RESEARCH AND DEVELOPMENT

FEDRATINIB

RISK MANAGEMENT PLAN

Version Number: 3.1

Data-lock Point for this RMP:15-Aug-2023

Date of final sign off: 15-Jul-2024

Bristol-Myers Squibb
P.O. Box 4000
Princeton, NJ 08543-4000
USA

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LIST OF ABBREVIATIONS

Term	Definition
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ASCT	allogeneic stem cell transplantation
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATMP	Advanced Therapy Medicinal Product
AUC	area under the concentration-time curve
AUC_{inf}	area under the plasma concentration time curve from time zero to infinity
AUC_{tau}	area under the plasma concentration time curve over the dosing interval
BAT	best available therapy
BCRP	Breast Cancer Resistance Protein
BMS	Bristol-Myers Squibb Company
BSEP	Bile Salt Export Pump
CCDS	Company Core Data Sheet
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events (NCI-CTCAE)
CYP	cytochrome P450
DBL	Database Lock
DILI	drug-induced liver injury
DIPSS	Dynamic International Prognostic Scoring System
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EEA	European Economic Area
ET	essential thrombocythaemia
EU	European Union
EURD	European Union reference dates
F1	first filial
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3

Term	Definition
FSFD	First Subject First Dose
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GI	Gastrointestinal
GL	Global Labeling
GLP	Good Laboratory Practice
GPV&E	Global Pharmacovigilance and Epidemiology
HA	health authority
hERG	human ether-a-go-go related gene
HI	hepatic impairment
HMRN	Haematological Malignancy Research Network
HR	heart rate
IC_{50}	half maximal inhibitory concentration
ICSRs	Individual Case Safety Reports
ICU	Intensive care unit
IITs	investigator-initiated trials
IND	investigational new drug
INN	nonproprietary name
IP	investigational product
IRB	institutional review board
JAK	Janus Associated Kinase
KP	Korsakoff's psychosis
LLN	Lower limit of normal
LSLV	Last Subject Last Visit
LVEF	left ventricular ejection fraction
MAH	Marketing Authorisation Holder
MATE	multi-antimicrobial extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MPL	myeloproliferative leukaemia
MPN	myeloproliferative neoplasm
MRP	multidrug resistance-associated protein
N/A	not applicable
OATP	organic anion-transporting polypeptide

Term	Definition
OCT	organic cation transporter
PASS	Post-authorisation safety study
PBPK	physiologically-based pharmacokinetic
P-gp	P-glycoprotein
PI	Product Information
PIL	Patient Information Leaflet
PK	pharmacokinetic(s)
PL	Package leaflet
PMF	primary myelofibrosis
Post-ET MF	post-essential thrombocythaemia myelofibrosis
Post-PV MF	post-polycythaemia vera myelofibrosis
PPI	proton pump inhibitor
PSMF	Pharmacovigilance System Master File
PSUR	periodic safety update report
PT	preferred term
PV	polycythaemia vera
Q	Quarter
QD	once daily
QPPV	Qualified Person Responsible for Pharmacovigilance
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia
RBC	red blood cell
RMP	Risk Management Plan
RR	relative risk
SAE	serious adverse event
SBD	Summary Basis of Decision
SmPC	Summary of product characteristics
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
SVR	spleen volume reduction
TBL	total bilirubin
TEAE	treatment-emergent adverse event
THTr	thiamine transporter
TYK2	tyrosine kinase 2
ULN	upper limit of normal

Term	Definition
US	United States
UTI	urinary tract infection
VEGF	vascular endothelial growth factor
WE	Wernicke's encephalopathy

EU RISK MANAGEMENT PLAN (RMP) FOR FEDRATINIB

RMP version to be assessed as part of this application:

Version Number: 3.1

Data-lock Point for this RMP: 15-Aug-2023

Date of Final Sign-off: 15-Jul-2024

Rationale for submitting an updated RMP:

Administrative merge of the recently EMA approved EU RMP version 2.0 and version 3.0.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	Update to main treatment options in Table 2.1.1-1	3.1 / pending
SII Non-clinical part of the safety specification	Updated key safety findings in Table 2.2-1	3.1 / pending
SIII Clinical trial exposure	N/A	1.0 / 08 Feb 2021
SIV Populations not studied in clinical trials	Updated exposure in Table 2.4.3-1	3.1 / pending
SV Post-authorisation experience	Updated post-authorisation exposure	3.1 / pending
SVI Additional EU requirements for the safety specification	N/A	1.0 / N/A
SVII Identified and potential risks	Updated to remove “use in patients with severe HI” as missing information from list of safety concerns Updated risk factor section with observation for fedratinib	3.1 / pending
SVIII Summary of the safety concerns	Updated to remove “use in patients with severe HI” as missing information from list of safety concerns	3.1 / pending
Part III Pharmacovigilance Plan	Updated status of study CP-001 from ongoing to complete	3.1 / pending
Part IV Plan for post-authorisation efficacy studies	N/A	1.0 / 08 Feb 2021
Part V Risk Minimization Measures	Updated to remove “use in patients with severe HI” as missing information from list of safety concerns	3.1 / pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
	Update to Table 5.1-1 for WE	
Part VI Summary of the Risk Management Plan	Updated to align with changes made in body of RMP Update to Section IIb for WE	3.1 / pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Updated status of study CP-001 from ongoing to complete	3.1 / pending
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	N/A	1.0 / 08 Feb 2021
ANNEX 4 Specific adverse drug reaction follow-up forms	Updated to include new version of questionnaires	3.1 / pending
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	N/A	1.0 / 08 Feb 2021
ANNEX 6 Details of proposed additional risk minimisation activities	N/A	1.0 / 08 Feb 2021
ANNEX 7 Other supporting data	Administrative update to include MedDRA terms	3.1 / pending
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include Version 3.1	3.1 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None	N/A	N/A

Details of the currently approved RMP:

Version number: Version 2.0

Approved with procedure: EMEA/H/C/005026/II/0019

Date of approval (opinion date): 30-May-2024

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	fedratinib
Pharmacotherapeutic group(s) (ATC Code)	L01XE57
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	INREBIC
Marketing authorisation procedure	Centralised
Brief description of the product	*N*-tert-butyl-3-[(5-methyl-2-{ [4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino]benzenesulfonamide dihydrochloride monohydrate. Summary of mode of action: Fedratinib is a kinase inhibitor with activity against wild type and mutationally activated JAK2 and FLT3. Fedratinib is a JAK2-selective inhibitor with higher inhibitory activity for JAK2 over family members JAK1, JAK3 and TYK2. Fedratinib reduced JAK2-mediated phosphorylation of signal transducer and activator of transcription (STAT)3/5 proteins, and inhibited malignant cell proliferation *in vitro* and *in vivo.*
Hyperlink to the Product Information	Refer to proposed Product Information (PI)

Table 1-1: Product Details

Indication(s) in the EEA	**Current:** INREBIC is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post polycythaemia vera (PV) myelofibrosis (post-PV MF) or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, or have been treated with ruxolitinib. **Proposed:** Not applicable.
Dosage in the EEA	**Current:** The recommended dose of INREBIC is 400 mg QD. **Proposed:** Not applicable.
Pharmaceutical form (s) and strength(s)	**Current:** Fedratinib hard capsule, 100 mg. **Proposed:** Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Myelofibrosis

Table 2.1.1-1: Epidemiologic Characteristics of Myelofibrosis

Myelofibrosis	
Incidence	• Based on an exhaustive literature review of the published peer-reviewed literature in EMBASE and by reviewing online documentation from disease registries and relevant health registries in European countries, the incidence rate of PMF ranged from 0.3 to 0.5 per 100,000 per year.[1] • Age-adjusted incidence rate per 100,000 per year from two large United States (US) health plans between 2008 and 2010 were: 2.2 to 3.2 for any type of MF; 0.8 to 1.3 for PMF; 0.1 to 0.4 for post-PV MF; 0.2 to 0.4 for post-ET MF. Regardless of health plan, incidence rates were similar by year.[2] • Age-standardised incidence rate of PMF per 100,000 per year from the Haematological Malignancy Research Network (HMRN, covering a population of 3.8 million with detailed information about all patients diagnosed with a haematological malignancy within the HMRN region in the United Kingdom) was 0.6.[3]

Table 2.1.1-1: Epidemiologic Characteristics of Myelofibrosis

Myelofibrosis	
Prevalence	• The Swedish Myeloproliferative Neoplasm (MPN) Registry collected data for newly diagnosed MPN patients between January 2008 and December 2014. The incidence per 100,000 inhabitants was 0.66 for MF and 0.53 for MPN unclassified.[4] • The calculated incidence of MF from the Norwegian Cancer registry between 1995 and 2012 was between 0.2 to 0.5 per 100,000.[5] • Orphanet reported a prevalence for any MF of 2.7 per 100,000, while RARECARE reported a 15-year period prevalence of only 0.51 per 100,000 on 01 Jan 2003, for any MF.[1] • Age-adjusted prevalence per 100,000 from two large US health plans between 2008 and 2010 were: 3.6 to 5.7 for any type of MF; 1.3 to 2.3 for PMF; 0.3 to 0.7 for post-PV MF; 0.5 to 1.1 for post-ET MF. In both health plans, prevalence increased over time.[2] • The Working Group of MPN of the Bulgarian Society of Hematology (10 centres) reported a prevalence of MF in Bulgaria of 5.4/100,000 between 2014 and 2015.[6] • The calculated prevalence of MF from the Norwegian Cancer registry between 1995 and 2012 was 3.0 per 100,000.[5]
Demographics of the population: age, gender, racial and/or ethnic origin	• Based on an exhaustive literature review of the published peer-reviewed literature in EMBASE and by reviewing online documentation from disease registries and relevant health registries in European countries, there was a higher incidence of MF in males than females, while the median age of diagnosis was between 69 and 76 years.[1] • Women accounted for 49.5% and 47.6% MF cases, respectively, in two large US health plans between 2008 and 2010. The mean ages of patients with MF in the two health plans were 61 and 67 years, respectively.[2]
Risk factors for the disease	• Exposure to petrochemicals, such as benzene and toluene, and ionising radiation may increase the risk of developing MF.[7] • About 50% of people with MF have a mutation called “V617F JAK2” found in the JAK2 gene.[8] • Accumulation of mutated alleles such as JAK2V617F and CALR plays a role in the process of transformation of PV and ET to MF.[9] Myeloproliferative leukaemia (MPL) mutated ET patients had a greater likelihood of transforming to post-ET MF compared to other genotypes, but the difference did not reach statistical significance.[9] • In a Mayo Clinic study with 120 patients who underwent therapeutic splenectomy for MF, driver mutations were known in 89 patients: JAK2 - 67 (75%), CALR - 13 (15%), MPL - 4 (4%) and triple-negative - 5 (6%).[10]
Main treatment options	• Allogeneic stem cell transplantation (ASCT) is currently the only treatment that can induce long-term remission in patients with MF. The average age at diagnosis of MF is 65 years; thus, the majority of patients are not eligible for ASCT. Therefore, the treatment options are primarily symptom oriented, to help mitigate the clinical presentation of anaemia, splenomegaly, constitutional symptoms and, less commonly, increased levels of platelets, and white blood cells. So far, none of these has shown an anticlonal effect, although

Table 2.1.1-1: Epidemiologic Characteristics of Myelofibrosis

Myelofibrosis	

alleviation in spleen size and splenic discomfort, symptoms and anaemia have been shown.[11]

- The understanding of MPNs and the molecular mechanisms of the disease have been expanding. In 2005, the JAK2V617F mutation was discovered and observed in approximately 50% to 60% of patients with PMF or ET and 90% to 95% of patients with PV. JAK2V617F and other mutations in patients with MPNs were found to activate the JAK/signal transducers and STAT pathway (JAK2 exon 12, myeloproliferative leukaemia and adaptor protein LNK).[12,13,14] These findings established the dysregulation of the JAK signalling pathway as the major contributor to the pathogenesis of MPNs. It has also translated into the development of small molecule JAK inhibitors.
- The JAK1/2 inhibitor ruxolitinib is approved in the EU for the treatment of disease related splenomegaly or symptoms in adult patients with PMF (also known as chronic idiopathic MF), post-PV MF or postET MF. Another JAK inhibitor, momelotinib, received CHMP opinion on 09-Nov-2023, recommending the granting of a marketing authorization for the medicinal product Omjjara, intended for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate-to-severe anaemia who have primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis.
- The registration of ruxolitinib was based on two randomised, controlled studies (COMFORT-I and COMFORT-II) that compared ruxolitinib to placebo and to the best available therapy (BAT), respectively.[15,16] The studies demonstrated benefit, with a higher proportion of subjects in the ruxolitinib arms exhibiting a ≥ 35% reduction in spleen volume as measured by magnetic resonance imaging (MRI) at 24 weeks in COMFORT-I (41.9% ruxolitinib versus 0.7% placebo) and at 48 weeks in COMFORTII (28% ruxolitinib versus 0% BAT). In COMFORT-I, there was a > 50% improvement in the Myelofibrosis Symptom Assessment Form (MFSAF) Total

  Symptom Score at 24 weeks in 45.9% of subjects on ruxolitinib compared with 5.3% of subjects on placebo. Improvement of survival compared with BAT was also demonstrated based on the recent 3-year follow-up data from the COMFORT-II study. The Kaplan-Meier estimated probability of survival at 144 weeks was 81% in the ruxolitinib arm and 61% in the BAT arm.[17]

  The positive CHMP opinion of momelotinib was based on wo Phase III trials (MOMENTUM and SIMPLIFY-1) that compared momelotinib to danazol and to ruxolitinib, respectively.[18,19] In the MOMENTUM trial, a significantly greater proportion of subjects in the momelotinib arm reported a 50% or more reduction in MFSAF Total Symptom Score vs the danazol arm (25% vs 9%) and a higher proportion of subjects achieved transfusion independence at Week 24 in the momelotinib arm vs the danazol arm (30% vs 20%). A higher proportion of subjects in the momelotinib arm also reported a 35% or more reduction in spleen volume from baseline at Week 24 vs the danazol arm (22% vs 3%). In the SIMPLIFY-1 trial, a similar proportion of subjects in the momelotinib arm achieved a 35% or more reduction in spleen volume from baseline at Week 24 vs the ruxolitinib arm (26.5% vs 29%, respectively), demonstrating noninferiority of momelotinib compared to ruxolitinib.

  Other therapeutic options for MF include erythropoiesis-stimulating agents, danazol, and immunomodulatory drugs for improvement of anaemias and hydroxyurea, interferon, and rarely splenectomy for the treatment of splenomegaly and/or constitutional symptoms.[20]

Table 2.1.1-1: Epidemiologic Characteristics of Myelofibrosis

Myelofibrosis	
Mortality and morbidity (natural history)	• Myelofibrosis is a serious and life-threatening MPN that is characterised by stem cell-derived clonal myeloproliferation, abnormal cytokine expression, bone marrow fibrosis, anemia, splenomegaly, extramedullary hematopoiesis, constitutional symptoms, cachexia, leukemic progression, and shortened survival. [21] • Myelofibrosis can either present de novo as PMF or following a previously diagnosed PV and ET (post-PV MF and post ET MF, respectively [ie, secondary MF]).[20,22] Post-PV and MF post-ET MF are both clinically indistinguishable from PMF and develop from prior PV and ET due to fibrotic transformation and progressive bone marrow fibrosis. These conditions are clinically named MPN associated MF.[23] • MF causes no symptoms in 30% of patients initially, whereas other patients have symptoms caused by cytopenias, leukocytosis, thrombocytosis, thrombosis, infections, aquagenic pruritus, splenomegaly, bone pain and constitutional symptoms.[24] • Leukaemic transformation is common in patients with MF. The 10-year risk of leukaemic transformation for patients with PMF has been estimated at 12% to 31%, depending on the presence of thrombocytopenia and/or unfavourable karyotype.[25] Patients with MPN associated MF have similar survival and prognoses to that of patients with PMF and a 5% to 10% cumulative risk of transformation to acute myeloid leukaemia (AML).[26] • Multivariate analysis of 649 patients with MF identified a bone marrow blast level of 10% or greater and high-risk karyotype (17p–, –5, –7, or complex karyotype) as independent predictors of leukaemic transformation; the risk at 1 year was 13% for those with one or both risk factors versus 2% for those with neither of these. Certain somatic mutations (TET2, ASXL1, IDH1/2, EZH2, DNMT3A and TP53) are associated with transformation to AML.[24] • Several prognostic scoring systems that predict survival in patients with MF are used, including the Dynamic International Prognostic Scoring System (DIPSS).The DIPSS scoring system takes into account several individual prognostic variables such as age, constitutional symptoms, haemoglobin, white blood cell count and presence of peripheral blood blasts, and can be utilized at the time of disease diagnosis and at any point during the course of their disease. In assigning a point value for each of these independent risk factors, (age > 65 years, presence of constitutional symptoms, leukocyte levels > 25 × 10^9/L, and blood myeloblasts ≥ 1%) each are associated with a point value of 1, whereas a haemoglobin concentration < 10 g/dL accounts for 2 points. Together, these factors and associated point values stratify patients into one of four different prognostic risk categories: low risk (0 points), intermediate-1 (1 or 2 points), intermediate-2 (3 or 4 points), and high-risk (5 or 6 points) categories. Median survival was not reached in low-risk patients; it was 14.2 years in intermediate-1, 4 years in intermediate-2 and 1.5 years in high-risk categories.[27] Patients with MF might progress into blast-phase disease. For post-ET MF, reported risk factors for leukemic transformation include advanced age, extreme thrombocytosis, anaemia, leukocytosis and sequence variants/mutations involving TP53 and EZH2; for post-PV MF, advanced age, leukocytosis, abnormal karyotype, mutations involving SRSF2 and IDH2, and treatment with pipobroman, chlorambucil, or P32; and for PMF, increased blast percentage, thrombocytopenia, abnormal karyotype, triple-negative driver mutational status, and sequence variants/mutations involving SRSF2, RUNX1, CEBPA, and SH2B3. For MF patients with blast-phase disease, the median survival from time of diagnosis ranges anywhere from 1.5 to 10 months. The 10-year incidence rates for

Table 2.1.1-1: Epidemiologic Characteristics of Myelofibrosis

Myelofibrosis	
	development of transformation to blast phase in PMF, post-ET MF and post-PV MF is 10% to 20%, 2.3% and < 1%, respectively.[28]
Important co-morbidities	Important comorbidities of MF are:[29,30] • Hypertension • Diabetes mellitus • Solid tumours • Angina/coronary artery disease • Venous disease.

2.2 Nonclinical Part of the Safety Specification

A summary of the significant nonclinical findings and their relevance to human usage is outlined in Table 2.2-1

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (non-clinical studies)	Relevance to Human Usage
Toxicology	
• Bone Marrow and Lymphoid Tissue In repeat-dose studies, bone marrow hypoplasia was observed in mice, rats and dogs. In dogs, increased myeloid progenitor cells consistent with ineffective myelopoiesis were also observed. Infiltrates of myeloid progenitor cells were also noted in the spleen and liver in the 9-month study in dogs; this increase in myeloid progenitor cells was considered to represent an attempt at bone marrow/haematologic recovery. Lymphoid depletion and/or atrophy was observed in the spleen, thymus, gut-associated lymphoid tissue and/or lymph nodes in all species. In rats, histiocytic infiltrates were observed in the mesenteric lymph nodes. Pneumonia and/or abscesses were also observed at lethal dosages in both studies, possibly secondary to effects on the immune system associated with the changes in the bone marrow and lymphoid organs.	In clinical studies, anaemia was the most frequent haematological toxicity and thrombocytopenia was observed in patients previously exposed to ruxolitinib. Dose modifications (including reductions) to be made in case of haematologic toxicity are described in Section 4.2 of the SmPC. Monitoring of complete blood counts is recommended in Section 4.4 of the SmPC. Anaemia and thrombocytopenia are described in Section 4.8 of the SmPC. There is an increased risk of infections both in patients with MF, as well as in patients treated with other JAK inhibitors. Although a review of the fedratinib Pool 1 safety data did not reveal evidence of an increased risk of severe infections in MF patients treated with fedratinib, severe infections, including viral reactivation, will be monitored in ongoing clinical studies and in the post-marketing environment.
• Gastrointestinal (GI) Tract GI tract-associated clinical signs, including vomiting, soft stool and diarrhoea, were prominent observances in the repeat-dose studies in dogs, at all doses. The highest dose group in the 9-month study, which was sacrificed early, showed internal bleeding related to	In the clinical program, GI toxicities including nausea, vomiting and diarrhoea were amongst the most frequently reported TEAEs for fedratinib. Despite the high rate of GI toxicities early on, permanent discontinuation was infrequent. The risk can be successfully managed by supportive treatments and dose

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

ulcers and chronic-active inflammation of the oesophagus and stomach. This finding was likely secondary to stress and severe toxicity observed in these animals. Since no histologic correlates were observed at lower doses, the GI signs observed in dogs were considered related to nausea and alterations in GI motility, perhaps through interactions with non-JAK receptors in the gut. GI tract-associated clinical signs were observed at non-tolerated doses in the nonpivotal studies in rats. In mice, non-glandular ulceration/inflammation and glandular hypertrophy of the stomach was noted.	interruption in more severe cases. This advice is included in Sections 4.2 and 4.4 in the SmPC.
• Reproductive and Developmental Toxicity In a rat fertility study, fedratinib had no effect on oestrous cycle parameters, mating performance, delay before mating, fertility, pregnancy rate or reproductive parameters at any dosage level. Fedratinib produced evidence of embryo-foetal toxicity in the rat including: increased post-implantation loss, lower foetal body weights and skeletal effects (additional ossification centres on the cervical vertebral neural arches). Fedratinib produced no evidence of embryo-foetal toxicity in the rabbit. In a rat pre- and post-natal development study, treatment with fedratinib resulted in decreased maternal body weight gain and first filial (F1) generation pup body weight and food consumption at various intervals during the study. There was no effect on any developmental landmark or behavioural assessments. F1 mating, fecundity and fertility indices and Gestation Day 13 caesarean section parameters were unaffected. In a 28-day toxicity study in dogs, epididymal and testicular aspermia and oligospermia and seminiferous tubule degeneration were observed in moribund sacrificed animals.	There are no studies with the use of fedratinib in pregnant women to inform drug-associated risks. In assessing the relevance of the observations from reproductive and developmental toxicity studies, it is important to point out that, because humans are less sensitive to the toxicities of fedratinib than animals, the plasma exposures (maximum concentration [C_{max}] and AUC) achieved in patients in clinical studies have exceeded the highest exposures achieved in rats and rabbits in these studies. This limits the value of these studies in predicting the exposures that may be associated with potential effects on reproduction and development in humans.
• Nephrotoxicity No separate studies were performed to investigate nephrotoxicity. In a repeat-dose toxicity study, mice exhibited renal tubule degeneration and necrosis.	Generally asymptomatic Grade 1 and 2 increases of creatinine were observed in patients taking fedratinib. These effects are described in Section 4.8 of the SmPC. Dose reductions and monitoring for patients with severe renal impairment are described in Section 4.2 of the SmPC.
• Hepatotoxicity No separate studies were conducted to assess hepatotoxicity. In repeat-dose toxicity studies, bile duct hypertrophy and necrosis were observed in rats and bile duct epithelial hypertrophy and proliferation were	Primarily asymptomatic Grade 1 and 2 increases of ALT and AST were observed in patients taking fedratinib. Monitoring of hepatic function at baseline, at least monthly for the first 3 months and as clinically indicated is recommended in Section 4.4 of the SmPC, dose modifications are described in Section 4.2 of the SmPC

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

observed in dogs. Also in dogs, more exaggerated liver effects were observed at lethal dosages. These effects included bile duct epithelial degeneration/regeneration and necrosis (sometimes with fibrosis and inflammation), hepatocellular necrosis, Kupffer cell hyperplasia, cholestasis and arterial mural necrosis.	and ALT and AST elevations are described in Section 4.8 of the SmPC.
• Genotoxicity Fedratinib was negative in the in vitro Ames assay in bacterial cells, the in vitro chromosomal assay in Chinese hamster ovary cells and the in vivo micronucleus test in rats.	Not applicable
• Carcinogenicity In a 6-month carcinogenicity study in transgenic mice, there were no neoplasms that were attributed to treatment with fedratinib.	Transformation to AML is not unexpected in MPN subjects, in particular in the MF population. No transformation to AML occurred in solid tumour subjects (ISS Listing 6.2). A review of the clinical database confirmed that the rate of transformation to AML for all fedratinib-treated subjects was within the expected rate for this population; however, this assessment is confounded by limited long-term follow-up data due to the clinical hold and termination of the clinical development programme by the sponsor. No trends for increased rates of other secondary malignancies were observed. There were no reports of lymphoma. The review of the cases of secondary malignancies, including transformation to AML, does not suggest an increased risk in fedratinib-treated subjects.
General Safety Pharmacology	
• Cardiovascular The half maximal inhibitory concentration (IC_{50}) values for inhibition of human ether-a-go-go related gene (hERG) channel assessed in one non-Good Laboratory Practice (GLP) and one GLP study were 17.5 µM and 2.1 µM, respectively. In a study of 11 cardiac ion channels, IC_{50} values ranged from 2.8 to 31.2 µM. In a cardiovascular and respiratory study at dosages up to 20 mg/kg (400 mg/m^2) in conscious telemetered beagle dogs, fedratinib produced no clinical observations. Body weights, core body temperature and food consumption were not altered. There were no fedratinib-related changes in blood pressure (diastolic, systolic and mean arterial pressure), heart rate (HR), or electrocardiogram (ECG) intervals (PR, QRS, QT and corrected QT interval [QTc]). Respiratory rate and arterial blood gases were not altered by fedratinib.	In assessing the relevance of the observations from in vivo safety pharmacology studies, it is important to point out that, because humans are less sensitive to the toxicities of fedratinib than are animals, the plasma exposures (C_{max} and AUC) achieved in patients in clinical studies have exceeded the highest exposures achieved in rats and dogs in these studies. This limits the value of these studies in predicting the exposures that may be associated with potential effects on safety pharmacology parameters in humans. In humans, a lack of significant QTc prolongation by fedratinib is confirmed in the dedicated QT study TES13519, with the upper bound of the 2-sided 90% CI being lower than 10 msec for the largest time-matched mean difference in corrected QT interval by Fridericia (QTcF) between fedratinib and placebo. Supportive information was provided by two additional studies. No large changes in the mean QTc interval (ie, > 20 msec) from baseline were detected in fedratinib-treated patients in the Phase 1 study, TED12037, and the pivotal study Phase 3 study, EFC12153. Fedratinib treatment,

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

	furthermore, did not induce clinically relevant HR changes.
• Nervous system Fedratinib inhibited ligand binding at a number of central nervous system (CNS) receptors and/or transporters (eg, adenosine, muscarinic, serotonin, sigma and Na+ channel receptors and norepinephrine, dopamine and serotonin transporters) and had low nanomolar IC_{50} values for two muscarinic receptors and the dopamine transporter. However, in an in vivo neurobehavioural study in the rat, fedratinib produced no changes in CNS activity and excitability, autonomic nervous system activity, sensorimotor activity, or neuromuscular activity, nor was there evidence for neurobehavioural effects related to activity at CNS receptors in the repeat-dose mouse, rat and dog toxicology studies; the clinical signs that were observed in these studies were considered to be related to poor health and/or a moribund state.	Effects of fedratinib on the nervous system include primarily Grade 1 or 2 headaches and dizziness (10% and 9%, respectively, in patients taking 400 mg in the clinical studies) and are included in SmPC Section 4.8. Additionally, 8 patients with potential encephalopathy, including Wernicke's, were identified in 608 patients treated with multiple doses of fedratinib in the clinical programme. Wernicke's encephalopathy is an acute neurological condition resulting from thiamine (Vitamin B1) deficiency. Signs and symptoms of Wernicke's encephalopathy (WE) may include ataxia, mental status changes and ophthalmoplegia (eg, nystagmus, diplopia) (see Section 4.4 of the SmPC). Of the eight patients, seven with potential encephalopathy, including Wernicke's, were taking fedratinib at 500 mg daily prior to the onset of neurologic findings and had predisposing factors for WE such as malnutrition, weight loss and/or GI adverse events (AEs) that could have led to thiamine deficiency. One case was confirmed to be WE and one case was determined to be hepatic encephalopathy (patient was treated with fedratinib at 400 mg). Most events resolved with some residual neurological symptoms including memory loss, cognitive impairment and dizziness, except for one patient (who was included in a study for another indication) with head and neck cancer, brain metastasis, difficulty eating secondary to partial mandibulectomy and severe malnutrition, who had a fatal outcome.
Mechanisms for Drug Interactions	
• Fedratinib as a Substrate and Effect of Other Drugs on Fedratinib Fedratinib is metabolised by multiple cytochrome P450s (CYPs) in vitro with the predominant contribution from CYP3A4 and with a lesser contribution from CYP2C19 and flavin-containing monooxygenases (Module 2.7.2, Section 3.2.3, Section 3.4). In vitro, fedratinib is a substrate of P-glycoprotein (P-gp) but not Breast Cancer Resistance Protein (BCRP), Bile Salt Export Pump (BSEP), multidrug resistance-associated protein (MRP), MRP2, organic anion-transporting polypeptide (OATP)1B1 and OATP1B3. Based on cumulative data, clinically significant interaction with P-gp inhibitors is not expected to occur with fedratinib (Module 2.7.2, Section 3.4.5).	Agents that strongly or moderately induce CYP3A4 (eg, phenytoin, rifampicin, efavirenz) may decrease fedratinib plasma concentrations and should be avoided in patients receiving fedratinib. Concomitant administration of fedratinib with strong CYP3A4 inhibitors increases fedratinib exposure (Study INT12893; Fedratinib-DMPK-2852), requiring fedratinib initial dose to be reduced to 200 mg with a strong CYP3A4 inhibitor. Concomitant administration of fedratinib with a dual inhibitor of CYP2C19 and CYP3A4 increases fedratinib exposure (Study FEDR-CP-004). Therefore, patients taking concomitant inhibitors of CYP3A4 and CYP2C19 may require more intensive safety monitoring and if necessary, dose modifications of Inrebic based on adverse reactions. No clinically meaningful effect on the pharmacokinetics (PK) of fedratinib was observed upon administration of fedratinib with the proton pump inhibitor (PPI), pantoprazole (Study INT12894).

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

• Effect of Fedratinib on Other Drugs In vitro, fedratinib inhibits P-gp, BCRP, multi-antimicrobial extrusion protein (MATE)1, MATE2-K, OATP1B1, OATP1B3, organic cation transporter (OCT)2, but not BSEP, MRP2, OAT1 and OAT3. While the simulations suggest a minor potential of drug interaction from inhibition of transporters by fedratinib, the clinical significance of these potential drug interactions is not known (Module 2.7.2, Section 3.4.6 and Section 3.4.6.2).	Co-administration of fedratinib with drugs that are CYP3A4 substrates, CYP2C19 substrates, or CYP2D6 substrates increases the concentrations of these drugs, which may increase the risk of adverse reactions of these drugs. Monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates as necessary when co-administered with fedratinib.
Other Toxicity-related Information or Data	
In an in vitro study, the maximum percentage of inhibition of thiamine transporter (THTr)1 and THTr2 observed at 300 μM fedratinib was 24.5% and 44.2%, respectively. The IC_{50} values were estimated to be > 300 μM for both transporters. Rats administered fedratinib for 28 days at a dose comparable to that used to treat human cases of MF (2.27 mg per day, intraperitoneal) showed no evidence of clinical signs of thiamine deficiency or any effect on erythrocyte transketolase activity and thiamine status. Also, treatment of cultured astrocytes with fedratinib did not diminish the uptake of thiamine into these cells. An additional, pivotal 28-day repeat-dose study conducted in rats showed that fedratinib administration up to 80 mg/kg had no effect on thiamine concentration in the plasma or brain.	Although a previous in vitro study showed no direct inhibition on human thiamine transporters (IC50 > 300 μM), a recent external study indicated that fedratinib inhibited thiamine transport in Caco-2 (IC50 = 6.5 μM) and thiamine uptake in HEK293-hTHTR2 cells (IC50 = 1.2 μM).[31] In vivo studies demonstrated a lack of effect of fedratinib on thiamine concentration in plasma or brain in rats, and no evidence of thiamine deficiency or any effect on erythrocyte transketolase activity and thiamine status. Information on the risk of encephalopathy, including Wernicke's, is provided in the SmPC. A recommendation for prophylaxis and monitoring of thiamine levels and nutritional status for all patients prior to starting treatment, periodically during treatment and as clinically indicated is included in Section 4.4 of the SmPC. Guidance on thiamine replenishment is provided in Section 4.2 of the SmPC. Language in Section 4.4 of the SmPC describes the signs and symptoms of WE, and the need for immediate evaluation and intervention should WE be suspected. Based on the concern of GI AEs contributing to thiamine deficiency, recommendations for appropriate prophylaxis for nausea and vomiting during fedratinib treatment and supportive treatment initiated at the first signs of diarrhoea are included in Section 4.4 of the SmPC. Dose modification guidelines for ≥ Grade 3 nausea, vomiting or diarrhoea not responding to supportive measures within 48 hours, thiamine abnormalities and symptomatic WE are included in Section 4.2 of the SmPC.

2.2.1 Conclusions on Nonclinical Data

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 2.2.1-1

Table 2.2.1-1: Nonclinical Safety Concerns

Important Identified Risks	Anaemia
	Thrombocytopenia/bleeding
	Encephalopathy, including Wernicke's
	Gastrointestinal toxicities (diarrhoea, nausea, vomiting)
Important Potential Risks	Pancreatitis
	Severe hepatotoxicity
	Severe infections including viral reactivation
Missing Information	Use in patients with severe hepatic impairment
	Long-term safety, including secondary malignancies

2.3 Clinical Trial Exposure

2.3.1 Clinical Study Information

An overview of the fedratinib clinical program summarized in this RMP is in Table 2.3.1-1.

Table 2.3.1-1: Fedratinib Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number	Study Title/Design	Last patient last visit dates
Myelofibrosis		
	Safety Pool 1	
EFC12153 (JAKARTA)	A multicentre, randomised, double blind, placebo controlled, 3 arm Phase 3 study to evaluate the efficacy and safety of daily doses of 400 mg or 500 mg of fedratinib (SAR302503) compared with placebo in patients with intermediate-2 or high-risk PMF, post PV MF, or post ET MF with splenomegaly	24-Jul-2014
ARD12181 (JAKARTA2)	A Phase 2, single-arm, open label, multicentre study to determine the efficacy, safety, PK and pharmacodynamics of fedratinib (SAR302503) in patients previously treated with ruxolitinib and with a current diagnosis of intermediate-1	12 Jun 2014

Table 2.3.1-1: Fedratinib Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number	Study Title/Design	Last patient last visit dates
	with symptoms, intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF	
ARD11936	A Phase 2, multicentre, randomised, open label, dose ranging, study to evaluate the efficacy, safety, PK and pharmacodynamics of fedratinib (SAR302503) in patients with intermediate 2 or high risk MF, post PV MF, or post ET MF with splenomegaly	21 May 2014

2.3.2 Clinical Trial Exposure

Exposure for the studies varied due to study start date because all clinical development was placed on hold by the US FDA on 15-Nov-2013 and subsequently terminated by the sponsor on 18-Nov-2013 following reports of WE in patients treated with fedratinib across the fedratinib clinical development programme. As the primary endpoint for JAKARTA was 6 cycles, patients in the placebo arm were treated for 6 cycles and then had the option to crossover to active treatment. The median duration of treatment exposure in JAKARTA2 was 24.4 weeks (approximately 6 cycles); therefore, the 6-cycle duration of treatment was determined as the best comparison for safety data for the cumulative presentation (EFC12153 [JAKARTA], ARD12181 [JAKARTA2] and ARD11936; Table 2.3.2-1).

The duration of exposure in patients with MF treated with fedratinib with exposure by gender, age group, and race are provided in Table 2.3.2-2,Table 2.3.2-3, and Table 2.3.2-4 respectively.

Table 2.3.2-1: Duration of Exposure (Cumulative for All Indications)

Duration of Exposure (at least)	**Patients,** n (%)	**Person Time,** years
1 cycle	321 (100)	280.91
3 cycles	290 (90)	278.64
6 cycles	234 (73)	263.19
12 cycles	159 (50)	218.88
18 cycles	75 (23)	121.15
24 cycles	16 (5)	32.86
Total person time	321 (100)	280.91

Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Table 2.3.2-2: Clinical Exposure by Gender (Cumulative for All Indications)

Gender	**Patients,** n (%)	**Person Time,** years
Male	184 (57)	166.63
Female	137 (43)	114.28
Total	321 (100)	280.91

Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Table 2.3.2-3: Clinical Exposure by Age Group (Cumulative for All Indications)

Age Group	**Patients,** n (%)	**Person Time,** years
≥ 85 years	1 (0.3)	0.88
< 85 years	320 (99.7)	280.03
≤ 75 years	283 (88)	254.64
> 75 years	38 (12)	26.27
≤ 65 years	170 (53)	164.16
> 65 years	151 (47)	116.75
< 18 years[a]	0	0
Total	321 (100)	280.91

[a] Paediatric patients were excluded from the clinical study programme.

Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Table 2.3.2-4: Clinical Exposure by Ethnic or Racial Origin (Cumulative for All Indications)

Ethnic/racial origin	**Patients,** n (%)	**Person Time,** years
White	286 (89.1)	246.40
Black or African American	6 (1.9)	4.04
Asian	28 (8.7)	29.03
Other	1 (0.3)	1.44
Other – Hispanic	1 (0.3)	1.44
Total	321 (100)	280.91

Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

400mg Fedratinib

The duration of exposure in patients with MF assigned to 400 mg fedratinib in Safety Pool 1 is provided in Table 2.3.2-5, with exposure by gender, age group, and race provided in Table 2.3.2-6, Table 2.3.2-7 and Table 2.3.2-8 respectively.

Table 2.3.2-5: Duration of Exposure (Cumulative for All Indications) - Patients Assigned to 400mg Fedratinib

Duration of Exposure (at least)	**Patients,** n (%)	**Person Time,** years
1 cycle	203 (100)	164.02
3 cycles	189 (93)	162.92
6 cycles	147 (72)	151.02
12 cycles	87 (43)	116.25
18 cycles	41 (20)	63.88
24 cycles	4 (2)	8.44
Total person time	203 (100)	164.02

By assigned dose group
Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Table 2.3.2-6: Clinical Exposure by Gender (Cumulative for All Indications) - Patients Assigned to 400mg Fedratinib

Gender	**Patients,** n (%)	**Person Time,** years
Male	113 (56)	91.73
Female	90 (44)	72.29
Total	203 (100)	164.02

By assigned dose group
Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Table 2.3.2-7: Clinical Exposure by Age Group (Cumulative for All Indications) - Patients Assigned to 400mg Fedratinib

Age Group	**Patients,** n (%)	**Person Time,** years
≥ 85 years	1 (0.5)	0.88
< 85 years	202 (99.5)	163.15
≤ 75 years	178 (88)	148.59
> 75 years	25 (12)	15.43
≤ 65 years	107 (53)	96.65
> 65 years	96 (47)	67.37
< 18 years[b]	0	0
Total	203 (100)	164.02

[a] Paediatric patients were excluded from the clinical study programme.

By assigned dose group.
Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Table 2.3.2-8: Clinical Exposure by Ethnic or Racial Origin (Cumulative for All Indications) - Patients Assigned to 400mg Fedratinib

Ethnic/racial origin	**Patients,** n (%)	**Person Time,** years
White	187 (92.1)	148.25
Black or African American	2 (1.0)	1.64
Asian	13 (6.4)	12.70
Other	1 (0.5)	1.44
Other – Hispanic	1 (0.5)	1.44
Total	203 (100)	164.02

By assigned dose group.
Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Placebo

The duration of exposure in patients with MF in Safety Pool 1 assigned to placebo is provided in Table 2.3.2-9, with exposure by gender, age group, and race provided in Table 2.3.2-10, Table 2.3.2-11 and Table 2.3.2-12, respectively.

Table 2.3.2-9: Duration of Exposure (Cumulative for All Indications) - Patients Assigned to Placebo

Duration of Exposure (at least)	**Patients,** n (%)	**Person Time,** years
1 cycle	1 cycle	95 (100)
3 cycles	3 cycles	80 (84)
6 cycles	6 cycles	61 (64)
12 cycles	12 cycles	0
18 cycles	18 cycles	0
24 cycles	24 cycles	0
Total person time	95 (100)	36.03

Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Table 2.3.2-10: Clinical Exposure by Gender (Cumulative for All Indications) - Patients Assigned to Placebo

Gender	**Patients,** n (%)	**Person Time,** years
Male	54 (57)	19.87
Female	41 (43)	16.16
Total	95 (100)	36.03

Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Table 2.3.2-11: Clinical Exposure by Age Group (Cumulative for All Indications) - Patients Assigned to Placebo

Age Group	**Patients,** n (%)	**Person Time,** years
≥ 85 years	1 (1.1)	0.46
< 85 years	94 (98.9)	35.57
≤ 75 years	89 (94)	33.51
> 75 years	6 (6)	2.52
≤ 65 years	44 (46)	16.72
> 65 years	51 (54)	19.30
< 18 years[c]	0	0
Total	95 (100)	36.03

[a] Paediatric patients were excluded from the clinical study programme.
Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

Table 2.3.2-12: Clinical Exposure by Ethnic or Racial Origin (Cumulative for All Indications) - Patients Assigned to Placebo

Ethnic/racial origin	**Patients,** n (%)	**Person Time,** years
White	89 (93.7)	33.49
Black or African American	1 (1.1)	0.46
Asian	5 (5.3)	2.08
Other	0	0
Other – Hispanic	0	0
Total	95 (100)	36.03

Person time (years) is calculated as ((date of last dose – date of first dose) + 1)/365.25.
Includes data from Studies EFC12153, ARD12181 and ARD11936.

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Age < 18 years	Studies were conducted in the target population for the indication.	No	Fedratinib is not indicated for the treatment of patients aged < 18 years.
Hepatic impairment (AST or ALT ≥ 2.5 × ULN and TBL ≥ 3.0 × ULN)	Safety reasons. Fedratinib is metabolised in the liver.	No	In CP-001 a study conducted to characterize the effects of moderate and severe HI on the PK of fedratinib has been completed. In this study 8 patients had moderate and received 300 mg fedratinib and 8 patients had severe hepatic impairment and received 200 mg fedratinib. Instructions for this populatopm are addressed in the SmPC (Section 4.2).
Significant active cardiac disease	Interference with study endpoint analysis. Significant active cardiac disease (including New York Heart Association Class III or IV congestive heart failure or left ventricular ejection fraction [LVEF] < 40%) was an exclusion criterion for all fedratinib studies to avoid interference with the study endpoints.	No	No effects on LVEF, ECG variables, or vital signs have been observed in studies with fedratinib. In humans, a lack of significant QTc prolongation by fedratinib is confirmed in the dedicated QT study TES13519, with the upper bound of the 2-sided 90% CI being lower than 10 msec for the largest time-matched mean difference in QTcF between fedratinib and placebo. The type and incidence of cardiovascular treatment-emergent adverse events (TEAEs) were consistent with what could be expected in the population of older patients with advanced haematological malignancies especially MF.
Pregnant women	Safety reasons based on results from the nonclinical embryo foetal development toxicity studies.	No	Effects of fedratinib on pregnancy included increased post implantation loss, reduced foetal weights and increased incidence of skeletal variations in rats, all at exposures lower than achieved in human subjects at the currently recommended highest human dose. There was one report of ectopic pregnancy from ARD12042, a study in patients with PV and essential thrombocytosis. The patient had essential thrombocytosis, which carries a risk of ectopic pregnancy. Otherwise there are no other data on the use of fedratinib in pregnant women.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			Fedratinib is contraindicated during pregnancy (Section 4.3 of the SmPC).
Breast-feeding	Many drugs are excreted in human milk. It is not known whether fedratinib or its metabolites are excreted in human milk. Due to potential serious adverse reactions in the nursing child.	No	There are no data on exposure of breast-feeding patients. It is not known whether fedratinib is excreted in human milk. Studies of lacteal excretion of fedratinib in animals have not been conducted. A risk to human newborns/infants cannot be excluded.
Platelet count below 50×10^9/L	Safety reasons. Patients with low platelet counts at the start of therapy are more likely to develop thrombocytopenia of Grade 3 or above during treatment.	No	Guidance that initiating treatment with fedratinib is not recommended in patients with a baseline platelet count below 50×10^9/L is included in Sections 4.2 and 4.4 of the SmPC.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure (Table 2.4.2-1). Furthermore, patients with severe comorbidities in *Safety Pool 1* were excluded through exclusion criteria.

Table 2.4.2-1: Limitation of Study Programme Adverse Event Detection

Ability to Detect Adverse Reactions	Limitation of Study Programme	Discussion of Implications for Target Population
Which are rare or very rare	Patient numbers may not be sufficient to capture all rare (≥ 1/10,000 to < 1/1000) or very rare (< 1/10,000) adverse drug reactions (ADRs). A total of 321 patients with MF were exposed to fedratinib in Safety Pool 1 (Studies EFC12153, ARD12181, ARD11936).	With 321 patients with MF exposed to fedratinib in Safety Pool 1 (Studies EFC12153, ARD12181, ARD11936), at least one TEAE would be observed with a 95% probability of the true incidence being 0.929%.
Due to prolonged exposure	Of 321 MF patients treated with fedratinib in Safety Pool 1 (Studies EFC12153, ARD12181, ARD11936), 11 (3.4%) have been treated for at least 2 years.	It is not anticipated that the safety profile will be substantially different over time.

Table 2.4.2-1: Limitation of Study Programme Adverse Event Detection

Ability to Detect Adverse Reactions	Limitation of Study Programme	Discussion of Implications for Target Population
Due to cumulative effects which have a long latency	The clinical study programme may be limited in its ability to assess cumulative effects and effects with a long latency.	No cumulative effects have been identified for fedratinib.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

To ensure patient safety, specific populations of patients were excluded from the pivotal and supportive studies (Table 2.4.3-1). Thus, experience in these populations is limited.

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not applicable. These patients were excluded from the clinical study programme. There were no reports of pregnancy in patients with PMF, post PV MF, or post ET MF in Safety Pool 11.
Breastfeeding women	There was one report of pregnancy in Study ARD12042. A 35 year old patient with ET in the < 300 mg group in Study ARD12042 was reported with ectopic pregnancy on Day 418. Study drug was interrupted, and the patient underwent surgical evacuation of retained products of conception. The patient recovered on Day 460. Study drug was resumed.
Paediatric population	Not applicable. These patients were excluded from the clinical study programme and a paediatric product specific waiver is in place.
Patients > 75 years of age	A total of 38 (12%) patients in Safety Pool 1 were > 75 years old of which 25 were in the 400 mg dose group.
Patients with relevant comorbidities:	
Patients with hepatic impairment	In Safety Pool 1, 109 (34%) patients had mild to moderate baseline hepatic dysfunction of which 76 were in the 400 mg dose group. Patients with severe HI were excluded. In CP-001 a total of 38 patients were treated with a single oral dose of fedratinib on the morning of Day 1 administered under fasted conditions. 8 patients had moderate hepatic impairment and received 300 mg fedratinib (Group 1) and 8 patients had severe hepatic impairment and received 200 mg fedratinib (Group 3).
Patients with renal impairment	In Safety Pool 1, 218 (68%) patients had mild to moderate baseline renal dysfunction of which 135 were in the 400 mg dose group. Patients with severe renal impairment were excluded.
Patients with cardiovascular impairment	In Safety Pool 1, various cardiac disorders were reported in 99 (31%) patients, of which 59 were in the 400 mg dose group. Patients with Uncontrolled congestive heart failure (New York Heart Association Classification 3 or 4), angina, myocardial infarction, cerebrovascular accident, coronary/peripheral artery

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
	bypass graft surgery, transient ischaemic attack, or pulmonary embolism within 3 months prior to initiation of investigational medicinal product were excluded.
Immunocompromised patients	Not applicable. These patients were excluded from the clinical study programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable. These patients were excluded from the clinical study programme.
Population with relevant different ethnic origin	Fedratinib is primarily metabolised by CYP3A4 that is not polymorphically expressed and is not different in Black or African American and Caucasian populations. Of a total of 321 fedratinib-treated patients in Safety Pool 1[a], there were 286 (89%) white patients, 28 (9%) Asian patients, 6 (1.9%) Black or African American patients and 1 (0.3%) patient in the race subgroup 'Other'. Of the 38 fedratinib-treated subjects in CP-001, 32 (84.2%) were White, 5 (13.2%) were Black or African American, and 1 (2.6%) was American Indian or Alaska Native.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.

Safety Pool 1 includes data from Studies EFC12153, ARD12181 and ARD11936.

2.5 Post-Authorisation Experience

Fedratinib is authorized for marketing in 41 countries for the treatment of adult patients with intermediate-2 or high-risk PMF or secondary (post-PV or post-ET) MF. The first marketing authorization was granted to the Company on 16-Aug-2019 in the US. Fedratinib was granted approval by the European Commission on 08-Feb-2021.[32]

2.5.1 Method Used to Calculate Exposure

The methodology for estimating commercial patient exposure utilizes 2 data sources:[32]

1) The Company's Sales/Shipment Data – this data consists of all shipments of the company's product to all applicable countries and includes commercial and free-of-charge units for both branded and generic product (as applicable). The data are used to determine the units (eg, milligrams) of a product that was sold to a geography to estimate the number of patients who would have been exposed to that product, based on expected dosing in the geography. Shipment data are used to estimate the active patients for a period of time by dividing the total units sold by the average units per patient (note that average units per patient is derived from epidemiologic or market research).

2) Claims Data – this data consists of 2 distinct sources of electronic health care claims data in the USA. Claims data consisting of distinct patient IDs and prescription fill rates for each

product are used to understand usage patterns. For newly approved products, until sufficient claims data are available, patterns are based on discontinuation rates derived from clinical trial experience.

2.5.2 Exposure

The cumulative number of patients treated from 16-Aug-2019 through 06-Aug-2023 is estimated to be 3516 patients exposed. The person-time of exposure has been estimated to be 2631 patient-years exposed. This estimate of the number of patients exposed should be interpreted with caution, considering the assumptions and the limitations of the available sales data.[32]

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

No potential for drug dependence, misuse or abuse has been noted for fedratinib in any of the clinical studies, which is in accordance with the pharmacological properties of fedratinib.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP are summarized in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	Anaemia
	Thrombocytopenia/bleeding
	Encephalopathy, including Wernicke's
	Gastrointestinal toxicities (diarrhoea, nausea, vomiting)
Important potential risks	Pancreatitis
	Severe hepatotoxicity
	Severe infections including viral reactivation
Missing information	Use in patients with severe hepatic impairment
	Long-term safety, including secondary malignancies

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	
Elevated creatinine	In patients with MF treated with 400 mg fedratinib, blood creatinine increased was among the most frequent laboratory abnormalities, reported for 68% of patients. The median time to onset of any grade creatinine elevation was 17 days, with 75% of cases occurring within 2 months of starting treatment.

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

	Most events were Grade 1 or Grade 2, with Grade 3 events occurring in only 1.5% of patients. There were no Grade 4 events. Elevated creatinine was not a common reason for dose modification or treatment discontinuation. These elevations were generally reversible following treatment discontinuation. This identified risk is therefore not considered to be an important identified risk. Blood creatinine increased is listed as a very common ADR in Section 4.8 of the SmPC.
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	
Drug-drug interactions with strong CYP3A4 inhibitors	Concomitant administration of fedratinib with a strong CYP3A4 inhibitor increases fedratinib exposure. Increased exposure of fedratinib may increase the risk of adverse reactions. In place of strong CYP3A4 inhibitors, alternative therapies that do not strongly inhibit CYP3A4 activity should be considered. If strong CYP3A4 inhibitors cannot be replaced, the dose of fedratinib should be reduced when administering with strong CYP3A4 inhibitors, (eg, ketoconazole, ritonavir). Co-administration of a single 300 mg oral dose of fedratinib with the strong CYP3A4 inhibitor, ketoconazole, in healthy subjects, increased fedratinib area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) by approximately 3-fold. Additionally, using physiologically-based pharmacokinetic (PBPK) simulations, co-administration of ketoconazole (400 mg once daily) with fedratinib 400 mg once daily is predicted to increase fedratinib area under the plasma concentration-time curve over the dosing interval (AUC_{tau}) at steady state by 2-fold. Concomitant administration of fedratinib with dual CYP2C19 and CYP3A4 inhibitors should be avoided in patients receiving fedratinib. See Section 4.2 of the SmPC for dose modifications with concomitant use of a strong CYP3A4 inhibitor.
Drug-drug interactions with moderate or strong CYP3A4 inducers	Co-administration of rifampicin (strong CYP3A4 inducer: 600 mg once daily) or efavirenz (moderate CYP3A4 inducer: 600 mg once daily) with a single dose of fedratinib (500 mg) decreased AUC_{inf} of fedratinib by approximately 80% or 50%, respectively (SmPC Section 4.5). Agents that strongly or moderately induce CYP3A4 (eg, phenytoin, rifampicin, efavirenz), may decrease fedratinib exposure and should be avoided in patients receiving fedratinib (SmPC Section 4.2).
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised)	
None	
Known risks that do not impact the risk-benefit profile	
None	
Other reasons for considering the risks not important	
None	

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Anaemia	Fedratinib inhibits JAK2 which is critical for haematopoiesis and therefore leads to anaemia in patients with MF. In patients with MF treated with 400 mg of fedratinib, 43% of patients developed Grade 3 anaemia and no patients developed Grade 4 anaemia. The median time to first onset of Grade 3 anaemia event was approximately 45 days, with 75% of cases occurring within 3 months of starting treatment. Red blood cell transfusions were received by 51% of patients treated with 400 mg fedratinib, and permanent discontinuation of 400 mg fedratinib occurred due to anaemia in 1% of patients. While anaemia may be severe and lead to transfusion dependency, given the life-threatening nature of MF, including the nature of the underlying disease, which can also lead to severe anaemia as demonstrated in the placebo arm of the clinical studies, the risk-benefit of fedratinib remains acceptable.
Thrombocytopenia/bleeding	Fedratinib inhibits JAK2 which is critical for haematopoiesis and therefore leads to thrombocytopenia in patients with MF. In patients with MF treated with 400 mg of fedratinib, 13% and 4% of patients developed Grade 3 or 4 thrombocytopenia, respectively. The median time to first onset of Grade 3 or 4 thrombocytopenia was approximately 43 days with 75% of cases occurring within 3 months of starting treatment. Bleeding events associated with any grade thrombocytopenia (within 14 days prior and after onset of the thrombocytopenia) requiring clinical intervention were reported for approximately 6% of patients treated with 400 mg fedratinib. Platelet transfusions were received by 4% of patients treated with 400 mg fedratinib. Permanent discontinuation of treatment due to thrombocytopenia and bleeding that required clinical intervention occurred in 2% and 6% of patients treated with 400 mg fedratinib, respectively. Thrombocytopenia is generally reversible and is usually managed by supportive treatment such as dose interruptions, dose reduction and/or platelet transfusions (SmPC Section 4.4). While thrombocytopenia observed with fedratinib use may be severe and require platelet transfusions, given that it was generally not associated with bleeding events and the life-threatening nature of MF, the risk-benefit of fedratinib remains acceptable.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Encephalopathy, including Wernicke's	Eight patients with potential encephalopathy, including Wernicke's, were identified in 608 patients treated with multiple doses of fedratinib in the clinical programme. These patients were identified as having neurological symptoms that could be compatible with a diagnosis of WE. Wernicke's encephalopathy is characterised by acute symptoms of ophthalmoplegia, cerebellar abnormalities such as ataxia and/or altered mental status with specific neuroimaging findings. Seven of the eight patients with potential encephalopathy, including Wernicke's, were taking fedratinib at 500 mg daily prior to the onset of neurologic findings and had predisposing factors for WE, such as malnutrition, GI AEs and other risk factors that can lead to thiamine deficiency. One case was confirmed to be WE and one case was determined to be hepatic encephalopathy (patient was treated with 400 mg fedratinib). Most events resolved with some residual neurological symptoms including memory loss, cognitive impairment and dizziness except for one patient (who was included in a study for another indication) with metastatic head and neck cancer and severe malnutrition who had a fatal outcome. Preclinical studies have demonstrated that at clinically relevant doses, fedratinib does not inhibit thiamine transport in the GI tract or the brain in rats suggesting that the potential cases of WE in fedratinib-treated patients were likely related to predisposing risk factors. As WE can be prevented and treated with thiamine supplementation and thiamine replenishment, respectively, the risk-benefit of fedratinib remains acceptable.
Gastrointestinal toxicities (diarrhoea, nausea, vomiting)	Diarrhoea, nausea and vomiting were the most common nonhaematologic TEAEs reported with fedratinib in patients with MF, reported for 63%, 59% and 39% patients treated with 400 mg fedratinib, respectively. Despite the high rate of GI TEAEs, these events were mostly of mild severity and not a common reason for permanent treatment discontinuation. Grade 3 and 4 AEs of diarrhoea, nausea and vomiting were reported for 5.4%, 0.5% and 2.0% patients with MF who received 400 mg fedratinib, respectively. Successful management of GI toxicities is essential in order to increase tolerability, especially considering the background morbidity in this population, including malnutrition. Gastrointestinal toxicity, among other factors, could lead to thiamine deficiency and WE. Gastrointestinal AEs reported during the fedratinib development programme were managed by supportive treatment and dose modifications. Recommendations for prophylaxis treatment for nausea and vomiting and early supportive treatment for diarrhoea are included in Sections 4.2 and 4.4 of the SmPC.

Important potential risks

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Pancreatitis	Elevations of amylase (20%) and lipase (32%) were reported with fedratinib in patients with MF. Most of these events were Grade 1 or 2, with Grade 3 and 4 events that responded to dose modification in 1.5% and 9% of patients, respectively. The median time to onset of any grade amylase or lipase elevation was 15 days, with 75% of cases occurring within 1 month of starting treatment. During randomised treatment in the Phase 3 study, permanent discontinuation of treatment due to elevated amylase and/or lipase occurred in 1.0% of patients receiving 400 mg of fedratinib and no patients receiving placebo. Pancreatitis was observed in one 400 mg fedratinib-treated MF patient without prior elevations of lipase and amylase. The pancreatitis resolved with treatment discontinuation. There were no other reports of pancreatitis in the fedratinib development programme. Recommendations for dose modification for other non-haematologic toxicities in order to prevent the potential risk of pancreatitis are included in Section 4.2 of the SmPC.
Severe hepatotoxicity	Nonclinical studies showed that fedratinib targets the liver, primarily through bile duct epithelial hypertrophy and proliferation. In addition, elevations of bilirubin and alkaline phosphatase are inherent to MF patients secondary to many factors, including extramedullary haematopoiesis.[33] Grade 3 or 4 elevations of ALT and AST were reported in 1.5% or 1.0% of patients with MF treated with 400 mg fedratinib, respectively. The median time to onset of any grade transaminase elevation was approximately 1 month, with 75% of cases occurring within 2 months of starting treatment. Elevations of ALT and AST (Grade 3 or 4) were generally reversible with dose modifications or permanent treatment discontinuation. Recommendations for dose interruption followed by dose reduction for severe hepatic enzyme elevations in order to prevent the potential risk of severe hepatotoxicity are included in Section 4.2 of the SmPC. In a Phase 2 dose-range finding study (Study ARD11936), one patient treated with 300 mg fedratinib developed hepatic failure with Grade 4 elevations of ALT, AST and bilirubin. Fedratinib was permanently discontinued, and the patient recovered.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Severe infections including viral reactivations	Infections are a known cause of morbidity and mortality in patients with MF; the increased risk of infection in MF is believed to originate from deregulation of key mediators of the immune system.[34] An increased risk of infections (eg, urinary tract infections [UTIs] and pneumonia) has also been reported in patients treated with ruxolitinib, a JAK1/2 inhibitor.[15,16,35] In patients with MF treated with 400 mg fedratinib, UTI was reported for 10.8% of patients. In Study EFC12153, the frequencies of patients with infection TEAEs were similar between placebo and treatment arms (clinical study report [CSR] EFC12153, Section 12.3.1.3.4.2); however, given reports of more severe infections, including viral reactivation, with other JAK inhibitors, the entire safety pool was reviewed and there was no evidence of increased risk of severe infections in fedratinib-treated patients. As such, given the known effects of fedratinib on the bone marrow and the lymphoid system from preclinical studies and the risk observed in ruxolitinib patients, the potential for severe infections including viral reactivation will be monitored in ongoing clinical studies and in the post-marketing environment.
Missing Information	
Use in patients with severe hepatic impairment	The use of fedratinib in patients with severe HI should be avoided since fedratinib PK have not been evaluated in patients with severe HI. A study is ongoing in patients with severe HI (Study FEDR-CP-001). A population PK analysis demonstrated that dose adjustment is not required for patients with mild or moderate HI.
Long-term safety, including secondary malignancies	An analysis of 28 MF patients in the Phase 1 study who received fedratinib treatment for more than 24 cycles did not indicate that there were late-onset adverse effects of fedratinib treatment. A review of the clinical database confirmed that the rate of transformation to AML for all fedratinib-treated subjects was within the expected rate for this population and no trends for increased rates of other second malignancies were observed. However, given the small number of patients exposed for long periods of time as a result of the clinical hold which led to termination of all ongoing studies, long-term safety, including secondary malignancies, remains missing information and will be monitored in Study FEDR-MF-002 and in the post-marketing environment.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns with the submission of the updated RMP. Missing information "Use in patients with severe hepatic impairment" is removed from the list of safety concerns.

Table 2.7.2-1: Reclassification of Safety Concern with a Submission of an Updated RMP

Safety Concern	
Reclassification: Missing information "Use in patients with severe hepatic impairment" is removed from the list of safety concerns.	**Reasons for the reclassification:** With the completion of CP-001 (Category 3) and the availability of the results use in patients with severe hepatic impairment is no longer considered as missing information because no further relevant information is there expected and no new safety concerns in this population have been identified. Overall, the study results indicate that a different starting dose is not required in this group of patients.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The RMP search criteria have been defined for each study based on the MedDRA version as noted in Table 2.7.3-1. The important identified and potential risks of fedratinib are summarised in the Section 2.7.3.1 for the study cutoff dates listed in Section 2.3.1. Missing information for fedratinib is presented in Section 2.7.3.2. Clinical study exposure data are presented in Section 2.3.2.

Table 2.7.3-1: RMP Search Criteria

Study	MedDRA Version Used to Define RMP Search Criteria	MedDRA Version Used to Code AEs in Clinical Database	Final Data Lock Point
EFC12153 (JAKARTA)	20.1	20.1	24-Jul-2014
ARD11936	20.1	20.1	21-May-2014
ARD12181 (JAKARTA2)	20.1	20.1	12-Jun-2014

2.7.3.1 Presentation of Important Identified and Important Potential Risks

For all important risks, data are presented for the first six cycles of treatment, with the exception of the important identified risk of encephalopathy, including Wernicke's, and the important potential risk of pancreatitis, as these events did not fall within those parameters and the frequency of these risks was better characterised using the total population of patients who received continuous doses of fedratinib (n = 608), given their low incidence.

Table 2.7.3.1-1: Important Identified Risk: Anemia

Important Identified Risk: Anaemia	
Potential mechanisms	JAK2 is critical for normal erythropoiesis and thrombopoiesis. Cytokine receptors such as thrombopoietin receptor and MPL physically interact with and signal through JAK2 to

Table 2.7.3.1-1: Important Identified Risk: Anemia

Important Identified Risk: Anaemia

regulate these processes.[36] Thus, it is presumed, though not proven, that on-target effects in normal blood cells could contribute to anaemia and thrombocytopenia during treatment with JAK2 inhibitors like ruxolitinib and fedratinib.[37]

Fedratinib nonclinical data partially support this speculation. For instance, in a mouse model of PV, fedratinib treatment (120 mg/kg twice daily) reduced the frequencies of early erythroid precursors in bone marrow and late erythroid precursors in spleen, while improving erythroid hyperplasia and decreasing allele burden (Study PH-07-101348-068). However, in a mouse model of post-PV MF, fedratinib treatment (150 mg/kg, QD) restored proportion of bone marrow blood progenitors, including early progenitors ($Lin^{-}Sca1^{+}Kit^{+}$), common myeloid progenitors and megakaryocyte-erythroid progenitors, while improving circulating platelet counts, reducing splenomegaly and targeting JAK2V617F blood progenitors in spleen.[38]

Evidence source and strength of evidence

Grade 3 or 4 anaemia frequently leads to the need for RBC transfusions including RBC transfusion dependence. In PMF, anaemia and the need for RBC transfusions is associated with a shorter overall survival and shorter leukaemia-free survival.[63] Given the prognostic implications and the observation of Grade 3 anaemia as a very common adverse reaction in patients treated with fedratinib, this risk is considered an important identified risk.

Characterisation of risk

Frequency with 95% CI

Anaemia	Fedratinib 400 mg (N = 203)	Fedratinib Pool 1 (N = 321)	Placebo (N = 95)
Total number of patients, n	203	321	95
Patients with ≥ 1 serious adverse event (SAE), n (%)	3 (1.5)	10 (3.1)	1 (1.1)
Patients with ≥ 1 AE, n (%)	87 (43)	130 (40)	13 (14)
Incidence (%) of patients with ≥ 1 AE (95% CI)	43 (36.0, 50.0)	41 (35.1, 46.1)	14 (7.5, 22.3)
Exposure-adjusted incidence rate / 100 person-years	155.6	147.5	40.1

In patients treated with 400 mg fedratinib, the relative risk (RR) of fedratinib to placebo for all-grade anaemia was 3.1 (95% CI: 1.7-5.6), with an RR of 3.9 ($p < 0.001$) when adjusted by patient time.

Seriousness/Outcomes

In Studies EFC12153, ARD11936 and ARD12181, serious anaemia events were recorded in 3/203 (1.5%) patients with MF who were treated with 400 mg fedratinib. In fedratinib Pool 1, serious anaemia events were recorded in 10/321 (3.1%) patients; the reported preferred term (PT) was anaemia in all patients.

The outcomes of these SAEs are summarised below.

Outcome	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n(%)	Placebo (N = 95), n (%)
Not recovered/Not resolved	1 (0.5)	2 (0.6)	0
Recovering/Resolving	0	1 (0.3)	0
Recovered/Resolved	2 (1.0)	7 (2.2)	1 (1.1)

Table 2.7.3.1-1: Important Identified Risk: Anemia

Important Identified Risk: Anaemia

	Total: 3 (1.5) / 10 (3.1) / 1 (1.1)

Severity and Nature of Risk

Anaemia	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n(%)	Placebo (N = 95), n (%)
All AEs	87 (43)	130 (40)	13 (14)
Grade 3 or 4	69 (34)	106 (33)	7 (7)
AEs leading to discontinuation	2 (1.0)	4 (1.2)	0
AEs leading to dose reduction	13 (6)	27 (8)	1 (1.1)
AEs leading to dose interruption	6 (3.0)	10 (3.1)	0

Risk factors and risk groups	Patients with baseline haemoglobin < 10 g/dL are more likely to develop severe anaemia. The median time to first onset of Grade 3 anaemia event was approximately 45 days with 75% of cases occurring within 3 months of starting treatment. Patients with underlying renal disease may be at an increased risk of anaemia. In patients with MF, anaemia may occur as part of the primary disease and patients may be transfusion dependent at the start of the study.
Preventability	A complete blood count should be obtained prior to starting treatment with fedratinib, periodically during treatment and as clinically indicated. A total of 75% of cases of Grade 3 anaemia occurred within 3 months of starting treatment. Patients with anaemia may require blood transfusions and/or dose modifications.
Impact on the risk-benefit balance of the product	The impact on the risk-benefit balance due to anaemia is acceptable. Risk minimisation measures in the SmPC with appropriate warnings regarding anaemia, the need for periodic blood tests and dose modifications for anaemia are in place.
Public health impact	Anaemia is a very common ADR of fedratinib treatment (SmPC Section 4.8) and an underlying manifestation of MF. All fedratinib-treated patients should be monitored with periodic blood counts for anaemia and given RBC transfusions as clinically indicated. Anaemia does not commonly lead to hospitalisation and can be managed in the ambulatory or clinical setting.

Table 2.7.3.1-2: Important Identified Risk: Thrombocytopenia/Bleeding

Important Identified Risk: Thrombocytopenia/Bleeding

Potential mechanisms	The potential mechanisms for fedratinib-induced thrombocytopenia/bleeding are provided in Table 2.7.1.2-1.
Evidence source and strength of evidence	While Grade 3 or 4 thrombocytopenia was similar in fedratinib-treated patients and patients receiving placebo patients in the randomised controlled Phase 3 study in the JAK inhibitor naïve setting, the rate of Grade 3 or 4 thrombocytopenia was higher in MF patients previously treated with ruxolitinib. These previously exposed patients fulfil an area of high unmet medical need and it is expected that fedratinib will be primarily utilised in this setting. As thrombocytopenia may lead to bleeding events, thrombocytopenia/bleeding is considered an important identified risk of fedratinib.

Table 2.7.3.1-2: Important Identified Risk: Thrombocytopenia/Bleeding

Important Identified Risk: Thrombocytopenia/Bleeding

Characterisation of risk

Frequency with 95% CI

Thrombocytopenia	Fedratinib 400 mg (N = 203)	Fedratinib Pool 1 (N = 321)	Placebo (N = 95)
Total number of patients, n	203	321	95
Patients with ≥ 1 SAE, n (%)	2 (1.0)	3 (0.9)	0
Patients with ≥ 1 AE, n (%)	39 (19)	60 (19)	8 (8)
Incidence (%) of patients with ≥ 1 AE (95% CI)	19 (14.0, 25.3)	19 (14.6, 23.4)	8 (3.7, 15.9)
Exposure-adjusted incidence rate / 100 person-years	53.9	52.8	23.7

Bleeding Associated with Any Grade Thrombocytopenia that Needed Clinical Intervention	Fedratinib 400 mg (N = 203)	Fedratinib Pool 1 (N = 321)	Placebo (N = 95)
Total number of patients, n	203	321	95
Patients with ≥ 1 SAE, n (%)	6 (3.0)	11 (3.4)	2 (2.1)
Patients with ≥ 1 AE, n (%)	12 (5.9)	19 (5.9)	3 (3.2)
Incidence (%) of patients with ≥ 1 AE (95% CI)	5.9 (3.1, 10.1)	5.9 (3.6, 9.1)	3.2 (0.7, 9.0)
Exposure-adjusted incidence rate / 100 person-years	15.3	15.3	8.7

In patients treated with 400 mg fedratinib, the RR of fedratinib to placebo for all-grade thrombocytopenia was 2.3 (95% CI: 1.1-4.9), with an RR of 2.3 (p = 0.034) when adjusted by patient time. For all-grade bleeding associated with thrombocytopenia, the RR of fedratinib to placebo was 1.9 (95% CI: 0.5-6.6), with an RR of 1.8 (p = 0.385) when adjusted by patient time.

Seriousness/Outcomes

In Studies EFC12153, ARD11936 and ARD12181, serious thrombocytopenia events were recorded in 2/203 (1.0%) patients with MF who were treated with 400 mg fedratinib; the reported PTs were thrombotic thrombocytopenic purpura and platelet count decreased. In fedratinib Pool 1, serious thrombocytopenia events were recorded in 3/321 (0.9%) patients; PTs reported included platelet count decreased, thrombotic thrombocytopenic purpura and thrombocytopenia in one patient each.

Serious bleeding events associated with thrombocytopenia were recorded in 6/203 (3.0%) patients with MF who were treated with 400 mg fedratinib. In fedratinib Pool 1, serious bleeding events associated with thrombocytopenia were recorded in 11/321 (3.4%) patients.

The outcomes of these SAEs are summarised below.

Thrombocytopenia Outcome	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n (%)	Placebo (N = 95), n (%)
Not recovered/Not resolved	1 (0.5)	2 (0.6)	0
Recovered/Resolved	1 (0.5)	1 (0.3)	0

Table 2.7.3.1-2: Important Identified Risk: Thrombocytopenia/Bleeding

Important Identified Risk: Thrombocytopenia/Bleeding

Total	2 (1.0)	3 (0.9)	0
Bleeding Associated with Any Grade Thrombocytopenia that Needed Clinical Intervention Outcome	**Fedratinib 400 mg (N = 203), n (%)**	**Fedratinib Pool 1 (N = 321), n (%)**	**Placebo (N = 95), n (%)**
Recovered/Resolved	5 (2.5)	9 (2.8)	2 (2.1)
Recovered/Resolved with sequelae	1 (0.5)	1 (0.3)	0
Fatal	0	1 (0.3)	0
Total	6 (3.0)	11 (3.4)	2 (2.1)

Severity and Nature of Risk

Thrombocytopenia	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n (%)	Placebo (N = 95), n (%)
All AEs	39 (19)	60 (19)	8 (8)
Grade 3 or 4	29 (14)	46 (14)	6 (6)
AEs leading to discontinuation	6 (3.0)	12 (3.7)	0
AEs leading to dose reduction	8 (3.9)	12 (3.7)	0
AEs leading to dose interruption	5 (2.5)	9 (2.8)	0

Bleeding Associated with Any Grade Thrombocytopenia that Needed Clinical Intervention	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n (%)	Placebo (N = 95), n (%)
All AEs	12 (5.9)	19 (5.9)	3 (3.2)
Grade 3 or 4	6 (3.0)	9 (2.8)	1 (1.1)
AEs leading to discontinuation	1 (0.5)	2 (0.6)	0
AEs leading to dose reduction	0	0	1 (1.1)
AEs leading to dose interruption	1 (0.5)	3 (0.9)	1 (1.1)

Risk factors and risk groups

Patients with baseline platelets < 100×10^9/L are more likely to develop severe thrombocytopenia. Thrombocytopenia generally occurs within the first 3 months of treatment, then stabilises. Previous chemotherapies including ruxolitinib and severity of the underlying disease are also an important contributor to thrombocytopenia and subsequent bleeding risks.

Preventability

A complete blood count should be obtained prior to starting treatment with fedratinib, periodically during treatment and as clinically indicated. Thrombocytopenia is generally reversible and is usually managed by supportive treatment such as dose interruptions, dose reduction and/or platelet transfusions. The risk minimisation activities put in place to control the thrombocytopenias are thus considered adequate to prevent the risk of severe thrombocytopenia and bleeding risks.

Table 2.7.3.1-2: Important Identified Risk: Thrombocytopenia/Bleeding

Important Identified Risk: Thrombocytopenia/Bleeding	
Impact on the risk-benefit balance of the product	While bleeding episodes in the presence of thrombocytopenia may significantly contribute to morbidity and mortality, risk minimisation measures in the SmPC with appropriate warnings regarding thrombocytopenia, the need for periodic blood tests and dose modifications for thrombocytopenia are in place to manage this risk. Therefore, the impact on the risk-benefit balance due to thrombocytopenia/bleeding is acceptable.
Public health impact	Thrombocytopenia is a very common ADR of fedratinib treatment (SmPC Section 4.8) especially in patients previously exposed to ruxolitinib. All fedratinib-treated patients should be monitored with periodic blood counts for thrombocytopenia and dose reduced and/or given platelet transfusions as clinically indicated.

Table 2.7.3.1-3: Important Identified Risk: Encephalopathy, Including Wernicke's

Important Identified Risk: Encephalopathy, Including Wernicke's	
Potential mechanisms	Preclinical studies conducted in rats have demonstrated that at clinically relevant doses, fedratinib does not inhibit thiamine transport in the GI tract or the brain.[39] Additionally, in an in vivo neurobehavioural study in the rat and repeat-dose mouse, rat and dog toxicology studies, there was no evidence for neurobehavioural effects related to activity at CNS receptors.[40] Patients with neurological symptoms that could be compatible with a diagnosis of WE had predisposing factors such as malnutrition and/or GI AEs that can lead to thiamine deficiency. Conditions associated with WE include chronic alcoholism, hyperemesis, malabsorption, poor dietary intake, increased loss by the kidneys (eg, in diabetes or renal disease), or an increased metabolic requirement.[41] Fedratinib inhibited ligand binding at a number of CNS receptors and/or transporters (eg, adenosine, muscarinic, serotonin, sigma and Na^+ channel receptors and noradrenaline, dopamine and serotonin transporters) and had low nanomolar IC_{50} values for two muscarinic receptors and the dopamine transporter. However, in an in vivo neurobehavioural study in the rat, fedratinib produced no changes in CNS activity and excitability, autonomic nervous system activity, sensorimotor activity or neuromuscular activity. There was no evidence for neurobehavioural effects related to activity at CNS receptors in the repeat-dose mouse, rat and dog toxicology studies: the clinical signs that were observed in these studies were considered to be related to poor health and/or a moribund state.
Evidence source and strength of evidence	Due to the limited understanding of the causal association of fedratinib with this risk based on the fact that fedratinib does not interfere with thiamine receptors and that WE can be fatal if not recognised and treated properly, the risk of encephalopathy, including Wernicke's is considered an important identified risk. To evaluate any possible association between concerns of encephalopathy, including Wernicke's, in fedratinib-treated patients, the fedratinib clinical database of 608 patients receiving continuous daily doses of fedratinib for MPNs or solid tumours was searched for reports of encephalopathy of any type, including Wernicke's, and any signs or symptoms (eg, mental status changes, ophthalmoplegia (eg, nystagmus, diplopia) and cerebellar findings) that could be suggestive of thiamine deficiency or encephalopathy, including Wernicke's. Eight fedratinib-treated patients with neurological signs or symptoms suggesting the potential diagnosis of encephalopathy, including Wernicke's, were identified. Only one patient had thiamine levels evaluated at the time of symptoms and it was normal. These patients' case histories and neuro-imaging data were reviewed by five independent experts. Based on the

Table 2.7.3.1-3: Important Identified Risk: Encephalopathy, Including Wernicke's

Important Identified Risk: Encephalopathy, Including Wernicke's	
	experts' reviews, all agreed that one patient was identified as having WE. One patient was identified as not having WE, but rather hepatic encephalopathy. For the remaining six patients, there was no consensus among the experts. Therefore, taken conservatively, at most seven cases of WE occurred in over 600 fedratinib-treated patients.
Characterisation of risk	All seven cases of potential WE occurred in patients receiving 500 mg fedratinib at the time of experiencing neurological symptoms. There was no contribution of alcohol suspected in these patients. Time to onset of neurological symptoms ranged from Cycle 2 to Cycle 13. Most events resolved with some residual neurological symptoms including memory loss, cognitive impairment and dizziness, except for one patient (who was included in a study for another indication) with head and neck cancer, brain metastasis, difficulty eating secondary to partial mandibulectomy and severe malnutrition, who had a fatal outcome. Chronic nausea, vomiting and weight loss resulting in malnutrition as well as severe diarrhoea in the absence of thiamine supplementation are recognised causes of thiamine deficiency, which can lead to WE. All seven of these potential cases had preexisting malnutrition, weight loss and/or significant GI AEs that were not adequately controlled as well as other risk factors that may have contributed to thiamine deficiency. A thiamine level was normal for one patient and not obtained for any other patients at the time of symptoms. In one case, the patient had stopped fedratinib for 2 weeks and was only treated with intravenous fluids prior to the onset of symptoms. Two patients continued receiving fedratinib treatment while their neurological symptoms improved. The analysis suggested that the potential causes of WE in these patients treated with fedratinib were multifactorial, including malnutrition, nausea, vomiting and diarrhoea. In Study FEDR-MF-002, 1 patient receiving Cycle 3 of fedratinib experienced a Grade 1 WE with confusion, ataxia, and diplopia in the setting of an unrecognized and untreated low thiamine level (52 nmol/L) 20 days prior. The patient had full and rapid resolution after delayed initiation of thiamine supplementation without changes in fedratinib dosing.
Risk factors and risk groups	Four common and distinct (but overlapping) presentations of encephalopathies the physician is likely to encounter in clinical practice are: encephalopathy from metabolic disorder or deficiency, encephalopathy due to a severe systemic illness or organ failure, encephalopathy due to medication-related toxicity and encephalopathies diagnosed primarily by findings on brain imaging. For WE, specifically, conditions associated with thiamine deficiency and subsequent development of WE include chronic alcoholism, hyperemesis, malabsorption, poor dietary intake, increased loss of thiamine by the kidneys (eg, in diabetes or renal disease), or an increased metabolic requirement of thiamine.[41] Myelofibrosis patients may be malnourished due to splenomegaly causing a feeling of fullness or loss of appetite. In addition, fedratinib is very commonly associated with GI AEs including nausea, vomiting and diarrhoea. Inadequate treatment of these GI AEs, especially in the thiamine setting of underlying malnutrition, may predispose to thiamine deficiency and thus WE. Based on a draft of the primary CSR for EU PASS FEDR-MF-002, a validated signal of low thiamine, a risk factor for WE, was identified, reviewed, and closed following review of central laboratory values and AEs in subjects ranodmized to fedratinib (n = 134) vs. those randomized to BAT (n = 67) (total N = 201). The incidence of thiamine levels below the LLN (70 nmol/L) was 20.9% (28/134) for the fedratinib arm vs. 4.5 (3/67) for the BAT arm. The median time to the first low thiamine level after initiation of fedratinib was 29.5 days. Thiamine levels < 30 nmol/L were not observed in the study. Besides low thiamine, no safety concerns for fedratinib emerged from this study, despite a larger sample size and longer exposure and follow up compared to prior trials. The observed rate of 1 Grade 1 WE (1/134 = 0.7%) was consistent with the current product labelling.

Table 2.7.3.1-3: Important Identified Risk: Encephalopathy, Including Wernicke's

Important Identified Risk: Encephalopathy, Including Wernicke's	
Preventability	For those causes of encephalopathy that will lead to irreversible neurological dysfunction if not recognised and reversed immediately. Therefore, the immediate approach to treatment of any encephalopathic patient is directed at correction of any circulatory deficiency and replacement of any potentially deficient metabolic substrate (eg, oxygen, thiamine, or glucose). This should be followed by correction of any other potentially causative metabolic abnormality, treatment of any underlying causative acute systemic illness or complication of organ failure, and attempt at discontinuation or removal of any likely offending medication or toxin. A specific aetiological diagnosis can be made through history, examination, laboratory studies and in some cases, imaging, which may lead to a specific medical intervention, more rapid clinical resolution and may help prevent irreversible neurologic dysfunction.[42] In addition, a specific diagnosis would allow for neurology expert consultation for further diagnosis and management of these patients. Wernicke's encephalopathy is a neurological condition resulting from acute thiamine (vitamin B1) deficiency which can present with ataxia, mental status changes and ophthalmoplegia (eg, nystagmus, diplopia). Any change in mental status should raise concern for potential WE. Thiamine levels and nutritional status should be assessed prior to starting treatment and periodically during treatment as clinically indicated. Before treatment initiation and during treatment, thiamine levels should be replenished if they are low. If encephalopathy, including Wernicke's, is suspected, treatment with fedratinib should immediately be discontinued and parenteral thiamine treatment should be initiated. Patients should be monitored until symptoms have resolved or improved and thiamine levels have normalised. Details for monitoring and management of abnormal thiamine levels and signs or symptoms of encephalopathy, including Wernicke's, are provided in Sections 4.2 and 4.4 of the SmPC.
Impact on the risk-benefit balance of the product	The risk minimisation measures identified in the label include well described posology with prescriptive language for dose modifications due to thiamine deficiency or signs or symptoms of encephalopathy, including Wernicke's, recommendations for thiamine replenishment, prophylaxis, and assessment in Section 4.2 of the SmPC, and information on the signs and symptoms of encephalopathy, including Wernicke's, and recommendations for thiamine prophylaxis and the monitoring of thiamine levels as clinically indicated, nutritional status and neurological symptoms in Section 4.4 of the SmPC. Well described risk factors for WE, including GI symptoms that are associated with fedratinib and may increase the risk of thiamine deficiency are also provided. Details of WE and GI events are provided in Section 4.8 of the SmPC. Following a protocol amendment in FEDR-MF-002 mandating thiamine prophylaxis, no further cases of WE were observed. Therefore, the risk of encephalopathy, including Wernicke's, can be prevented or mitigated by the recommendations described in the SmPC, enabling the risk-benefit balance to be acceptable in this patient population with high unmet medical need.
Public health impact	The term encephalopathy describes a general alteration in brain function manifesting as an attentional disorder anywhere within the continuum between a hyperalert agitated state and coma, and typically refers to the commonly encountered clinical scenario of diffuse brain dysfunction felt to be due to a systemic, metabolic, or toxic derangement. The incidence of toxic-metabolic encephalopathy occurring during hospitalisation in patients over age 65 has been reported to be as high as 56% (up to 87% in the intensive care unit [ICU] setting) with high in-hospital mortality, and with a 1-year mortality rate of up to 40%.[42] Although encephalopathy may resolve with treatment of the underlying disorder, there is mounting evidence that cerebral dysfunction persists beyond the acute phase of critical illness. ICU survivors of encephalopathy often suffer chronic impairments in cognitive ability, suggesting occult brain injury.[43]

Table 2.7.3.1-3: Important Identified Risk: Encephalopathy, Including Wernicke's

Important Identified Risk: Encephalopathy, Including Wernicke's	
	WE is considered under-recognised in clinical practice, particularly in non-alcoholic patients. Estimates of the prevalence of WE in the general population is 0.4% to 2.8%, based on typical brain lesions found in autopsy studies.[44] Magnetic resonance imaging is useful in confirming a diagnosis of acute WE as typical brain lesions can be found.[45,46] Failure to diagnose WE and institute adequate parenteral therapy results in death in 20% of patients, while 75% will be left with permanent brain damage involving short-term memory loss (Korsakoff's psychosis [KP]). Twenty-five percent of patients with KP will be sufficiently affected to require long-term institutionalisation.[47]

Table 2.7.3.1-4: Important Identified Risk: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)

Important Identified Risk: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)

Potential mechanisms

Despite the ubiquitous nature of GI signs in animals, there was no significant, associated GI tract histopathology to provide an understanding of the mechanism. In the absence of histologic evidence of GI tract toxicity, it is likely that the GI signs observed in dogs were related to nausea and alterations in GI motility.

Evidence source and strength of evidence

Diarrhoea (62.6%), nausea (58.6%) and vomiting (39.4%) were the most common nonhaematologic TEAEs (all grades) in MF patients who received 400 mg fedratinib. Most of the GI events were Grade 1 or 2. f Despite the high rate of GI TEAEs, these events were not a common reason for permanent treatment discontinuation.

Characterisation of risk

Frequency with 95% CI

Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)	Fedratinib 400 mg (N = 203)	Fedratinib Pool 1 (N = 321)	Placebo (N = 95)
Total number of patients, n	203	321	95
Patients with ≥ 1 SAE, n (%)	3 (1.5)	5 (1.6)	0
Patients with ≥ 1 AE, n (%)	162 (79.8)	267 (83.2)	26 (27.4)
Incidence (%) of patients with ≥ 1 AE (95% CI)	79.8 (73.6, 85.1)	83.2 (78.6, 87.1)	27.4 (18.7, 37.5)
Exposure-adjusted incidence rate / 100 person-years	759.8	901.5	94.1

In patients treated with 400 mg fedratinib, the RR of fedratinib to placebo for all-grade GI toxicities was 2.9 (95% CI: 1.9-4.4), with an RR of 8.1 ($p < 0.001$) when adjusted by patient time.

Seriousness/Outcomes

In Studies EFC12153, ARD11936 and ARD12181, serious GI events were recorded in 3/203 (1.5%) patients with MF who were treated with 400 mg fedratinib; of these 3 patients, 1 patient experienced nausea and all 3 patients experienced diarrhoea.

In fedratinib Pool 1, serious GI events were recorded in 5/321 (1.6%) patients; of these 5 patients, 4 patients experienced diarrhoea, 2 patients experienced nausea and 2 patients experienced vomiting.

Table 2.7.3.1-4: Important Identified Risk: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)

Important Identified Risk: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)

The outcomes of these SAEs are summarised below.

Outcome	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n (%)	Placebo (N = 95), n (%)
Recovered/Resolved	3 (1.5)	5 (1.6)	0
Total	3 (1.5)	5 (1.6)	0

Severity and Nature of Risk

Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n (%)	Placebo (N = 95), n (%)
All AEs	162 (79.8)	267 (83.2)	26 (27.4)
Grade 3 or 4	13 (6.4)	30 (9.3)	0
AEs leading to discontinuation	9 (3.9)	13 (4.0)	0
AEs leading to dose reduction	16 (7.9)	30 (9.3)	0
AEs leading to dose interruption	15 (7.4)	29 (9.0)	0

Risk factors and risk groups	In the clinical development program, GI toxicities were observed across all indications including patients with MF, with solid tumours and in heathy volunteers.
Preventability	Despite the high rate, especially at the beginning of treatment, GI toxicities can be successfully managed by way of supportive treatment with anti-emetics (eg, 5HT3 receptor antagonists) and antidiarrhoeal medications as clinically indicated. For GI symptoms that are not responsive to supportive treatment fedratinib should be interrupted temporarily until symptoms resolve and be restarted at a lower dose.
Impact on the risk-benefit balance of the product	While GI toxicities may be of concern due to the impact on patient well-being and potential complications including dehydration and malabsorption (including thiamine), the risk can be successfully managed by way of supportive treatments and dose interruption, and dose reduction. During long-term treatment, early onset followed by a steady decrease during the following cycles also mitigates the impact. For these reasons the impact on the risk-benefit balance of the product is considered to be acceptable.
Public health impact	While nausea, vomiting and diarrhoea are frequent, most of these events are low-grade, as a whole have not been associated with other serious GI toxicities and can be managed by routine risk minimisation. Healthcare professionals in this area are expected to be well familiar with the management of these manifestations of GI toxicities.

Table 2.7.3.1-5: Important Potential Risk: Pancreatitis

Important Potential Risk: Pancreatitis

Potential mechanisms	No evidence has been found for pancreatitis or pancreatic injury from fedratinib treatment based on nonclinical toxicology studies. Cases of pancreatitis and asymptomatic elevations of lipase and amylase have been reported with other tyrosine kinase inhibitors, including sorafenib[48] and pazopanib[49]. The mechanism for pancreatic toxicity induced by tyrosine

Table 2.7.3.1-5: Important Potential Risk: Pancreatitis

Important Potential Risk: Pancreatitis	
	kinase inhibitors is unknown. One proposed mechanism includes pancreatic ischaemia involving vascular endothelial growth factor (VEGF), with anti-VEGF activity producing acinar cell apoptosis, causing the release of autodigestive enzymes and resulting pancreatitis. Another mechanism could be the activation of pancreatic enzymes caused by reflux of duodenal contents induced by decreased GI motility.
Evidence source and strength of evidence	Grade 3 and 4 elevations of lipase were a dose-limiting toxicity in the Phase 1 dose finding study at high dose (up to 800 mg). Elevations of amylase (20%) and lipase (32%), all grades, were reported with fedratinib in patients with MF. Most of these events were Grade 1 or 2 and the more severe elevations responded to dose modification. During the clinical development programme, only one case of pancreatitis was observed in a patient in the Phase 3 study who presented with acute onset of abdominal pain and Grade 4 lipase increased by laboratory evaluation. The event occurred at the beginning of Cycle 7, and no elevations of lipase or amylase were detected by laboratory assessment before this event, including at the End-of-Cycle 6 visit. The event resolved with treatment discontinuation. Given the above, the risk of pancreatitis is considered an important potential risk.
Characterisation of risk	**Frequency with 95% CI**

Pancreatitis	Fedratinib 400 mg (N = 203)	Fedratinib Pool 1 (N = 321)	Placebo (N = 95)
Total number of patients, n	203	321	95
Patients with ≥ 1 SAE, n (%)	1 (0.5)	1 (0.3)	0
Patients with ≥ 1 AE, n (%)	1 (0.5)	1 (0.3)	0
Incidence (%) of patients with ≥ 1 AE (95% CI)	0.5 (0.0, 2.7)	0.3 (0.0, 1.7)	0
Exposure-adjusted incidence rate / 100 person-years	0.6	0.4	-

Seriousness/Outcomes

In Studies EFC12153, ARD11936 and ARD12181, serious pancreatitis events were recorded in 1/203 (0.5%) patients with MF who were treated with 400 mg fedratinib. In fedratinib Pool 1, serious pancreatitis events were recorded in 1/321 (0.3%) patients.

Severity and Nature of Risk

Pancreatitis	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n (%)	Placebo (N = 95), n (%)
All AEs	1 (0.5)	1 (0.3)	0
Grade 3 or 4	1 (0.5)	1 (0.3)	0
AEs leading to discontinuation	1 (0.5)	1 (0.3)	0
AEs leading to dose reduction	0	0	0
AEs leading to dose interruption	0	0	0

Table 2.7.3.1-5: Important Potential Risk: Pancreatitis

Important Potential Risk: Pancreatitis	
Risk factors and risk groups	Higher doses of fedratinib were associated with more severe elevations of amylase and lipase. Risk factors for pancreatitis include gallstones, prolonged alcohol use, high triglycerides and pancreatitis is commonly associated with diabetes, obesity and smoking.[50]
Preventability	Pancreatitis can be prevented or minimised by modifying risk factors such as obesity, gallstones and alcohol use that predispose to pancreatitis. Lipase and amylase increased are included in Section 4.8 of the SmPC; therefore, prescribers can be made aware that these events may occur. The SmPC advises that patients should have their amylase and lipase monitored at baseline, at least monthly and as clinically indicated (Section 4.4) and also includes recommendations for dose modifications (including dose reductions) for Grade 3 or 4 non-haematologic toxicities (Section 4.2).
Impact on the risk-benefit balance of the product	Severe pancreatitis has the potential to be fatal, especially if not diagnosed and treated promptly; however, given the life-threatening nature of MF, the impact on the risk-benefit balance due to the potential risk of pancreatitis is acceptable.
Public health impact	The mean incidence of acute pancreatitis in Europe over the past 20 years is about 26 per 100,000 persons per year (95% CI: 19.6, 32.0), and the frequency of cases is increasing.[51] Approximately 80% of patients admitted with acute pancreatitis have mild, self-limiting disease and are discharged within several days. Mortality associated with acute pancreatitis has decreased over time, and overall mortality is now approximately 2%.[50] For patients with severe pancreatitis, requiring care in an intensive care unit, mortality can be as high as 20% to 25%.[51] Overall, about 15% to 20% of patients with acute pancreatitis progress to a severe illness with a prolonged disease course. The recurrence rate has been reported to be from 10% to 30% in various studies. Progression to chronic pancreatitis has been reported in 6.4% of patients after a first attack of acute pancreatitis.[52]

Table 2.7.3.1-6: Important Potential Risk: Severe Hepatotoxicity

Important Potential Risk: Severe Hepatotoxicity	
Potential mechanisms	The causes of serum enzyme elevations, and thus the potential mechanism for severe hepatotoxicity during fedratinib therapy are not known. Fedratinib is metabolised in the liver primarily via the CYP3A4 pathway, and liver injury may be related to the production of a toxic intermediate. Fedratinib may lead to drug-drug interactions with agents that inhibit or induce hepatic CYP3A4 activity. Nonclinical studies showed that fedratinib targets the liver, primarily through bile duct epithelial hypertrophy and proliferation.
Evidence source and strength of evidence	Elevations of ALT (43%) and AST (52%), all grades, were reported with 400 mg fedratinib in MF patients. Most of these elevations were Grade 1 or 2; however, Grade 3 and 4 ALT, AST and TBL elevations in the Phase 1 study (TED12037/TED12015) at higher fedratinib doses (patients received up to 800 mg) were observed and in a Phase 2 dose-range finding study, one patient at 300 mg developed hepatic failure with Grade 4 elevations of ALT, AST and bilirubin. Fedratinib was withdrawn, and the patient recovered. Grade 3 or 4 elevations of ALT and AST were generally reversible with dose modification and permanent treatment discontinuation. Recommendations for dose modifications (including dose reductions) for severe hepatic enzyme elevations in order to prevent the potential risk of severe hepatotoxicity are included in Section 4.2 of the SmPC.

Table 2.7.3.1-6: Important Potential Risk: Severe Hepatotoxicity

Important Potential Risk: Severe Hepatotoxicity

Characterisation of risk

Frequency with 95% CI

Severe Hepatotoxicity (Grade ≥ 3)	Fedratinib 400 mg (N = 203)	Fedratinib Pool 1 (N = 321)	Placebo (N = 95)
Total number of patients, n	203	321	95
Patients with ≥ 1 SAE, n (%)	1 (0.5)	3 (0.9)	3 (3.2)
Patients with ≥ 1 Grade ≥ 3 AE, n (%)	1 (0.5)	5 (1.6)	3 (3.2)
Incidence (%) of patients with ≥ 1 (Grade ≥ 3) AE (95% CI)	0.5 (0.0, 2.7)	1.6 (0.5, 3.6)	3.2 (0.7, 9.0)
Exposure-adjusted incidence rate / 100 person-years	1.2	3.9	8.5

In patients treated with 400 mg fedratinib, the RR of fedratinib to placebo for severe hepatotoxicity events (Grade ≥ 3) was 0.2 (95% CI: 0.0-1.5), with an RR of 0.1 (p = 0.094) when adjusted by patient time.

Seriousness/Outcomes

In Studies EFC12153, ARD11936 and ARD12181, serious hepatotoxicity events were recorded in 1/203 (0.5%) patients with MF who were treated with 400 mg fedratinib. In fedratinib Pool 1, serious hepatotoxicity events were recorded in 3/321 (0.9%) patients.

The outcomes of these SAEs are summarised below.

Outcome	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n (%)	Placebo (N = 95), n (%)
Not recovered/Not resolved	0	0	1 (1.1)
Recovered/Resolved	1 (0.5)	3 (0.9)	2 (2.1)
Total	1 (0.5)	3 (0.9)	3 (3.2)

Severity and Nature of Risk

Severe Hepatotoxicity	Fedratinib 400 mg (N = 203), n (%)	Fedratinib Pool 1 (N = 321), n (%)	Placebo (N = 95), n (%)
Grade ≥ 3	1 (0.5)	5 (1.6)	3 (3.2)
AEs leading to discontinuation	0	1 (0.3)	0
AEs leading to dose reduction	0	0	0
AEs leading to dose interruption	0	1 (0.3)	1 (1.1)

Risk factors and risk groups

Risk factors may include higher doses of fedratinib. In the Phase 1 study (TED12037/TED12015), Grade 3 and 4 ALT, AST and TBL elevations were observed at higher fedratinib doses (patients received up to 800 mg). Risk factors for severe hepatotoxicity from drugs include medication dose, drug lipophilicity and extent of hepatic metabolism.[53] Pre-existing liver disease/extramedullary haematopoiesis is also commonly observed in the liver in MF patients, and may increase the risk of severe hepatotoxicity.

Table 2.7.3.1-6: Important Potential Risk: Severe Hepatotoxicity

Important Potential Risk: Severe Hepatotoxicity	
	Host-related risk factors include the patient's age, sex, genetics, previous episodes of drug-induced liver injury (DILI), and underlying chronic liver disease. Environmental risk factors include the patient's metabolic features (eg, obesity), diet type, alcohol, coffee, and tobacco consumption, multidrug therapy, immune state (eg, immunocompromised), and nutritional status.[54]
Preventability	The low incidence of hepatic toxicity (DILI) coupled with the limited knowledge of the biochemical mechanisms or pathways responsible for this idiosyncratic event make it difficult to identify patients who are at increased risk.[55] Section 4.2 of the SmPC includes language to help prevent severe hepatotoxicity including: Interrupt fedratinib dose until resolved to ≤ Grade 1 (AST/ALT [> ULN - 3.0 × ULN] or bilirubin [> ULN - 1.5 × ULN]) or baseline. Restart dose at 100 mg daily below the last given dose. Monitor ALT, AST and bilirubin (total and direct) every 2 weeks for at least 3 months following the dose reduction. If re-occurrence of a Grade 3 or higher elevation, discontinue treatment with fedratinib. In addition, Section 4.4 of the SmPC advises that patients should have their hepatic function monitored at baseline, at least monthly for the first 3 months, periodically during treatment and as clinically indicated. After observed toxicity, patients should be monitored at least every 2 weeks until resolution. In place of strong CYP3A4 inhibitors, alternative therapies that do not strongly inhibit CYP3A4 activity should be considered. If strong CYP3A4 inhibitors cannot be avoided, the dose of fedratinib should be reduced when administering with strong CYP3A4 inhibitors. Agents that strongly or moderately induce CYP3A4 should be avoided in patients receiving fedratinib. Use of fedratinib in patients with severe HI (Child-Pugh class C or total bilirubin > 3 times ULN and any AST increase) should be avoided.
Impact on the risk-benefit balance of the product	Severe DILI has the potential to be fatal, especially if not diagnosed and treated promptly; however, given the life-threatening nature of MF, the impact of the potential risk of severe hepatotoxicity on the risk-benefit balance is acceptable.
Public health impact	Drug-induced liver injury is an infrequent but potentially severe event. The idiosyncratic nature and poor prognosis of DILI make this type of reaction a major safety issue during drug development, as well as the most common cause for the withdrawal of drugs from the pharmaceutical market. According to the US Acute Liver Failure Study Group, DILI accounts for more than 50% of acute liver failure, including hepatotoxicity caused by overdose of acetaminophen (39%) and idiosyncratic liver injury triggered by other drugs (13%[56]). Because of the significant patient morbidity and mortality associated with DILI, the US Food and Drug Administration has removed several drugs from the market, including bromfenac, ebrotidine and troglitazone. DILI can affect both parenchymal and nonparenchymal cells of the liver, leading to a wide variety of pathological conditions, including acute and chronic hepatocellular hepatitis, fibrosis/cirrhosis, cholestasis, steatosis, as well as sinusoidal and hepatic artery/vein damage. The predominant forms of DILI include acute hepatitis, cholestasis and a mixed pattern. Acute hepatitis is defined as a marked increase in aminotransferases coinciding with hepatocellular necrosis. Cholestasis is characterised by jaundice with a concurrent elevation in alkaline phosphatase, conjugated bilirubin and gamma-glutamyltransferase. Mixed pattern DILI includes clinical manifestations of both hepatocellular and cholestatic injury. Two prospective studies showed the incidence of DILI to be 14 per 100,000 and 19 per 100,000.[57]

Table 2.7.3.1-6: Important Potential Risk: Severe Hepatotoxicity

Important Potential Risk: Severe Hepatotoxicity	
	The natural history of DILI is dominated by complete recovery for most patients, but approximately 10% may not survive the initial injury, or may require liver transplantation. Another 5% to 10% may be at risk from chronic injury and potential long-term morbidity and mortality.[58]

Table 2.7.3.1-7: Important Potential Risk: Severe Infections Including Viral Reactivation

Important Potential Risk: Severe Infections Including Viral Reactivation

Potential mechanisms

Immunomodulatory drugs that affect intracellular signalling are involved in immune responses, and therefore treatment could result in infections, including viral reactivation. Infections and viral reactivation associated with ruxolitinib are mediated through the potent inhibitory effects of ruxolitinib on JAK1 and TYK2.[59,60,61] Fedratinib is selective for JAK2 over JAK1 and TYK2, and less potent than ruxolitinib in the inhibition of JAK1 And TYK2.

Evidence source and strength of evidence

Infections including tuberculosis, UTI and herpes zoster are an important identified risk of treatment with ruxolitinib, a JAK1/JAK2 inhibitor. In Study EFC12153, the frequencies of patients with infection TEAEs was similar between placebo and treatment arms (CSR EFC12153, Section 12.3.1.3.4.2) however there was an increased frequency of UTI in fedratinib-treated patients compared to placebo but these were Grade 1 or 2 events. Therefore, the risk of severe infections including viral reactivation is considered an important potential risk for fedratinib.

Characterisation of risk

Frequency with 95% CI

Severe Infections Including Viral Reactivations (Grade ≥ 3)	**Fedratinib 400 mg (N = 203)**	**Fedratinib Pool 1 (N = 321)**	**Placebo (N=95)**
Total number of patients, n	203	321	95
Patients with ≥ 1 SAE, n (%)	0	0	0
Patients with ≥ 1 Grade ≥ 3 AE, n (%)	1 (0.5)	1 (0.3)	0
Incidence (%) of patients with ≥ 1 Grade ≥ 3 AE (95% CI)	0.5 (0.0, 2.7)	0.3 (0.0, 1.7)	0
Exposure-adjusted incidence rate / 100 person-years	0.6	0.4	0

As there was only one fedratinib-treated patient and no placebo-treated patients with ≥ Grade 3 severe infections, the difference and RR were not estimated.

Seriousness/Outcomes

There were no reported SAEs in MF patients treated at 400 mg and in the overall study population.

Severity and Nature of Risk

Severe Infections Including Viral Reactivations	**Fedratinib 400 mg (N = 203), n (%)**	**Fedratinib Pool 1 (N = 321), n (%)**	**Placebo (N = 95), n (%)**
All AEs	6 (3.0)	9 (2.8)	3 (3.2)

Table 2.7.3.1-7: Important Potential Risk: Severe Infections Including Viral Reactivation

Important Potential Risk: Severe Infections Including Viral Reactivation				
	Grade 3 or 4	1 (0.5)	1 (0.3)	0
	AEs leading to discontinuation	0	0	0
	AEs leading to dose reduction	0	0	0
	AEs leading to dose interruption	0	0	0
Risk factors and risk groups	Risk factors include underlying neutropenia, immunosuppressive disease or taking immunosuppressive agents. Prolonged hospitalisation may also increase the risk of serious infections.			
Preventability	As fedratinib-treated patients are monitored by obtaining a complete blood count at baseline, periodically during treatment and as clinically indicated, patients can be monitored for abnormalities in the white count and neutrophil count which may increase the risk of severe infections.			
Impact on the risk-benefit balance of the product	Severe infections including viral reactivation in the presence of neutropenia may contribute significantly to morbidity and mortality.			
Public health impact	As fedratinib-treated patients are monitored for haematological toxicities by obtaining a complete blood count at baseline, periodically during treatment and as clinically indicated, patients can be monitored for abnormalities in the white count and neutrophil count which may increase the risk of severe infections. Febrile neutropenia and infections should be treated aggressively in MF patients, as these contribute significantly to morbidity and mortality.[62] These infections may necessitate treatment with antibiotics and/or G-CSF for neutropenic infection.			

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information – Long-term Safety, Including Secondary Malignancies

Missing Information	**Evidence Source**
Population in need of further characterisation: Long-term Safety, Including Secondary Malignancies	
Overall, long-term observations indicate that, in general, toxicities did not increase over time and were tolerable during long-term treatment with fedratinib (> 24 cycles) in a limited number of patients with MF. Furthermore, up to 3 years of follow up is planned in Study FEDR-MF-002 to further investigate long-term safety of fedratinib, including secondary malignancies.	Due to the placement of the clinical hold and subsequent termination of all on-going studies, there has been no collection of long-term safety data in fedratinib-treated patients. An analysis performed for the subset of patients from Study TED12037/TED12015 who received long-term treatment, defined as > 24 cycles initiated (N = 28) indicate that there were no late-onset TEAEs noted. A review of the clinical database confirmed that the rate of transformation to AML for all fedratinib-

Table 2.7.3.2-1: Missing Information – Long-term Safety, Including Secondary Malignancies

	treated subjects was within the expected rate for this population and no trends for increased rates of other second malignancies were observed. Given the small numbers of patients with treatment beyond 24 cycles, long-term safety, including secondary malignancies, is considered missing information.

2.8 Summary of the Safety Concerns

Table 2.8-1: Summary of Safety Concerns

Important identified risks	Anaemia
	Thrombocytopenia/bleeding
	Encephalopathy, including Wernicke's
	Gastrointestinal toxicities (diarrhoea, nausea, vomiting)
Important potential risks	Pancreatitis
	Severe hepatotoxicity
	Severe infections including viral reactivation
Missing information	
	Long-term safety, including secondary malignancies

3 PART III: PHARMACOVIGILANCE PLAN

Routine Pharmacovigilance activities in BMS as described in the BMS Pharmacovigilance System Master File and Drug Safety's Standard Operating Procedures are in accordance with "Good Pharmacovigilance Practices in the European Union." BMS's Routine Pharmacovigilance System is detailed in the current version of the BMS Pharmacovigilance System Master File.

In addition to expedited reporting, BMS vigilantly undertakes follow-up on all AEs, including serious AEs that are provided to health authorities to ensure that all details of the case are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the AEs.

Emerging potential safety signals can be detected by periodic and if appropriate, cumulative evaluation of the AEs. The results will be compiled in the PSUR, in accordance with Guidelines on Good Pharmacovigilance Practices in the EU/EEA. Periodicity of the PSUR submissions will be in accordance with the published list of EU reference dates (EURD-List).

In addition, data regarding AEs of special interest, which are referred to as risks in the PSUR will be targeted for review and will be specifically discussed in the PSUR document. These data will include all case reports collected during the specified period together with cumulative data.

Using the data obtained from this plan, the benefit/risk profile of fedratinib will be re-evaluated on a periodic basis via the PSUR. If necessary, the related sections of the RMP will be updated accordingly.

3.1 Routine Pharmacovigilance Activities

Targeted follow-up questions for thrombocytopenia/bleeding and encephalopathy, including Wernicke's are included in Annex 4.

3.2 Additional Pharmacovigilance Activities

A summary of ongoing and completed pharmacovigilance study protocols is provided in Annex 2.

Table 3.2-1: Post-Authorisation Safety Studies Short Name Summary

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestone(s)	Due Date(s)
FEDR-MF-002 "FREEDOM 2" A Phase 3, multicentre, open-label, randomized study to evaluate the efficacy and safety of fedratinib compared to best available therapy in subjects with DIPSS-intermediate or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib	MPN-associated MF is a serious and life-threatening disease. The only approved therapy currently available in the EU is the JAK1/2 inhibitor, ruxolitinib. For patients in Europe who have been previously treated with ruxolitinib and who failed first-line treatment, there is no approved therapy and prognosis for these patients is poor. Fedratinib is a potent and selective, orally available JAK2 inhibitor. The primary objective of the study is: • To evaluate the efficacy of fedratinib (the proportion of subjects who have a ≥ 35% reduction in spleen volume) as compared to BAT and to further evaluate the safety of fedratinib. Secondary objectives of the study include: • To evaluate the safety of fedratinib. • To assess the effectiveness of the risk mitigation strategy for GI events and encephalopathy, including Wernicke's. For a full list of secondary objectives, see Annex 3. Safety concerns covered are: Anaemia; Thrombocytopenia/ bleeding; Encephalopathy, including Wernicke's; GI toxicities (diarrhoea, nausea, vomiting); Pancreatitis; Severe hepatotoxicity; Severe infections including viral reactivation; Long-term safety, including secondary malignancies.	Phase 3 multicentre, open-label, randomised, efficacy and safety study.	Patients with DIPSS-intermediate-2 or high-risk PMF, post-PV MF or post-ET MF and previously treated with ruxolitinib.	Original protocol Protocol amendment No. 1 Protocol amendment No. 2 FSFV LSLV (treatment discontinuation) DBL CSR with FUP	26-Sep-2018 01-Feb-2019 08-Oct-2019 09-Sep-2019 24-May-2022[a] 23-Aug-2025[a] 22-Nov-2025[a]

[a] At this point in time, it is unknown how coronavirus disease-19 (COVID-19) pandemic could impact the timeline.

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study/ Status	Summary of Objectives	Safety Concerns Addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
FEDR-MF-002/ Ongoing	Primary objective: • To evaluate the efficacy of fedratinib (the proportion of subjects who have a ≥ 35% reduction in spleen volume) as compared to BAT and to further evaluate the safety of fedratinib. Secondary objectives of the study include: • To evaluate the safety of fedratinib. • To assess the effectiveness of the risk mitigation strategy for GI events and encephalopathy, including Wernicke's. For a full list of secondary objectives, see Annex 3.	Anaemia Thrombocytopenia/bleeding Encephalopathy, including Wernicke's Gastrointestinal toxicities (diarrhoea, nausea, vomiting) Pancreatitis Severe hepatotoxicity Severe infections including viral reactivation Long-term safety, including secondary malignancies	Original Protocol Protocol Amendment No. 1 Protocol Amendment No. 2 FSFD LSLV DBL CSR with FUP	26 Sep 2018 01 Feb 2019 08 Oct 2019 09 Sep 2019 24 May 2022[a] 23 Aug 2025[a] 22 Nov 2025[a]

[a] At this point in time, it is unknown how coronavirus disease 19 (COVID-19) pandemic could impact the timeline.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No studies are planned or required.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Anaemia	Routine risk communication: SmPC Section 4.8 Undesirable effects Details of anaemia events. Anaemia listed as a very common ADR. Package Leaflet (PL) Section 4 Possible side effects Anaemia listed as a very common side effect. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration Includes details of dose reductions to be made in the event of Grade 3 and higher anaemia (transfusion indicated), during treatment with fedratinib. Section 4.4 Special warnings and precautions for use Warnings that treatment with fedratinib may cause anaemia (generally within the first 3 months of treatment), that a baseline complete blood count should be obtained prior to starting treatment with fedratinib, periodically during treatment and as clinically indicated, and that blood transfusions and/or dose reductions may be required. PL Section 2 What you need to know before you take Inrebic Warnings to talk to a doctor or pharmacist if signs of low red blood cell counts are present before starting fedratinib treatment and during treatment, that blood tests will be performed before and during treatment with fedratinib, and that the dose of fedratinib may be changed or treatment stopped based on the results of the blood tests. Other routine risk minimisation measures beyond the Product Information: None. Legal status: Fedratinib is subject to restricted medical prescription.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Thrombocytopenia/ bleeding	Routine risk communication: SmPC Section 4.8 Undesirable effects Details of thrombocytopenia events. Thrombocytopenia listed as a very common ADR. PL Section 4 Possible side effects Thrombocytopenia listed as a very common side effect. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration Includes details of dose adjustments to be made in the event of Grade 3 thrombocytopenia with active bleeding or Grade 4 thrombocytopenia. Section 4.4 Special warnings and precautions for use Warnings that treatment with fedratinib may cause thrombocytopenia (generally within the first 3 months of treatment), that a baseline complete blood count should be obtained prior to starting treatment with fedratinib, periodically during treatment and as clinically indicated, and that thrombocytopenia is generally reversible and usually managed by supportive treatment such as dose interruptions, dose reduction and/or platelet transfusions. PL Section 2 What you need to know before you take Inrebic Warnings to talk to a doctor or pharmacist if signs of a low platelet count are present before and during fedratinib treatment, that blood tests will be performed before and during treatment with fedratinib, and that the dose of fedratinib may be changed or treatment stopped based on the results of the blood tests. Other routine risk minimisation measures beyond the Product Information: None. Legal status: Fedratinib is subject to restricted medical prescription.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Encephalopathy, including Wernicke's	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use Includes statement that patients treated with fedratinib have experienced encephalopathy, including Wernicke's, with details of signs and symptoms. Section 4.8 Undesirable effects Details of WE ADRs: WE listed as a common ADR. PL Section 4 Possible side effects Details of side effects of encephalopathy, including Wernicke's. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration Guidance on replenishment of thiamine if levels are low, prior to treatment and on thiamine prophylaxis and assessment during treatment. Dose modification guidelines for GI toxicity and thiamine abnormalities. Section 4.4 Special warnings and precautions for use Includes a warning that fedratinib treatment should not be started in patients with thiamine deficiency and that thiamine levels and nutritional status should be assessed prior to starting treatment with fedratinib. Includes guidance that while on treatment, all patients should receive thiamine prophylaxis and should have thiamine levels assessed as clinically indicated. Warning regarding GI toxicity and thiamine levels. Warning that fedratinib treatment should be immediately discontinued if encephalopathy, including Wernicke's, is suspected, and that parenteral thiamine treatment should be initiated while evaluating for all possible causes. Patients should be monitored until symptoms have resolved or improved and thiamine levels have normalised. PL Section 2 What you need to know before you take Inrebic Warning to talk to a doctor or pharmacist if signs of encephalopathy, including Wernicke's, are present before and during fedratinib treatment, statements that blood tests will be performed to check vitamin B1 levels before and during treatment with fedratinib, and that the dose of fedratinib may need to be adjusted or treatment stopped based on the results of the blood tests. Other routine risk minimisation measures beyond the Product Information: None. Legal status: Fedratinib is subject to restricted medical prescription.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Gastrointestinal toxicities (diarrhoea, nausea, vomiting)	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use Includes warning that nausea, vomiting and diarrhoea are among the most frequent ADRs in fedratinib-treated patients. Section 4.8 Undesirable effects Diarrhoea, vomiting and nausea listed as very common ADRs. PL Section 4 Possible side effects Diarrhoea, vomiting and nausea listed as very common side effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration Recommendation that prophylactic anti-emetics be used according to local practice for the first 8 weeks of treatment and continued as clinically indicated. Administration with a high fat meal may reduce the incidence of nausea and vomiting. Section 4.4 Special warnings and precautions for use Includes advice regarding prophylactic treatment and the treatment that should be given following the onset of symptoms. Advice that thiamine levels should be monitored and replenished as needed. PL Section 2 What you need to know before you take Inrebic Warning to talk to a doctor or pharmacist if symptoms including nausea, vomiting or diarrhoea, are present before and during fedratinib treatment. Other routine risk minimisation measures beyond the Product Information: None. Legal status: Fedratinib is subject to restricted medical prescription.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Pancreatitis	Routine risk communication: SmPC Section 4.8 Undesirable effects Details of events of pancreatitis, lipase increased and amylase increased. Lipase increased and amylase increased listed as very common ADRs. PL Section 4 Possible side effects Changes in blood test results (increase in amylase and lipase levels) listed as very common side effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration Includes dose recommendations for other ≥ Grade 3 non-haematologic toxicities. Section 4.4 Special warnings and precautions for use Includes a statement that patients should have their amylase and lipase monitored at baseline, at least monthly for the first 3 months and as clinically indicated. After observed toxicity, patients should be monitored at least every 2 weeks until resolution. PL Section 2 What you need to know before you take Inrebic Warning to talk to a doctor or pharmacist during fedratinib treatment if the patient has or has ever had any history of problems with the pancreas or liver, or history of kidney problems. Statements that blood tests will be performed before and during fedratinib treatment to check pancreatic function and that the dose of fedratinib may need to be adjusted or treatment stopped based on the results of the blood tests. Other routine risk minimisation measures beyond the Product Information: None. Legal status: Fedratinib is subject to restricted medical prescription.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Severe hepatotoxicity	Routine risk communication: SmPC Section 4.8 Undesirable effects Details of events of ALT increased and AST increased. ALT increased and AST increased listed as very common ADRs. PL Section 4 Possible side effects Changes in blood test results (ALT increased and AST increased) listed as very common side effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration Includes dose recommendations in the event of ≥ Grade 3 ALT, AST or bilirubin. Section 4.4 Special warnings and precautions for use Includes a statement that patients should have their hepatic function monitored at baseline, at least monthly for the first 3 months, periodically during treatment and as clinically indicated. After observed toxicity, patients should be monitored at least every 2 weeks until resolution. PL Section 2 What you need to know before you take Inrebic Warnings to talk to a doctor or pharmacist during fedratinib treatment if the patient has or has ever had any liver problems, statements that blood tests will be performed before and during fedratinib treatment to check liver function and that the dose of fedratinib may need to be adjusted or treatment stopped based on the results of the blood tests. Other routine risk minimisation measures beyond the Product Information: None. Legal status: Fedratinib is subject to restricted medical prescription.
Severe infections including viral reactivation	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None. Legal status: Fedratinib is subject to restricted medical prescription.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Long-term safety, including secondary malignancies	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None. Legal status: Fedratinib is subject to restricted medical prescription.

5.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Section 5.1 are sufficient to manage the safety concerns of the medicinal product.

5.3 Summary of Risk Minimisation Measures

A summary of risk minimisation measures and pharmacovigilance activities by safety concern is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Anaemia	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4 and PL Section 2 – warnings, advice and management of anaemia discussed. SmPC Section 4.8 and PL Section 4 – details of events and anaemia listed as a very common ADR. Additional risk minimisation measures: None. Legal status: Fedratinib is subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Category 3 studies: FEDR-MF-002
Thrombocytopenia/ bleeding	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4 and PL Section 2 – warnings, advice and management of thrombocytopenia discussed. SmPC Section 4.8 and PL Section 4 – details of events and thrombocytopenia listed as a very common ADR.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questions. Additional pharmacovigilance activities: Category 3 studies: FEDR-MF-002

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None. Legal status: Fedratinib is subject to restricted medical prescription.	
Encephalopathy, including Wernicke's	Routine risk minimisation measures: SmPC Section 4.2 – includes guidance on thiamine replenishment if levels are low prior to treatment, on thiamine prophylaxis and assessment as clinically indicated during treatment, and dose recommendations. SmPC Section 4.4 – advice on prophylaxis and monitoring of thiamine levels and nutritional status, warnings regarding WE and GI toxicity and recommendations for prophylaxis and supportive treatment of encephalopathy, including Wernicke's. SmPC Section 4.8 – details of encephalopathy, including Wernicke's, ADRs and WE listed as a common ADR. PL Sections 2 and 4 – warnings regarding encephalopathy, including Wernicke's, details of encephalopathy, including Wernicke's, side effects, signs of encephalopathy, including Wernicke's. Additional risk minimisation measures: None. Legal status: Fedratinib is subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questions. Additional pharmacovigilance activities:
Gastrointestinal toxicities (diarrhoea, nausea, vomiting)	Routine risk minimisation measures: SmPC Section 4.2 –recommendations regarding prophylactic anti-emetics and administration with a high fat meal. SmPC Section 4.4 –advice regarding prophylactic treatment, treatment that should be given on the onset of symptoms, and monitoring and replenishment of thiamine levels. SmPC Section 4.8 – diarrhoea, vomiting and nausea listed as very common ADRs. PL Sections 2 and 4 – warning to talk to a doctor or pharmacist if symptoms including nausea, vomiting or diarrhoea, are present before and during fedratinib treatment. Diarrhoea, vomiting and nausea listed as very common side effects. Additional risk minimisation measures: None. Legal status: Fedratinib is subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Category 3 studies: FEDR-MF-002

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pancreatitis	Routine risk minimisation measures: SmPC Section 4.2 – includes dose recommendations for other ≥ Grade 3 non-haematologic toxicities. SmPC Section 4.4 – advice on monitoring of amylase and lipase. SmPC Section 4.8 – details of events of pancreatitis, elevated amylase/lipase. Amylase increased and lipase increased listed as very common ADRs. PL Sections 2 and 4 – warnings regarding history of problems with the pancreas (and the liver) and history of kidney problems, details of side effects of increased lipase and amylase. Additional risk minimisation measures: None. Legal status: Fedratinib is subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Category 3 studies: FEDR-MF-002
Severe hepatotoxicity	Routine risk minimisation measures: SmPC Section 4.2 – dose recommendations are provided. SmPC Section 4.4 – advice on monitoring of hepatic function. SmPC Section 4.8 – details of events of ALT increased and AST increased. ALT increased and AST increased listed as very common ADRs. PL Sections 2 and 4 – warnings regarding liver problems, details of side effects of ALT increased and AST increased. Additional risk minimisation measures: None. Legal status: Fedratinib is subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Category 3 studies: FEDR-MF-002
Severe infections including viral reactivation	Routine risk minimisation measures: None. Additional risk minimisation measures: None. Legal status: Fedratinib is subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Category 3 studies: FEDR-MF-002
Long-term safety, including	Routine risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
secondary malignancies	Additional risk minimisation measures: None. Legal status: Fedratinib is subject to restricted medical prescription.	reactions reporting and signal detection: None. Additional pharmacovigilance activities: Category 3 studies: FEDR-MF-002

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for INREBIC (fedratinib)

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

INREBIC's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how INREBIC should be used.

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

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

I. The medicine and what it is used for

INREBIC is authorised for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (post-PV MF) or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, or have been treated with ruxolitinib. It contains fedratinib as the active substance and it is given by oral route.

Further information about the evaluation of INREBIC’s benefits can be found in INREBIC’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://ema.europa.eu/en/medicines/human/EPAR/inrebic

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

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

II.A List of important risks and missing information

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

List of important risks and missing information

Important identified risks	Anaemia
	Thrombocytopenia/bleeding
	Encephalopathy, including Wernicke's
	Gastrointestinal toxicities (diarrhoea, nausea, vomiting)
Important potential risks	Pancreatitis
	Severe hepatotoxicity
	Severe infections including viral reactivation
Missing information	Long-term safety, including secondary malignancies

II.B Summary of Important Risks

Important identified risk: Anaemia

Evidence for linking the risk to the medicine	Grade 3 or 4 anaemia frequently leads to the need for red blood cell (RBC) transfusions including RBC transfusion

Important identified risk: Anaemia

	dependence. In PMF, anaemia and the need for RBC transfusions is associated with a shorter overall survival and shorter leukaemia-free survival.[63] Given the prognostic implications and the observation of Grade 3 anaemia as a very common adverse reaction in patients treated with fedratinib, this risk is considered an important identified risk.
Risk factors and risk groups	Patients with baseline haemoglobin < 10 g/dL are more likely to develop severe anaemia. The median time to first onset of Grade 3 anaemia event was approximately 45 days with 75% of cases occurring within 3 months of starting treatment. Patients with underlying renal disease may be at an increased risk of anaemia. In patients with myelofibrosis (MF), anaemia may occur as part of the primary disease and patients may be transfusion dependent at the start of the study.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4 and PL Section 2 – warnings, advice and management of anaemia discussed. SmPC Section 4.8 and PL Section 4 – details of events and anaemia listed as a very common adverse drug reaction (ADR).
	Additional risk minimisation measures: None.
	Legal status: Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: FEDR-MF-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Thrombocytopenia/Bleeding

Evidence for linking the risk to the medicine	While Grade 3 or 4 thrombocytopenia was similar in fedratinib-treated patients and patients receiving placebo in the randomised controlled Phase 3 study in the JAK inhibitor naïve setting, the rate of Grade 3 or 4 thrombocytopenia was higher in MF patients previously treated with ruxolitinib. These previously exposed patients fulfil an area of high unmet medical need and it is expected that fedratinib will be primarily utilised in this setting. As thrombocytopenia may lead to bleeding events, thrombocytopenia is considered an important identified risk of fedratinib.
Risk factors and risk groups	Patients with baseline platelets < 100×10^9/L are more likely to develop severe thrombocytopenia. Thrombocytopenia generally occurs within the first 3 months of treatment, then stabilises. Previous chemotherapies including ruxolitinib and severity of the underlying disease are also an important contributor to thrombocytopenia and subsequent bleeding risks.

Important identified risk: Thrombocytopenia/Bleeding

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4 and PL Section 2 – warnings, advice and management of thrombocytopenia discussed. SmPC Section 4.8 and PL Section 4 – details of events and thrombocytopenia listed as a very common ADR.
	Additional risk minimisation measures: None.
	Legal status: Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: FEDR-MF-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Encephalopathy, Including Wernicke's

Evidence for linking the risk to the medicine	Due to the limited understanding of the causal association of fedratinib with this risk based on the fact that fedratinib does not interfere with thiamine receptors and that Wernicke's encephalopathy can be fatal if not recognised and treated properly, the risk of encephalopathy, including Wernicke's is considered an important identified risk. To evaluate any possible association between concerns of encephalopathy, including Wernicke's in fedratinib-treated patients, the fedratinib clinical database of 608 patients receiving continuous daily doses of fedratinib for MPNs or solid tumours was searched for reports of encephalopathy of any type, including Wernicke's, and any signs or symptoms (eg, mental status changes, ophthalmoplegia (eg, nystagmus, diplopia) and cerebellar findings) that could be suggestive of thiamine deficiency or encephalopathy, including Wernicke's. Eight fedratinib-treated patients with neurological signs or symptoms suggesting the potential diagnosis of encephalopathy, including Wernicke's, were identified. Only one patient had thiamine levels evaluated at the time of symptoms and it was normal. These patients' case histories and neuro-imaging data were reviewed by five independent experts. Based on the experts' reviews, all agreed that one patient was identified as having WE. One patient was identified as not having WE, but rather hepatic encephalopathy. For the remaining six patients, there was no consensus among the experts. Therefore, taken conservatively, at most seven cases of WE occurred in over 600 fedratinib-treated patients.
Risk factors and risk groups	Four common and distinct (but overlapping) presentations of encephalopathies the physician is likely to encounter in clinical practice are: encephalopathy from metabolic disorder or deficiency, encephalopathy due to a severe systemic illness or

Important identified risk: Encephalopathy, Including Wernicke's

	organ failure, encephalopathy due to medication-related toxicity, and encephalopathies diagnosed primarily by findings on brain imaging. For WE, specifically, conditions associated with thiamine deficiency and subsequent development of WE include chronic alcoholism, hyperemesis, malabsorption, poor dietary intake, increased loss of thiamine by the kidneys (eg, in diabetes or renal disease), or an increased metabolic requirement of thiamine.[41] Myelofibrosis patients may be malnourished due to splenomegaly causing a feeling of fullness or loss of appetite. In addition, fedratinib is very commonly associated with gastrointestinal (GI) adverse events (AEs) including nausea, vomiting and diarrhoea. Inadequate treatment of these GI AEs, especially in the thiamine setting of underlying malnutrition, may predispose to thiamine deficiency and thus WE.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 – includes guidance on thiamine replenishment if levels are low prior to treatment, on thiamine prophylaxis and assessment during treatment, and dose recommendations. SmPC Section 4.4 – advice on prophylaxis and monitoring of thiamine levels and nutritional status, warnings regarding WE and GI toxicity and recommendations for prophylaxis and supportive treatment of encephalopathy, including Wernicke's. SmPC Section 4.8 – details of encephalopathy, including Wernicke's, ADRs and WE listed as a common ADR. PL Sections 2 and 4 – warnings regarding encephalopathy, including Wernicke's, details of encephalopathy, including Wernicke's, side effects, signs of encephalopathy, including Wernicke's.
	Additional risk minimisation measures: None.
	Legal status: Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: FEDR-MF-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)

Evidence for linking the risk to the medicine	Diarrhoea (62.6%), nausea (58.6%) and vomiting (39.4%) were the most common nonhaematologic TEAEs (all grades) in MF patients who received 400 mg fedratinib. Most of the GI events were Grade 1 or 2. Grade 3 and 4 AEs of diarrhoea, nausea and vomiting were reported for 5.4%, 0.5% and 2.0% patients with

Important identified risk: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)

	MF who received 400 mg fedratinib, respectively. Despite the high rate of GI TEAEs, these events were not a common reason for permanent treatment discontinuation.
Risk factors and risk groups	In the clinical development program, GI toxicities were observed across all indications including patients with MF, with solid tumours and in heathy volunteers.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 –recommendations regarding prophylactic anti-emetics and administration with a high fat meal. SmPC Section 4.4 –advice regarding prophylactic treatment, treatment that should be given on the onset of symptoms, and monitoring and replenishment of thiamine levels. SmPC Section 4.8 – diarrhoea, vomiting and nausea listed as very common ADRs. PL Sections 2 and 4 – warning to talk to a doctor or pharmacist if symptoms including nausea, vomiting or diarrhoea, are present before and during fedratinib treatment. Diarrhoea, vomiting and nausea listed as very common side effects.
	Additional risk minimisation measures: None.
	Legal status: Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: FEDR-MF-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Pancreatitis

Evidence for linking the risk to the medicine	Grade 3 and 4 elevations of lipase were a dose-limiting toxicity in the Phase 1 dose finding study at high dose (up to 800 mg). Elevations of amylase (20%) and lipase (32%), all grades, were reported with fedratinib in patients with MF. Most of these events were Grade 1 or 2 and the more severe elevations responded to dose modification. During the clinical development programme, only one case of pancreatitis was observed in a patient in the Phase 3 study who presented with acute onset of abdominal pain and Grade 4 lipase increased by laboratory evaluation. The event occurred at the beginning of Cycle 7, and no elevations of lipase or amylase were detected by laboratory assessment before this event, including at the End-of-Cycle 6 visit. The event resolved with treatment discontinuation. Given the above, the risk of pancreatitis is considered an important potential risk.

Important identified risk: Pancreatitis

Risk factors and risk groups	Higher doses of fedratinib were associated with more severe elevations of amylase and lipase. Risk factors for pancreatitis include gallstones, prolonged alcohol use, high triglycerides and pancreatitis is commonly associated with diabetes, obesity and smoking.[50]
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 – includes dose recommendations for other ≥ Grade 3 non-haematologic toxicities. SmPC Section 4.4 – advice on monitoring of amylase and lipase. SmPC Section 4.8 – details of events of pancreatitis and elevated amylase/lipase. Amylase increased and lipase increased listed as very common ADRs. PL Sections 2 and 4 – warnings regarding history of problems with the pancreas (and the liver) and history of kidney problems, details of side effects of increased lipase and amylase.
	Additional risk minimisation measures: None.
	Legal status: Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: FEDR-MF-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Severe Hepatotoxicity

Evidence for linking the risk to the medicine	Elevations of alanine aminotransferase (ALT) (43%) and aspartate aminotransferase (AST) (52%), all grades, were reported with 400 mg fedratinib in MF patients. Most of these elevations were Grade 1 or 2; however, Grade 3 and 4 ALT, AST and total bilirubin (TBL) elevations in the Phase 1 study (TED12037/TED12015) at higher fedratinib doses (patients received up to 800 mg) were observed and in a Phase 2 dose-range finding study, one patient at 300 mg developed hepatic failure with Grade 4 elevations of ALT, AST and bilirubin. Fedratinib was withdrawn, and the patient recovered. Grade 3 or 4 elevations of ALT and AST were generally reversible with dose modification and permanent treatment discontinuation. Recommendations for dose modifications (including dose reductions) for severe hepatic enzyme elevations in order to prevent the potential risk of severe hepatotoxicity are included in Section 4.2 of the SmPC.

Important Potential Risk: Severe Hepatotoxicity

Risk factors and risk groups	Risk factors may include higher doses of fedratinib. In the Phase 1 study (TED12037/TED12015), Grade 3 and 4 ALT, AST and TBL elevations were observed at higher fedratinib doses (patients received up to 800 mg). Risk factors for severe hepatotoxicity from drugs include medication dose, drug lipophilicity and extent of hepatic metabolism.[53] Pre-existing liver disease/extramedullary haematopoiesis is also commonly observed in the liver in MF patients, and may increase the risk of severe hepatotoxicity. Host-related risk factors include the patient's age, sex, genetics, previous episodes of drug-induced liver injury, and underlying chronic liver disease. Environmental risk factors include the patient's metabolic features (eg, obesity), diet type, alcohol, coffee and tobacco consumption, multidrug therapy, immune state (eg, immunocompromised), and nutritional status.[54]
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 – dose recommendations are provided. SmPC Section 4.4 – advice on monitoring of hepatic function. SmPC Section 4.8 – details of events of ALT increased and AST increased. ALT increased and AST increased listed as very common ADRs. PL Sections 2 and 4 – warnings regarding liver problems, details of side effects of ALT increased and AST increased.
	Additional risk minimisation measures: None.
	Legal status: Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: FEDR-MF-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Severe Infections Including Viral Reactivation

Evidence for linking the risk to the medicine	Infections including tuberculosis, urinary tract infections (UTI) and herpes zoster are an important identified risk of treatment with ruxolitinib, a JAK1/JAK2 inhibitor. In Study EFC12153, the frequencies of patients with infection treatment-emergent adverse events was similar between placebo and treatment arms (clinical study report EFC12153, Section 12.3.1.3.4.2) however there was an increased frequency of UTI in fedratinib-treated patients compared to placebo but these were Grade 1 or 2 events. Therefore, the risk of severe infections including viral

Important Potential Risk: Severe Infections Including Viral Reactivation

	reactivation is considered an important potential risk for fedratinib.
Risk factors and risk groups	Risk factors include underlying neutropenia, immunosuppressive disease or taking immunosuppressive agents. Prolonged hospitalisation may also increase the risk of serious infections.
Risk minimisation measures	Routine risk minimisation measures: None.
	Additional risk minimisation measures: None.
	Legal status: Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: FEDR-MF-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important missing information: Long-term Safety, Including Secondary Malignancies

Risk minimisation measures	Routine risk minimisation measures: None.
	Additional risk minimisation measures: None.
	Legal status: Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: FEDR-MF-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

No studies are conditions of the marketing authorisation.

II.C.2 Other Studies in Post-authorisation Development Plan

Study short name: **FEDR-MF-002**

Purpose of the study: the primary objective of the study is to evaluate the efficacy of INREBIC (the proportion of subjects who have a ≥ 35% reduction in spleen volume) as compared to BAT and to further evaluate the safety of INREBIC. The secondary objectives of the study include to evaluate the safety of INREBIC and to assess the effectiveness of the risk mitigation strategy for GI events and encephalopathy, including Wernicke's.

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

11 page(s) excluding cover page

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Follow-up forms

Adverse Event Report Questionnaire
TL Thrombocytopenia-Bleeding

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐Male ☐ Female Age: _____

Race/Ethnicity: _____ ☐ Aboriginal ☐African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander ☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
	Platelets					
	PT					
	aPTT					
	INR					
	ESR					
	LFTs					
	Factor VIII					
	Factor IX					

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes [please complete below; Please provide relevant concomitant medications, including thromboprophylaxis (type/dose/dates as well as corresponding lab monitoring values if applicable), and possible platelet transfusion need to prevent hemorrhagic event]
☐ No ☐ Unknown

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date (DD-MMM-YYYY)

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Please provide location of the bleeding/hemorrhage.

Relevant medical history:
Does the patient have:

History of anemia?

Was patient transfusion dependent? If yes, since when and how frequent?

Episodes of Hypotension? Hypertension? Gingivorrhagia or epistaxis? Headaches? Pallor? Dyspnea? Weakness?

Please describe. History of bleeding/hemorrhage? Coagulation disorder? Please describe.

Please provide date of diagnosis of underlying disease, stage at the time of diagnosis and stage of the patient's disease at the time of the event.

Please include bone marrow studies / x-ray / CT scan results for the event of thrombocytopenia/ bleeding/hemorrhage.

What treatments were given for the thrombocytopenia/ bleeding/ hemorrhage? Please include dates/dose.

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Adverse Event Report Questionnaire
TL Encephalopathy Including Wernickes

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐Male ☐ Female Age: _____

Race/Ethnicity: _____ ☐ Aboriginal ☐African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander ☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date (DD-MMM-YYYY)

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Please provide the type of encephalopathy
☐ Thiamine deficiency (Wernicke's)
☐ Hypoxic/ischemic
☐ Septic
☐ Hepatic
☐ Uremic
☐ Toxic metabolic
☐ Hyponatremic
☐ Hypernatremic
☐ Hypoglycemic
☐ Hyperosmolar hyperglycemic/ diabetic ketoacidosis
☐ Post-transplantation
☐ Hypertensive
☐ Posterior reversible *encephalopathy* syndrome (PRES)

☐Infectious
☐Other to specify:

Please characterize encephalopathy as
☐Acute
☐Subacute
☐Chronic

Please check and provide a description of the signs and symptoms that led to a diagnosis of encephalopathy
☐Ocular abnormalities such as nystagmus, diplopia, etc. Specify:
☐Confusion
☐Memory impairment
☐Mental status changes
☐Ataxia, Gait abnormalities
☐Seizures
☐Speech abnormalities
☐Hallucination/Delirium
☐Lethargy
☐Coma (stage)
☐Other findings (describe below)

Please provide relevant clinical examination results of the event of encephalopathy:
☐Blood pressure
☐Eye examination
☐Cranial nerve examination
☐Motor functions
☐Mental status changes
☐Gait
☐Seizures
☐Coma (stage)
☐Other findings (describe below)

Please provide relevant diagnostic laboratory results (Serum thiamine levels, glucose levels, CSF chemistry and cytology) including reference ranges and dates.

Please provide relevant diagnostic imaging results (EEG, CT, MRI, etc.) including dates and results

Please provide prior exposure to other CNS toxic elements (including solvents, paints, industrial chemicals, and metals)

Please provide pertinent medical history including risk factors such as previous head traumatic events, brain tumors, brain ischemia, stroke, hypertensive crisis or hypertensive encephalopathy, thiamine deficiency, nutritional deficiencies, alcohol abuse, hepatic disturbances, kidney disturbances etc.

Please provide infectious work up (relevant culture/serology results with dates)

Please provide full blood count with differential and chemistry tests at time of symptoms (electrolytes, glucose levels, calcium, ammonia, kidney function, liver function, blood gases) including reference ranges and dates

Please provide the treatment/intervention measures

If suspect product was temporarily interrupted or dose reduced in response to the event, please specify dates and dosages:

If temporarily interrupted, did the event recur after reintroducing INREBIC (fedratinib):
☐Yes ☐No

Please provide date of diagnosis of disease under treatment with INREBIC (fedratinib), status at the time of diagnosis and status of the patient's disease at the time of the event.

Diagnosis date of underlying disease_____
Status of underlying disease at time of diagnosis_____
Status of underlying disease at time of event_____

Additional Questions:

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event:

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

None.