10 December 2020
EMA/705612/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inrebic

International non-proprietary name: fedratinib

Procedure No. EMEA/H/C/005026/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File = Drug Master File
AST	Aspartate aminotransferase
ASXL-1	Additional sex combs like 1
ATC	Anatomic therapeutic code
AUC	Area under the plasma concentration-time curve
AUC_{inf}	Area under the curve over time to infinity
AUC_{0-24}	Area under the plasma concentration versus time curve from time 0 to 24 hours
AUC_{C1-C6}	Area under the plasma concentration-time curve from Cycle 1 to Cycle 6
AUC_T	Area under the plasma concentration time curve over the dosing interval
BAT	Best available therapy
BCRP	Breast cancer resistance protein
BID	Twice daily
CALR	Calreticulin
CEP	Certificate of Suitability of the European Pharmacopoeia
CI	Confidence interval
Cl	Clearance
CLcr	Creatinine clearance
CL/F	Apparent clearance of drug from plasma after extravascular administration
C_{max}	Maximum plasma concentration
CPPs	Critical Process Parameters
CQA	Critical Quality Attributes
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	predose concentration during repeated dosing
%CV	Percent coefficient of variation
CYP	Cytochrome P450
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DIPSS	Dynamic International Prognostic Scoring System
DIPSS Plus	Dynamic International Prognostic Scoring System Plus
DL	Detection Limit
DLT	Dose limiting toxicity
DP	Drug Product

DS	Drug Substance
EC_{50}	Half maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EOC6	End of Cycle 6
EORTC	European Organisation for Research and Treatment of Cancer
ER	Exposure-response
ESA	Erythropoiesis-stimulating agents
ET	Essential thrombocythemia
EU	European Union
FDA	United States Food and Drug Administration
fedratinib	also known as SAR302503 or TG101348
FLT3	Fibromyalgia syndrome-like tyrosine kinase 3
FLT3ITD	FLT3 internal tandem duplication
FMEA	Failure mode effect analysis
FMO	Flavin-containing monooxygenases
GC	Gas Chromatography
GCP	Good Clinical Practices
GI	Gastrointestinal
GLP	Good laboratory practice
GMP	Good manufacturing practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HRQOL	Health-related quality of life
HU	Hydroxyurea
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IDH-1/2	Isocitrate dehydrogenase 1 or 2
IND	Investigational New Drug
IPC	In-process control
IPSS	International Prognostic Scoring System
IRC	Independent Review Committee
ITT	Intent to treat
IVRS	Interactive Voice Response System
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus kinase or Janus Associated Kinase, depending on context
JAK2	Janus kinase 2 or Janus Associated Kinase 2, depending on context
JAKV617F	Substitution of valine for phenylalanine at codon 617 of JAK2
JP	Japanese Pharmacopoeia
JPE	Japanese Pharmaceutical Excipients
KF	Karl Fischer titration
LC-MS/MS	Liquid chromatography with mass spectrometric identification and detection
LDH	Lactate dehydrogenase
LDPE	Low-density polyethylene
LOCF	Last observation carried forward
LTMMD	Largest time-matched mean difference
MAA	Marketing Authorisation Application
MAIC	Matching adjusted indirect treatment comparison
MedDRA	Medical Dictionary for Regulatory Activities

MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MO	Major objection
MOE	Margin of exposure
MPL	Myeloproliferative leukemia virus oncogene
MPN	Myeloproliferative neoplasm
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
MS/MS	tandem mass spectrometry
MTD	Maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate
NF	National formulary
NLT	Not Less Than
OAT	organic anion transporter
OATP	organic anion transporting protein
OCT	organic cation transporter
OS	Overall survival
OVAT	One Variable At a Time
PBPK	physiologically-based pharmacokinetic
PD	Pharmacodynamic(s) or progressive disease, depending on context
PDE	Permitted Daily Exposure
PFS	Progression-free survival
Ph. Eur.	European Pharmacopoeia
PGI	Potential genotoxic impurity
P-gp	P-glycoprotein
Ph1	Philadelphia chromosome
PK	Pharmacokinetic(s)
PMF	Primary myelofibrosis
PopPK	population pharmacokinetics
post-ET MF	Post-essential thrombocythemia myelofibrosis
post-PV MF	Post-polycythemia vera myelofibrosis
PP	Per-Protocol
PP	Polypropylene
PPI	Proton pump inhibitor
PS	Performance status
PSD	Particle Size Distribution
pSTAT3	Phosphorylated signal transducer and activator of transcription 3
PT	Preferred term
PV	Polycythemia vera
PXR	pregnane X receptor
QbD	Quality by Design
QC	Quality Control
QD	Once daily
QL	Quantification Limit
QLQ-C30	Quality of Life Questionnaire-Core 30
QoL	Quality of life
QT	QT interval
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia’s formula
QTcB	QT interval corrected for heart rate by Bazett’s formula

QTcN	QT interval corrected for heart rate by the FDA Neuropharmacological Division's formula
QTTP	Quality target product profile
RBC	Red blood cell
Rpm	Revolutions per minute
RR	Response rate
R/R	Relapsed/refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR302503	fedratinib
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SCT	Stem-cell transplantation
SMCC	Silicified Microcrystalline Cellulose
SmPC	Summary of Product Characteristics
SOC	System organ class
STAT	Signal transducer and activator of transcription
SVR	Spleen volume reduction
$t_{1/2,z}$	terminal elimination half life
TBL	Total bilirubin
TD	Thiamine deficient
TEAE	Treatment-emergent adverse event
TET2	Ten-eleven translocation–2
TG101348	fedratinib
t_{max}	time to maximum concentration
TSS	Total symptom score
TTC	Threshold of Toxicological Concern
TYK2	Tyrosine kinase 2
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet
Vss/F	Apparent volume of distribution at steady state
XRPD	X-Ray Powder Diffraction
WBC	White blood cell
WE	Wernicke's encephalopathy
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celgene Europe BV submitted on 20 December 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Inrebic, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 March 2018.

Inrebic, was designated as an orphan medicinal product EU/3/10/794 on 1/10/2010, EU/3/10/810 and EU/3/10/811 on 26/11/2010 in the following conditions:

- for the treatment of primary myelofibrosis (EU/3/10/794),
- for the treatment of post-essential thrombocythaemia myelofibrosis (EU/3/10/810),
- for the treatment of post-polycythaemia vera myelofibrosis (EU/3/10/811)

The applicant applied for the following indication: "Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, who are JAK inhibitor naïve or have been treated with ruxolitinib."

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Inrebic as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/inrebic

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0261/2012 on the granting of a (product-specific) waiver for the treatment of polycythaemia vera, essential thrombocythaemia and primary myelofibrosis.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance fedratinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 April 2011	EMEA/H/SA/2107/1/2011/PA/II	Dr Pierre Demolis; Dr Bertil Jonsson

The Protocol assistance pertained to the following clinical aspects:

- the adequacy of the Phase 1 efficacy, safety and PK data to support the two selected dosages of 400 mg and 500 mg for the pivotal Phase 3 trial;
- the proposed definitions of response, response rate (RR), progression and progression-free survival (PFS), based on modification of the IWG-MRT criteria.
- the proposed design of the randomised, placebo controlled 3-arm Phase 3 trial in patients with myelofibrosis who are either Intermediate-2 or High Risk by IWG-MRT criteria and whether RR with symptom improvement assessed at 24 weeks could support a MAA;
- whether positive results in at least one of the dose arms in the proposed single pivotal study would be sufficient for approval.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik CoRapporteur: Outi Mäki-Ikola

The appointed co-rapporteur had no such prominent role in Protocol assistance relevant for the indication subject to the present application.

The application was received by the EMA on	20 December 2019
The procedure started on	30 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 April 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 May 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 May 2020

The applicant submitted the responses to the CHMP consolidated List of Questions on	13 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	25 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2020
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	09 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	04 December 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Inrebic on	10 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis. Patients can be either JAK inhibitor naïve or have been previously treated with ruxolitinib.

2.1.2. Epidemiology

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) that can present as an apparently *de novo* disorder termed primary MF (PMF) or evolve from other MPNs and can be termed secondary MF, post polycythaemia Vera MF (Post PV-MF) or post essential thrombocythaemia MF (Post ET-MF). Myelofibrosis has an incidence of about 0.58 new cases per 100,000 person-years, but a higher prevalence of 6 per 100,000 person-years because of its chronic and disabling course. Median age at diagnosis is 67 years, without any significant difference in distribution between the sexes (Visser et al, 2012[1]). Median survival ranges from approximately 3.5 to 5.5 years, and the most frequent cause of death in patients with MF is transformation to acute myeloid leukaemia (20%). Most patients die because of other disease-related events, such as progression without transformation, infections, and thrombo-haemorrhagic complications.

2.1.3. Aetiology and pathogenesis

Primary myelofibrosis is a member of a group of Philadelphia chromosome (Ph1)-negative MPNs, which also includes PV and ET. MPNs are considered to arise from a somatic mutation of a pluripotent haematopoietic progenitor cell, but the exact cause of is unknown. Almost all patients with PV and about one half of patients with ET and PMF have a Janus kinase 2 (JAK2) mutation, typically JAK2V617F mutation. Increased JAK2 signaling, evidenced by constitutively phosphorylated signal transducer and activator of transcription (STAT3), is not strictly dependent on the presence of JAK2V617F mutation. Other mutations in patients with PMF include calreticulin (CALR) and myeloproliferative leukemia virus oncogene (MPL) (Tefferi, 2016[2]). About 10% of patients with PMF have no detectable mutation in JAK2, CALR, or MPL and are termed "triple negative" (Tefferi, 2016). Mutations in JAK2, CALR, and MPL activate the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway (Romano, 2017[3]), resulting in cell proliferation and inhibition of cell death and clonal expansion of myeloproliferative malignant cells. It is less clear how the driver mutations that are present in earlier myeloproliferative neoplasms, such as essential thrombocythemia or polycythemia vera, evolve to the more advanced phases of myelofibrosis. Factors may include epigenetic changes; additional somatic mutations in other genes, such as additional sex combs like 1

[1] Visser O, Trama A, Maynadié M, et al. Incidence, survival and prevalence of myeloid malignancies in Europe. *Eur J Cancer*. 2012;48:3257–3266.
[2] Tefferi A. Primary myelofibrosis: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016;91(12):1262-71.
[3] Romano M, Sollazzo D, Trabanelli, Barone M, Polverelli N, Perricone M, et al. Mutations in JAK2 and calreticulin genes are associated with specific alterations of the immune system in myelofibrosis. Oncoimmunology. 2017;16(10):e1345402.

(*ASXL1*), ten-eleven translocation–2 (*TET2*), and isocitrate dehydrogenase 1 (*IDH1*) and 2 (*IDH2*); and contributions of the bone marrow microenvironment, particularly regarding inflammation.

2.1.4. Clinical presentation, diagnosis prognosis

Myeloproliferative myelofibrosis can present as a *de novo* disorder (PMF) or evolve secondarily from previous polycythaemia vera or essential thrombocythaemia (Post-PV MF or Post-ET MF respectively). Post-PV MF and 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 (Sangle, 2014[4]). These conditions are clinically named MPN-associated myelofibrosis (MF). Regardless of whether myelofibrosis is primary or secondary, the disease is characterised by a clonal haemopoietic stem cell proliferation associated with associated with reactive bone marrow fibrosis, osteosclerosis, angiogenesis, extramedullary haematopoiesis (EMH) and abnormal cytokine expression. Cytokine elevations in MF occur regardless of mutational status or disease subtype and MF is considered to be a condition with a considerable inflammatory potential (Lussana, 2017[5]). Clinical manifestations in PMF include severe anemia, marked hepatosplenomegaly, constitutional symptoms (e.g., fatigue, night sweats, fever, weight loss), bone marrow reticulin and collagen fibrosis, cachexia, bone pain, splenic infarct, pruritus, thrombosis and bleeding. Ineffective erythropoiesis and EMH are the main causes of anemia and organomegaly, respectively. Other disease complications include symptomatic portal hypertension that might lead to variceal bleeding or ascites and non-hepatosplenic EMH that might lead to cord compression, ascites, pleural effusion, pulmonary hypertension or diffuse extremity pain. It is currently assumed that aberrant cytokine production by clonal cells and host immune reaction contribute to PMF associated bone marrow stromal changes, ineffective erythropoiesis, EMH, cachexia and constitutional symptoms. Causes of death include leukemic progression that occurs in approximately 20% of patients but many patients also die of comorbid conditions including cardiovascular events and consequences of cytopenias including infection or bleeding (Tefferi 2016[2], Stahl 2017[6]).

A diagnosis of MPN is based on the 2016 World Health Organization (WHO) diagnostic criteria and requires a combination of clinical, laboratory, cytogenetic, and molecular testing (O' Sullivan, 2018[6]). This includes the presence of 1 of the 3 driver mutations (JAK2, CALR and MPL). In patients with triple-negative disease, the detection of one of the associated somatic mutations (eg, EZH2, TET2, IDH1/2, ASXL1, SRSF2, or SF3B1) suffices as the presence of a clonal marker for diagnostic purposes. Because the natural course of secondary MF (post-PV MF and post-ET MF) may differ from that of PMF, the diagnosis of post-PV or post-ET MF should adhere to criteria published by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) (O' Sullivan, 2018[7]; Tefferi, 2016[2]).

Several prognostic scoring systems have been developed to facilitate risk assessment for patients with MF. The prognostic scorings were originally developed for primary MF, but the same models and parameters are applied in post-PV and post-ET MF, partly because the therapeutic approach is quite similar. The International Prognostic Scoring System (IPSS) is used to predict survival at diagnosis, and the Dynamic International Prognostic Scoring System (DIPSS) is used to predict survival at any time during the disease. Variables included in the IPSS are age > 65 years, constitutional symptoms, haemoglobin level < 10 g/dL, white blood cell (WBC) counts > 25 x 10^9/L and circulating blast

[4] Sangle N, Cook J, Perkins S, Teman CJ, Bahler D, Hickman K, et al. Myelofibrotic transformations of polycythemia vera and essential thrombocythemia are morphologically, biologically and prognostically indistinguishable from primary myelofibrosis. Appl Immunohistochem Mol Morphol. 2014;22(9):663-8.
[5] Lussana F, Rambaldi, A. Inflammation and myeloproliferative neoplasms. J Autoimmun 2017; 85: 58-63.
[6] Stahl M, Zeidan AM. Management of myelofibrosis: JAK inhibition and beyond. Expert Review of Hematology. 2017;10(5):459-77.
[7] O'Sullivan JM. Myelofibrosis: Clinicopathologic features, prognosis, and management. Clin Adv Hematol Oncol. 2018;16(2):121-31.

frequency ≥1%. DIPSS puts more emphasis on anaemia. DIPSS Plus incorporates 3 additional independent risk factors: platelet count < 100 x 10^9/L, red blood cell (RBC) transfusion need, and unfavourable karyotype (Gangat, 2011[8]). A strong association between DIPSS Plus risk category and overall survival (OS) for MF patients has been reported; intermediate-1, intermediate-2, or high-risk disease has been associated with median survival of 6.5, 2.9, and 1.3 years, respectively (Gangat, 2011[7]; Tefferi, 2016[2]). Approximately 90% of individuals with MF are in the intermediate or high-risk categories according to DIPSS Plus (Gangat, 2011[7]), comprising a large population with symptomatic disease and shortened survival and representing the greatest unmet medical need.

2.1.5. Management

Allogeneic stem-cell transplantation (SCT) is the only treatment that is potentially curative and can induce long-term remission in patients with MF (Barbui, 2018[9]; Vannucchi, 2017[10]). However, the majority of MF patients are not eligible for the procedure due to age, comorbidities and an overall frail condition (Stahl, 2017[5]; Vannucchi, 2017[10]). Therefore, the existing treatment options are primarily symptom oriented. Treatment goals include reduction of spleen size, improvement of cytopenias and symptom burden, reduction of bone marrow fibrosis, restoration of transfusion-independence, and prevention and delay of progression to acute myeloid leukemia (AML) (Stahl, 2017[5]; Vannucchi, 2017[10]).

The selection of appropriate treatment is based on the risk score and presence of symptoms (European LeukemiaNet (ELN), Barbui, 2018[9]; the European Society for Medical Oncology (ESMO) clinical practice guidelines, Vannucchi 2015[11]). For patients with intermediate-risk 2 or high-risk score and not eligible for alloSCT, ruxolitinib is the core treatment of MF. Ruxolitinib (Jakavi), a JAK1/2 inhibitor, which is the only centrally approved drug in the EU for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. It improves splenomegaly symptoms in patients with intermediate-2–risk and high-risk myelofibrosis (COMFORT-II study Cervantes, 2013[12]). It is also used in patients with symptomatic intermediate-1–risk myelofibrosis who are not responding or are intolerant to hydroxyurea. Whether ruxolitinib improves survival is uncertain, as meta-analyses have not been able to conclude on estimates of survival advantage of ruxolitinib and the benefit of ruxolitinib is currently seen as being control of splenomegaly and constitutional symptoms (Barbui, 2018[9]). Other therapeutic options for MF include erythropoiesis-stimulating agents (ESAs), corticosteroids, danazol, and immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide) for improvement of anaemias and hydroxyurea and interferon for the treatment of splenomegaly and/or constitutional symptoms (Stahl, 2017[5]). Hydroxyurea (HU) is the only approved on a national basis in a few countries (e.g. France, Italy, Sweden and Spain) in the EU. Splenectomy and splenic irradiation are treatment options in refractory disease and disease specific complications (Tefferi 2016[2]).

[8] Gangat N, Caramazza D, Vaidya R, George G, Begna K, Schwager S, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol. 2011;29(4):392-7.
[9] Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leukemia. 2018;32:1057-69.
[10] Vannucchi AM, Harrison CN. Emerging treatments for classical myeloproliferative neoplasms. Blood. 2017;129(6):693-703.
[11] Vannucchi AM, Barbui T, Cervantes F, Harrison C, Kiladjian JJ, Kröger n, et al. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 (Supplement 5):v85-v99.
[12] Cervantes F, Vannucchi AM, Kiladjian JJ, Al-Ali HK, Sirulnik A, Stalbovskaya V, et al. Three year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood. 2013;122:4047–4053.

Currently, there is no approved treatment option or standard of care for patients who have been treated with ruxolitinib, and the prognosis for these patients is poor with median survival of 6 to 16 months (Kuykendall, 2018[13]; Newberry, 2017[14]).

About the product

Pharmacological classification

Fedratinib is an oral kinase inhibitor with activity against wild type and mutationally activated JAK2 and fibromyalgia syndrome-like tyrosine kinase 3 (FLT3). It belongs to the pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE57.

Note: Fedratinib is also known as SAR302503 or TG101348.

Mode of action

Fedratinib is a JAK2-selective inhibitor with higher inhibitory activity for JAK2 over family members JAK1, JAK3 and TYK2. Abnormal activation of JAK2 is associated with MPNs, including MF and PV. In cell models expressing mutationally active JAK2V617F or FLT3 internal tandem duplication (ITD), fedratinib reduced phosphorylation of signal transducer and activator of transcription (STAT3/5) proteins, inhibited cell proliferation, and induced apoptotic cell death. In mouse models of JAK2V617F - driven myeloproliferative disease, fedratinib blocked phosphorylation of STAT3/5, and improved survival, white blood cell counts, haematocrit, splenomegaly, and fibrosis.

Claimed indication and recommendation for use

The initial claimed indication was:

Fedratinib is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis:

- who are JAK inhibitor naïve
- who have been treated with ruxolitinib

The agreed indication is: " Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib."

The proposed dose of fedratinib is 400 mg once daily. Treatment may be continued for as long as patients derive benefit.

Special pharmaceutical aspects

Not applicable.

[13] Kuykendall AT, Shah S, Talati C, Al Ali, N, Sweet K, Padron E, et al. Between a rux and a hard place: evaluating salvage treatment and outcomes in myelofibrosis after ruxolitinib discontinuation. Ann Hematol. 2018;97:435–41.
[14] Newberry KJ, Patel K, Masarova L, Luthra R, Manshouri T, Jabbour E, et al. Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation. Blood. 2017;130(9):1125-31.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an immediate release hard capsule containing 100 mg of fedratinib. The product contains the hydrated salt form fedratinib dihydrochloride monohydrate.

Other ingredients are:

- for the capsule content: silicified microcrystalline cellulose (contains microcrystalline cellulose (E460) and silica colloidal anhydrous (E551)) and sodium stearyl fumarate.
- for the capsule shell: gelatin (E441), titanium dioxide (E171), red iron oxide (E172).
- for the White printing ink: shellac (E904), titanium dioxide (E171), propylene glycol (E1520).

The product is available in high density polyethylene (HDPE) bottle with polypropylene child resistant cap and heat induction seal.

2.2.2. Active substance

General information

The chemical name of fedratinib is benzenesulfonamide, N-(1,1-dimethylethyl)-3-[[5-methyl-2-[[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]amino]-4-pyrimidinyl]amino]-, hydrochloride, hydrate (1:2:1) corresponding to the molecular formula $C_{27}H_{36}N_6O_3S \cdot 2HCl \cdot H_2O$. It has a relative molecular mass of 615.62 (dihydrochloride monohydrate) and the following structure:

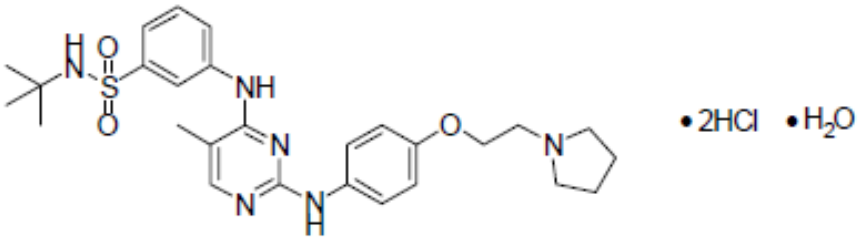


Figure 1: fedratinib active substance structure

The chemical structure of fedratinib was elucidatedby a combination of elemental analysis, nuclear magnetic resonance spectroscopy, mass spectrometry, ultraviolet spectrophotometry (UV), Fourier Transform infrared spectrophotometry. The solid state properties of the active substance were measured by single crystal X-ray analysis, dynamic vapor sorption, scanning electron microscopy differential scanning calorimetry, X-ray powder diffraction (XRPD), thermogravimetric analysis, and particle size distribution (PSD).

Fedratinib is a white to off-white, non-hygroscopic crystalline solid that exhibits pH-dependent aqueous solubility: it is freely soluble in acidic buffers and practically insoluble in neutral buffer (pH 6.8).

Fedratinib does not have chiral centres and does not exhibit stereoisomerism.

Polymorphism has been observed for fedratinib. Several polymorphic solid forms of the fedratinib active substance have been identified. As confirmed by x-ray powder diffraction pattern analysis, the proposed manufacturing process of fedratinb consistently yields the desired polymorphic form, which is the thermodynamically stable form. The desired polymorph is controlled at release and monitored in stability studies.In response to a MO, the NAS status of fedratinib has been adequately demonstrated during the procedure: no previously authorised medicinal products were identified using structural and CAS number searches.

Manufacture, characterisation and process controls

Fedratinib is manufactured in several steps using a convergent synthetic process. In case of unexpected deviation or out of specification results, any intermediate or active substance batch can be reprocessed in accordance with ICH Q7 guideline by repeating all or part of the related process; this is accepted.

Fedratinib is synthesised using well defined commercially available starting materials with acceptable specifications. In response to a major objection (MO), one of the proposed starting materials has been adequately justified in line ICH Q11.The starting material in question has defined chemical properties and structure. It is incorporated as a significant structural fragment into the structure of the active substance and it is a commodity in pre-existing non-pharmaceutical market. The step upstream does not impact the impurity profile of the active substance. Batch analysis data of starting material show that the level of impurities is low.

For the non-critical process parameters, target settings are provided in line with ICH Q11. The normal operating ranges (NORs) are within proven acceptable ranges (PARs), which have been justified using a combination of conventional univariate studies and elements of QbD by performing a risk assessment. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Fedratinib is non-mutagenic. During the assessment, in response to a MO on the evaluation and assessment of potential genotoxic impurities (PGIs), data have been provided confirming that three impurities presenting the sulfonylchloride alerting structure, are present at the level below 30% of the TTC (Threshold of Toxicological Concern) in seven consecutive batches of the process intermediate Additionally, the three PGIs are controlled at the level of the starting material and/or as process intermediate, in line with Option 3 of ICH M7. Overall, the proposed control strategy for the discussed potential genotoxic impurities is acceptable.

All potential residues of solvents are either demonstrated to be absent, or sufficiently controlled by IPCs or in the active substance specification. A palladium catalyst is used in the synthesis. Potential residues are controlled at a specified level. Adequate in-process controls are applied during the synthesis. Several intermediate impurities and the assay limits h have been tightened during the procedure, as requested. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are satisfactory.

The synthetic route for the active substance has remained essentially unchanged from the beginning of development; changes to improve the purity profile of the active substance were made by the manufacturer of the clinical batches and minor improvements were made during the transfer to the proposed commercial site. As demonstrated by batch data the only difference between the batches

manufactured by the proposed commercial manufacturer and earlier batches is a decrease in impurity level.

The active substance is packaged in in double low-density polyethylene (LDPE) bags which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification, , includes tests for appearance (visual), identification (HPLC, IR (Ph. Eur.), XRPD (Ph. Eur.)), chloride content (Ph. Eur.), assay (HPLC, anhydrous solvent free basis), starting material content (HPLC), related impurities (HPLC), water content (KF; Ph. Eur.), sulfated ash (Ph. Eur.), residual solvents (isopropanol and benzene GC), isopropyl chloride content (GC) and PSD (laser light diffraction; Ph. Eur.).

The specification limit set for the starting material conforms to the ICH Q3A qualification level; the control of impurities is in line with ICH Q3 for the specified and unspecified impurities.

Isopropanol, used throughout the synthesis and in the final crystallisation step, is controlled as residual solvent, together with benzene, a Class 1 solvent, that is potentially present as an impurity in alcohol solvents and in isopropanol. Isopropyl chloride is controlled in the specification at a limitwhich is below the TTC The absence of a test for palladium in the active substance specification is justified as it is controlled in an active substance intermediate during the synthesis. Testing of elemental impurities is not necessary in light of the risk assessment performed in accordance with the ICH Q3D. The absence of this test is deemed acceptable in accordance with the NfG ICH Q6A, Decision Tree #6.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines the applicant is recommended to modify the analytical method for determination of assay and related substances in fedratinib active substance (REC 1).

Satisfactory information regarding the reference standards used for assay and impurity testing has been presented.

Batch analysis data on 6 commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three pilot scale batches of active substance from the proposed manufacturer and three clinical pilot scale batches according to the ICH guidelines were provided.

The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications and no trend was observed.

Photostability testing, using conditions equivalent to three times those described ICH Q1B, was performed on one batch. Batch data from forced degradation studies performed under acid, base, oxidation and thermal stress conditions were also provided on one batch. Degradation was quite modest in most forced degradation conditions; however, degradation was observed in oxidative conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container, with no additional storage conditions.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as an immediate release hard capsule containing 100 mg of fedratinib (as fedratinib dihydrochloride monohydrate). The finished product composition is provided. The composition of the capsule shell components and of the printing ink – 00A1 White have been provided.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards with the exception of silicified microcrystalline cellulose (SMCC) which complies with USP-NF and contains microcrystalline cellulose and silica colloidal anhydrous, which are of Ph. Eur. quality. SMCC is used in a number of centralised products and its specification is acceptable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The pharmaceutical development of the finished product contains QbD elements.

Compatibility with the excipients of the proposed formulation has been confirmed.

Fedratinib capsules are manufactured using a process which includes blending and encapsulation.

The formulation and manufacturing development have been evaluated. The proposed QC dissolution method conditions have been defined. During the procedure the applicant has demonstrated that other dissolution conditions or the use of a different apparatus exhibited greater variability than the proposed method, additionally they did not result in an improvement of the discriminatory power. In conclusion, the development of the dissolution method is considered sufficiently described. Although, the proposed QC dissolution method was not shown to be discriminatory towards the applied deliberate changes based on the data provided, the test method together with the agreed dissolution limit, which have been tightened in response to a MO are considered adequate for its intended purpose.

The formulation used during pivotal clinical studies is the same as that intended for marketing differences in clinical trial batches did not lead to differences in dissolution.

The finished product batches for pivotal clinical study, also used for supportive stability data, were produced by a different manufacturer from the proposed commercial manufacturer, using a comparable manufacturing process. The comparability between the capsules manufactured by the two sites has been demonstrated with an *in vitro* comparative dissolution study. The primary packaging is high density polyethylene (HDPE) bottle with polypropylene child resistant cap and heat induction seal. The material complies with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of several steps including blending and encapsulation. The process is considered to be a standard manufacturing process.

During the procedure the PARs have been redefined. The claimed ranges are acceptable. The PARs are considered acceptable based on the available development data, which confirmed that the finished product CQAs were not affected within the evaluated ranges.

The manufacturing process has been satisfactorily validated and validation data on three full scale consecutive batched have been provided. It has been demonstrated that the manufacturing process is

capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this of type of pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (UV and HPLC), assay HPLC), degradation products (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (KF- Ph. Eur.) and microbiological quality (Ph. Eur.).

The release and end of shelf life limits are the same for all involved parameters except water content. The dissolution limit is set based on dissolution profiles of relevant clinical batches and it has been updated during the procedure in response to a MO.

The control of impurities is in line with ICH Q3B (R2). Residual solvents are tested at the level of the active substance, as the manufacturing process of the finished product does not utilise any solvent, this is accepted. The desired polymorphic form is routinely tested only in the active substance since it has been demonstrated that it does not change during finished product manufacture and storage. The omission of the polymorphic form test is considered as justified.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach, in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

To address an MO, a risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. However, the applicant is recommended to modify the analytical method for determination of assay and related substances in fedratinib finished product (REC 2).

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for nine commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of finished product stored under long term conditions and under accelerated conditions according to the ICH guidelines were provided. The batches of finished product were packed in the primary packaging proposed for marketing and are representative to those proposed for marketing,

Stability data from 1 pilot scale batch of finished product, stored under long term conditions and under accelerated conditions according to the ICH guidelines were also provided.

Additional stability data pilot scale batches manufactured by the manufacturer of the clinical batches stored under long term conditions and under accelerated conditions according to the ICH guidelines were also provided.

Samples were tested for the specification tests.

No significant changes have been observed in the data from the formal stability studies, further confirming the comparability between the clinical material and the proposed commercial product.

In addition, one batches was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed.

Samples of the finished product were exposed to forced degradation under acid, base, oxidation and thermal stress conditions. Mass balance was confirmed under the stress conditions; the analytical procedures used were shown to be stability indicating.

Gelatin capsule shells are known to be sensitive to very high, but also to very low humidity conditions. Therefore, the precautionary storage condition "Keep the bottle tightly closed in order to protect from moisture" has been added. This is in accordance with the CHMP Guideline on Declaration of Storage Conditions and is acceptable. An in-use stability study was not performed as there is no indication from stability and/or stress studies that the finished product may be susceptible to degradation under long term, and hence in-use, conditions.

Based on available stability data, the proposed shelf-life of 4 years without any special storage condition but with the recommendation "Keep the bottle tightly closed in order to protect from moisture." as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the capsule shells of the finished product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The MO raised during the procedure on the suitability of a starting material has been addressed by further justifying its suitability and no redefinition was needed. Satisfactory data have been provided confirming that the proposed control strategy is adequate with regards to the control of three PGIs, in line with Option 3 of ICH M7, and hence additional controls were not deemed needed in response to a MO raised. To address a MO, the dissolution acceptance criteria for the finished product have been tightened. In response to a MO, a satisfactory risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed confirming that no risk has been identified. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Additionally, in response to a MO, the NAS status has been adequately substantiated.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to assay and related

substances/degradation product in the active substance and finished product. These points are put forward and agreed as recommendations for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant is recommended to modify the analytical method for determination of assay and related substances in fedratinib active substance (REC1)
- The applicant is recommended to modify the analytical method for determination of assay and related substances in Inrebic finished product. (REC 2)

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

In a cell free enzyme activity assay, fedratinib was shown to be a potent inhibitor of wild-type and mutant (V617F) JAK2, with IC50 values ranging from 1.26 – 12 nM in different assays. Also FLT3 is potently inhibited with an IC50 of 15 nM. The Janus family kinases were further investigated in 2 different assays. JAK3 and TYK2 showed much reduced potency with at least 38-fold reduced IC50 values, and concordance between the experiments. However, for JAK1 IC50 values varied from 13 to 45.5 µM in these assays. The lowest IC50 value of 13 nM is only 6-fold higher than the IC50 of JAK2 and in the same range as FLT3. The main difference appears to be the ATP concentration used in the assays, being 140 µM for the lowest IC50 and 10 µM for the highest. These data could indicate that fedratinib also has inhibitory effect via JAK1. However, in a further study evaluating the effect of fedratinib on cellular proliferation, it was shown that the IC50 for JAK2 was 0.36 µM, whereas no IC50 was reached in the test system for JAK1, JAK3 and TYK2. It can therefore be concluded that within the Janus family of kinases, fedratinib has high affinity for JAK2 inhibition, although some activity against JAK1 cannot be ruled out.

Table 1: IC50 values of kinases inhibited by fedratinib with greater than 50% inhibition at 0.5 µM

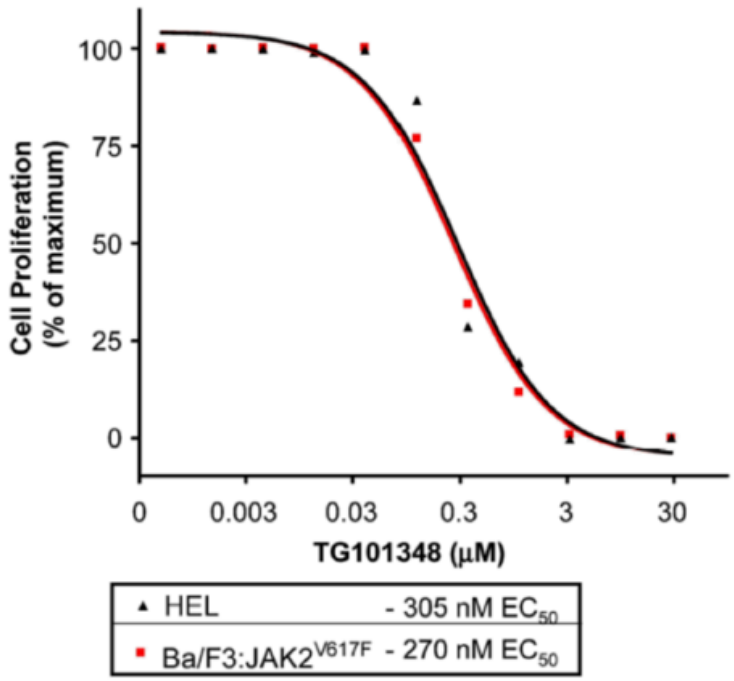
Kinase Tested	IC_{50} (nM)	Fold Selectivity IC_{50} kinase/ JAK2 IC_{50}
JAK2 JH1 JH2 V617F	3	1
JAK2 JH1 JH2	3	1
JAK2	12	4
FLT3	15	5
FLT3 D835Y	26	9
RET	48	16
NTRK1 (TRKA)	53	18
DAPK3 (ZIPK)	54	18
LCK	56	19
ABL1	69	23
ROS1	73	24
ABL1 G250E	73	24
RET Y791F	81	27
FYN	82	27
ABL1 E255K	84	28
FGR	86	29
SRC N1	96	32
RET V804L	99	33
–	–	–

Kinase Tested	IC_{50} (nM)	Fold Selectivity IC_{50} kinase/ JAK2 IC_{50}
ABL1 Y253F	102	34
MUSK	107	36
FES (FPS)	128	43
SRC	131	44
YES1	138	46
LYN A	155	52
ABL2 (Arg)	162	54
STK22D (TSSK1)	166	55
FGFR2	188	63
PTK2 (FAK)	198	66
LYN B	202	67
FGFR1	223	74
EPHA1	232	77
AURKC (Aurora C)	239	80
ABL1 T315I	265	88
CSF1R (FMS)	280	93
FLT4 (VEGFR3)	356	119
IKBKB (IKK beta)	454	151
KDR (VEGFR2)	506	169

Table 2: IC50 values of Janus family kinases, from 2 experiments

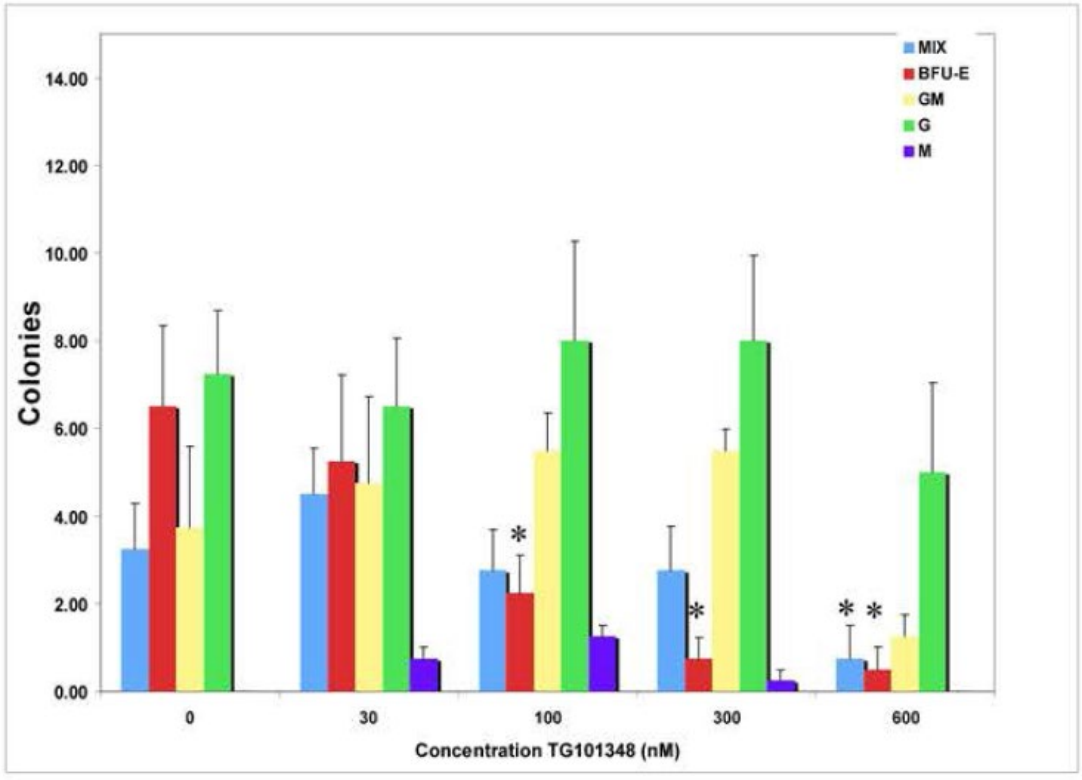
	Experiment 1 (ONVT0048)		**Experiment 2 (PH-07-101348-041)**	
Kinase	**ATP µM**	**IC50 nM**	**ATP µM**	**IC50 nM**
JAK2	50	2.4	10	1.26
$JAK2^{V617F}$	80	2.3	-	-
JAK1	140	13	10	45.5
JAK3	10	91	5	95.6
TYK2	50	169	25	171

Fedratinib inhibited cell proliferation of patient derived (human erythroid leukaemia) or transgenic mouse JAK2 expressing cells harbouring the most commonly found mutation V617F, with EC50 values ranging from 0.27 – 0.94 µM. The inhibition of cell proliferation is caused by reduced STAT5 phosphorylation and leads to apoptosis of cells. Similar results were obtained from experiments with $JAK2^{V617F}$ positive patient derived PV HSCs. Erythroid colonies that were formed were largely eliminated by treatment with fedratinib with an EC50 of less than 0.3 µM. These results indicate that fedratinib can induce an anti-tumour effect through binding to the mutant JAK2 receptor.



EC50 = half-maximal effective concentration; HEL = human erythroid leukaemia.

Figure 2: Fedratinib inhibits proliferation of cells expressing JAK2^{V617F}



MIX = granulocyte, erythroid, macrophage, megakaryocyte; BFU-E = burst-forming unit erythroid; GM =granulocyte-macrophage; G =granulocyte; M =macrophage.

Figure 3: Inhibition of PV progenitor erythroid differentiation by fedratinib

Three metabolites of fedratinib were identified, SAR317753, SAR317793, and SAR317981. In terms of inhibition of cellular proliferation tested in patient derived JAK2^{V617F}-expressing cell lines, the most active metabolite SAR317981was about 2-fold less active than fedratinib. SAR317753 and SAR317793 were at least 10-fold less active.

Table 3: Antiproliferative activity of fedratinib and its metabolites in patient-derived JAK2^{V617F}-expressing cell lines

Cell Line	IC_{50} (µM)			
	Fedratinib	SAR317753	SAR317793	SAR317981
SET-2	0.269	8.54	3.35	0.569
UKE-1	0.538	> 10[a]	4.26	1.71
HEL	0.940	> 10[a]	4.28	1.43

Resistance to fedratinib seems limited. While common mutations in JAK2 confer resistance to other JAK inhibitors, there was only a 2 to 3-fold increase in EC50 for fedratinib. Induced resistant clones obtained from patient derived cell lines endogenously expressing JAK2^{V617F} were about 10-fold less sensitive to fedratinib but harboured no missense mutations. Despite the lack of mutations, increased phosphorylation of JAK1 and 2, and STAT3/5 was shown, indicating increased downstream signalling. The mechanism of resistance formation is unknown.

Different AML cell lines were used to investigate the effect of fedratinib on cells with mutations other than JAK2^{V617F}. Cell lines harbouring the internal tandem duplication (ITD) mutation in the FLT3 receptor (FLT3-ITD) were particularly sensitive to treatment with fedratinib, with EC50 values ranging from 57 to 69 nM. Reduced phosphorylation of the receptor and of downstream effector molecules STAT5, Erk and Akt, as well as increased apoptosis was shown in a dose dependent manner. Together with the high affinity for the FLT3 receptor, it can be concluded that fedratinib has the potential to induce an anti-tumour effect through binding to FLT3-ITD.

Several cell lines harbouring other mutant proteins or receptors were also tested for their responsiveness to fedratinib. All cell lines responded to treatment with EC50 values to around 1 µM.

Numerous *in vivo* mouse models have been used to investigate the efficacy of fedratinib. In a bone marrow transplantation model in which mice injected with JAK2^{V617F} transduced haematopoietic cells, a positive effect on survival, WBC counts, and splenomegaly was observed after 6 weeks treatment from the lowest dose tested of 60 mg/kg BID fedratinib. Mutant cells were reduced in the spleen at this dose, but a higher dose of 120 mg/kg BID was needed to also reduce these cells in bone marrow. A similar effect on spleen size was seen in JAK2^{V617F} knock-in mice, also at 60 mg/kg BID. However, treatment of up to 120 mg/kg BID did not eliminate disease-initiating JAK2^{V617F} cells, either in the transplantation or knock-in model.

Table 4: Overview of *in vivo* mouse models

Mouse model	Type of cells & route	Doses & duration fedratinib	Findings	Study number
Transplantation	Mouse JAK2^{V617F} transduced haematopoietic cells Bone marrow transplantation	60, 120 mg/kg BID 6 weeks	**≥60**: ↑ survival, ↓ WBC counts and haematocrit, ↓ splenomegaly, haematopoiesis markers, reticulin fibrosis, ↓	PH-07-101348-068

			JAK2^{V617F} allele frequency spleen, ↓ BFU-E cells and pSTAT5 in bone marrow **=120**: ↓ JAK2^{V617F} allele frequency bone marrow and blood	
Knock-in	JAK2^{V617F}	60 mg/kg BID 6 weeks	↓ spleen size	Mullaly, 2010
Xenograft	Human JAK2^{V617F} progenitor cells from PV patients Intrahepatic	150 mg/kg BID 12 days	↓ of erythroid engraftment	PH-07-101348-081
Xenograft	Human umbilical cord cells transduced with JAK2^{V617F} or wt JAK2 Intrahepatic	150 mg/kg BID 12 days	**JAK2^{V617F}**: ↓ of erythroid engraftment **wtJAK2, thymus JAK2^{V617F}**: no ↓ of erythroid engraftment	PH-07-101348-081
Xenograft	Human SET-2 cells, JAK2$^{wt/V617F}$ Subcutaneous	108 mg/kg Single dose	↓ pSTAT5 at 3 hours post dose ↓ pSTAT3 from 3 to 7 hours postdose	ONVV0047
Xenograft	Human SET-2 cells, JAK2$^{wt/V617F}$ Subcutaneous	60, 90, 120 mg/kg Single dose	Fedratinib concentration ratio of 3.3-3.9 for tumour versus plasma ↓ pSTAT5 more prolonged with higher dose. pSTAT5 EC50 3490 ng/ml pSTAT3 EC50 3230 ng/ml	ONVV0057
Xenograft	Human SET-2 cells, JAK2$^{wt/V617F}$ Subcutaneous	26.9, 53.9, 80.9, and 107.9 mg/kg BID	**≥80.9**: ↓ tumour volume	ONVV0048

		2 weeks		
Disseminated	Ba/F3-JAK2^{V617F}-GFP cells Intravenous	0, 10, 20, 30, 40, 80, 100 mg/kg BID 18 days	**≥40**: ↓ pSTAT5 **≥80**: ↑ survival, ↓ tumour cell burden	PH-07-101348-065
Xenograft	human myelomonocytic AML cell line MV411, FLT3-ITD Subcutaneous	60, 120 mg/kg BID 32 days	**≥60**: ↓ tumour growth, ↓pFLT3 **=120**: complete tumour regression, ↓ pSTAT5	PH-07-101348-078

Two studies with of JAK2^{V617F} or wild-type JAK2 human cells in a xenograft mouse model using intrahepatic administration showed reduction of erythroid engraftment of JAK2^{V617F} mutant cells. No reduction of wild-type JAK2 cells was seen, while *in vitro* experiments indicate that fedratinib is also a potent inhibitor of wild-type JAK2. It is not clear what is the cause of this discrepancy between *in vitro* and *in vivo* results, but specificity for mutant JAK2 is favourable. Also no reduction of thymic engraftment of JAK2^{V617F} cells was seen. This indicates that fedratinib only inhibits myeloid progenitor cells. There was only one high dose level of 150 mg/kg BID used in these studies. Other xenograft studies used subcutaneous administration of human SET-2 cells, heterozygous for the JAK2^{V617F} allele. Single doses of up to 120 mg/kg showed 3 to 4-fold higher concentration of fedratinib within the tumour as compared to blood. JAK2 downstream signalling was reduced as shown by reduction of STAT5 and STAT3 phosphorylation, with EC50 values of 3490 ng/ml and 3230 ng/ml respectively. Dosing for 2 weeks in this xenograft model demonstrated a reduced tumour volume from 80.9 mg/kg BID fedratinib and higher. A dose of 53.9 mg/kg BID or lower had no significant effect on tumour volume.

In a disseminated mouse tumour model where mice were injected Ba/F3-JAK2^{V617F}-GFP cells intravenously, survival was increased and circulating tumour cell burden was reduced from 80 mg/kg BID and higher. Lower doses (40 mg/kg BID) had no effect on these parameters, although a reduction in STAT5 phosphorylation was already seen after a dose of 40 mg/kg BID fedratinib.

A single xenograft mouse model was used to investigate the effect of fedratinib on human AML cells harbouring the FLT3-ITD mutation. The tumour volume was tracked over time and showed a reduced growth in the low dose group of 60 mg/kg BID. This indicates that although growth of the tumour is slower as compared to vehicle, treatment of 60 mg/kg BID still allows for the tumour to grow. Complete regression was however demonstrated in the high dose group of 120 mg/kg BID.

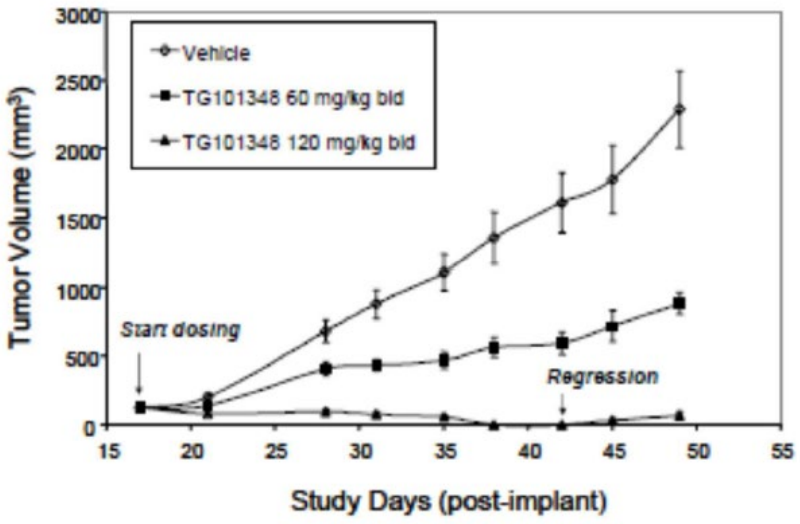


Figure 4: Oral administration of fedratinib inhibits tumour growth in MV411 xenograft model

Overall the *in vivo* mouse model studies indicate that fedratinib reduced downstream signalling through mutated JAK2 and FLT3, resulting in reduced tumour volume, growth or engraftment, and reduced splenomegaly. These effects were evident at doses from 60 mg/kg BID or higher, while lower doses had no effect. Although no kinetic data is available for these studies, extrapolation from other mouse data indicate that high concentrations are required to show an effect in these mouse models. The Cavg and Cmax at the effective mouse dose of 60 mg/kg BID would be around 1700 ng/ml and 3500 ng/ml respectively, while human Cavg and Cmax at the MRHD is only 1213 ng/ml and 2022 ng/ml respectively. It should also be noted that at the mentioned mouse plasma concentrations, growth of AML tumour cells was still possible, and 2-fold higher doses were required for complete regression. Further, when *in vitro* IC50 values are compared to *in vivo* data there appears to be a large difference. While *in vitro* effects on cell proliferation and downstream signalling were evident at EC50 values around 300 nM, the *in vivo* concentration needed for an effect appears to be 10-fold higher (Cavg of 1700 ng/ml corresponds to 3.24 µM).

Secondary pharmacodynamic studies

A screen has been performed to assess the binding of fedratinib to a panel of receptors and transporters. Significant binding was observed at the M1 and M5 muscarinic receptors and at the dopamine transporter, with IC50 values of 33 nM, 21 nM and 36 nM respectively.

It should be noted that a substantial number of other receptors was also inhibited by fedratinib at concentrations ranging from 150 to 730 nM. Although this is within the range of EC50 values for cell proliferation and downstream effects through JAK2 and FLT3, a comparison to a cell free system in which IC50 values of 3-12 nM and 15 nM for JAK2 and FLT3 were reported, is more appropriate. It can therefore be concluded that other than M1 and M5 muscarinic receptors and dopamine transporter, no other significant inhibition of fedratinib is evident.

Due to reports of clinical cases of encephalopathy in patients receiving fedratinib, and the link between thiamine deficiency and encephalopathy, a direct effect of fedratinib on thiamine transporters was investigated. *In vitro* results show an IC50 for both thiamine transporters THTr1 and THTr2 of >300 µM.

In a 28-day rat study, normal rats treated with fedratinib were compared to a thiamine deficient (TD) rat model and TD rat model treated with fedratinib, as well as controls. Results indicate that fedratinib

had no effect on TD progression in the model, or on thiamine status of the animals. A further GLP 28-day rat study was conducted to evaluate thiamine levels in plasma and brain after fedratinib treatment up to 80 mg/kg/day. No effect on thiamine levels was observed. These results indicate that fedratinib has no direct inhibitory effect on the thiamine transporter. Of note, at the highest dose tested, the exposure was only about 0.25-fold the human exposure at the recommended dose. However, the results together with the *in vitro* data suggesting very high IC50 values for thiamine transporters, and the lack of effect on thiamine levels in the clinic after fedratinib treatment are sufficient to exclude a direct inhibitory effect of fedratinib on the thiamine transporter.

Safety pharmacology programme

After a single dose fedratinib of up to 30 mg/kg there were no effects on the central nervous system of rats as measured by the functional observation battery. However, the exposure in these rats is anticipated to be far below the human exposure at the Maximum Recommended Human Dose (MRHD), when extrapolated from other rat toxicokinetic data, with an exposure multiple of 0.05 based on AUC. This study therefore did not provide information relevant for the human situation.

With regards to effects on the cardiovascular system, the hERG channel was inhibited with an IC50 of 2.1 µM. In the *in vivo* dog study where no effects on cardiovascular parameters were observed, this IC50 concentration was presumably not reached, as the highest dose tested was 20 mg/kg which resulted in only 0.2-fold the human exposure at the MRHD based on Cmax (extrapolated from other dog TK data). Although the IC50 for the hERG channel is below the Cmax and Cavg in humans, there is high protein binding of at least 91% in human plasma. Therefore, the unbound Cmax in humans of around 0.35 µM is below the IC50 for hERG channel inhibition. Further, a dedicated clinical QT study was performed which showed no effect on the cardiac action potential.

Effects on the respiratory system were evaluated in the same study as the dog cardiovascular study. Therefore, although no effects were observed on respiratory parameters, the exposure margin was too low (0.2 at best), and this study is not very informative. However, no effects on breathing were seen in the repeated dose toxicity studies, and no signs of effect on the respiratory system were seen in the clinical studies. Therefore, it can be concluded that fedratinib has no effect on the respiratory system.

Pharmacodynamic drug interactions

No studies of pharmacodynamic drug interactions were conducted.

2.3.3. Pharmacokinetics

Absorption was investigated *in vitro* and *in vivo* after single dose in mice, rats, dogs and monkeys and after repeated dose in mice, rats and dogs. Tissue distribution was investigated in rats. Metabolism was investigated *in vitro* and *in vivo* in mice, rats and dogs. Excretion was investigated in mass balance studies in mice, rats (intact and bile-duct cannulated rats) and dogs. Distribution to milk and placenta was not investigated.

Methods of analysis

In the toxicokinetic studies, fedratinib was analysed in plasma of mice, rats, dogs and rabbits with validated LC-MS/MS methods. The validation was adequate regarding calibration, accuracy, precision, LLOQ, carry-over, dilution integrity, matrix effect, selectivity and stability."

Absorption

In vitro apical to basolateral permeability in Caco-2 cells was high at pH 7.4 but very low at pH 6.5, at concentrations of 20 µM. At 100 µM, the permeability at pH 6.5 was markedly increased.

After oral single dose administration, tmax was around 3 h for rats, dogs (except in one dog study where it was only 0.5-0.75 h) and monkeys and 1 h for mice. In rats, Cmax and AUC0-inf were approximately 2 times higher in fasted conditions compared to fed conditions. In fed dogs, uptake of fedratinib appears to be delayed compared to fasted dogs (tmax increased and Cmax decreased and no significant difference in AUC0-24). Volume of distribution was 32, 13.5-17.4, 22, and 10.7 L/kg in mice, rats, dogs, and monkeys, respectively, which implies a wide distribution beyond the total body water. Absolute oral bioavailability was 28 – 37% in mice, rats, dogs and monkeys. After administration of fedratinib to the portal vein in rats, the exposure was approximately half the exposure compared to when fedratinib was administered into the femoral vein, indicating a first pass effect. Elimination half-life was longer in dogs and monkeys (9-11 h after IV and 18-19 h after oral administration) than in mice and rats (3-7 h after IV administration). Clearance after IV dosing was 125 mL/min/kg in mice, 42-46 mL/min/kg in rats, 38 mL/min/kg in dogs and 19 mL/min/kg in monkeys. Since only males were used in these studies, no conclusion can be drawn regarding gender differences after a single dose.

After repeated oral administration of up to 30 mg/kg/day, fedratinib exposure increased more than dose-proportionally in mice and rats (mice up to 11x more than the dose increase, rat up to nearly 5x more than the dose increase), while this was less clear at higher doses. Exposure in dogs increased more than dose-proportionally (up to 8x more than the dose increase). Also, in pregnant rats and in pregnant rabbits the exposure increased more than dose-proportionally (up to 11-12x more than the dose increase). No explanation was given for the high maximal exposure increases. However, all exposures, including those at the highest doses, were lower than the human exposure. In pregnant rats, the exposure was somewhat lower than in non-pregnant rats. In rats and mice, the exposure was slightly higher in females than in males, approximately 2-fold at maximum. In dogs, no clear gender difference was visible. No accumulation was observed in the mouse carcinogenicity study. In rats and dogs, slight accumulation was observed, but no more than approximately 2-fold. In pregnant rats, no accumulation was observed between gestation days 6 and 17. In pregnant rabbits, the exposure was increased at gestation day 18 compared to gestation day 6 (approximately 2-4-fold).

Table 5: **Fedratinib plasma pharmacokinetic parameters after single dose in various species**

Species (Strain)	Sex	Route	Study number	Food	Dose (mg/kg)	t_{max} (h)	C_{max} (ng/mL)	$t_{½}$ (h)	AUC (ng•hr/mL)	V_{ss} (L/kg)	CL (mL/min /kg)	F (%)
Mouse (BALB/c)	M	IV bolus [a]	PDM-07-101348-022	Fed	4.7	NA	NA	3.0	618	32	125	NA
		PO [b]	PDM-07-101348-022	Fed	23.3	1.0	236	NA	620	NA	NA	20
Rat (Sprague Dawley)	M	IV bolus [a]	PDM-07-101348-025	Fed	5	NA	NA	6.68	1990	13.5	42.0	NA
		PO [c]	PDM-07-101348-025	Fasted	25	3.0 [d]	436	NA	3640	NA	NA	37
		PO [c]	PDM-07-101348-025	Fed	25	3.0 [d]	196	NA	1810	NA	NA	19
		IV bolus [a]	PDM-07-101348-046	Fed	5	NA	NA	4.99	1820	17.4	45.7	NA
		PO [e]	PDM-07-101348-046	Fed	25	3.0	318	NA	2330	NA	NA	25.6
		PO [f]	PDM-07-101348-046	Fed	25	2.33	254	NA	1750	NA	NA	17.7
Dog (Beagle)	M	IV bolus [a]	PDM-07-101348-056	Fasted	2	NA	NA	9.2	894	22	38	NA
		PO [c]	PDM-07-101348-056	Fasted	10	3.7	105	NA	1180	NA	NA	26
		PO [g]	ABS0601	Fasted	~2	0.75 [d]	10.6	19.4	121	NA	NA	NA
		PO [h]	ABS0601	Fasted	~2	0.5 [d]	11.4	18.1	132	NA	NA	NA
Monkey (Cynomolgus)	M	IV bolus [a]	PDM-07-101348-015	Fasted	2	NA	NA	11.0	1810	10.7	18.6	NA
		PO [c]	PDM-07-101348-015	Fasted	10	3.3	207	NC	1970	NA	NA	23

AUC = area under the concentration-time curve; Captisol = sulfobutylether-β-cyclodextrin; CL = total body plasma clearance, C_{max} = maximum plasma concentration; F = oral bioavailability; h = hours; HPMC = hydroxypropyl methylcellulose; IV = intravenous; M = male; MC = methylcellulose; NA = not applicable; PG = propylene glycol; PO = per os (orally); $t_{½}$ = terminal elimination half-life; t_{max} = time to maximum plasma concentration; V_{ss} = volume of distribution at steady state.

[a] Solution in 9.5% Captisol®.
[b] Solution in 1% HPMC.
[c] Solution in 0.5% MC and 0.05% Tween 80.
[d] Median.
[e] Solution in 50% PG and 10% Tween 80.
[f] Suspension in 0.5% MC and 0.05% Tween 80.
[g] Regis capsule formulation at 20 mg (~2 mg/kg) in pentagastrin-treated dog.
[h] Sisteron capsule formulation at 20 mg (~2 mg/kg) pentagastrin-treated dog.

Distribution

Plasma protein binding of fedratinib was slightly higher in humans (91-96%) than in mice, rats, rabbits, dogs and monkeys (83-89%). Protein binding in human plasma was not concentration dependent up to 5000 ng/mL, but slightly lower binding was observed at 10000 ng/mL.Fedratinib was highly bound to α1-acid glycoprotein (98%) and moderately bound to human serum albumin (57%). Protein binding to human serum albumin was not concentration dependent. Protein binding to α1-acid glycoprotein appears to show saturation at concentrations ≥ 5000 ng/mL.

Some distribution of fedratinib-derived radioactivity into red blood cells was observed in rats and dogs (blood to plasma ratio 1.1-2.0 in rats and 1.1-1.2 in dogs). In humans, distribution into red blood cells was limited (blood to plasma ratio of 0.6 to 0.8). In rats, AUC was approximately 2-fold higher when calculated from concentrations in whole blood compared to plasma. Also $t_{1/2}$ was increased when based on concentrations in whole blood, especially in females.

Following single dose oral administration to rats, fedratinib was widely distributed in the body with the highest concentrations in the GI tract, the liver (tissue/plasma ratio 161-244 at 4 h post-dose), kidney (tissue/plasma ratio 93-256 at 4 h post-dose), spleen, lung, adrenal gland and thyroid. Maximum concentrations were found at 4 h after dosing for most tissues. Fedratinib distributed to the eye (uveal tract) and to pigmented skin. After 96h, fedratinib was still found in lacrimal glands, eye, kidney, liver and preputial gland. Fedratinib could still be found in the eye at 672 h (1 month) after dosing. The potential for phototoxicity has been studied and no phototoxic potential was found *in vitro* in 3T3 cells. Fedratinib distributed to the brain in low concentrations (concentrations lower than plasma concentrations at 4 h after dosing), but it eliminated slower from brain tissue than from plasma: following a single IV administration to rats, $t_{1/2}$ from brain was 27 h, whereas it was 4.3 h from plasma. No studies were conducted regarding placental transfer and distribution into milk. Evidence of embryo-foetal toxicity was found in rats, indicating that fedratinib crosses the placenta.

Metabolism

In vitro, the major compound found in human microsomes and in rat, dog and human hepatocytes was the parent compound (58-87% of total radioactivity). Four metabolic pathways were identified based on *in vitro* results. The major pathway in all species involved oxidations on the ethyl pyrrolidine moiety of fedratinib. Minor pathways found in all species were oxidation on the methyl-diphenylpyrimidine-diamine group and oxidation on the terbutyl group of fedratinib. Direct glutathione conjugation was a fourth pathway, which was found in the rat but not in human. Main metabolites in humans were SAR317981 (pyrrolidone of fedratinib, 3.6-4.0% of total radioactivity), metabolite 7 (formed by hydroxylation on the ethyl pyrrolidone, 5.1-8.5% of total radioactivity) and metabolite 5 (aminophenol derivative of fedratinib, 4.2% of total radioactivity). These metabolites were formed by successive oxidations on the ethyl pyrrolidine moiety. SAR317981 and metabolite 7 were also found in rat and dog hepatocytes (SAR317981 at 1.8-3.6% and metabolite 7 at 1.2-2.9%). Metabolite 5 was found in rat (1.6%), but not in dog hepatocytes. All other human metabolites accounted for less than 3.5% of total radioactivity. SAR317981 was also found following incubation without NADPH, indicating that it was formed not (only) by CYP enzymes. Main metabolites in rats and dogs were SAR318031 (successive oxidations on pyrrolidine ethyl group leading to the carboxylic acid group, 16% in dog and 8.3% in rat) and SAR317753 (N-oxidation on the pyrrolidine ethyl group, 7.6% in dog and 5.5% in rat).

Table 6: **Relative percentage of fedratinib and metabolites in rat, dog and human hepatocytes and human microsomes (study MIV0640)**

Species (Dose)	Percent Radioactivity			
	Human (pooled male and female)		Dog (male)	SD Rat (male)**
Test System	Liver Microsomes*	Hepatocytes*	Hepatocytes*	Hepatocytes*
% Biotransformation	42	13	34	39
SAR302503 (fedratinib, UD)	57.9	87.4	66.1	61.1
1 (di-oxidation on pyrrolidine of UD)	3.2	BLQ	BLQ	BLQ
2 =SAR317981 (di-oxidation on pyrrolidine of UD)	4.0	3.6	1.8	3.6
3 (di-oxidations on pyrrolidine + oxidation on benzene sulfonide)	3.4	0.8	BLQ	BLQ
4 (pyrrolidine hydrolysis + oxidations on ethane group)	3.4	0.8	1.1	BLQ
5 (O-dealkylation of ethane pyrrolidine)	4.2	1.3	BLQ	1.6
6 (tri-oxidations on ethane pyrrolidine)	BLQ	BLQ	1.4	BLQ
7 (tri-oxidations on ethane pyrrolidine)	8.5	5.1	2.9	1.2
8 = SAR317753 (N-oxidation on pyrrolidine of UD)	2.9	BLQ	7.6	5.5
10 (oxidation on benzene sulfonide of UD)	2.8	1.0	BLQ	BLQ
12 (N-dealkylation on pyrrolidine)	2.4	BLQ	BLQ	BLQ
13 = SAR317793 (oxidation on methyl pyrimidine of UD)	1.5	BLQ	1.6	1.2
14 = SAR318031(oxidations on pyrrolidine)	2.8	BLQ	15.7	8.3
16 (terbutyl oxidation of UD)	1.3	BLQ	BLQ	BLQ
17 (oxidations on ethane pyrrolidine)	2.0	BLQ	1.7	2.6
18 (glutathione conjugation)	BLQ	BLQ	BLQ	2.2
19 (glutathione conjugation)	BLQ	BLQ	BLQ	1.3
20 (O-dealkylation + glutathione conjugation)	BLQ	BLQ	BLQ	3.0
21 (O-dealkylation + glutathione conjugation)	BLQ	BLQ	BLQ	4.7

BLQ = below the limit of quantification (0.7% of radioactivity); UD = unchanged drug
* Results obtained at 6 hours in hepatocytes and 60 minutes with NADPH regenerating system in liver microsomes.
** Only metabolites representing at least 1.2% of radioactivity are reported in this table.
Source: Report MIV0640.

In vivo metabolism was investigated in mice, rats and dogs. In all species, parent drug was the main circulating compound in plasma (66%, 79-88%, 72% and 80% of radioactivity AUC0-24h in mice, rats, dogs and humans respectively).

Table 7: Interspecies comparison of the *in vivo* metabolic profiles of [14C]-fedratinib in plasma

Species (Strain)	Mouse (C57Bl/6)	Rat (Sprague Dawley)		Dog (beagle)	Human
Sex	Male	Male and Female		Male	Healthy Male
Study number	[MET0910]	[MET0895]		[MET0893]	[MEH0082]
Vehicle/ formulation	0.5% Methylcellulose	0.5% Methylcellulose		0.5% Methylcellulose	Water
Feeding conditions	Fasted	Fasted		Fasted	Fasted
Method of Administration	Single oral	Single oral		Single oral	Single oral
Dose	100 mg/kg	25 mg/kg		5 mg/kg	200 mg
Number of animals and human	4/sampling time	3/sampling time/sex		3	6
Analytical Method	HPLC with radioactivity detection and/ or mass spectrometry				
	Plasma - % of radioactivity AUC [ngEq.h/mL]				
Biotransformation	Mouse (0-24 h)	Rat (0-24 h)		Dog (0-24 h)	Human [a] (0-6 h to 12 h)
	C57Bl/6	Male	Female	Male	Male
SAR302503 (fedratinib, UD)	66.2 [25884]	78.7 [1731]	87.7 [3569]	72.3 [304]	79.8 [2221]
2=SAR317981 (pyrrolidone of UD)	5.2 [2033]	21.3 [469]	12.3 [501]	BLQ	9.4 [262]
7 (hydroxylation on ethyl pyrrolidone of UD)	5.4 [2111]	BLQ	BLQ	BLQ	BLQ
14=SAR318031 (N-butyric acid of UD)	3.6 [1408]	BLQ	BLQ	BLQ	BLQ[b]
20a (pyrimidine acid derivative of UD)	5.2 [2033]	BLQ	BLQ	BLQ	BLQ
22a*	BLQ	BLQ	BLQ	27.7 [117]	BLQ
Total radioactivity	[39100]	[2200]	[4070]	[421]	[2783]

BLQ = below the limit of quantification; HPLC = high-performance liquid chromatography; UD = unchanged drug SAR302503.
[a] Mean data (n=6).
[b] Detected in only one subject.
* Not identified.

In mice, 4 metabolites were observed in plasma, among which the main human metabolite, SAR317981, at 5.2%. The other metabolites in plasma of mice were SAR318031, metabolite 7 and metabolite 20a (hydroxylation on methyl pyrimidine of SAR317981), representing 3.6-5.4% of radioactivity. In faeces of mice, 72-83% of the dose was excreted after 24 h; 4% of the dose was excreted in urine after 48 h. A total of 30-42% of the dose was excreted as unchanged drug. Thirteen metabolites were found in the excreta of mice, among which the main one was SAR318031 (6.6-8.1% of dose). Other metabolites represented ≤ 5% of dose. No significant difference in metabolite profile was observed between C57Bl/6 and wild-type RasH2 mice.

In rats, the main human metabolite SAR317981 was the only circulating metabolite, at 12-21% of radioactivity. SAR317981 was found in liver at 4 h after dosing (tissue:plasma ratio 156 and 55 in males and females resp.). In faeces of rats, 78-88% of the dose was excreted after 48h; 1.5% of the dose was excreted in urine after 24 h. A total of 39-55% of the dose was excreted as unchanged drug. Thirteen metabolites were found in the excreta of rats, among which the main ones were SAR318031 (10-11% of dose) and metabolite 17 (8.3-8.6% of dose). Other metabolites in excreta represented ≤ 6% of dose. In bile of cannulated rats, 49% of the dose was excreted within 24 h, among which only 1.2% as the parent compound. Three major phase II metabolites were found in bile: metabolite 19a (S-cysteine-glutamine derivative of glutathione conjugate of fedratinib) at 7.6% of dose, and metabolites 20 and 21c (glutathione and glucuronide conjugate derivatives of metabolite 5) at 4.6% and 7.0% of dose. In addition, SAR318031 and 2 other phase I metabolites were found in bile at 5%. The amount of 49% of dose found in bile, was higher than the oral bioavailability of 18-37%. It is possible that part of the absorbed fedratinib is metabolised immediately, but this does not match with approximately 80% parent compound in plasma.

In dogs, one major metabolite was found in plasma, M22a, an unidentified ultra-polar compound, at 28% of radioactivity. In faeces of dogs, 87% of the dose was excreted after 48h; in urine, 0.5% of the dose was excreted after 48 h. A total of 21% of the dose was excreted as unchanged drug. Eleven metabolites were found in the excreta of dogs, among which SAR317981 at 40% of the dose. Other metabolites in excreta represented ≤ 6% of the dose. The fact that of the 87% which was excreted in faeces, only 21% was unchanged drug suggests that fedratinib, after having been absorbed, undergoes first-pass metabolism in the liver, primarily to metabolite SAR318031, to be excreted in the faeces. This explains why in faeces there is a low proportion of unchanged drug, while the bioavailability of fedratinib is also relatively low. In humans, the main circulating metabolite was SAR317981 at 9.4%. SAR318031 was detected in only one subject.

The main metabolic pathway in all species is ethyl pyrrolidine oxidation. Minor pathways found in most investigated species are tri-aromatic group (TAG) oxidation and terbutyl oxidation. Two additional minor pathways found only in rats are glutathione conjugation and glucuronide conjugation.

There are no unique human metabolites. The main circulating metabolite in humans SAR317981 (9.4% of radioactivity) was also formed in substantial amounts in rats (12-21%) and to a lesser extent in mice (5.2%). It is not found in quantifiable amounts in dog plasma. With its presence in substantial amounts in rats, this metabolite is however sufficiently investigated in non-clinical species.

Excretion

In mouse, rat and dog, the major part of fedratinib-related radioactivity was excreted via the faeces (78-95% of dose) and only a minor part was excreted through the urine (0.6-4.8% of dose). In bile-duct cannulated rats, 51% of the dose was excreted via the bile following administration of [14C]-fedratinib (after 48 h). Only a minor part of this represented the parent compound (2.3% excreted in bile 24 h after administration of fedratinib to bile-duct cannulated rats). In humans, the same pattern was observed (77% excreted in faeces and 5.2% in urine).

2.3.4. Toxicology

Single dose toxicity

Single-dose toxicity was assessed in Sprague-Dawley rats and Beagle dogs at doses up to 1000 mg/kg and 300mg/kg fedratinib respectively. Bodyweight loss and diarrhoea was observed in rats treated with ≥400mg/kg, but mortality only occurred in one female rat treated with 400mg/kg. In dogs, diarrhoea, vomiting and decreased activity was observed in all animals treated with fedratinib ≥ 100mg/kg.

Repeat dose toxicity

Repeat-dose toxicity studies were conducted in mice, Sprague-Dawley rats and beagle dogs given fedratinib for up to 1 month, 6 months and 9 months respectively. Exposure levels to fedratinib were low for rats (6 months, up to 30 mg/kg/day, margin-of-exposure (MOE): 0.106-0.153), dogs (9 months, up to 15 mg/kg/day, MOE: 0.099-0.132) and slightly higher in mice (1 month, up to 400/300 mg/kg/day, MOE: 0.9-1.2; 200 mg/kg/day, MOE: 2.3-3.4). It is apparent that exposures are much lower in animals than in humans, and therefore the human appears to tolerate fedratinib significantly better than toxicity animal species despite much higher systemic exposures.

In mice, the main target organs of toxicity included: bone marrow, lymphoid tissue, kidney, stomach and urinary bladder. Bone marrow hypoplasia, thymus atrophy, non-glandular hyperplasia in the

stomach and vacuolation of transitional cells in the urinary bladder was observed in mice treated with ≥200 mg/kg/day (MOE: 2.3-3.4) fedratinib. All mice treated with 400/300 mg/kg/day (MOE:0.9-1.2) were euthanised prematurely in moribund condition. In addition to the above-mentioned observations, these mice displayed lymphocyte depletion and/or necrosis in the spleen, GALT and mesenteric lymph nodes, renal tubule degeneration and necrosis in the kidney, non-glandular ulceration/inflammation and glandular hypertrophy in the stomach.

In rats, the main target organs of toxicity included the bone marrow and liver. Effects were also observed in the lymphoid tissues, lungs and heart. Rats treated with ≥30 mg/kg/day (1 month, MOE: 0.06-0.1; 6 months, MOE: 0.106-0.153) showed decreased weight gain, bone marrow hypoplasia and lymphoid atrophy in the thymus, spleen and mesenteric lymph nodes. In addition, histiocytic infiltrates were observed in the lungs and mesenteric lymph nodes. Rats treated with 80 mg/kg/day (1 month, MOE: 0.2-0.4) additionally showed liver bile duct hypertrophy and/or necrosis/fibrosis, accompanied by increased alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values. In these rats, myocardial degeneration and necrosis of the heart was also observed.

In dogs, the main target organs of toxicity included the bone marrow and liver. Effects were also noted in lymphoid tissues and testis. Lymphocyte depletion was observed in the thymus, spleen, lymph nodes in dogs, increasing in severity in a dose-dependent fashion. In dogs treated with ≥10 mg/kg/day (1 month, MOE: 0.1), bone marrow hypoplasia and bile duct hypertrophy and proliferation in the liver was noted. In 20/15 mg/kg/day (9 months, MOE: 0.1) and 40/30 mg/kg/day (1 month, MOE: 0.2-1.0) the bone marrow hypoplasia was accompanied by increased myeloid progenitor cells (MPCs) consistent with ineffective myelopoiesis. Infiltrates of myeloid progenitor cells were also noted in the spleen and liver in the 9-month study; this increase in myeloid progenitor cells was considered to represent an attempt at bone marrow/haematologic recovery. More exaggerated liver effects were observed in moribund animals. 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, accompanied by increases in ALT, AST, ALP and bilirubin levels. Other findings in moribund animals in the 9-month study included internal bleeding related to ulcers, chronic-active inflammation of the oesophagus and stomach. 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 conclusion, fedratinib-related effects on the bone marrow (hypoplasia) and lymphoid tissues (lymphocyte depletion in the spleen, thymus and lymph nodes) in all three species are likely symptoms of exaggerated pharmacology and indicate clear immunosuppressive properties of fedratinib (also see immunotoxicity section). In addition, liver toxicity was observed in both rats and dogs, which is also relevant for humans, where increased ALT and AST levels have been observed. Liver toxicity is mentioned as an important potential risk in the RMP. Another target organ effected in all three species is the stomach. Clinical relevance is apparent, since in humans nausea and vomiting are common adverse effects. Effects on heart were seen in rats and mice (cardiomyopathy in rats and increased weight in mice), but not in dogs. As discussed in the section on safety pharmacology, heart is not likely to be a target organ in humans, since a clinical QT study revealed no effects. In mice, renal tubule degeneration and necrosis was observed in the kidney, but no other kidney findings were observed in other non-clinical species. In humans however, increased creatinine levels were noted. Other target organs identified in the repeat-dose toxicity studies are likely not clinically relevant since they were only observed in one single species. These include effects on urinary bladder, vagina, muscle and lungs. Effects on testes were seen in dogs (epidiymides/testis aspermia) and rats (seminal vesicles weight reduction).

Genotoxicity

Fedratinib was negative in the Ames assay in bacterial cells, *in vitro* chromosomal assay in Chinese hamster ovary cells and in the *in vivo* micronucleus test in rats. Fedratinib has no genotoxic potential.

Carcinogenicity

In a 6-month carcinogenicity study in transgenic Tg.RasH2 mice, there were no neoplasms that were attributed to treatment with fedratinib. No 2-year carcinogenicity study in rats was performed.

Reproduction Toxicity

Fedratinib produced no effects on fertility or reproductive performance in male and female rats at dosages up to 30 mg/kg/day (MOE: 0.100-0.132). However, testes effects related to possible effects on sperm quality/quantity were seen in the repeated dose toxicity studies in rats (seminal vesicles weight reduction) at dosages of 80 mg/kg/day (1 month, MOE: 0.2) and dogs (epidiymides/testis aspermia) at dosages of 40/30 mg/kg/day (1 month, MOE: 0.5).

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) at dosages of 30 mg/kg/day (MOE: 0.112). Fedratinib produced no evidence of embryo-foetal toxicity in the rabbit at very low dosages up to 30 mg/kg/day (MOE: 0.080).

In a rat pre- and post-natal development study, treatment with fedratinib resulted in decreased maternal body weight gain and F1 generation pup body weight and food consumption at dosage levels of 30 mg/kg/day (MOE: 0.132). There was no effect on any developmental landmark or behavioural assessments. F1 mating, fecundity and fertility indices and GD13 caesarean section parameters were unaffected.

Toxicokinetic data

In TK, low exposure levels were obtained in mice, rats and dogs following repeated administration, resulting in no safety margin. The exposure increased more than dose-proportionally in mice from 3 to 30 mg/kg/day. This was less clear from 100 to 200 mg/kg/day: AUC increased more than dose-proportionally in female mice, but this was not the case in males and also not for Cmax. In rats, exposure increased more than dose-proportionally up to 30 mg/kg/day. This was less clear from 30 to 80 mg/kg/day. Exposure in dogs increased more than dose-proportionally. In rats and mice, the exposure was slightly higher in females than in males, approximately 2-fold at maximum. In dogs, no clear gender difference was visible. No accumulation was observed in the mouse carcinogenicity study. In rats and dogs, slight accumulation was observed, but no more than 2-fold. No measurable concentrations were found in control samples.

Exposure was very low in the embryo-foetal development studies. The exposure multiple based on AUC0-24 was at most 0.1 in pregnant rats and at most 0.08 in pregnant rabbits. In pregnant rats, the exposure was somewhat lower than in non-pregnant female rats. Like in non-pregnant rats, the exposure increased more than dose-proportionally in pregnant rats. Also, in pregnant rabbits the exposure increased more than dose-proportionally.

Local Tolerance

No specific studies have been conducted.

Other toxicity studies

Fedratinib demonstrated no phototoxic potential *in vitro* in 3T3 cells.

The impurity SM3 showed an *in-silico* alert for mutagenicity. Several non-GLP micronucleus assays in mouse lymphoma L5178Y cells resulted in equivocal results, but SM3 was negative in a GLP Ames test and chromosomal aberrations test in human peripheral blood lymphocytes. Therefore, SM3 is not considered genotoxic. Two genotoxic impurities were identified: 1) isopropyl chloride, a potential synthesis byproduct; and 2) 1-(2-chloroethyl) pyrrolidine hydrochloride, a precursor of starting material SAR311801A. Both are below the threshold of toxicological concern for all drug substance batches representative of the commercial process and used in clinical trials.

2.3.5. Ecotoxicity/environmental risk assessment

PBT screening: The octanol-water partitioning coefficient was determined according to OECD 107 at three pH values, resulting in log D_{ow} values of -0.3, 2.1 and >3.1 at pH 5, 7 and 9, respectively. The D_{ow} value at pH 7 is below the trigger values for performance of a bioaccumulation study (log K_{ow} >3) or PBT assessment (log K_{ow} >4.5).

Phase I calculations result in a PECsw of 2.0 µg/L, which exceeds the trigger value for Phase II. Phase II calculations were not provided as part of the initial Marketing Authorisation Application.

Table 8: Summary of main study results

Substance (INN/Invented Name): fedratinib			
CAS-number (if available): 936091-26-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OECD107	pH 5: -0.2 pH 7: 2.1 pH 9: >3.1 hydrophobicity of the neutral species is potentially high	potentially PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	pH 5: -0.2 pH 7: 2.1 pH 9: >3.1 hydrophobicity of the neutral species is potentially high	potentially PBT
	BCF	TBD	B/not B
Persistence	DT50 or ready biodegradability	TBD	P/not P
Toxicity	NOEC or CMR	TBD	T/not T
PBT-statement :	TBD		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater	2.0	µg/L	> 0.01 threshold (Y), documentation

					on prevalence is not up to date.
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	TBD			
Ready Biodegradability Test	OECD 301…	TBD			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	TBD			
Phase IIa Effects studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	TBD	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	TBD	µg/L	
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	TBD	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	TBD	µg/L	

2.3.6. Discussion on non-clinical aspects

The proof of concept for efficacy of fedratinib was shown through *in vitro* and *in vivo* experiments. Fedratinib appears to have high specificity for mutant JAK2 and FLT3. Although fedratinib showed lower selectivity against JAK1, JAK3 and TYK2 the IC_{50} values for these recombinant kinases in two commercial kinase screens were still within clinically relevant concentrations (free C_{max} in plasma of MF patients = 304 nM). Although in enzyme kinetic assays the IC50 values for other JAK family members JAK1, JAK3 and TYK2 are below the clinical Cmax of 304 nM which marks them as potential targets of fedratinib, when further evaluation on inhibitory potential was performed in a cell-based assay, no IC50 was reached for JAK1, JAK3 and TYK2, when tested up to 1 µM. This indicates that although binding is possible, there is no downstream consequence on inhibition of cell proliferation through these kinases. Therefore, within the JAK family of kinases, it can be concluded that fedratinib is specific for JAK2. The data concerning wild-type JAK2 is conflicting. While enzyme kinetics and a single cell-based assay show high affinity binding and reduced proliferation, a xenograft mouse model showed no reduction of engraftment of wild-type JAK2. However, a contribution of wild-type JAK2 to the effect of fedratinib cannot be excluded.

For other kinases outside the JAK family and FLT3, only enzyme kinetics data is available. These data indicate that binding of fedratinib to several kinases, including but not limited to ZIPK, FGFR1 V561M, and NUAK, is possible at clinically relevant concentrations. There is however no data in cell-based assays, and it is therefore not known if binding also leads to relevant inhibition of cell proliferation. In the context of the intended indication, effects through inhibition of other kinases besides JAK2 and FLT3 will likely not contribute to the overall effect. However, secondary effects through inhibition of other kinases cannot be excluded and could be related to some of the adverse effects seen in animals and humans. Since the safety profile of fedratinib is known, no further studies regarding the contribution of inhibition of other kinases is considered necessary.

While other off-target binding appears to be possible for CNS related receptors, since adenosine, muscarinic, serotonin, sigma, and Na+ channel receptors and norepinephrine, dopamine and serotonin

transporters were inhibited with more than 50% at 1 µM, the weight of evidence suggests that these interactions are not important *in vivo*.

Numerous *in vivo* mouse models were used to evaluate the efficacy of fedratinib. Although proof of concept is shown in these studies, it appears that in mice a higher exposure to fedratinib than the exposure reached in humans is required to result in an effect on tumour cells. Additionally, in the xenograft mouse model, no toxicity was observed which raises doubts about exposure. However, the systemic exposure may have been lower in the xenograft model mice due to accumulation of fedratinib in tumour tissue relative to plasma (tumour/plasma ratio 1.65 to 25.2). The true efficacy potential is determined on a clinical level (please see clinical section below).

Safety pharmacology studies were conducted with doses that resulted in exposures far below the clinical exposure at the MRHD, and they are therefore not very informative. However, for aspects of the central nervous system, cardiovascular system and respiratory system sufficient data is available from repeated dose toxicity studies with higher doses and from clinical trial data, to conclude that there are no effects anticipated on these major organs systems.

The pharmacokinetics of fedratinib were investigated adequately.

The high melanin binding and the relatively long persistence of fedratinib in the eye were not associated with toxicity in mice and Beagle dog studies of up to 1 and 9 months duration and are therefore not considered a safety issue. Moreover, fedratinib demonstrated no phototoxic potential *in vitro* in 3T3 cells.

There appears to be a large discrepancy between sensitivity to fedratinib in animals and humans, illustrated by the low exposure margins across the studies. However, because clinically relevant exposures cannot be attained in the toxicity species, the general lack of utility of these studies in producing clinically relevant safety data on fedratinib is acknowledged. The existing clinical data of fedratinib can be considered to supersede the (lack of) nonclinical toxicity data.

Fedratinib is not genotoxic in the performed studies. It should be noted however, that the exposure in the *in vivo* rat micronucleus study was low (animal/human exposure ratios based on C_{max} (ng/mL) and $AUC_{0\text{-}24h}$ (ng*h/mL) values were in range of 0.008 to 0.306 and 0.004 to 0.259). No long-term carcinogenicity study has been conducted, and this was justified by the applicant by referring to ICH guideline S9 (treatment of advanced cancer). However, this is not applicable to fedratinib and instead ICH S1 applies. According to ICH S1A/S1B carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months and in long-term carcinogenicity study in a second rodent species the rat is normally a species of choice. The applicant justified to the lack of value of rodent carcinogenicity studies, due to the low tolerability of rodents to fedratinib, resulting in low exposures in the studies. This is agreed, and therefore carcinogenicity studies can be waived. During the assessment the applicant submitted a weight of evidence approach to assess the carcinogenic potential of fedratinib. From the non-clinical evidence, the only concern is a prominent immunosuppressive effect of fedratinib, which is a known risk factor for tumorigenesis in humans. Secondary malignancies will be monitored in patients in an ongoing clinical study and in the postmarketing setting (please see clinical section below).

Although no teratogenic effects were observed in rat or rabbit embryo-foetal toxicity studies, the exposure to fedratinib in these studies was well below the clinical exposure. The relevance of these studies for human safety is therefore limited. Based on the role of JAK2 in development described in literature, and the known class effects of other marketed JAK inhibitors, concern for exposure to fedratinib during pregnancy has been established. Due to this class effect and since other JAK inhibitors have a contraindication for pregnancy, a contraindication for pregnancy has been included in section 4.3 of the SmPC of Inrebic.

Regarding Ecotoxicity and environmental risk assessment the applicant is currently performing the Phase II testing. An updated ERA/PBT assessment will be provided by the end of 4Q2021. It is therefore not yet possible to conclude on the risk of Inrebic to the environment. However, considering that the data will be available soon, this is considered acceptable for this orphan medicine.

2.3.7. Conclusion on the non-clinical aspects

Marketing authorisation for Inrebic could be approvable from a non-clinical point of view. From the non-clinical evidence, the only concern is a prominent immunosuppressive effect of fedratinib, which is a known risk factor for tumorigenesis in humans. Secondary malignancies will be monitored in patients in an ongoing clinical study and in the post-marketing setting (please see clinical section below).

The CHMP considers the following measures necessary to address the non-clinical issues:

For the completion of the Environmental Risk Assessment, the applicant commits to performing a bioconcentration study in fish according to OECD 305. Further, the applicant is currently performing the Phase II testing. An updated ERA/PBT assessment is due by the end of Q4 2021.

2.4. Clinical aspects

2.4.1. Introduction

On 15 Nov 2013, the fedratinib US investigational new drug (IND) was placed on clinical hold by United States Food and Drug administration (FDA) after Sanofi provided cases of heart failure and preliminary case reports of Wernicke's encephalopathy (WE) that occurred in subjects being treated with fedratinib. On 18 Nov 2013, Sanofi (previous sponsor) decided to terminate the fedratinib clinical development programme. Seven clinical studies including the pivotal studies EFC12153 and ARD12181 did not run to completion with various impact on study results (additional studies ongoing at time of clinical hold: TES13519, a QT interval (QT) study; Study TED12015, the long-term extension study to TED12037; Study ARD11936, a phase 2 dose-range finding study; Study ARD12888, a phase 2 study in Japan in MF subjects; Study ARD12042, a phase 2 study in subjects with PV or ET who were resistant or intolerant to HU). Overall, long-term follow-up is limited.

On 18 Aug 2017, FDA removed the clinical hold after a detailed review of all data regarding possible cases of Wernicke's encephalopathy and cardiac failure/cardiomyopathy was provided, including evaluation of thiamine levels in subjects on fedratinib therapy.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 9: Overview of clinical studies

KEY STUDIES IN MYELOFIBROSIS			
Study	**Study Title**	**Doses**	**Number of Subjects [a]**
Subjects who are JAK Inhibitor Naïve			
EFC12153 (JAKARTA) Phase 3	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-Controlled, 3-arm Study of fedratinib (SAR302503) in Patients with Intermediate-2 or High-risk Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis with Splenomegaly	Placebo 400 or 500 mg fedratinib daily	289 total Placebo: N = 96 400 mg/day: N = 96 500 mg/day: N = 97 71 placebo subjects were re-randomised and crossed over to active treatment[b]
Subjects who Have Been Treated with Ruxolitinib			
ARD12181 (JAKARTA2) Phase 2	A Phase 2, Multicenter, Open-label, Single-arm Study of fedratinib (SAR302503) in Subjects Previously Treated With Ruxolitinib and With a Current Diagnosis of Intermediate or High-risk Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis	400 mg fedratinib daily[c]	97 total Overall: N = 97 Cohort 1: N = 79 [d] Cohort 1a: N = 66 [d]
SUPPORTIVE STUDIES IN MYELOFIBROSIS			
Subjects who are JAK Inhibitor Naïve			
ARD11936 Phase 2	A Phase 2 Randomized, Open-label, Dose-ranging Study of the Efficacy and Safety of Orally Administered fedratinib (SAR302503) in Patients With Intermediate-2 or High-risk Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, Post-essential Thrombocythemia Myelofibrosis With Splenomegaly	300, 400, or 500 mg fedratinib daily	31 total 300 mg/day, N = 10 400 mg/day, N = 10 500 mg/day, N = 11
TED12037 Phase 1	A Phase 1, Open-label, Dose-escalation Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Orally Administered fedratinib (TG101348) in Patients With Primary, Post-polycythemia Vera, or Post-essential Thrombocythemia Myelofibrosis	30 to 800 mg fedratinib daily	59 total 30 mg/day, N = 4 60 mg/day, N = 3 120 mg/day, N = 3 240 mg/day, N = 3 360 mg/day, N = 3 520 mg/day, N = 3 680 mg/day, N = 34 800 mg/day, N = 6
SUPPORTIVE STUDIES IN MYELOFIBROSIS			
Study	**Study Title**	**Doses**	**Number of Subjects [a]**
TED12015[e] Phase 1/2	An Open-label Study to Evaluate the Long-term Effects of Orally Administered fedratinib (SAR302503) in Patients With Primary or Secondary Myelofibrosis	Subjects continued at their assigned dose from the prior study, TED12037	43 total 30 mg/day, N = 3 60 mg/day, N = 3 120 mg/day, N = 2 240 mg/day, N = 2 360 mg/day, N = 3 520 mg/day, N = 2 680 mg/day, N = 25 800 mg/day, N = 3

- JAK = Janus kinase
- [a] Total randomised/assigned to treatment.
- [b] Placebo subjects were re-randomized to receive 400 mg or 500 mg at the end of Cycle 6 or at the time of progressive disease prior to the end of Cycle 6.
- [c] Up-titration to 500 mg or 600 mg if predefined efficacy and safety criteria were met.
- [d] Cohort 1 includes subjects meeting newly defined criteria for relapsed/refractory or intolerant to ruxolitinib. Cohort 1a is a subgroup of Cohort 1 that includes subjects who had received Cycle 6 of fedratinib treatment or who had discontinued fedratinib treatment for reasons other than "study terminated by sponsor".
- [e] Subjects enrolled in TED12015 had to have been enrolled in TED12037.
- Note: Fedratinib is also known as SAR302503 or TG101348.

2.4.2. Pharmacokinetics

Fedratinib is a small molecule kinase inhibitor of wild type and mutationally activated Janus kinase 2 (JAK2) and FMS-like tyrosine (FLT) kinase 3 (FLT3). Fedratinib is formulated as a 100 mg immediate release capsule. The recommended dose of Inrebic is 400 mg once daily for patients with a baseline

platelet count of ≥50 x 10^9/L. Fedratinib has not been studied in patients with a baseline platelet count <50 x 10^9/L.

Inrebic may be taken with or without food. According to the applicant, administration with a high fat meal may reduce the incidence of nausea and vomiting; therefore, it is recommended to be taken with food.

Fedratinib is a weak base, with 2 pKa values of 6.3 and 9.5. It exhibits pH-dependent solubility and permeability *in vitro*. It is freely soluble under acidic conditions (>100 mg/mL at pH 1) and practically insoluble in the neutral condition (4 µg/mL at pH 7.4). Fedratinib is not a stereoisomer, so interconversion is not an issue.

Bioanalysis. In general, fedratinib plasma concentrations in clinical studies were determined with liquid chromatography methods, coupled with tandem mass spectrometry (LC-MS/MS). Analytical methods for fedratinib appear validated to a reasonable extent, with accuracy, specificity and stability meeting appropriate requirements.

Models. A population pharmacokinetic model FEDR-MPK-001 was fitted to time-concentration data from six studies (one Phase 1 study: TED12037, four Phase 2 studies: ARD11936, ARD12042, ARD12181, ARD12888 and one Phase 3 study: EFC12153), all of which were patient studies. The developed model features first-order absorption and elimination, absorption lagtime and two-compartment distribution. The popPK model has been validated to a reasonable extent.

Further, a PBPK model was developed in Study FEDR-DMPK-2852, with the purpose to predict drug-drug interactions between fedratinib (victim) and cytochrome P450 modulators, drug-drug interactions between fedratinib (perpetrator) and cytochrome P450 substrates, and drug-drug interactions between fedratinib (perpetrator) and transporter substrates. The developed PBPK models were validated against the clinical observation including *1*) PK data following repeated doses of fedratinib in patients with myelofibrosis (MF), *2*) drug-drug interaction data between fedratinib (as the victim) and ketoconazole in healthy subjects, and *3*) drug-drug interaction data between fedratinib (as the perpetrator) and cocktail probe substrates consisting of midazolam, omeprazole, and metoprolol in patients with refractory solid tumours. Based on the standard PBPK model, the applicant developed a 'low QGut' PBPK model at 300 mg, in which the gut blood flow parameter (QGut) was reduced from the default 6.5 L/h to 1.34 L/h. This model was validated against the situation of a single dose of fedratinib (victim) with and without ketoconazole. Results demonstrate reasonable performance of the model in both situations. Therefore, the PBPK model is considered sufficiently validated for prediction of effects on 300 mg single dose fedratinib PK of mild to strong CYP3A4 inhibitors.

Table 10: Studies characterising clinical pharmacology, pharmacokinetics, and pharmacodynamics of fedratinib

Study Type	Study Number	Fedratinib Dose Strength(s)	Population	Number Enrolled
Biopharmaceutic studies				
Food effect	ALI13451[a]	500 mg single dose	Healthy	19
Relative bioavailability	BDR12462[a]	500 mg single dose (tablet and capsule)	Healthy	16
Pharmacokinetics, pharmacodynamics, and initial tolerability in healthy subjects				
Single ascending dose oral	TDU12620	10, 30, 80, 150, 300, 500, and 680 mg single dose	Healthy	6/Cohort; 14 (placebo) 57 total
Food effect	FED12258	100 and 500 mg single dose	Healthy	9 (100 mg); 8 (500 mg) 17 total
Excretion balance, pharmacokinetics, metabolism	BEX12257	200 mg single dose as [^{14}C]-fedratinib	Healthy	6
Intrinsic factors				
Renal impairment (RI)	POP13449	300 mg single dose	Healthy, RI	36
Hepatic impairment (HI)	POP13450	300 mg single dose	Healthy, HI	17
Extrinsic factors				
Ketoconazole DDI	INT12893	50 and 300 mg	Healthy	7/Cohort 14 total
Pantoprazole DDI	INT12894	500 mg	Healthy	26
Effect of fedratinib on other drugs				
DDI Cocktail Study (CYP3A4, 2C19, and 2D6)	INT12497	500 mg	Solid tumor	16
Pharmacokinetics and pharmacodynamics in efficacy/safety studies				
Phase 1	TED12037	30-800 mg	MF	59
Phase 1/2	TED12015[b]	30-800 mg	MF	43
Phase 2	ARD11936	300, 400, and 500 mg	MF	31
Phase 2	ARD12042	100, 200, 400, 600 mg	PV or ET	81
Phase 2	ARD12888	300, 400, 500 mg	MF	8
Phase 2 (JAKARTA2)	ARD12181	400 mg	MF	97
Phase 3 (JAKARTA)	EFC12153	400 and 500 mg	MF	289
Pharmacokinetics/pharmacodynamics				
Dedicated QT study	TES13519	500 mg	Solid tumor	60

[b] Study TED12015 was an open-label extension of Study TED12037.

Absorption

In healthy subjects, fedratinib was absorbed rapidly with a median tmax ranging from 0.5 to 4 hours following single oral doses of 10 to 680 mg. Likewise, after single oral administration of a 400 mg dose to MF patients, fedratinib was absorbed rapidly, with a C_{max} of approximately 1430 ± 750 ng/ml reached after 1 to 4 hours.

No absolute bioavailability study in human was conducted.

Clinical and commercial formulations. Three different types of capsule formulations (formulations initial, 1A1, and 1B1) have been used in all the clinical studies. No major differences exist between the three capsule formulations used in the clinical studies. The provided analysis FEDR-MPK-003 did not indicate major differences in PK obtained from the different capsule formulations under fasting conditions. Therefore, PK data obtained with the various capsules under fasting conditions are considered representative for the commercial formulation.

Effect of food. Based on the results from Study FED12258, administration of the 100 mg fedratinib capsule with a high-fat breakfast resulted in a 14% and 13% decrease in fedratinib C_{max} and AUC_{last}, respectively, whereas, at 500 mg (5 x 100 mg capsules), administration of a high-fat breakfast resulted in a 14% and 26% increase in fedratinib C_{max} and AUC_{lasth}, respectively. The t_{max} at the 100 mg and 500 mg dose was somewhat delayed, i.e. from 1.5 to 2h, and from 2 to 4 h, respectively.

Data from Study ALI13451 at a 500 mg dose in 19 healthy subjects are also used in support of the hypothesis that nausea and vomiting occur less frequently when given with food. Indeed, the most frequently reported gastrointestinal TEAEs such as nausea and vomiting were less frequent in the fed state (62.5% and 16.7%) than in the fasted state (87.5% and 66.7%), in subjects receiving a 500 mg fedratinib dose.

Distribution

The mean apparent volume of distribution of fedratinib at steady-state, measured as the sum of apparent central and peripheral volume of distribution in popPK Study FEDR-MPK-001, was approximately 1770 L in patients with myelofibrosis at a 400 mg QD dose. This large volume of distribution indicates extensive tissue distribution of fedratinib. Approximately 95% of fedratinib is bound to human plasma protein, mostly to α1-acid glycoprotein. In the mass-balance Study BEX12257, limited distribution of fedratinib and/or its metabolites into red blood cells (blood to plasma ratio of 0.615 to 0.753) was observed.

Metabolism and Elimination

In the mass-balance Study BEX12257, fedratinib was the predominant component (approximately 80% of plasma radioactivity) in systemic circulation after oral administration of fedratinib. None of the fedratinib metabolites contributed greater than 10% of total drug-related exposure in plasma. Metabolite M2 was the main circulating metabolite accounting for approximately 9% of the total radioactivity AUC. *In vitro* data indicate that fedratinib is metabolised by multiple CYPs, with the predominant contribution from CYP3A4 and with lesser contributions from CYP2C19 and flavin-containing monooxygenases (FMOs).

Both the parent compound and total radioactivity peaked at approximately 3 hours post-dose in plasma. Moreover, the kinetic profiles of the parent drug and its prominent metabolite M2 were similar from 3 to 12 hours, the last sampling time analysed, suggesting that M2 will not disproportionally accumulate.

Since M2 was approximately 2-fold less active than the parent compound, fedratinib activity is determined mainly by fedratinib parent. When adjusted for reduced potency, metabolite M2 is estimated to contribute less than 5% to this activity.

Fedratinib is mainly (approximately 77%) excreted via the faeces, and to a low extend (5%) via urine. Unchanged drug was the major component in excreta, accounting on average for approximately 23% and 3% of the dose in faeces and urine, respectively. In addition, in faeces, 19 fedratinib metabolites were detected, each accounting for 10% of the dose or lower.

The popPK estimated apparent Cl is 13 L/h for a typical MF patient with a median creatinine clearance of 78.3 mL/min. The fedratinib $t_{1/2}$ estimated from popPK Study FEDR-MPK-001 is 114 h. The long terminal half-life indicates slower redistribution and subsequent elimination of fedratinib from peripheral tissue.

Consequences of possible genetic polymorphism. Fedratinib is metabolised by CYP3A4 and CYP2C19. Both enzymes are known to harbour potentially relevant functional polymorphic forms. In the provided PG investigations PMH0143 in healthy subjects and PMH0144 in MF patients, no relationship was observed between fedratinib AUC and C_{max} in relation to *CYP2C19* genotype. However, an apparent relationship was noted between *CYP3A4* gene and fedratinib exposure. I.e., for one variant (*CYP3A4_rs2740574* (*CYP3A4*3*)), fedratinib exposure appeared to be decreased, whereas for another variant (*CYP3A4_rs2740574* (*CYP3A4*1B*)) fedratinib exposure appeared to be increased. These results should be considered with caution, due to the low numbers of subjects. For *CYP2C19*, it was also investigated if a relationship exists in this dataset between genotype-predicted metabolising phenotype (poor metaboliser (PM), intermediate metaboliser (IM), extensive metaboliser (EM), ultrarapid metaboliser (UM)) for *CYP2C19, CYP2C9, CYP2D6, NAT1* and *NAT2* genes and fedratinib C_{max} and AUC_{inf}. In both PG studies, no such relationship was apparent.

Dose proportionality and time dependencies

In healthy subjects, a more than dose-proportional increase in AUC and C_{max} is observed between single doses of 10 to 680 mg. In MF patients, in the clinically relevant dose range of 100 mg or greater, and more specifically, the 300 mg to 500 mg dose range, PK following single and multiple doses was approximately dose proportional.

Time-dependency. After repeated QD oral fedratinib doses in MF patients, steady state appeared to have been achieved by Cycle 1 Day 15, with approximately 2-3-fold accumulation of $AUC_{0\text{-}24h}$ and C_{max} at the 400 mg QD dose level. Based on *in vitro* results, fedratinib administration results in autoinhibition of CYP3A4 and CYP2C19, and autoinduction of CYP3A4, which may lead to time-dependent changes in fedratinib PK.

The total intersubject variability of PK parameters in PV and MF/ET patients is moderate to large, with a %CV of >50%. The total intrasubject variability of PK parameters in PV and MF/ET patients, based on PopPK appears moderate to large, with a %CV of approximately 30%.

PK in the target population

For patients included in the proposed indication (MF, post ET-MF and post PV-MF) no apparent differences in fedratinib exposure are apparent. PV patients have been observed to have 30% lower fedratinib exposure. Further, the applicant provided a comparison of the single dose AUC_{inf} and C_{max} in healthy subjects and the steady state AUC_T and C_{max} in patients. Fedratinib AUC_T in patients appeared higher than AUC_{inf} in healthy subjects.

Special populations

Impaired renal function. In renal impairment Study POP13449, as compared to matched subjects with normal renal function, fedratinib C_{max} and AUC_{inf} increased by 1.4-fold and 1.5-fold, respectively, in subjects with moderate renal impairment, and by 1.8-fold and 1.9-fold, respectively, in subjects with severe renal impairment following a single 300 mg dose of fedratinib. Creatinine clearance was identified as a significant covariate on CL/F of fedratinib in the final PopPK model in Study FEDR-MPK-

001, and an effect or renal impairment on fedratinib exposure was observed: in MF patients with mild (60 ≤ CLcr < 90 mL/min) and moderate renal impairment (30 ≤ CLcr < 60 mL/min) had 10% and 37% increases in fedratinib plasma AUC exposure, respectively.

Impaired hepatic function. After a 300 mg single dose administration in hepatic impairment study POP13450, fedratinib exposure (total and unbound C_{max} and AUC) in the subjects with mild hepatic impairment (Child-Pugh total score from 5 to 6) was not appreciably different from those observed in subjects with normal hepatic function. Hepatic function parameters like albumin, ALT, AST and NCI ODWG liver function classification were not significant covariates in the popPK analysis FEDR-MPK-001. No clinically meaningful effect on the pharmacokinetics of fedratinib was observed with regards to mild hepatic impairment (defined as total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 1.5 times ULN and any AST increase) or moderate hepatic impairment (defined as total bilirubin > 1.5 to 3 times ULN and any AST). Further, in patients receiving fedratinib, the frequencies and distributions of TEAEs were generally similar across baseline hepatic functions (normal hepatic function, n=126; mild/moderate impairment, n=66) in the pivotal study EFC12153.

Gender, race, weight. In popPK analysis FEDR-MPK-001, gender and race were not a statistically significant covariates affecting fedratinib PK exposure. In the popPK model, weight was a significant covariate, affecting V2/F. The large volume of distribution of fedratinib suggests that fedratinib may be distributed by diffusion into the extracellular fluids, the volume of which increases with body weight; thus, the estimated increases in the central volume of distribution of fedratinib with increased body weight are consistent with the physiological effects of weight. Within the 40 to 135 kg weight range, the maximum change as compared to a typical patient of 70.1 kg, was less than 30%.

Age. In the popPK model, age (20-95 years) was not a significant covariate affecting fedratinib PK exposure. The number of patients that was included per age category is indicated in the Table 11. A waiver for the conduct of paediatric studies was granted by EMA (EMA Decision P/0261/2012). No paediatric patients have therefore been included in the provided clinical studies.

Table 11: Number of elderly patients included in the population PK analysis

	Age 65-74 (Older subjects number/total number)	**Age 75-84 (Older subjects number/total number)**	**Age 85+ (Older subjects number/total number)**
Population PK analysis	170/452	54/452	4/452

PK = pharmacokinetic

Pharmacokinetic interaction studies

Based on the *in vitro* data, fedratinib levels could potentially be increased when co-administered with drugs that are inhibitors of CYP3A. Indeed, in the presence of ketoconazole (a strong CYP3A4 inhibitor) in *in vivo* DDI Study INT12893, an approximately 3-fold increase in fedratinib exposure following a single 300 mg dose of fedratinib was noted.

The results of the PBPK simulation Study FEDR-DMPK-2852 may indicate that, probably due to the long $t_{1/2}$ of 114 h, the effect of strong inhibition of CYP3A4 is maintained relatively long after stopping the co-administration of a strong CYP3A4 inhibitor.

Based on the results from the *in vivo* ketoconazole Study INT12893 and the PBPK Study FEDR-DMPK-2852 simulations, agents that increase fedratinib plasma concentrations (i.e., strong CYP3A4 inhibitors) need to be used with caution and the fedratinib dose needs to be initially reduced to 200 mg QD with strong CYP3A4 inhibitors. Further, the PBPK simulations indicate that DDI with mild and moderate inhibitors of CYP3A4 are less severe than observed with strong inhibitors of CYP3A4.

Fedratinib is a substrate for P-gp, but not for BCRP, BSEP, MRP2, OAT-, OATP-, OCT- and MATE-type transporters. The applicant concludes that no significant effects on fedratinib PK are expected upon inhibition of P-gp.

In vivo DDI study FEDR-CP-002, investigating the effect of co-administration of the potent CYP3A4 inducer rifampicin and the moderate CYP3A4 inducer efavirenz on fedratinib exposure was provided during the procedure. The study was conducted in an appropriate manner, and showed that fedratinib exposures when co-administered with the strong CYP3A4 inducer rifampin were 19.5% and 30.2%, for AUC_{∞} and C_{max}, respectively, of that when administered alone. Further, fedratinib exposures when co-administered with the moderate CYP3A4 inducer efavirenz were 53.2% and 71.5%, for AUC_{∞} and C_{max}, respectively, of that when administered alone.

Fedratinib is an inhibitor of multiple CYP isoforms (2D6, 2C8, 2C9 and 3A4), but with relatively high IC_{50} values ≥10 µM *in vitro*. With a free fedratinib C_{max} of 0.16 µM, no *in vivo* interaction via these enzymes is to be expected. Further, fedratinib is a mechanism-based inhibitor of CYP2C19 and CYP3A4, and also inhibits several transporters with IC_{50} values ≤ 10 µM *in vitro*. Considering the expected luminal fedratinib concentration of approximately 300 µM, it is expected that P-gp is saturated (*in vitro* at a concentration of 40 µM), and the effect of inhibition of P-glycoprotein on fedratinib exposure is expected to be small. Based on *in vivo* data from the cocktail DDI Study INT12497, concomitant administration of fedratinib with the CYP3A4 substrate midazolam, the CYP2C19 substrate omeprazole, and the CYP2D6 substrate metoprolol, increases midazolam, omeprazole, and metoprolol AUC_{inf} by 3.8-, 2.8-, 1.8-fold respectively. Dose modifications of CYP3A4, CYP2C19, or CYP2D6 substrate drugs should be considered based on these results, with close monitoring of safety and efficacy.

Fedratinib did not induce CYP1A2 and CYP2B6 (based on enzyme activity and gene expression). Fedratinib exhibited a concentration-dependent increase in CYP3A4 gene expression for all donors but did not induce CYP3A4 enzymatic activity. This net decrease in CYP3A4 enzymatic activity in the presence of an increase in CYP3A4 gene expression is likely the result of the observed time-dependent inhibitory effect of fedratinib on CYP3A4.

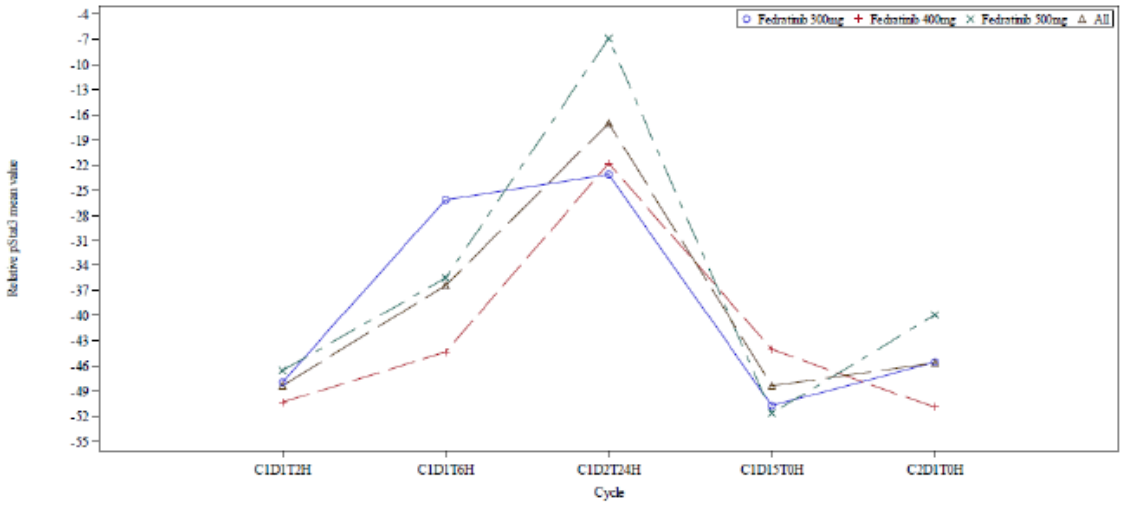
2.4.3. Pharmacodynamics

Mechanism of action

Fedratinib is an oral kinase inhibitor with activity against wild type and mutationally activated Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). Fedratinib is a JAK2-selective inhibitor with higher potency for JAK2 over family members JAK1, JAK3 and TYK2.

Primary and Secondary pharmacology

In patients, the pharmacodynamics (PD) effects of fedratinib were measured by inhibition of substrate (STAT3) phosphorylation in the JAK-STAT signal transduction pathway (phase 2 study ARD11936), changes in the expression of circulating proteins (CPs) (phase 2 study ARD11936, phase 1 study TED12037/ TED12015), and by changes in JAK2V617F allele burden (phase 1 study TED12037/ TED12015, phase 2 study ARD11936, phase 3 study EFC12153). Fedratinib showed a time-dependent, but not dose-related inhibition of STAT3 phosphorylation in all treatment groups (300 mg, 400 mg, 500 mg) at 2 hours post-dose on Cycle 1 Day 1.



Fedratinib 300mg	7	7	7	6	7
Fedratinib 400mg	10	10	10	10	10
Fedratinib 500mg	9	9	9	9	9
All	26	26	26	25	26

C = cycle; D = day; H = hour; ITT = intent-to-treat; STAT3 = signal transducer and activator of transcription 3.
Source: Report ARD11936 Figure 16.

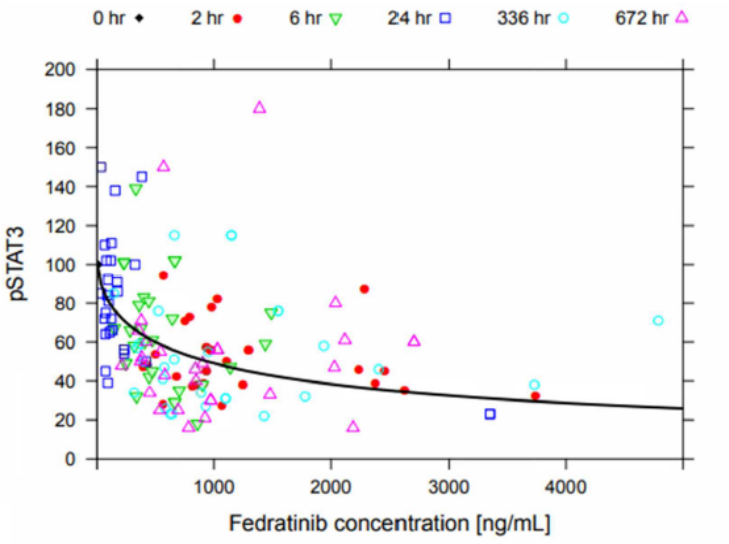
Figure 5: Mean percent changes (%) in pSTAT3 relative to baseline in myelofibrosis patients receiving fedratinib – (ITT Population) (study ARD11936)

Further, several immune/inflammatory cytokines were downregulated, including amongst IL-1, IL-6, and TNF-a. An effect (reduction) on JAK2V617F mutant allele burden was shown in the phase 1 study TED12037; in patients who completed at least 6 cycles of therapy and who had baseline allele burden values > 20% (range 23%-100%, n = 20), 45% had a ≥ 50% reduction in JAK2V617F allele burden in granulocytes at the end of Cycle 6 relative to the baseline. This was maintained during longer follow-up (up to cycle 48) in the extension part (study TED12015). However, an effect on allele burden was not shown in study ARD11936 and study EFC12153. The relationship of pSTAT3 and fedratinib plasma concentrations was described by an inhibitory Emax model (see table below) and is graphically shown in the Figure below.

Table 12: PK/PD relationship of pSTAT3 (% remaining of baseline) and fedratinib plasma concentration following repeated doses of fedratinib of 300 mg, 400 mg, and 500 mg (study ARD11936)

Parameter	Maximum Effect	Mean	RSE (%)
E_{max}	Maximum Effect	1 (fix)	NA
EC_{50} (ng/mL)	Fedratinib concentration producing half maximal effect	915	29.3
$pSTAT_0$	pSTAT3 at baseline	101	0.73
Hill	Hill coefficient	0.628	18.2
ω_{EC50}	Interindividual variability of EC_{50}	128%	46.0

EC_{50} = half maximal effective concentration; E_{max} = maximum effect; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; pSTAT = phosphorylated signal transducer and activator of transcription; RSE = relative standard error.
Source: Report ARD11936 Table 38.



hr= hour; PD = pharmacodynamics; PK = pharmacokinetics; pSTAT3 = phosphorylated STAT3.
Note: Symbol is observed pSTAT3 and solid line represents model prediction.
Source: Report ARD11936 Figure 15.

Figure 6: PK/PD relationship of pSTAT3 (% remaining of baseline) and fedratinib plasma concentration following repeated doses of fedratinib of 300 mg, 400 mg, and 500 mg (study ARD11936)

There are no data on inhibition of STAT3 phosphorylation in patients previously treated with ruxolitinib.

Secondary Pharmacology

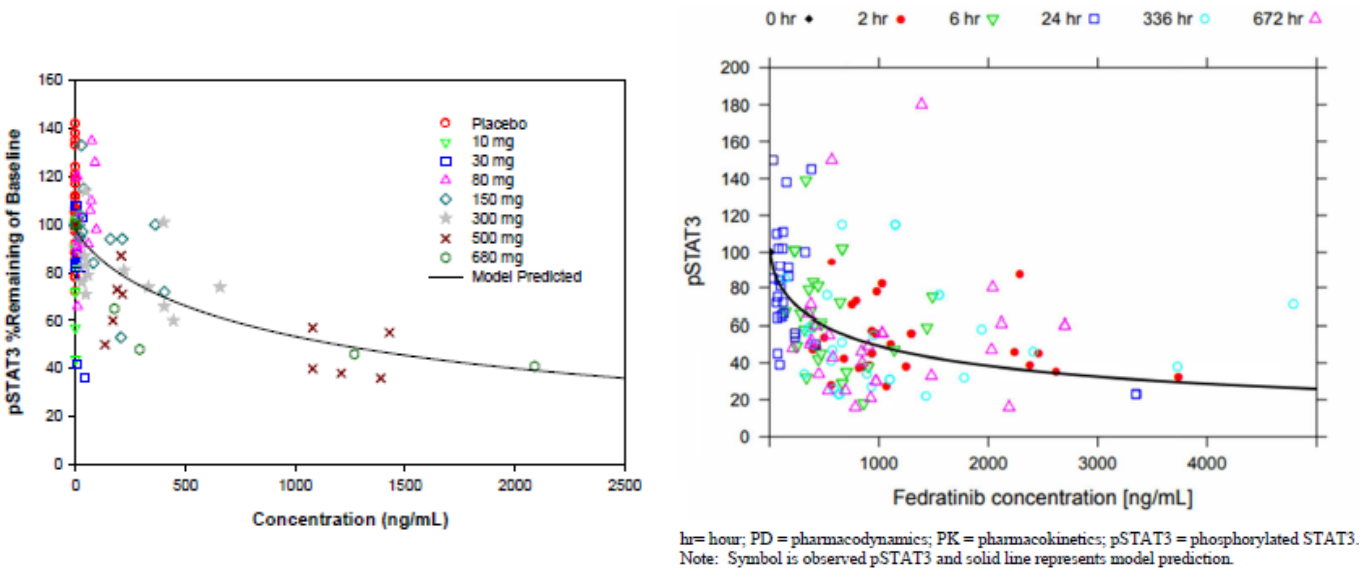
Effect on corrected QT interval (QTc)

The effect of fedratinib on ventricular repolarisation was studied in a phase 1 study in solid malignancies with patients receiving a 500 mg dose (study TES13519). A total of 59 subjects received placebo (5 capsules) on Day 1 and fedratinib 500 mg (5 ×100 mg capsules) QD for 14 days (Days 2 to 15). There was no significant effect on QTc using Fridericia's formule (QTcF) following fedratinib treatment in cancer subjects. The estimated largest time-matched mean difference (LTMMD) for the QTcF interval, observed at T4H, was 4.32 msec (90% CI: 1.16; 7.49). The upper bound of the 2-sided 90% CI was lower than 10 msec. Supportive information was provided by a secondary analysis; the

mean difference estimate at t_{max} vs placebo was -2.54 msec (90% CI: -5.93, 0.84). No subjects had an increase in QTcF, QTcB or QTcN > 60 msec. There were no notable changes during fedratinib treatment in safety 12-lead electrocardiogram (ECG), rhythm and conduction analysis or vital signs.

Pharmacokinetic-pharmacodynamic analyses of pSTAT3

Overall, there was a clear trend observed for a fedratinib concentration dependent inhibition of pSTAT3 levels in whole blood leukocytes, both in healthy subjects and MF patients. The estimated EC_{50} in the various studies are generally around 1000 ng/ml, a concentration that appears to be reached at fedratinib doses of 300 mg and higher (see also figure below).



hr= hour; PD = pharmacodynamics; PK = pharmacokinetics; pSTAT3 = phosphorylated STAT3.
Note: Symbol is observed pSTAT3 and solid line represents model prediction.

(a) (b)

Figure 7: PK/PD relationship of pSTAT3 and fedratinib plasma concentration following a) following a single-dose in healthy subjects (Study TDU12620) and b) repeated doses of fedratinib of 300, 400, and 500 mg in in patients with MF (Study ARD11936)

Exposure-efficacy analyses

With respect to exposure-efficacy relationships, significant relationships were established between the cumulative AUC from cycle 1 to cycle 6 (AUC_{C1-C6}) and percent change in spleen volume at the end of cycle 6, spleen volume response rate (RR, percentage of patients with >35% reduction at the end of cycle 6), and total symptom score response (TSSR).

Results for Spleen volume are shown in figure and table below:

Table 13: Predicted percent change of spleen volume from linear regression model(Study FEDR-MPK-002)

Dose (mg)	Mean $logAUC_{C1-C6}$	Δ (Mean $logAUC_{C1-C6}$)	Δ (% spleen volume change)
300	14.99062	-	-
400	15.36874	0.37812	-3.86
500	15.52616	0.15742	-1.61

AUC = area under the concentration-time curve; C1-C6 = Cycle 1 to Cycle 6.

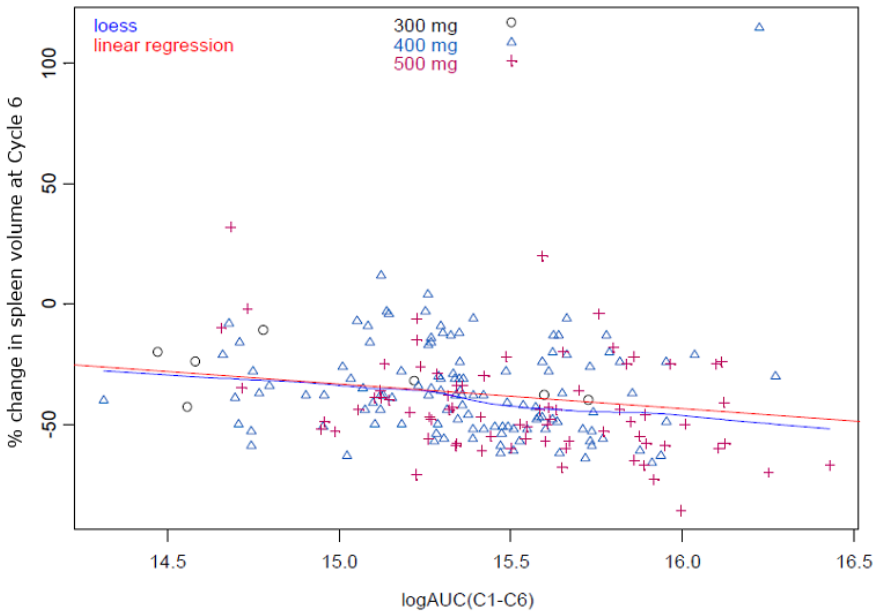
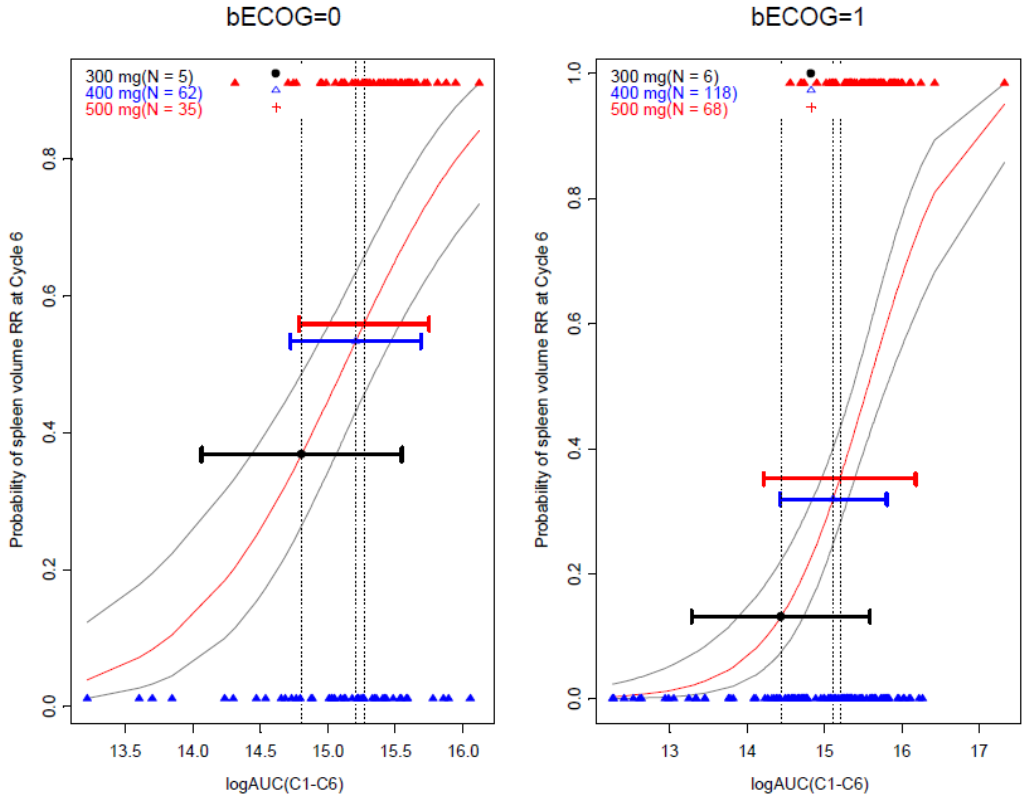


Figure 8: Local weighted scatterplot smoothing and fitting curve from linear regression of percent change in spleen volume at cycle 6 versus logAUC$_{C1-C6}$ (Study FEDR-MPK-002)

Results for spleen volume response rate are shown in figure and table below:



bECOG = baseline Eastern Cooperative Oncology Group; ECOG = Eastern Cooperative Oncology Group; logAUC$_{(C1-C6)}$ = log-transformed area under the curve from the start of Cycle 1 to the end of Cycle 6; RR = response rate.
The red line is the fitted line and the two gray lines are the 95% confidence band. The three vertical dotted lines represent the mean logAUC$_{C1-C6}$ (taking into account dose reduction and dose interruption) for 300 mg, 400 mg, and 500 mg dose. The three horizontal error bars represent observed means and standard deviations of logAUC$_{C1-C6}$ (taking into account dose reduction and dose interruption). Red triangles represent responders and blue triangles represent non-responders.

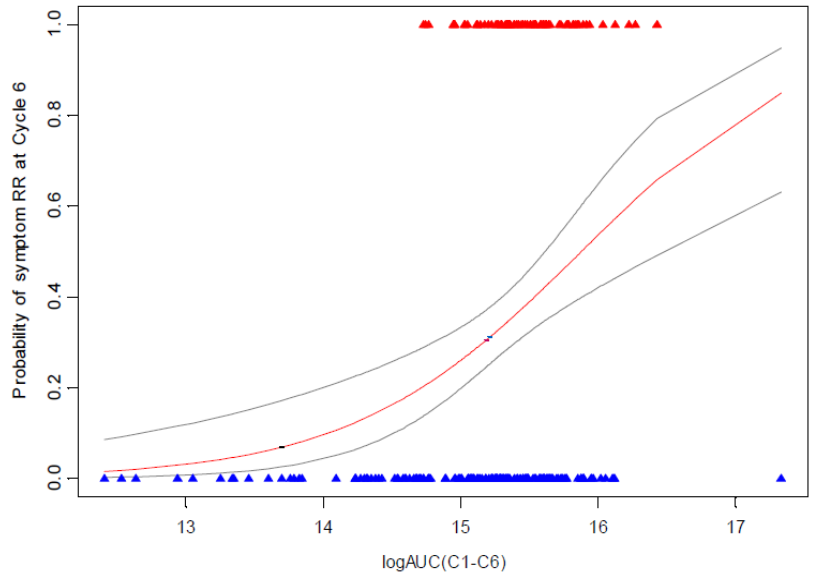
Figure 9: Logistic model of spleen volume response rate (RR) at cycle 6 versus logAUC$_{C1-C6}$ at cycle 6 by baseline ECOG status (Study FEDR-MPK-002)

Table 14: Predicted odds ratio of spleen volume response rate (RR) of 400 mg versus 300 mg and 500 mg versus 400 mg, from logistic regression (Study FEDR-MPK-002)

Dose (mg)	Mean $logAUC_{C1-C6}$	Δ (Mean $logAUC_{C1-C6}$)	Odds Ratio
300	14.607	-	-
400	15.148	0.541	2.48
500	15.225	0.077	1.14

$logAUC_{C1-C6}$ = log-transformed area under the curve from the start of Cycle 1 to the end of Cycle 6.

Results for *total symptom score response (TSSR)*are shown in figure and table below:



logAUC(C1-C6) = log-transformed area under the curve from the start of Cycle 1 to the end of Cycle 6; TSSR = total symptom score response
The red line is the fitted line and the two gray lines are the 95% confidence band. Red triangles represent responders and blue triangles represent non-responders.

Figure 10: Logistic model of total symptom score response (TSSR) at cycle 6 versus cumulative $logAUC_{C1-C6}$ at cycle 6 (Study FEDR-MPK-002)

Table 15: Predicted odds ratio of total symptom score response (TSSR) of 400 mg versus 300 mg and 500 mg versus 400 mg, from logistic regression analysis (Study FEDR-MPK-002)

Dose (mg)	Mean $logAUC_{C1-C6}$ (log (ng·h/mL))	Δ (Mean $logAUC_{C1-C6}$) (log (ng·h/mL))	Odds Ratio
300	14.607	-	-
400	15.148	0.541	1.90
500	15.225	0.077	1.10

$logAUC_{C1-C6}$ = log-transformed area under the curve from the start of Cycle 1 to the end of Cycle 6

In general, the increase in effect on these efficacy parameters going from the 400 to the 500 mg dose is limited. This may be attributable to the dose reductions and dose interruptions, resulting in significantly overlapping cumulative AUC_{C1-C6} for the 400 mg and 500 mg dose cohorts.

Exposure-safety analyses

PK-PD analysis Study FEDR-MPK-002 was conducted using fedratinib PK exposures and safety data from Phase 3 Study EFC12153 and Phase 2 studies ARD11936, ARD12888, ARD12181, and ARD12042.

ER models were developed to characterize the relationships between fedratinib exposure and various safety endpoints in patients with MF, PV or ET. The PK exposure parameter of the fedratinib steady state $AUC_{0\text{-}24,ss}$ at the nominal starting dose was used for exposure-safety analysis since the safety endpoints were based on the worst values across all Cycles from Cycle 1 to Cycle 6.

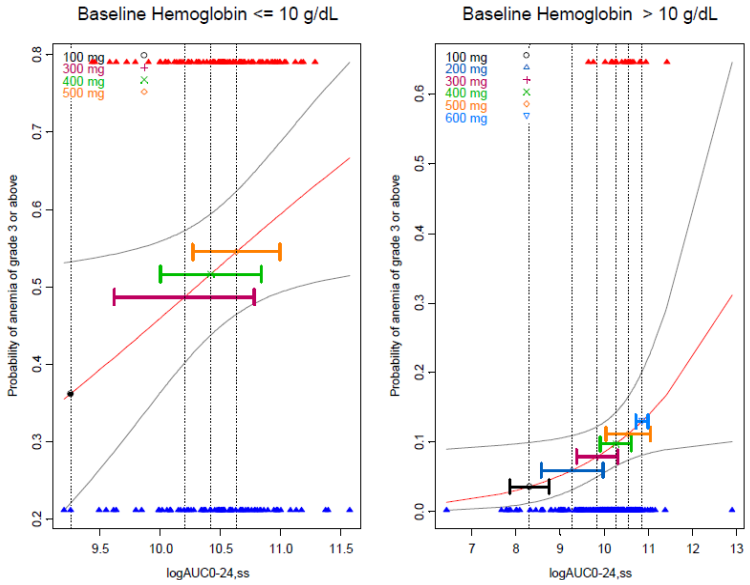
The safety endpoints analysed were:

- Anaemia of Grade 3 or above (worst across Cycles 1-6)
- Thrombocytopenia of Grade 3 or above (worst across Cycles 1-6)
- Nausea and vomiting of any grade (worst across Cycles 1-6)
- Diarrhoea of any grade (worst across Cycles 1-6)

The PopPK model developed for fedratinib (Study FEDR-MPK-001*)* was used to estimate the steady state $AUC_{0\text{-}24,ss}$. The log-transformed steady state $AUC_{0\text{-}24,ss}$ ($logAUC_{0\text{-}24,ss}$) at the nominal starting dose was used as the predictor variable for safety endpoints in subsequent ER analyses. A total of 404 subjects, who had both post-hoc estimated PK exposures ($logAUC_{0\text{-}24,ss}$) from the final PopPK model and safety data, were included in the PK-safety relationship analysis.

Anaemia of grade 3 or above

The stepwise logistic model identified both fedratinib exposure and the baseline haemoglobin levels as the significant factors affecting the probability of anaemia of Grade 3 or above. Results are shown in figure and table below:



$logAUC_{0\text{-}24,ss}$ = log-transformed area under the curve from Time 0 to 24 hours post dose at steady state.
The red line is the model predicted probability and the two grey lines are the 95% confidence bands from logistic regression. The six symbols with horizontal error bars represent predicted probability at the observed means (± standard deviations) of $LogAUC_{0\text{-}24,ss}$ at different dose levels. Red triangles represent responders and blue triangles represent non-responders.

Figure 11: Logistic model of probability of anaemia of grade 3 or above versus log $AUC_{0\text{-}24,ss}$ (Study FEDR-MPK-002)

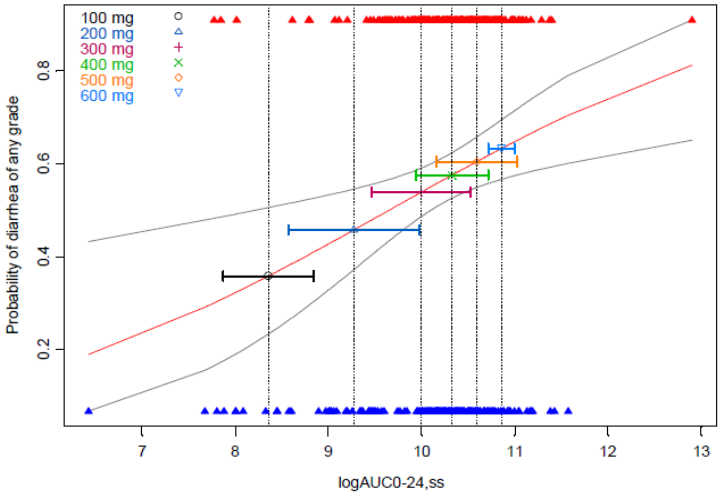
Table 16: Predicted odds ratio from logistic regression of anaemia of grade 3 or above (Study FEDR-MPK-002)

Dose (mg)	Mean $logAUC_{0\text{-}24,ss}$ (log (ng·h/mL))	Δ (Mean $logAUC_{0\text{-}24,ss}$) (log (ng·h/mL))	Odds Ratio
300	10.001	-	-
400	10.328	0.327	1.19
500	10.594	0.266	1.16

$logAUC_{0\text{-}24,ss}$ = log-transformed area under the curve from Time 0 to 24 hours post dose at steady state

Diarrhoea of any grade

Logistic model identified $logAUC_{0\text{-}24,ss}$ as a statistically significant factor affecting the probability of diarrhoea of any grade (p = 0.0039). An increasing trend between $logAUC_{0\text{-}24,ss}$ and probability of diarrhoea of any grade analysis was observed, however the statistical tests indicated a lack of fit. Results are shown in figure and table below:



$logAUC_{0\text{-}24,ss}$ = log-transformed area under the curve from Time 0 to 24 hours post dose at steady state
The red line is the model predicted probability and the two grey lines are the 95% confidence bands from logistic regression. The six symbols with horizontal error bars represent predicted probability at the observed means (± standard deviations) of $LogAUC_{0\text{-}24,ss}$ at different dose levels. Red triangles represent responders and blue triangles represent non-responders.

Figure 12: Logistic model of probability of diarrhoea of any grade versus $logAUC_{0\text{-}24,ss}$ (Study FEDR-MPK-002)

Table 17: Predicted odds ratio from logistic regression of diarrhoea of any grade (Study FEDR-MPK-002)

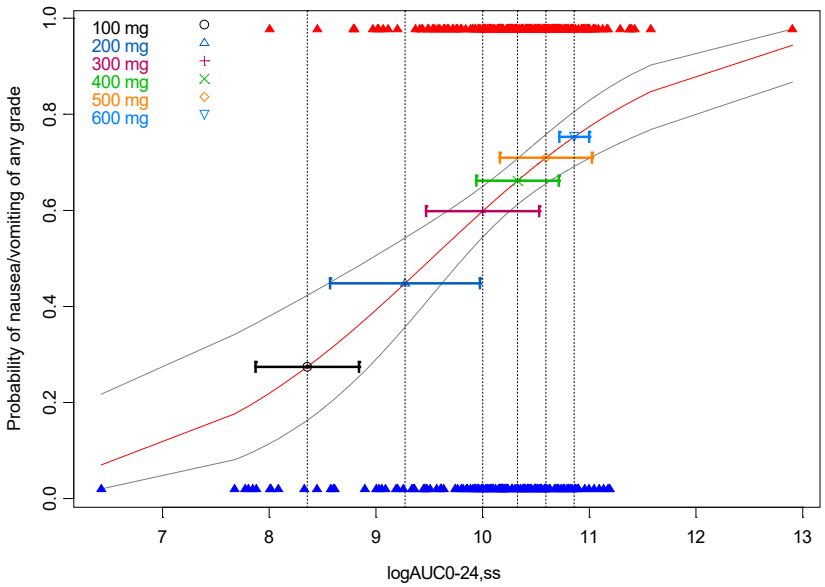
Dose (mg)	Mean $logAUC_{0\text{-}24,ss}$ (log (ng·h/mL))	Δ (Mean $logAUC_{0\text{-}24,ss}$) (log (ng·h/mL))	Odds Ratio
300	10.001	-	-
400	10.328	0.327	1.16
500	10.594	0.266	1.13

$logAUC_{0\text{-}24,ss}$ = log-transformed area under the curve from Time 0 to 24 hours post dose at steady state

Nausea/vomiting of any grade

Logistic regression model identified $logAUC_{0\text{-}24,ss}$ as a statistically significant factor affecting the probability of nausea/vomiting of any grade (p < 0.0001). An increasing trend between $logAUC_{0\text{-}24,ss}$ and probability of nausea/vomiting of any grade was apparent and the statistical tests indicated

adequate goodness-of-fit for the logistic regression model. Results are shown in figure and tables below:



$logAUC_{0\text{-}24,ss}$ = log-transformed area under the curve from Time 0 to 24 hours post dose at steady state.
The red line is the model predicted probability and the two grey lines are the 95% confidence bands from logistic regression. The six symbols with horizontal error bars represent predicted probability at the observed means (± standard deviations) of $LogAUC_{0\text{-}24,ss}$ at different dose levels. Red triangles represent responders and blue triangles represent non-responders.

Figure 13: Logistic model of probability of nausea/vomiting of any grade versus $logAUC_{0\text{-}24,ss}$ (Study FEDR-MPK-002)

Table 18: Odds ratio estimates and confidence intervals of nausea/vomiting of any grade(Study FEDR-MPK-002)

Effect	Unit	Estimate	95% Confidence Interval	
$logAUC_{0\text{-}24,ss}$	1	2.303	1.638	3.239

$logAUC_{0\text{-}24,ss}$ = log-transformed area under the curve from Time 0 to 24 hours post dose at steady state

Table 19: Predicted odds ratio from logistic regression of nausea/vomiting of any grade (Study FEDR-MPK-002)

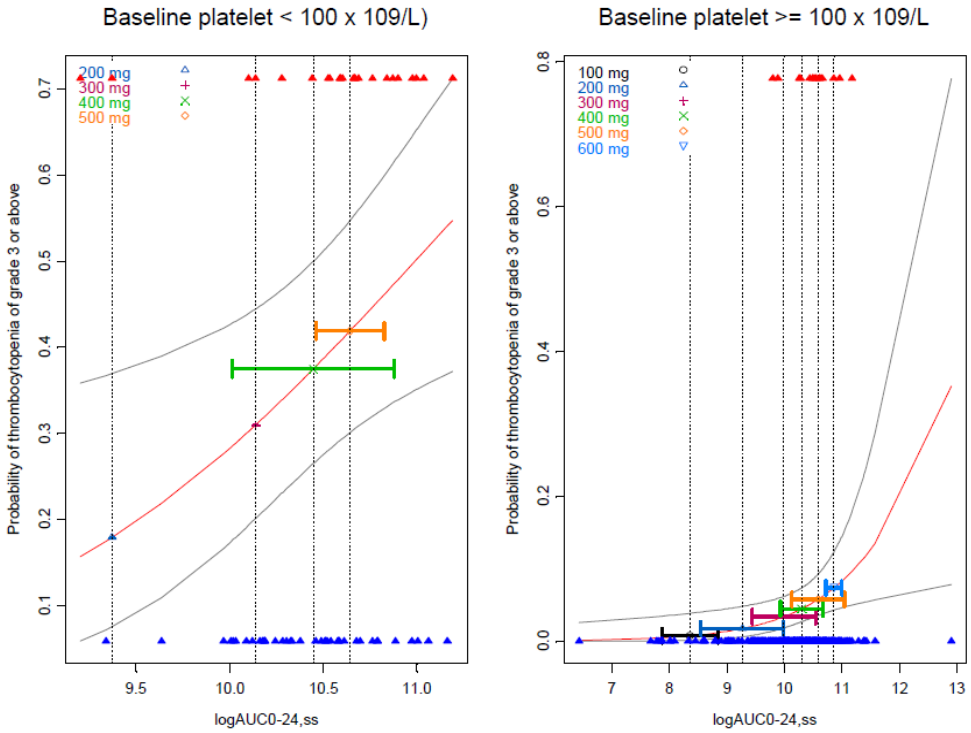
Dose (mg)	Mean $logAUC_{0\text{-}24,ss}$ (log (ng·h/mL))	Δ (Mean $logAUC_{0\text{-}24,ss}$) (log (ng·h/mL))	Odds Ratio
300	10.00	-	-
400	10.33	0.33	1.31
500	10.59	0.27	1.25

$logAUC_{0\text{-}24,ss}$ = log-transformed area under the curve from Time 0 to 24 hours post dose at steady state

Grade 3 and above thrombocytopenia

The stepwise logistic model identified both fedratinib exposure and the baseline platelet count as the significant factors affecting the probability of thrombocytopenia of Grade 3 or above. There was a marginal effect of the fedratinib PK exposure on the probability of thrombocytopenia of Grade 3 or above ($p = 0.03$). An increasing trend between $logAUC_{0\text{-}24,ss}$ and probability of thrombocytopenia of Grade 3 or above was apparent. However, the baseline platelet count was a statistically significant covariate affecting probability of thrombocytopenia of Grade 3 or above ($p < 0.0001$) suggesting that

the baseline disease characteristic of platelet count had outweighed fedratinib exposure to increase probable incidents of thrombocytopenia of Grade 3 or above. Results are shown in figure and table below:



$logAUC_{0\text{-}24,ss}$ = log-transformed area under the curve from Time 0 to 24 hours post dose at steady state.
The red line is the model predicted probability and the two gray lines are the 95% confidence bands from logistic regression. The six symbols with horizontal error bars represent predicted probability at the observed means (± standard deviations) of $LogAUC_{0\text{-}24,ss}$ at different dose levels. Red triangles represent responders and blue triangles represent non-responders.

Figure 14: Logistic model of probability of thrombocytopenia of grade 3 or above versus $logAUC_{0\text{-}24,ss}$ (Study FEDR-MPK-002)

Table 20: Predicted odds ratio from logistic regression of thrombocytopenia of grade 3 or above (Study FEDR-MPK-002)

Dose (mg)	Mean $logAUC_{0\text{-}24,ss}$ (log (ng·h/mL))	Δ (Mean $logAUC_{0\text{-}24,ss}$) (log (ng·h/mL))	Odds Ratio
300	10.001	-	-
400	10.328	0.327	1.36
500	10.594	0.266	1.28

$logAUC_{0\text{-}24,ss}$ = log-transformed area under the curve from Time 0 to 24 hours post dose at steady state

With respect to exposure-safety relationships, increasing fedratinib exposure at steady-state ($AUC_{0\text{-}24,ss}$) appeared to be related with increased anaemia Grade 3 or above, thrombocytopenia of Grade 3 or above, diarrhoea of any grade, and nausea and vomiting of any grade. However, the baseline haemoglobin level (≤ 10g/dl vs >10 g/dl) and the baseline platelet count (< 100 x 10^9 vs ≥ 100 x 10^9/l) appeared to be more important for the occurrence of anaemia or thrombocytopenia than fedratinib exposure.

Wernicke's encephalopathy (WE)

Seven patients with potential Wernicke's encephalopathy (WE) were identified out of 608 patients treated with multiple doses of fedratinib in the clinical programme. These potential cases occurred at the 500 mg QD dose level.

Pharmacokinetic-pharmacodynamic analyses on ECG

Based on a linear mixed-effect model applied to exposure and QTc data from Phase 3 Study EFC12153, there was a weak relationship between the difference from placebo in mean change of QTcF from baseline and fedratinib concentration, with an estimated slope of 0.002 msec/(ng/mL) (95% CI: [0.001, 0.004]). The predicted mean effect for the placebo corrected change from baseline in QTcF at the geometric mean C_{max} at steady state with the 400 mg and 500 mg repeated doses (1804 ng/mL and 2294 ng/mL, respectively) were 4.6 msec (90% CI: [2.4, 6.8]) and 5.7 msec (90% CI: [3.3, 8.2]), respectively (Study EFC12153). This result is considered supportive for the findings in the dedicated QTc Study TES13519, where no clinically meaningful QTcF prolongation induced by fedratinib up to 500 mg/day was noted.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalysis. According to the applicant, the validation of the method(s) and sample analysis were conducted in compliance with the appropriate FDA and EMA regulations in place at the time studies were conducted.

Models. The main outcomes of the pop-PK model are to simulate fedratinib exposures for the exposure-response analysis, and to investigate covariates, the outcome of which affects the SmPC text on special populations. The initial population PK model presented by the applicant did not investigate dose affecting F instead of V2/F, and fedratinib PK time-dependency, although both autoinduction and autoinhibition are present. In order to evaluate a model with dose as a covariate of bioavailability (F) instead of apparent central volume of distribution (V2/F), additional data obtained with such a modified model were provided. AUCs predicted with the original and modified model appeared similar, arguing against a major dose-dependency of the AUC.

Further, no healthy subject PK data were included in the popPK model in Study FEDR-MPK-001. Since exposure in healthy subjects is stated to be lower than in patients and drug-drug interactions may therefore be quantitatively different in healthy subjects and patients, it was requested to optimise the popPK model by including such healthy subject PK data. However, the applicant rightfully argued that instead of via popPK methodology, DDI data from healthy subjects may be translated to patients via PBPK methods.

The 'low QGut' PBPK model FEDR-DMPK-2852 at 300 mg was validated against the situation of a single dose of fedratinib (victim) with and without ketoconazole in healthy subjects. Results demonstrate reasonable performance of the model in both situations. Therefore, the PBPK model is considered sufficiently validated for prediction of effects on 300 mg fedratinib PK of mild to strong CYP3A4 inhibitors. Further simulations were however conducted using a 400 mg dose using the standard baseline PBPK model. The applicant provided a comparison of the DDI predictions using the low QGut and the standard PBPK model. Based on this comparison, it can be concluded that the PBPK based DDI predictions for fedratinib either as victim or perpetrator for the two PBPK models are similar.

The PBPK model is considered not sufficiently validated for prediction of the effects of CYP3A4 inducers, since this is a situation outside the validated range of DDI, and quantitative predictions by this model regarding the effect of such inducers were therefore not included in the SmPC.

PBPK models for midazolam, omeprazole and metoprolol, as substrate/victim for effects of fedratinib (perpetrator), were validated to a limited extend. Since these models have only been used to mimic the data in the *in vivo* cocktail DDI Study INT12497, and no predictions were made based on these models, these will not be further discussed. No data were provided on the method development for

prediction of the effects of inhibition of transporters on fedratinib PK. Therefore, any simulations in this respect are only considered exploratory.

In the exposure-response analysis report, the applicant claims less than dose-dependent cumulative AUC due to dose reduction/interruption, especially at a 500 mg dose. However, the proposed posology (400 mg QD starting dose, downwards titration allowed until 200 mg QD) is not complicated by the uncertainty in dose proportionality. Furthermore, the dose of 500 mg dose, for which the dose proportionality was mainly questioned, is not currently not applied for.

Absorption. The absolute oral bioavailability of fedratinib in mice, rats, dogs, and monkeys ranged between 18% and 37%. No absolute bioavailability study in human was conducted. The applicant states that, since following oral administration of fedratinib to human subjects, 23% of the dose is recovered in faeces as unchanged drug, the absorption is at least 77%. A somewhat lower degree of fedratinib systemic absorption than 77% cannot fully be excluded. However, since PBPK-based DDI predictions in PBPK Study Fedratinib-DMPK-2852 have been conducted assuming a somewhat lower absorption of fedratinib, i.e., 65%, this issue is not pursued further.

Based on indirect comparison of the exposure following administration of 300 or 500 mg fedratinib as capsule and the 200 mg as solution, no major differences in bioavailability between the capsule and the oral solution used in the mass balance Study Bex12257, were observed.

Effect of food. Food-effect Study FED12258, using the 100 mg fedratinib capsules at a final dose of 100 mg and 500 mg was conducted with formulation 1A1 and not with the final formulation 1B1/1C1. Additional information on a food-effect was obtained in Study AL13451, using the 100 mg capsule formulation 1B1. The outcome of this Study ALI13415 is in line with food-interaction data obtained with formulation 1A1 in Study FED12258 and considering the minor differences between formulation 1B1 and commercial formulation 1C1, the food-interaction data obtained in Study ALI13451 are considered valid for the commercial 1C1 formulation as well.

Further, data obtained with the 100 mg capsule formulation in Study ALI13451 under fasting and fed conditions are supportive for the hypothesis that nausea and vomiting occur less frequently when given with food. Overall, the occurrence to the TEAEs nausea and vomiting, especially at higher fedratinib doses under fasting conditions, is acknowledged. Further, although the data indicating less nausea and vomiting under fed conditions are obtained from a limited number of subjects in Study ALI13451, the advice to take fedratinib with food for reasons of tolerance, is accepted.

Consequences of possible genetic polymorphism. Although potential effects of genetic polymorphisms of metabolising enzymes and drug transporters was investigated both in healthy subjects and MF patients, a drawback of the provided PG data regarding *CYP3A4* is that the relative enzymatic activity of *CYP3A4*1B* and **3* is not known (ref https://www.pharmvar.org/gene/CYP3A4), and that data have not been analysed for known functional polymorphisms of *CYP3A4*, i.e., polymorphisms leading to an increased or decreased CYP3A4 activity. The effect of other CYP3A4 variants will be evaluated in Study FEDR-MF-002. Considering the current knowledge from scientific literature on the effect of CYP3A4*22 heterozygous mutation (which is by far the most common encountered situation), resulting in an effect that is comparable to that of a mild to moderate inhibitor of CYP3A4, at this stage it is acceptable to assume that the effect of CYP3A4*22 on fedratinib exposure is not clinically relevant in such patients. In this respect, the information provided on the clinical relevance of the effect of mild and moderate inhibitors of 3A4 on fedratinib exposure is supportive.

Time-dependency The mean accumulation ratios are similar in adult patients with primary MF, post-PV MF or post-ET MF, ranging from 3- to 4-fold. Of note, 30% lower exposures (increased clearance) were observed in PV patients (being different from post-PV MF patients as in the indication) as compared to

primary MF, post-PV MF or post-ET MF patients. In healthy subjects, exposure and accumulation was even lower (increased clearance) than in PV patients.

PK in the target population. Fedratinib AUC_T in patients appeared higher than AUC_{inf} in healthy subjects. DDIs in patients was predicted using exposure data in healthy subjects. By doing so, DDIs related to effects of other medicines on fedratinib (victim) exposure are considered to be estimated in a conservative manner by using exposure data in healthy subjects. In the healthy subject *in vivo* DDI studies investigating fedratinib as perpetrator, the fedratinib doses applied were higher than the 400 mg dose advised in MF patients, i.e., 500 mg or 600 mg. This resulted in fedratinib steady-state exposures comparable to higher than those obtained in patients. Therefore, the outcome of these healthy subject DDI studies are considered applicable for patients as well.

Special populations

Impaired renal function. According to the mass balance Study BEX12257, total radioactivity excreted in urine was 5 % of the dose. However, unexpectedly increase of fedratinib AUC_∞ was 1.9 fold in subjects with severe renal impairment and 1.5 fold in subjects with moderate renal impairment compared to subjects with normal renal function. Exposure was also increased in subjects with mild renal impairment. This increased exposure may be due to increase in alpha1 acid glycoprotein (AAG) levels and resulting reduced unbound fraction in patients with renal impairment.

The applicant argues that the 1.5-fold increased fedratinib exposure in patients with moderate renal impairment is not clinically relevant, based on comparable frequencies and distributions of TEAEs in the pivotal Phase 3 trial EFC12153 (no of patients with normal renal function, n=57; mild/moderate impairment, n=128). This is agreed. However, in the absence of reassuring safety data for patients with severe renal impairment, a 2-fold dose-reduction is proposed for such patients which is acceptable.

Impaired hepatic function. After a 300 mg single dose administration in hepatic impairment study POP13450, fedratinib exposure (total and unbound C_{max} and AUC) in the subjects with mild hepatic impairment (Child-Pugh total score from 5 to 6) was not appreciably different from those observed in subjects with normal hepatic function. Hepatic function parameters like albumin, ALT, AST and NCI ODWG liver function classification were not significant covariates in the popPK analysis FEDR-MPK-001. No clinically meaningful effect on the pharmacokinetics of fedratinib was observed with regard to mild hepatic impairment (defined as total bilirubin $\leq$ ULN and AST > ULN or total bilirubin 1 to 1.5 times ULN and any AST increase) or moderate hepatic impairment (defined as total bilirubin > 1.5 to 3 times ULN and any AST). Further, in patients receiving fedratinib, the frequencies and distributions of TEAEs were generally similar across baseline hepatic functions (normal hepatic function, n=126; mild/moderate impairment, n=66) in the pivotal study EFC12153. Based on lack of significant differences in fedratinib PK in patients with mild and moderate hepatic impairment, as well a safety data from Phase 3 Study EFC12153, no dose adjustment is considered necessary for patients with mild or moderate hepatic impairment. The limited pharmacokinetic data in patients with moderate hepatic impairment has been addressed in the SmPC. In addition, the following warning has been added in section 4.4 of the SmPC: " 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. ALT and AST elevations were generally reversible with dose modifications or permanent treatment discontinuation (see sections 4.2 and 4.8)". At this stage the effect of severe hepatic impairment on fedratinib PK is not clear and a relevant effect cannot be ruled out since the predominant clearance pathway of fedratinib appears to be via hepatic metabolism. The proposal of the applicant that fedratinib should not be used in patients with severe hepatic impairment until data are available in these patients is supported. The results of the currently ongoing study in patients with severe hepatic impairment is awaited.

Gender, race, weight. The number of males (249) and females (203) included in the popPK analysis FEDR-MPK-001 has been indicated in the SmPC section 5.2. Likewise, the number of patients with White (399), Black (7), Asian (44) and Other (2) background included in this popPK analysis has been indicated in the SmPC section 5.2. In the popPK model, the estimated maximum increases in the central volume of distribution of fedratinib with increased body weight within the 40 to 135 kg weight range, as compared to a typical patient of 70.1 kg, was less than 30%. Information on the weight of patients included in the clinical studies, with information that no PK data is available for patients weighing more than 135 kg is provided in the SmPC.

Age. In the popPK model, age (20-95 years) was not a significant covariate affecting fedratinib PK exposure. The number of patients that was included per age category is indicated in the SmPC section 5.2.

Interactions

Effect other drugs on fedratinib PK. In the presence of the potent CYP3A4 inhibitor ketoconazole in *in vivo* DDI Study INT12893, an approximately 3-fold increase in fedratinib exposure following a single 300 mg dose of fedratinib was noted. Based on this *in vivo* DDI study and PBPK results, strong CYP3A4 inhibitors need to be used with caution and the fedratinib dose needs to be initially reduced to 200 mg QD with strong CYP3A4 inhibitors. In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, fedratinib dosage should be increased to 300 mg QD during the first 2 weeks after discontinuation of the CYP3A4 inhibitor, and then to 400 mg QD thereafter as tolerated. Subsequently, additional dose modifications should be made with monitoring of fedratinib related safety and efficacy. If AEs are still not resolved after reducing fedratinib dose, dose interruption of either fedratinib or strong CYP3A4 inhibitors, or alternative therapies that do not strongly inhibit CYP3A4 activity should be considered based on overall benefit/risk for the patient. The proposed dose advice in relation to concomitantly administered strong CYP3A4 is supported and described in section 4.4 of the SmPC. In case of combination of fedratinib with strong CYP3A4 inhibitors, next to dose reduction, a recommendation for more frequent monitoring of haematological parameters and of clinical signs and symptoms of fedratinib-related adverse drug reactions (at least weekly) is indicated in the SmPC.

Results of PBPK simulations indicate that the effect of strong inhibition of CYP3A4 is maintained relatively long after stopping the co-administration of a strong CYP3A4 inhibitor. In comparison with a 'reference' PBPK simulation, using the situation where the fedratinib dose is increased to 400 mg immediately after stopping the co-administration of the strong CYP3A4 inhibitor, the proposed stepwise increase after stopping the strong CYP3A4 inhibitor co-administration (first 2 weeks 300mg OD, then 400 mg fedratinib) yields less increased fedratinib exposure than in case the original 400 mg fedratinib dose is used immediately after stopping the CYP3A4 inhibitor.

The PBPK simulations further indicate that DDI with mild and moderate inhibitors of CYP3A4 are less severe than observed with strong inhibitors of CYP3A4, and the applicant considers no dose-modification appears necessary. Based on efficacy and safety data obtained with a 400 and 500 mg fedratinib, with the 400 mg dose being better tolerated, the applicant proposed an upper limit of the therapeutic margin of fedratinib of 1.25, which is agreed. Therefore, the 20% increased fedratinib exposure obtained following short term inhibition by a moderate CYP3A4 inhibitor is not considered clinically relevant. A safety consideration upon prolonged moderate inhibition of CYP3A4 is included in the SmPC. Since no quantitative dose advice is given for moderate inhibitors of CYP3A4, this part of the paragraph is included in section 4.4 of the SmPC.

An *in vivo* DDI with the dual CYP2C19/3A4 inhibitor fluconazole or upon simultaneous inhibition of CYP3A4 and 2C19 by separate inhibitors cannot be excluded based on the *in vitro* data. Indeed, an interaction was predicted based on a PBPK Study, however, the PBPK model was not validated for CYP2C19. The applicant stated that these potential interactions will be further investigated in dedicated

DDI studies. The submission of these studies is awaited. It is agreed that until data from this DDI study are received, dual CYP2C19 and CYP3A4 inhibitors like fluconazole and fluvoxamine should be avoided in patients receiving fedratinib. At this stage this is indicated both in in section 4.4 and 4.5 of the SmPC. It should however be indicated that not only combined inhibition of CYP2C19 and 3A4 by a single agent is of concern, but also the combination with a single inhibitor of CYP2C19 and a single inhibitor of CYP3A4 at the same time.

The *in vitro* predicted DDI with the strong and moderate CYP3A4 inducers (rifampicin and efavirenz, respectively) were further investigated in a dedicated *in vivo* DDI study. *In vivo* DDI study FEDR-CP-002, investigating the effect of co-administration of the potent CYP3A4 inducer rifampicin and the moderate CYP3A4 inducer efavirenz on fedratinib exposure which was provided during the procedure showed that fedratinib exposures were significantly reduced. Agents strongly or moderately inducing CYP3A4 (e.g., efavirenz, phenytoin, rifampicin), including herbal agents and foods should be avoided in patients receiving fedratinib. Further, information on the potential effect of induction is indicated in sections 4.4 and 4.5 of the SmPC.

Fedratinib has pH-dependent solubility and permeability (highly soluble at low pH, poorly soluble at neutral pH). However, based on *in vivo* DDI Study INT12894 with pantoprazol, fedratinib exposure was not affected to a relevant extent (1.09-fold for C_{max} and 1.15-fold for AUC). The fact that an increase in gastric pH is not expected to have impact on febratinib exposure and no dose adjustment is needed with concomitant administration with these drugs has been indicated in the SmPC.

Effect fedratinib on other drugs. When given in combination with fedratinib, dose modifications of CYP3A4, CYP2C19, or CYP2D6 substrate drugs should be considered, with close monitoring of safety and efficacy. This DDI is indicated in section 4.4 and 4.5 of the SmPC.

It is agreed that based on the *in vitro* data with regards to effects of fedratinib as perpetrator on CYP2C8 and 2C9 substrates, no *in vivo* drug-drug interaction studies are considered necessary. Of note, the outcome of the provided PBPK simulations bear no value to this conclusion, since the PBPK model was not validated for this purpose.

Based on *in vitro* data, an interaction between fedratinib as perpetrator and P-gp, BCRP, MATE1, MATE2-K, OATP1B1, OATP1B3, and OCT2 substrates cannot be excluded, and results of the planned *in vivo* study investigating this possibility is awaited. Of note, the outcome of the provided PBPK simulations bear no value to this conclusion, since the PBPK model was not validated for this purpose. The potential effect of fedratinib *in vivo* on drug transporters is unknown. Based on *in vitro* DDI data such interaction cannot yet be excluded: Results of study FEDR-CP-003 (drug transporter DDI Study) are due by September 2021. Until *in vivo* data are available, caution is advisable for agents that are sensitive substrates of these transporters with narrow therapeutic index.

Pharmacodynamics

The proof of concept for efficacy of fedratinib was shown through non-clinical *in vitro* and *in vivo* experiments, and thereby the mode of action is sufficiently demonstrated. In patients, fedratinib showed a time-dependent, but not dose-related inhibition of STAT3 phosphorylation in all treatment groups (300 mg, 400 mg, 500 mg) at 2 hours post-dose on Cycle 1 Day 1. Further, several immune/inflammatory cytokines were downregulated. These data are supportive for JAK2 inhibition. There are no data on inhibition of STAT3 phosphorylation in patients previously treated with ruxolitinib whereas a 2-3 fold increase in EC50 was observed in case of known resistance mutations in non-clinical studies. It remains uncertain whether the selected dose of fedratinib inhibits STAT3 phosphorylation to the same extent as in JAK inhibitor naïve patients. Nevertheless, clinical data support a beneficial effect of the proposed dose in the pre-treated patients. Data regarding an effect (reduction) on JAK2V617F mutant allele burden are inconclusive as results differed between studies. In

non-clinical studies, mutant allele burden was only reduced at high doses, which are not reached clinically, but complete elimination of mutant alleles was not observed in these studies. It remains unknown whether fedratinib could change the natural history of the disease. There were no reports on drug-drug interactions, however the potential for interactions was limited by the exclusion criteria. Interactions with agents acting through JAK2 signalling (e.g. EPO, G-CSF) may be expected, however the clinical impact remains unknown. The lack of data on concurrent use with haematopoietic growth factors is reflected in section 4.4 and 4.5. Given the lack of data, the statement on the use of G-CSF in case of neutropenia in section 4.2 is followed by a reference to section 4.4 and 4.5 on the lack of data. Further the applicant commits to follow up case reports of interactions with other agents through Janus Associated Kinase 2 (JAK2) signaling and comment on them in the Periodic Safety Update Reports (PSURs). The response to fedratinib appears independent of JAK2 mutation, though data from patients without JAK2 mutation were limited. Other mutations (e.g. in CALR and MPL genes) have been shown to be involved in aberrant JAK2-STAT signalling and response to ruxolitinib was also independent of JAK2 mutation. Additional information will become available from the ongoing FEDR-MF-002 Phase 3 trial.

Fedratinib at a dose of 500 mg did not result in a clinically relevant QTc prolongation in patients with solid tumours.

Exposure-*safety analyses*

Increasing fedratinib exposure at steady-state ($AUC_{0\text{-}24,ss}$) appeared to be related with increased anaemia Grade 3 or above, thrombocytopenia of Grade 3 or above, diarrhoea of any grade, and nausea and vomiting of any grade. However, the baseline haemoglobin level (≤ 10g/dl vs >10 g/dl) and the baseline platelet count (< 100 x 10^9 vs ≥ 100 x 10^9/l) appeared to be more important for the occurrence of anaemia or thrombocytopenia than fedratinib exposure. In the SmPC section 4.4, it is indicated that treatment with fedratinib may cause anaemia and thrombocytopenia, and that complete blood counts should be obtained at baseline, periodically during treatment and as clinically indicated. This is agreed. It is mentioned that patients with low platelet counts (< 100 x 10^9/l) at the start of therapy are more likely to develop thrombocytopenia during treatment and patients with a haemoglobin level below 10.0 g/dl at the start of therapy have a higher risk of developing anaemia Grade 3 or above during treatment compared to patients with a higher baseline haemoglobin level, and more frequent monitoring of haematology parameters and of clinical signs and symptoms of fedratinib-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

The exposure at a 500 mg fedratinib dose in 3 patients with potential Wernicke's encephalopathy were provided. It is agreed that, although the AUCss in these patients with evaluable exposure are higher than the median, no conclusions can be drawn due to the low number of patients. A warning on the potential occurrence of WE is adequately included in SmPC section 4.4.

2.4.5. Conclusions on clinical pharmacology

Overall, the PK and PD of fedratinib has been investigated to a fair extent. The PD is mainly based on non-clinical data and supported by the limited data available in patients. The submitted data adequately support the application.

The potential effect of fedratinib *in vivo* on drug transporters is unknown. Based on *in vitro* DDI data such interaction cannot yet be excluded: Results of study FEDR-CP-003 (drug transporter DDI Study) are due by September 2021.

Additional information on Pharmacodynamics will also become available from the ongoing FEDR-MF-

002 Phase 3 trial which is included as a Cat 3 PASS study in the RMP.

2.5. Clinical efficacy

Table 21: Clinical studies providing efficacy and safety data for fedratinib in myelofibrosis

Study ID First patient enrolled - Last patient completed	**Primary Objective**	**Patient Population**	**Design and Duration** (In all studies treatment could continue until progression or unacceptable toxicity.)	**Primary Endpoint** *(Spleen volume assessed by an independent central review)*	**Number of Subjects and Posology** Placebo used only in EFC12153 (JAKARTA)
EFC12153 (JAKARTA) Dec 2011 – Jun 2014	To evaluate the **efficacy** of daily doses of 400 or 500 mg fedratinib compared with placebo on the spleen volume reduction (SVR) as determined by MRI (or CT scan in subjects with contra-indications for MRI)	Subjects with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF. **JAK Inhibitor Naïve**	Phase 3, Multicentre, Randomised (1:1:1), double blind, placebo controlled, 3-arm, parallel-group At least 6 consecutive 28d cycles (6 months)	Spleen response rate (RR): Defined as the proportion of subjects with ≥35% SVR at End of Cycle 6 as measured by MRI/CT scan relative to baseline A confirmatory MRI/CT was required 4 weeks later.	**289 total** **Placebo:** N = 96 **Fedratinib:** 400 mg/day: N = 96 500 mg/day: N = 97 71 placebo subjects were re-randomised and crossed over to 400 or 500 mg at end Cycle 6 or at time of progression prior to end Cycle 6
ARD12181 (JAKARTA2) Apr 2012 – May 2014	To evaluate the **efficacy** of once daily dose of fedratinib based on the reduction of spleen volume at the end of 6 treatment cycles.	Subjects with intermediate-1 with symptoms, intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF. **Prior Ruxolitinib**	Phase 2, Multicentre, Open-label, Single-arm At least 6 consecutive 28d cycles (24 weeks)	Spleen response rate (RR): Defined as the proportion of subjects with ≥35% SVR at End of Cycle 6 as measured by MRI/CT scan relative to baseline.	**97 total** 400 mg daily Could be titrated in 100-mg increments up to 600 mg/day. *CSR Addendum post-hoc* Cohort 1: N=79 ***** Cohort 1a: N=66 *****
ARD11936 Aug 2011 – May 2014	To evaluate the **efficacy** of daily oral doses of 300, 400, and 500 mg fedratinib for the reduction of spleen volume as	Subjects with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly	Phase 2, Randomised (1:1:1), open-label, dose-ranging study of the efficacy and	Percent change in spleen volume based on MRI/CT at the End of Cycle 3.	**31 total** 300, 400, 500 mg daily: 300 mg/day, N = 10

	determined by MRI (or CT scan in subjects with contraindications for MRI)	**JAK Inhibitor Naïve**	safety of orally administered sar302503 At least 1 cycle;	Post-hoc analysis of spleen RR, defined as the proportion of subjects who had ≥35% SVR at the End of Cycle 3. Spleen RR at end of Cycle 6 was secondary EP.	400 mg/day, N = 10 500 mg/day, N = 11
TED12037 (MFTG101348-001) Feb 2008 - Oct 2009	**1.** To determine the **safety,** tolerability, **DLTs, MTD,** and recommended Phase 2 dose (**RP2D**) of orally administered fedratinib (SAR302503, TG101348) **2.** To assess the **PK** of TG101348. (Secondary objectives were to assess preliminary activity and PD activity.)	Subjects with high-risk or intermediate-risk PMF, post-PV MF, or post-ET MF and with symptomatic splenomegaly and/or unresponsive to available therapy	Phase 1, first-in-human, non-randomised, open-label, multicentre, dose escalation study of fedratinib. Up to 6 consecutive 28-day cycles (168 days) plus follow-up 30 days after last dose of study drug.	*Primary Safety Variables:* DLTs, AEs, laboratory assessments, vital signs assessments, ECG parameters, physical and neurological examinations. *Primary PK Variables:* Plasma concentration of TG101348 and PK parameters	**59 total** 30 to 800 mg daily 30 mg/day, N = 4 60 mg/day, N = 3 120 mg/day, N = 3 240 mg/day, N = 3 360 mg/day, N = 3 520 mg/day, N = 3 680 mg/day, N = 34 800 mg/day, N = 6 Study had 2 phases: - Dose-escalation to determine MTD. - Dose confirmatory evaluating RP2D.
TED12015 (MFTG101348-002) July 2008 - Nov 2012 **CSR Addendum**	To determine the **long-term effects** of continued treatment with fedratinib (SAR302503) on safety, clinical activity, and Pharmacodynamics. Updated key safety data on subjects still ongoing after cut-off date of the initial TED12015	Patients with primary or secondary MF who had stable disease, CI, PR, or CR (per IWG-MRT criteria), and tolerated 6 cycles in study 12037	Phase 1/2 open-label extension to TED12037 Subjects continued at their assigned dose from the prior study, TED12037	Safety, clinical activity, and PD Variables	**43 total** 30 mg/day, N = 3 60 mg/day, N = 3 120 mg/day, N = 2 240 mg/day, N = 2 360 mg/day, N = 3 520 mg/day, N = 2 680 mg/day, N = 25

	CSR and the 11 subjects who entered the Thiamine Supplementation Period.				800 mg/day, N = 3

*****Cohort 1 includes subjects meeting newly defined criteria for relapsed/refractory or intolerant to ruxolitinib.*
*****Cohort 1a is a subgroup of Cohort 1 that includes subjects who had received Cycle 6 of fedratinib treatment or who had discontinued fedratinib for reasons other than "study terminated by sponsor". CSR=clinical study report, MTD: maximal tolerated dose.*

Table 22: Study ARD12042, a dose-ranging study in PV and ET subjects previously treated with hydroxyurea

Study ID	Primary Objective	Patient Population	Design and Duration	Primary Endpoint	Number of Subjects and Posology
ARD12042 First patient enrolled - Last patient completed Oct 2011-May 2014	Evaluate efficacy and safety of fedratinib in patients with PV and ET who were **resistant to or could not tolerate hydroxyurea.**	PV or ET according to the revised WHO criteria and had been resistant to or intolerant of hydroxyurea (per LeukemiaNet consensus criteria).	Phase 2, Multicentre, Randomised (1:1:1) to 100, 200, 400 mg daily, open-label study with a dose ranging phase and dose expansion phase. At completion of randomisation: A 600 mg group of up to 15 ET patients was added. *Dose expansion* (PV): 400 mg/day. Up to 8 consecutive 28-day cycles. (Beyond 8 cycles if the subject was deriving benefit and had no progression or unacceptable toxicity.)	***Dose-Ranging Phase*** **PV:** absence of phlebotomy and a haematocrit < 45% for ≥3 months **ET:** Reducing platelet count to ≤400× 109/L for ≥3 months **ET *Dose-Ranging* (600 mg):** Reducing platelet count to ≤ 400 × 109/L cycle 4 thru cycle 6. **PV: *Dose-Expansion* (400 mg):** absence of phlebotomy cycle 4 thru cycle 6.	**81 total (45 PV, 36 ET)** 100, 200, 400 daily: 100 mg/day, N=23 200 mg/day, N=24 ≥400 mg/day, N=34 *Dose-Ranging Phase* (37 PV, 33 ET) + 3 ET with a starting dose of 600 mg *Dose-Expansion Phase* 8 PV with a starting dose of 400 mg

2.5.1. Dose response studies

Study TED12037 was a phase 1 multicentre, open-label, non-randomised, dose-escalation study, conducted in 2 phases in 59 patients with high-risk or intermediate-risk PMF, post-PV MF, or post-ET MF and with symptomatic splenomegaly and/or unresponsive to available therapy. The dose-escalation

phase was designed to determine the MTD and to evaluate its safety/tolerability, PK, PD, and preliminary clinical activity. The dose confirmation phase was a cohort expansion at or below the MTD (i.e., the RP2D). Doses from 30 mg to 800 mg QD in consecutive 28-day cycles were tested and 680 mg/day (n=31) was determined to be the MTD. Clinical improvement was achieved in 41.8% of subjects (23 of 55) across doses and 48.6% (18 of 37) of subjects in the MTD cohort. The lowest dose at which clinical improvement was observed was 240 mg/day (2 of 3 subjects). At that time, from a safety perspective, doses of ≥ 520 mg resulted in more anemia and increased transfusion requirement, supporting the selection of the 500 mg dose for further study.

Study ARD11936 was a phase 2 open-label dose-ranging study in 31 patients with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly to study efficacy and safety of fedratinib. Doses of 300 mg (n=10), 400 mg (n-10) and 500 mg (n=11) in 28-day cycles were further evaluated. Mean percent change in spleen volume to the End of Cycle 3 based on MRI/CT (primary endpoint) was -30.1%, -33.1%, and -43.3% for 300 mg, 400 mg and 500 mg fedratinib, respectively. The proportion of subjects with spleen RR (defined as ≥ 35% SVR at End of Cycle 3) was 30%, 50%, and 72.7% in the 300 mg, 400 mg, and 500 mg group, respectively (post-hoc analysis). Corresponding results for EOC6 were 60.0% and 63.6% in the 400 mg and 500 mg group, respectively, compared to 30% in the 300 mg group. Effect on symptoms was measured based using the total symptom score (TSS), defined as the sum of the scores for the 6 key MF-related symptoms assessed by the MPN-SAF (myeloproliferative neoplasm symptom assessment form): early satiety, abdominal pain, abdominal discomfort, bone pain, night sweats, and itching (Post-hoc analysis). Symptom response rates of ≥ 50% reduction in TTS at End of Cycle 3 and 6 were 44.4% and 33.3% in the 300 mg group, 40.0% and 60.0% in the 400 mg group, and 37.5% at both time points in the 500 mg group. The most common treatment-emergent adverse events (TEAEs, all grades) in all treatment groups (at least 40% of subjects in each treatment group) were diarrhoea, vomiting, nausea, and anemia. These were also the most common treatment-related TEAEs. No trends were noted in the most frequently reported TEAEs across the treatment groups. Grade 3 or 4 treatment-related TEAEs were reported in more subjects in the 500 mg treatment group (100%) than in the 300 mg or the 400 mg treatment groups (50.0% each). The most common Grade 3 or 4 treatment-related TEAE was anemia. Though numbers were small, efficacy data favored 400 mg and 500 mg over 300 mg fedratinib dose.

Based on these data, both doses were included in the pivotal trial ECF12153 as separate arms. In study ARD12181, the starting dose was 400 mg QD with the option for dose-escalation up to 60 mg QD.

2.5.2. Main studies

Study EFC12153 (JAKARTA): a phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of fedratinib (SAR302503) in patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis with splenomegaly.

Study ARD12181 (JAKARTA2): a phase II, multicentre, open-label, single-arm study of fedratinib (SAR302503) in subjects previously treated with ruxolitinib and with a current diagnosis of intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis.

Methods

Study EFC12153 was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-arm study in subjects with intermediate-2 or high-risk primary MF, post-PV MF, or post-ET MF with

splenomegaly. The study was designed to show the safety and efficacy of fedratinib in MF subjects naïve to JAK inhibitors and studied fedratinib at both 400 mg and 500 mg doses compared to placebo. Patients were initially randomised (1:1:1) to either placebo or fedratinib 400 mg or 500 mg. Eligible subjects in the placebo arm were allowed to cross over to receive treatment with 400 or 500 mg fedratinib (re-randomisation 1:1) after completing 6 cycles of treatment or when a subject experienced progressive disease (PD) prior to completing the first 6 cycles of treatment.

Study ARD12181 was a non-randomised, open-label, single-arm, multicentre study of fedratinib in patients with intermediate-1 with symptoms, intermediate-2 or high-risk PMF, post-PV MF or post-ET MF previously treated with ruxolitinib. The study was designed to evaluate efficacy and safety of fedratinib 400 mg in patients previously treated with ruxolitinib. The study consisted of a Screening Period of up to 28 days, followed by an approximately 6-month Treatment Period (6 cycles of 28 days), and a Follow-up Visit, which was performed approximately 30 days following the last administration of fedratinib. Retrospectively, subjects previously exposed to ruxolitinib were identified that met refractory, relapsed, or intolerant criteria as defined based on recommendations from MF experts and Health Authority feedback.

Though studies were performed in different target populations, in-and exclusion criteria as well as endpoints largely overlap. Therefore, the method section of both studies is combined and where relevant differences for study ARD1281 compared to EFC12153 are presented separately.

Study Participants

In Study EFC12153, eligible subjects were ≥ 18 years of age and were JAK-inhibitor naïve.

In study ARD12181, eligible subjects had had previous ruxolitinib treatment for at least 14 days (exposure of < 14 days was allowed for subjects who discontinued ruxolitinib due to intolerability or allergy) and were classified as resistant or intolerant to ruxolitinib per the investigators' assessments.

Main inclusion criteria:

1. Diagnosis of PMF or post-PV MF or post-ET MF, according to the 2008 World Health Organization (WHO) and IWG-MRT criteria.
2. Myelofibrosis classified as high-risk or intermediate-risk level 2, as defined by modified IWG-MRT criteria (according to Cervantes, 2009) at screening. In study ARD12181, patients with MF classified as intermediate-1 with symptoms, intermediate-2 or high-risk Dynamic International Prognostic Scoring System (DIPSS, Passamonti 2010) were included.
3. Enlarged spleen, palpable at least 5 cm below costal margin
4. Eastern Cooperative Oncology Group (ECOG) PS score of 0-2
5. The following laboratory values within 14 days prior to the initiation of fedratinib or placebo:
    - Absolute neutrophil count (ANC) ≥1.0 x 10^9/L
    - Platelet count ≥50 x 10^9/L
    - Serum creatinine ≤1.5 x upper limit of normal (ULN)
    - Serum amylase and lipase ≤1.5 x ULN

Main exclusion criteria:

1. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2.5 x ULN

2. Total bilirubin (TBL):
    - Exclude if ≥3.0 x ULN.
    - Subjects with TBL between 1.5 to 3.0 x ULN were excluded if the direct bilirubin fraction was ≥25% of the total.
3. Any chemotherapy, immunomodulatory drug therapy (eg, thalidomide, interferon-α), Anagrelide, immunosuppressive therapy, corticosteroids > 10 mg/day prednisone or equivalent, or growth factor treatment (eg, erythropoietin), or hormones (eg, androgens, danazol) within 14 days prior to initiation of fedratinib; darbepoetin use within 28 days prior to initiation of fedratinib. Subjects who had exposure to hydroxyurea in the past could be enrolled in study EFC12153 as long as the hydroxyurea had not been administered within 14 days prior to initiation of fedratinib or placebo. In study ARD12181, hydroxyurea was allowed within 1 day prior to initiation of fedratinib.
4. Concomitant treatment with or use of pharmaceutical or herbal agents known to be moderate or severe inhibitors or inducers of cytochrome P450 3A4 (CYP3A4).

Other exclusions criteria were related to significant comorbidities, amongst others active hepatitis and prior chronic liver disease, prior malignancies (except adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which subject had been disease-free for ≥ 5 years), active acute infection, and certain types of cardiovascular comorbidities.

Treatments

Fedratinib treatment

Fedratinib (400 or 500 mg) was taken orally once daily, at approximately the same time each day, on an outpatient basis for at least 6 consecutive 28-day cycles. The study drug was taken on an empty stomach (i.e. 1 hour before or 2 hours after a meal). Within study ARD12181, the dose could be uptitrated to a maximum of 600 mg daily based on response. Dose reductions or interruptions based on safety were allowed, the lowest dose being 200 mg/day. Subjects continued to receive fedratinib for as long as they showed signs of benefiting from the therapy and had not PD or relapse or unacceptable toxicity requiring discontinuation of study drug.

Placebo treatment (study EFC12153)

Placebo was taken orally once daily, at approximately the same time each day, on an outpatient basis for up to 6 consecutive 28-day cycles. Eligible subjects in the placebo arm were allowed to cross over to receive treatment with either 400 or 500 mg of fedratinib after a second 1:1 randomisation in either of the following 2 scenarios: 1. When a subject had completed the first 6 cycles of treatment and had completed the End-of-Cycle 6 imaging assessments or 2. when a subject had PD **prior** to completing 6 cycles of treatment and continued to meet study entry eligibility criteria.

Transfusions (blood/platelet), as clinically indicated were allowed. Granulocyte growth factors were permitted in study EFC12153, but not in study ARD12181. Other drugs for MF and erythropoietin and darbepoetin were prohibited.

Objectives

The primary objective was to evaluate the effect of fedratinib on the reduction of spleen volume at the end of 6 treatment cycles. Secondary objectives were amongst others effect on MF symptoms, PFS and safety.

Outcomes/endpoints

Primary endpoint: Spleen response rate (RR) defined as the proportion of subjects with ≥35% SVR at the End of Cycle 6 (EOC6) measured by MRI/computed tomography (CT) scan relative to baseline. A confirmatory MRI/CT was required 4 weeks later (not included in study ARD12181). The independent review committee (IRC) reviewed the MRI/CT images in a blinded manner.

Secondary endpoints
Symptom RR: Defined as the proportion of subjects with ≥50% reduction in the total symptom score (TSS) from baseline to the End of Cycle 6. Baseline TSS was the TSS value the week before randomisation or the week before an on-treatment assessment.

TSS: Defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified Myelofibrosis Symptom Assessment Form (MFSAF). *(The 6 symptoms according to the modified MFSAF diary are night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain.)* All 6 key symptom scores were required to calculate a TSS. These symptoms were measured on a scale from 0 (absent) to 10 (worst imaginable, TSS = 60).

Overall survival (OS): Defined as the time interval from the date of randomisation to the date of death due to any cause. In the absence of confirmation of death, OS was censored at the last date the subject was known to be alive.

Progression-free survival (PFS): Defined as the time interval from the date of randomisation to the date of the first investigator-assessed disease progression or the date of death due to any cause, whichever came first. In the absence of PD or death, PFS was censored at the date of the last valid assessment performed.

Spleen RR of ≥25% SVR (RR25) at the End of Cycle 6 and confirmed 4 weeks later. The IRC reviewed the MRI/CT images in a blinded manner.

Spleen RR at End of Cycle 3: Defined as the proportion of subjects who had a ≥ 35% reduction from baseline in spleen volume at the End of Cycle 3 as measured by MRI/CT scan (study ARD12181 only).

Duration of spleen response: Defined as the time from the date of the first response by IRC to the date of subsequent PD by IRC or death, whichever was earlier.

Safety assessment of fedratinib.

Of note, OS and PFS in EFC12153 were not analysed as the required number of 126 events was not reached due to early (follow-up) discontinuation. Endpoints/measurements beyond 6 cycles of treatment were not assessed in study ARD12181 due to early study discontinuation.

Sample size

Study ECF12153: Calculation was based on spleen RR, assuming the RR was 30% in either fedratinib arm and 5% in the placebo arm, 63 subjects per arm would provide 90% power at a 2-sided 2.5% alpha level. Assuming there was about a 15% dropout rate, the RR would be 26% in either fedratinib arm and 4.3% in the placebo arm in the intent-to-treat (ITT) Population. Thus, 75 subjects per study arm (total 225 subjects) were planned to be randomised.

Study ARD12181: Assuming the primary endpoint, spleen RR, was 25%, then 70 evaluable subjects were to provide at least 90% power at a 1-sided 2.5% α-level to test the null hypothesis of ≤ 10% RR. This also provided sufficient power for the subgroup of patients that had not responded to previous ruxolitinib treatment.

Randomisation and Blinding

Study EFC12153: Randomisation and treatment allocation was performed centrally via Interactive Voice Response System (IVRS) to 400 mg fedratinib, 500 mg fedratinib, or placebo treatment in a 1:1:1 ratio. A subject could be randomised by IVRS more than once in the study if they crossed over from placebo to fedratinib. Rerandomisation from placebo to either 400 or 500 mg fedratinib was 1:1.

At the time of rerandomisation, the IVRS system determined which treatment the subject had received in their initial randomisation and either:

1) rerandomised those subjects who had initially been treated with placebo to active drug or

2) assigned subjects who had initially received one of the active doses to their same treatment.

No stratification criteria were applied for these randomisations.

The study was double-blind. Following rerandomisation, treatment with fedratinib was open label; however, the blind for dose level was maintained.

Not applicable for Study ARD12181 which was a single arm, open label uncontrolled study.

Statistical methods

Analysis Populations

Study EFC12153 (JAKARTA) and ARD12181 (JAKARTA2)

- **The Intent-to-treat (ITT) Population** included all randomised subjects (in ARD12181 (JAKARTA2) all enrolled subjects).
- **All Treated (AT) Population:** subjects who took $\geqslant$ 1 dose (even if partial) of study medication.
- **The Symptom Analysis Population (modified MFSAF Population)** included subjects evaluable at baseline for symptom assessment. All analyses using this population were based on the treatment assigned by IVRS. (In study EFC12153 (JAKARTA) ITT subjects).
- **Pharmacokinetics (PK) Population:** subjects who received at least 1 (even partial) **cycle** of study drug (study EFC12153 (JAKARTA) / $\geqslant$ 1 **dose** of study drug (study ARD12181 (JAKARTA2) and had evaluable drug concentration data.

Study EFC12153 (JAKARTA)

- The Evaluable Subjects15 (EP) Population consisted of the subset of the ITT Population with a paired baseline and at least 1 post baseline MRI (CT in case of contraindications for MRI), and who had received a minimum of 50% of the targeted dose for 3 cycles, or who had progressed or died within first 3 treatment cycles. All analyses using this population were based on the treatment actually received.
- The **Bone Marrow Fibrosis Population** included subjects evaluable at baseline and with a post-baseline assessment evaluable according to central review, and who had received a minimum of 50% of the targeted dose for 3 cycles. Subjects evaluable at baseline were those with bone marrow fibrosis Grade > 0 by central review at baseline. All analyses using this population were based on the treatment assigned by IVRS.
- The **PD Population** comprised subjects who received at least 1 full cycle of study drug and who had evaluable PD marker concentration data.

- The **PK/PD-ECG Population** consisted of the subset of the All Treated Population with at least 1 paired ECG and predicted plasma fedratinib concentration data. Data from subjects after rerandomisation were not taken into account.

Study ARD12181 (JAKARTA2)

- **Per-protocol (PP) Population**: treated subjects with evaluable baseline and ≥ 1 postbaseline MRI/CT scan of spleen volume, and no important protocol deviations that could impact the efficacy outcome.
- **Thiamine Supplementation Follow-up Population:** subjects who took ≥ 1 dose of study drug and had at least 1 dose of thiamine during the Follow-up Period.

Safety Populations Study EFC12153 (JAKARTA)

- The All Treated Population was used for analysis of exposure and safety data before crossover. All analyses using this population were based on the treatment actually received. Randomised subjects for whom it was unclear whether they took the study drug were included in the Safety Population as randomised.
- The Crossover Safety Population included all subjects from the placebo arm who crossed over to receive fedratinib. This population was used for analysis of exposure and safety data after the crossover date.

Planned analyses

Study ECF12153:
The ITT Population was the primary analysis population for all efficacy parameters. All analyses using this population were based on the treatment assigned by IVRS.

Primary endpoint (RR): primary analysis was a Chi-square test for each dose vs placebo at 2.5% two-sided alpha, with 97.5%-CI based on normal approximation for each dose to placebo. The primary analysis regarded as non-responders: 1) patients without valid end cycle 6 assessment, 2) patients without a 4-weeks-later confirmation of the end cycle 6 assessment, and 3) patients with PD before end cycle 6. Secondary analyses regarded only 1) and 3) as non-responders. Sensitivity analyses included: the primary analysis but imputing patients without valid end cycle 6 assessment by the last available post-baseline value and requiring 3) to be non-responders.

Secondary endpoint TSS: the primary analysis is as for RR, with subjects with a missing TSS at the end of cycle 6 and patients with disease progression considered non-responders. One secondary analysis imputes the last observation carried forward (progression before end of cycle 6 again regarded as non-response).

Type 1 error was controlled by Bonferroni splitting for the two comparisons of doses vs placebo and within that by fixed sequence testing of: spleen RR ->TSS -> spleen RR using 25% cut-off -> OS -> PFS (the latter two not analysed). No interim analysis was performed.

Study ARD12181 (JAKARTA2)
The Per-protocol (PP) Population was to be used as the primary analysis population (reported in ARD12181 main CSR).
In the ARD12181 CSR Addendum, all analyses were done on the ITT Population (i.e., all subjects enrolled in the study who met the criteria for either R/R or intolerant to ruxolitinib).

NOTE:

Main Clinical Study Report (CSR) for study ARD12181 (JAKARTA2)

Study ARD12181 was initiated shortly after ruxolitinib was approved and at the time, there were no well-established criteria to define resistance or intolerance. Therefore, the original inclusion (protocol Sanofi Aventis) was based on investigators' judgement of relapsed/refractory or intolerant to ruxolitinib. To be eligible for the study, subjects were only required to have been treated with ruxolitinib for 14 days at a minimum.

In the main CSR for study ARD12181 (JAKARTA2), results and analyses are presented according to the investigators' judgement of relapsed/refractory or intolerant.

ARD12181 CSR Addendum,

Patients were also classified retrospectively as relapsed/refractory or intolerant to ruxolitinib according to criteria based on a meeting with MF experts from the United States (US) and European Union (EU) in April 2018 (with applicant Celgene) and these criteria were discussed with regulatory authorities.

The criteria were applied to the baseline information that was prospectively collected in the eCRF and adverse events (AEs) associated with prior ruxolitinib treatment were also collected.

In the ARD12181 CSR Addendum, results and analyses are presented for subjects who were reclassified as R/R or intolerant to ruxolitinib if they met at least one of the following criteria:

Relapsed: < 30% reduction in spleen size (or < 10% reduction in spleen volume) at the end of ruxolitinib treatment compared to baseline after an initial response (as defined below). Subjects must have had treatment with ruxolitinib for ≥ 3 months. Response to ruxolitinib is defined as: ≥ 50% reduction in spleen size for baseline spleen > 10 cm (or ≥ 35% reduction in spleen volume from baseline); non-palpable spleen for baseline spleen between 5 and 10 cm; not eligible for spleen response for baseline spleen < 5 cm.

Refractory: < 30% reduction in spleen size (or < 10% reduction in spleen volume) at the end of ruxolitinib treatment compared to baseline and failure to meet criteria for response (as defined above) during ruxolitinib treatment. Subjects must have had treatment with ruxolitinib for ≥ 3 months.

Intolerant: ruxolitinib treatment for ≥ 28 days complicated by either (i) the development of red blood cell (RBC) transfusion requirement (≥ 2 units/month for 2 months), or (ii) toxicity defined as Grade ≥ 3 AEs of thrombocytopenia, anaemia, haematoma, and/or haemorrhage while on treatment with ruxolitinib.

The subjects who met the above criteria were grouped into the following cohorts (ARD12181 CSR Addendum):

Cohort 1: all subjects who were relapsed/refractory (R/R) or intolerant to ruxolitinib treatment per the above criteria. This cohort includes 79 subjects out of the 97 subjects enrolled in Study ARD12181.

Cohort 1a: a "subgroup" of Cohort 1 that includes 66 of the 79 subjects who were R/R or intolerant to ruxolitinib treatment per the above criteria and who, at the time of the early study termination, either:
1. had received Cycle 6 of fedratinib treatment, OR
2. had discontinued fedratinib treatment before Cycle 6 due to reasons other than "Study terminated by the sponsor" (ie, had discontinued due to an "AE," "Withdrawal of consent," "Investigator decision," or "Progressive disease").

The final Sanofi statistical analysis plan (SAP) (11 JUN 2014) was abbreviated by the early termination of treatment and by the fact that all efficacy assessments were terminated.

- only the primary efficacy endpoint, spleen RR (≥ 35% SVR), and certain secondary endpoints (symptom RR, spleen RR [≥ 35% SVR] at the End of Cycle 3, spleen RR by palpation at End of Cycle 6, and percent change of spleen volume at the End of Cycle 3 and 6) were planned to be analysed, instead of all endpoints listed in the protocol .
- the chi square test for testing whether the primary endpoint was > 10%, was omitted.
- The primary efficacy analysis population was the PP Population. This way the effect in subjects with a baseline and post-baseline measurements could be described using last observation carried forward LOCF.
- Primary endpoint: the LOCF method was planned in the Protocol and Final Sanofi SAP: missing spleen volume at End of Cycle 6 was imputed with the end of cycle 3 (Day 1 Cycle 4) measurement unless a subject had progression before end of cycle 6.
- The symptom response was based on the modified MFSAF: all patients that are treated, have an evaluable baseline assessment of total symptom scores and at least one post-baseline evaluable assessment. Missing data was imputed as 'no event' (note that for the primary endpoint LOCF was used).
- An interim analysis for futility after approximately one-third of subjects were enrolled and completed 3 cycles of fedratinib treatment. If there is insufficient evidence of efficacy and/or unacceptable toxicity, the study would be stopped; this interim report was used for regulatory purposes.

Celgene included additional analyses (Celgene Supportive Statistical Document for the CSR, dated 28 Nov 2018) to address the potential bias that may have resulted from the administrative closure of the fedratinib programme by the former sponsor (Sanofi). These included:

- Addition of Cohort 1 and cohort 1a (Cohort 1a patients had a primary endpoint measurement before the termination of the trial and was intended to provide analyses as if the trial had not terminated early).
- All analyses in the CSR addendum were performed on Cohort 1 and Cohort 1a.
- Primary endpoint will analysed on the ITT set (not only the PP) and missing data for end of cycle 6 will not be imputed by LOCF on the end of cycle 3 value, but will be considered as non-responders (non-responder imputation).
- The secondary endpoints as above in the Sanofi break-off statistical analysis plan were analysed, but with additional analyses: not only on PP, but also on ITT;
  subgroup analyses for spleen RR by current expert criteria for R/R vs intolerant for both end of cycle 3 and 6, spleen reductions / response rate at end of cycle 6 without LOCF imputation
- endpoints additional to the Sanofi break-off statistical analysis were analysed:
  - duration of spleen response, spleen response using a ≥25% threshold, quality of life (QoL) using quality of life questionnaire-core 30 (QLQ-C30). These endpoints were already present in the last Sanofi protocol that was not impacted by early termination (v3, 28 NOV 2012).

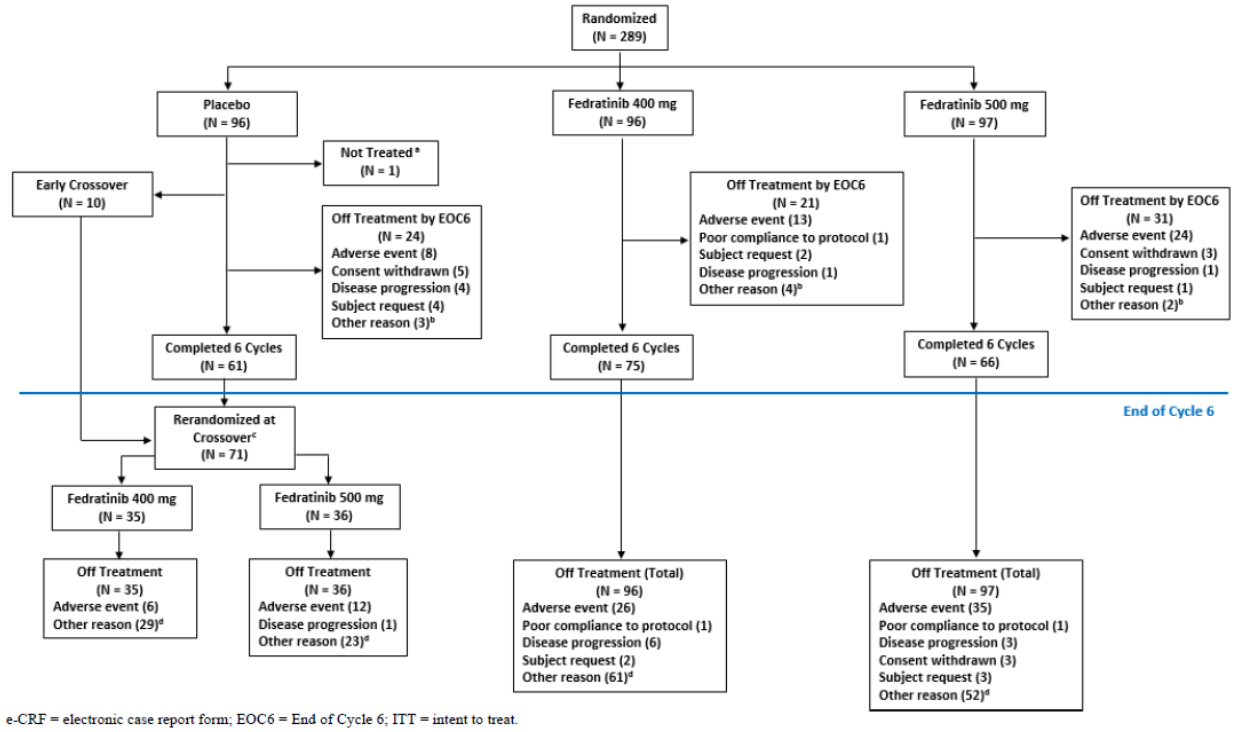
Subgroup analyses

Subgroup analysis of the primary endpoint were performed according to clinically relevant demographic factors and baseline disease/prognosis characteristics.

Study ARD12181: Subgroup analyses by the subgroups R/R vs intolerant based on the investigators' judgements (Sanofi) were also performed. Based on current experts' criteria (Celgene) the latter subgroups were also provided and by baseline platelet count. Both these analyses are without LOCF imputation and on both the ITT and PP set.

Results – Study EFC12153 (JAKARTA)

Participant flow



e-CRF = electronic case report form; EOC6 = End of Cycle 6; ITT = intent to treat.

[a] One subject randomized to placebo died before receiving treatment (Table 14.1.1.2).

[b] See Listing 16.2.1.2 for details regarding the "other reasons" for permanent treatment discontinuation at the EOC6. Note that the 1 subject in the placebo arm who died before receiving treatment is included because the End-of-treatment e-CRF page was completed, and the discontinuation reason was entered as "other reason."

[c] Includes subjects with early crossover and subjects rerandomized after completion of Cycle 6; see Section 9.1.1.1 for details regarding crossover. Three subjects received placebo past Cycle 6 due to rerandomization deviations at the site level (see Table 11 and Section 12.1).

[d] The most common "other reason" for permanent discontinuation after the EOC6 was study termination by Sanofi (see Listing 16.2.1.2 for details).

Note: Details regarding treatment-emergent adverse events leading to permanent treatment discontinuation are provided in Listing 16.2.7.6 (also see Section 12.3.1.3.1).

Sources: Table 14.1.2.2, Table 8, Table 9, and Table 10

Figure 15: Participant flow

Recruitment

Study EFC12153 was performed at 94 active centres in 24 countries in Europe, US, Canada, Brazil, Israel, Australia, Republic of Korea, Russian Federation, Singapore, South Africa, Taiwan.

Randomisation of subjects occurred from 10 Jan 2012 to 24 Sep 2012.

First subject enrolled: 22 Dec 2011. Last subject completed: 25 Jun 2014.

Subject Dispostion

Of 351 subjects screened, 62 subjects were screen failures (i.e. did not meet the eligibility criteria and 289 subjects (ITT population) were randomised in the study:96 to 400 mg; 97 to 500 mg; 96 to placebo (Table 23). One subject randomised to placebo died before receiving treatment. The All Treated Population consisted thus of 288 subjects.

Overall, 71 subjects in the placebo arm were rerandomised: 35 subjects to fedratinib 400 mg and 36 subjects to 500 mg (see Participants' flow above Figure 15). There were 10 subjects with early crossover before the End of Cycle 6 and 61 subjects rerandomised after completion of Cycle 6.

For the 25 placebo subjects who were not rerandomised to fedratinib, the reasons for permanent treatment discontinuation were AE (N=8), PD (ie, not eligible for crossover) N=4), and "other" (N=13).

In the 400 and 500 mg arms, the most common reason for permanent treatment discontinuation was "other reason" (63.5% and 53.6%, respectively), primarily study termination by Sanofi.

The frequency of fedratinib-treated subjects who permanently discontinued treatment due to AEs was lower in the 400 mg arm than in the 500 mg arm (26/96 subjects, 27.1% and 35/97 subjects, 36.1%, respectively).

For permanent discontinuation of treatment due to PD, the frequencies of fedratinib-treated subjects were 6.3% in the 400 mg arm and 3.1% in the 500 mg arm.

At the time of study termination, 144 subjects were still receiving fedratinib:
51/96 subjects randomised to 400 mg, 45/97 subjects randomised to 500 mg, 26 subjects who crossed over from placebo to 400 mg, and 22 subjects who crossed over from placebo to 500 mg.

The last fedratinib administration for this study was on 02 Dec 2013, by which date all 289 subjects had permanently discontinued treatment. The last subject's last visit was on 25 Jun 2014, which includes all available information on the 90-day Thiamine Supplementation Period.

Disposition of Subjects up to 6 Cycles

At the time of study termination, all subjects had either completed the first 6 cycles or had previously permanently discontinued treatment.

Altogether 76 (26.4%) subjects had permanently discontinued treatment before the end of Cycle 6: 21 (21.9%) subjects in the 400 mg arm, 31 (32.0%) subjects in the 500 mg arm, and 24 (25.3%) in the placebo arm (Table 23).

The most frequent reason for permanent treatment discontinuation up to 6 cycles in the fedratinib arms was Adverse Event (71 subjects, 15.6%), the rate being higher in the 500 mg arm (24 subjects, 24.7%) than in the 400 mg arm (13 subjects, 13.5%). In the placebo arm 8 subjects (8.4%) discontinued up to 6 cycles due to adverse events and 10 subjects due to early crossover.

Of the 76 subjects who permanently discontinued treatment by the End of Cycle 6, the majority (52 subjects; 68.4%) discontinued in the first 3 cycles:
25.0% (19/76) in Cycle 1; 22.4% (17/76) in Cycle 2; 21.1% (16/76) in Cycle 3; 11.8% (9/76) in Cycle 4; 9.2% (7/76) in Cycle 5; 10.5% (8/76) in Cycle 6.

The majority of the 45 subjects who permanently discontinued treatment due to an AE up to 6 cycles discontinued during the first 3 cycles:
500 mg arm: 18/24 (75.0%); 400 mg arm: 7/13 (53.8%); Placebo arm: 6/8 (75.0%).

Disposition of Subjects After Crossover

After crossover, the most common reason for permanent treatment discontinuation was "other reason" (82.9% and 63.9%, respectively), primarily study termination by Sanofi.

Permanent treatment discontinuation due to AEs was less frequent in placebo subjects who crossed over to 400 mg than in subjects who crossed over to 500 mg (6 subjects, 17.1% and 12 subjects, 33.3%, respectively) (Table 23). These results are consistent with the pattern of reasons for permanent treatment discontinuation in subjects initially randomised to fedratinib.

Table 23: Subject disposition - Study EFC12153 (ITT Population)

	Placebo [a] (N=96) n (%)	Fedratinib 400 mg (N=96) n (%)	Fedratinib 500 mg (N=97) n (%)
Permanently discontinued treatment up to 6 cycles	**24 (25.3)**	**21 (21.9)**	**31 (32.0)**
Permanently discontinued treatment as initially randomized	**96 (100.0)** [b]	**96 (100.0)**	**97 (100.0)**
Reason for Treatment Discontinuation Before End of Cycle 6			
Adverse event	8 (8.4)	13 (13.5)	24 (24.7)
Poor compliance to protocol	0	1 (1.0)	0
Disease progression	4 (4.2)	1 (1.0)	1 (1.0)
Other reason			
Consent withdrawn	5 (5.3)	0	3 (3.1)
Subject request	4 (4.2)	2 (2.1)	1 (1.0)
Other	3 (3.2)	4 (4.2)	2 (2.1)
Reason for Permanent Treatment Discontinuation			
Rerandomized[c]	71 (74.0)	NA	NA
Early crossover	10 (10.4)	NA	NA
Rerandomized after completion of Cycle 6 (completed placebo period)	61 (63.5)	NA	NA
Adverse event	8 (8.3)	26 (27.1)	35 (36.1)
Poor compliance to protocol	0	1 (1.0)	1 (1.0)
Disease progression	4 (4.2)	6 (6.3)	3 (3.1)
Other reason			
Consent withdrawn	5 (5.2)	0	3 (3.1)
Subject request	4 (4.2)	2 (2.1)	3 (3.1)
Other reason [c]	4 (4.2)[b]	61 (63.5)	52 (53.6)

eCRF = electronic case report form; ITT = intent to treat; NA = not applicable

[a] Placebo subjects are those without crossover.

[b] Note that the subject in the placebo arm who died before receiving treatment is included because the End of treatment e-CRF page was completed, and the discontinuation reason was entered as "other reason."

[c] The most common "other reason" for permanent treatment discontinuation after the End of Cycle 6 was study termination by Sanofi (previous sponsor)

Source: CSR EFC12153 in-text Table 8 and Table 9

	Placebo Crossed Over to	
	400 mg (N = 35) n (%)	500 mg (N = 36) n (%)
Permanently Discontinued Treatment After Crossover	35 (100.0)	36 (100.0)
Reason for Permanent Treatment Discontinuation After Crossover		
Adverse event[a]	6 (17.1)	12 (33.3)
Disease progression	0	1 (2.8)
Other reason[b]	29 (82.9)	23 (63.9)

[a] Details regarding treatment-emergent adverse events leading to permanent treatment discontinuation are provided in Listing 16.2.7.6 (also see Section 12.3.1.3.1).

[b] The most common "other reason" for permanent treatment discontinuation after crossover was study termination by Sanofi; see Listing 16.2.1.2 for additional details regarding the "other reasons."

Note: Only subjects from the placebo arm who crossed over to receive fedratinib 400 or 500 mg are included in this table.

Source: Table 14.1.2.3

Conduct of the study

Protocol Deviations

Important quantitative deviations were those identified from the clinical data available in the clinical database. Overall, 14.5% of all subjects in the ITT Population had ≥ 1 important protocol deviation:

13.5% in the placebo arm, 11.5% in the 400 mg arm, and 18.6% in the 500 mg arm, the most common being a rerandomisation issue. At rerandomisation, to protect the blind, subjects previously randomised to either 400 or 500 mg of fedratinib maintained the same dose level in a blinded fashion and were not permitted to cross over to a different dose level. Thus rerandomisation deviations would have only been expected to have an impact on subjects who received placebo past Cycle 6, which occurred for 3 subjects. As rerandomisation occurred after Cycle 6 (i.e. after assessment of the primary and other key efficacy endpoints) rerandomisation deviations had no impact on the interpretation of data. For 8 (2.8%) subjects, 2 subjects in the placebo arm and 6 subjects in the 500 mg arm, the treatment kit dispensed was not the same as the treatment kit authorised by IVRS.

Important qualitative deviations (i.e. that could not be derived using the clinical data based on the data review and surveillance plan and were identified by Sanofi during conduct of the study) at a minimum included critical audit observations, scientific misconduct, site closures due to noncompliance, and specific reasons for excluding site data in analysis. The most significant of these concerned one subject in the placebo arm who, although PD was shown in Cycle 4, did not crossover to active treatment at that time and another subject, who was initially randomised to the placebo arm, but continued to receive placebo after completing Cycle 6.

Significant GCP Noncompliance

During Study EFC12153, Sanofi observed and addressed significant GCP noncompliance at 2 study sites (one in Hungary and one in the UK). The deviations did not lead to exclusion of subjects from the ITT Population, as it was considered that none would affect the interpretation of the results. At the UK site (4 subjects randomised)/UK: A subject was screened and registered in the IVRS, but informed consent was not obtained due to a miscommunication between site staff. The investigator reported the case, with the corrective and preventive action plan, to the UK central ethics committee and the Research and Development office of the site. At the Hungary site (3 subjects randomised)/Hungary: Following persistent significant GCP noncompliance despite several actions put in place by the monitoring team, Sanofi decided to terminate the trial at this site. The subjects were transferred to another site, and the case was notified to the local ethics committee, the local health authority, and the US Food and Drug Administration. A directed site inspection conducted by the local health authority confirmed the notified significant GCP non-compliance.

Baseline data

Demographic Characteristics

The ITT Population consisted of 58.8% men and 41.2% women; subjects were mostly white (88.9%) and had a median age of 65.0 years (Table 24). The proportion of subjects who were ≤65 years of age was higher in the 400 mg arm (63.5%) compared with the placebo and 500 mg arms (45.8% and 50.5%, respectively). Overall, 9.0% of the ITT Population was older than 75 years. The highest proportion of subjects in each of the 3 treatment arms lived in Western Europe (43.6% overall) and Eastern Europe (26.0% overall) (Table 24). In general, demographic characteristics were well balanced across the 3 treatment arms.

Table 24: Demographics (ITT Population) Study EFC12153

	Placebo (N = 96)	Fedratinib 400 mg (N = 96)	Fedratinib 500 mg (N = 97)	Total (N = 289)
Age (years)				
Mean (SD)	64.9 (9.50)	62.9 (9.63)	64.7 (9.29)	64.2 (9.49)
Median	66.0	63.0	65.0	65.0
Minimum, maximum	27, 85	39, 86	39, 80	27, 86
Age Group, n (%)				
≤ 65 years	44 (45.8)	61 (63.5)	49 (50.5)	154 (53.3)
> 65 years	52 (54.2)	35 (36.5)	48 (49.5)	135 (46.7)
≤ 75 years	90 (93.8)	86 (89.6)	87 (89.7)	263 (91.0)
> 75 years	6 (6.3)	10 (10.4)	10 (10.3)	26 (9.0)
Sex, n (%)				
Male	55 (57.3)	54 (56.3)	61 (62.9)	170 (58.8)
Female	41 (42.7)	42 (43.8)	36 (37.1)	119 (41.2)
Race, n (%)[a]				
White	90 (93.8)	86 (89.6)	81 (83.5)	257 (88.9)
Asian	5 (5.2)	8 (8.3)	14 (14.4)	27 (9.3)
Black	1 (1.0)	1 (1.0)	2 (2.1)	4 (1.4)
Other[b]	0	1 (1.0)	0	1 (0.3)
Weight (kg)				
n	91	94	95	280
Mean (SD)	68.56 (14.450)	69.35 (12.050)	68.08 (12.527)	68.66 (12.996)
Median	66.30	68.95	67.30	67.70
Minimum, maximum	45.2, 115.1	45.0, 102.5	39.5, 100.0	39.5, 115.1
Height (cm)				
n	94	93	96	283
Mean (SD)	167.67 (9.711)	169.32 (9.342)	168.18 (9.479)	168.38 (9.503)
Median	167.25	169.00	169.25	169.00
Minimum, maximum	144.8, 188.0	150.0, 192.0	148.0, 192.0	144.8, 192.0
Region, n (%)[c]				
Western Europe	50 (52.1)	36 (37.5)	40 (41.2)	126 (43.6)
Eastern Europe	22 (22.9)	26 (27.1)	27 (27.8)	75 (26.0)
North America	9 (9.4)	14 (14.6)	9 (9.3)	32 (11.1)
Asia	3 (3.1)	8 (8.3)	13 (13.4)	24 (8.3)
South America	3 (3.1)	0	1 (1.0)	4 (1.4)
Other countries	9 (9.4)	12 (12.5)	7 (7.2)	28 (9.7)

ITT = intent to treat; SD = standard deviation.

[a] The race categories in the electronic case report form for this study were Caucasian/white, black, Asian/Oriental, and other (Appendix 16.1.2). The race categories in this this in-text table have been standardized for consistency across fedratinib clinical study reports.

[b] The race for this subject is not specified in Listing 16.2.4.1.

[c] Countries were grouped into geographical regions as follows: Asia (Republic of Korea, Singapore, and Taiwan [Province of China]), Eastern Europe (Hungary, Lithuania, Poland, Romania, and Russian Federation), North America (Canada and United States), South America (Brazil), Western Europe (Austria, Belgium, France, Germany, Ireland, Italy, Portugal, Spain, Sweden, and United Kingdom), and "other" countries (Australia, Israel, and South Africa).

Source: Table 14.1.4.1

Baseline Myelofibrosis Disease Characteristics

The largest proportion of subjects in the ITT Population had PMF (63.3%), followed by post-PV MF (26.3%) and post-ET MF (10.4%) (Table 25).

The overall median time since diagnosis of MF was 27.8 months. The overall frequency of subjects with intermediate-2 or high-risk status was 51.9% and 48.1%, respectively. The majority of all subjects (66.8%) had a mutant JAK2 allele profile. For most subjects, the baseline fibrosis grade was 2 (38.1%)

or 3 (48.8%). Overall, 73.7% of subjects had constitutional symptoms, and most subjects (93.4%) were not transfusion dependent. Most subjects had an ECOG PS score of 0 (35.6%) or 1 (54.7%). The median baseline TSS (using modified MFSAF) for all subjects was 14.7. The majority of all subjects (70.6%) had a spleen size > 10 cm. Prior hydroxyurea was taken by 63.0% of all subjects.

The disease characteristics at baseline were generally well balanced across the 3 treatment arms, with the following exceptions:

- The median time since diagnosis of MF was longer in the 400 mg arm (43.0 months) than in the placebo and 500 mg arms (28.3 and 22.0 months, respectively).
- A lower proportion of subjects in the 400 mg arm had high-risk status (40.6%) compared with the placebo and 500 mg arms (52.1% and 51.5%, respectively).
- A higher proportion of subjects in the 500 mg arm had mutant JAK2 profile (74.2%) compared with the placebo and 400 mg arms (61.5% and 64.6%, respectively).
- A higher proportion of subjects in the 400 mg arm had a baseline ECOG PS score of 0 (42.7%) compared with the placebo and 500 mg arms (32.3% and 32.0%, respectively).
- The median baseline TSS was lower in the placebo arm (12.43) compared with the 400 and 500 mg arms (15.3 and 16.0, respectively).
- A higher proportion of subjects in the 400 mg arm had received prior hydroxyurea (71.9%) compared with the placebo and 500 mg arms (56.3% and 60.8%, respectively).

Table 25: Baseline disease characteristics (ITT Population) Study EFC12153

	Placebo (N = 96)	Fedratinib 400 mg (N = 96)	Fedratinib 500 mg (N = 97)	Total (N = 289)
Type of Myelofibrosis, n (%)				
Primary MF	58 (60.4)	62 (64.6)	63 (64.9)	183 (63.3)
Post-PV MF	27 (28.1)	24 (25.0)	25 (25.8)	76 (26.3)
Post-ET MF	11 (11.5)	10 (10.4)	9 (9.3)	30 (10.4)
Time Since Diagnosis of MF (months)				
n	96	96	96	288
Mean (SD)	54.24 (69.091)	68.53 (73.585)	38.76 (46.419)	53.84 (65.069)
Median	28.34	42.99	21.98	27.79
Minimum, maximum	0.2, 412.5	0.8, 310.6	0.5, 232.1	0.2, 412.5
Risk Status[a], n (%)				
Intermediate-2	46 (47.9)	57 (59.4)	47 (48.5)	150 (51.9)
High risk	50 (52.1)	39 (40.6)	50 (51.5)	139 (48.1)
JAK2 Mutational Profile, n (%)				
Wild type	32 (33.3)	30 (31.3)	20 (20.6)	82 (28.4)
Mutant	59 (61.5)	62 (64.6)	72 (74.2)	193 (66.8)
Missing	5 (5.2)	4 (4.2)	5 (5.2)	14 (4.8)
Fibrosis Grade, n (%)				
0	3 (3.1)	1 (1.0)	3 (3.1)	7 (2.4)
1	2 (2.1)	7 (7.3)	11 (11.3)	20 (6.9)
2	40 (41.7)	36 (37.5)	34 (35.1)	110 (38.1)
3	47 (49.0)	49 (51.0)	45 (46.4)	141 (48.8)
Missing	4 (4.2)	3 (3.1)	4 (4.1)	11 (3.8)
Constitutional Symptoms, n (%)[b]				
Yes	70 (72.9)	73 (76.0)	70 (72.2)	213 (73.7)
No	26 (27.1)	23 (24.0)	27 (27.8)	76 (26.3)
ECOG PS Score, n (%)				
0	31 (32.3)	41 (42.7)	31 (32.0)	103 (35.6)
1	56 (58.3)	47 (49.0)	55 (56.7)	158 (54.7)
2	8 (8.3)	8 (8.3)	11 (11.3)	27 (9.3)
Missing	1 (1.0)	0	0	1 (0.3)
RBC Transfusion Dependence Status[c], n (%)				
Yes	6 (6.3)	8 (8.3)	5 (5.2)	19 (6.6)
No	90 (93.8)	88 (91.7)	92 (94.8)	270 (93.4)
Total Symptom Score[d]				
n	85	91	91	267
Mean (SD)	14.72 (11.954)	17.56 (13.530)	16.98 (11.969)	16.46 (12.530)
Median	12.43	15.29	16.00	14.71
Minimum, maximum	0, 52.7	0, 57.0	0, 47.6	0, 57.0
Spleen Size > 10 cm, n (%)[e]				
Yes	71 (74.0)	68 (70.8)	65 (67.0)	204 (70.6)
No	25 (26.0)	28 (29.2)	32 (33.0)	85 (29.4)
Prior Hydroxyurea, n (%)				
Yes	54 (56.3)	69 (71.9)	59 (60.8)	182 (63.0)
No	42 (43.8)	27 (28.1)	38 (39.2)	107 (37.0)

ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat; JAK2 = Janus kinase 2; MF = myelofibrosis; post-ET = post-essential thrombocythemia; post-PV = post-polycythemia vera; PS =performance status; RBC = red blood cell; SD = standard deviation.

[a] Risk status as defined in Cervantes, 2009.

[b] Constitutional symptoms were defined as one or more of the following: weight loss > 10% over a year before screening, fever persisting for > 1 month, or sweats persisting for > 1 month (Appendix 16.1.2).

[c] Transfusion dependence was defined as receiving ≥ 2 units/month of RBC transfusions over 3 months per Gale, 2011.

[d] The total symptom score was defined as the average value of the daily total score of the 6-item measures of the week: night sweats, pruritus (itching), abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain.

[e] Spleen size by palpation.

Source: Table 14.1.4.2

Baseline Spleen Volume and Spleen Size

The overall median spleen volume at baseline was 2568 mL (Table 26), which is approximately 12 times the median normal spleen volume of 215 mL (Prassopoulos, 1997). The median spleen size at

baseline was 15.0 cm. The baseline spleen volume and spleen size were balanced among the treatment arms.

Table 26: Baseline spleen volume and spleen size (ITT Population) Study EFC12153

	Placebo (N = 96)	Fedratinib 400 mg (N = 96)	Fedratinib 500 mg (N = 97)	Total (N = 289)
Baseline Spleen Volume (mL)				
n	91	94	92	277
Mean (SD)	2927.7 (1483.80)	2754.7 (1353.32)	2524.1 (1342.92)	2734.9 (1398.88)
Median	2660.0	2652.0	2366.0	2568.0
Minimum, maximum	662, 7911	316, 6430	388, 8244	316, 8244
Baseline Spleen Size[a] (cm)				
n	95	96	97	288
Mean (SD)	16.4 (6.99)	16.1 (7.50)	14.4 (6.86)	15.6 (7.15)
Median	17.0	16.0	14.0	15.0
Minimum, maximum	5, 40	5, 40	4, 32	4, 40

ITT = intent to treat; SD = standard deviation.
Note: Baseline was defined as the last non-missing record on or before the treatment start date.
[a] Spleen size by palpation.
Sources: Table 14.1.4.8 and Table 14.1.4.9

Baseline Total Symptom Score by Modified MFSAF

Median baseline TSS in the Symptom Analysis Population was 14.1 for the placebo arm, 15.3 for the 400 mg arm, and 16.1 for the 500 mg arm (Table 27).

Table 27: Baseline total symptom score as measured by modified MFSAF (Symptom Analysis Population) Study EFC12153

	Placebo (N = 81)	Fedratinib 400 mg (N = 89)	Fedratinib 500 mg (N = 89)	Total (N = 259)
Baseline Total Symptom Score[a]				
Mean (SD)	15.4 (11.78)	18.0 (13.42)	17.4 (11.82)	17.0 (12.38)
Median	14.1	15.3	16.1	15.3
Minimum, maximum	0.3, 52.7	0.4, 57.0	0.2, 47.6	0.2, 57.0

MFSAF = myelofibrosis symptom assessment form; SD = standard deviation; TSS = total symptom score.
[a] The total symptom score was defined as the average value of the daily total score of the 6-item measures of the week: night sweats, pruritus (itching), abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain.
Note: The baseline TSS was defined as the TSS of the week ending at the last non-missing record before the treatment start date.
Source: Table 14.1.4.10

Prior myelofibrosis therapies

Per the study entry criteria, no subject in this study had received prior treatment with a JAK2 inhibitor. Most (73.4%) subjects had received prior therapy for MF, but this was somewhat lower in the placebo arm (65.6%) than in the 400 and 500 mg arms (80.2% and 74.2%), respectively (Table 28).

Most subjects had received only 1 prior MF therapy: 71.4% in the placebo arm, 77.6% in the 400 and 81.7% in the 500 mg arm. Hydroxycarbamide (hydroxyurea) was the most frequently used prior MF therapy among all subjects (63.0%), with a higher usage in the 400 mg arm (71.9%) compared with the placebo and 500 mg arms (56.3% and 60.8%, respectively). Other frequently used therapies were immunomodulatory agents (18.7% overall) and corticosteroids (10.4% overall).

Table 28: Proportion of subjects with prior myelofibrosis therapies (ITT Population) Study EFC12153

	Placebo (N = 96) n (%)	Fedratinib 400 mg (N = 96) n (%)	Fedratinib 500 mg (N = 97) n (%)	Total (N = 289) n (%)
Prior Myelofibrosis Therapies				
Yes	63 (65.6)	77 (80.2)	72 (74.2)	212 (73.4)
No	33 (34.4)	19 (19.8)	25 (25.8)	77 (26.6)
Number of Prior Myelofibrosis Therapies				
n	63	76	71	210
1	45 (71.4)	59 (77.6)	58 (81.7)	162 (77.1)
2	11 (17.5)	6 (7.9)	11 (15.5)	28 (13.3)
≥ 3	7 (11.1)	11 (14.5)	2 (2.8)	20 (9.5)
Class of Antimyelofibrosis Therapy[a] Medication				
Antineoplastic agents	56 (58.3)	70 (72.9)	60 (61.9)	186 (64.4)
Hydroxycarbamide	54 (56.3)	69 (71.9)	59 (60.8)	182 (63.0)
Other	14 (14.6)	8 (8.3)	8 (8.2)	30 (10.4)
Immunomodulatory agent	16 (16.7)	23 (24.0)	15 (15.5)	54 (18.7)
Interferon	8 (8.3)	12 (12.5)	9 (9.3)	29 (10.0)
Other	10 (10.4)	11 (11.5)	7 (7.2)	28 (9.7)
Corticosteroids	9 (14.3)	6 (7.8)	7 (9.7)	22 (10.4)
Platelet-reducing agent	5 (7.9)	8 (10.4)	6 (8.3)	19 (9.0)
Other	3 (4.8)	4 (5.2)	5 (6.9)	12 (5.7)
Hormone	4 (6.3)	1 (1.3)	3 (4.2)	8 (3.8)
Hematopoietic agent	1 (1.6)	0	0	1 (0.5)

ITT = intent to treat; WHO = World Health Organization.
[a] Medications were coded using the WHO Drug Dictionary (Version WHODrug-DDE_HD-B3-201706-English). A medication could be counted in several anatomic classes. The anatomic and therapeutic classes are sorted by decreasing frequency in the Total column.
Notes: Prior medications were any medications the subject used before the date of the first dose of study drug.
Source: Table 14.1.5.2

Baseline Haematology

The median values for baseline haematology parameters were generally similar for the 3 treatment arms.

The median Hb concentration at baseline for all subjects was 10.2 g/dL. The baseline Hb concentration was ≤10 g/dL for 45.8% of all subjects, with a lower proportion in the 400 mg arm (34.4%) than in the placebo and 500 mg arms (49.5% and 53.6%, respectively).

The median platelet count at baseline for all subjects was 213.5 x 10^9/L, most subjects (83.7%) had platelet counts ≥100 x 10^9/L.

The median WBC count at baseline for all subjects was 11.8 x 10^9/L; 26.0% of all subjects had a WBC count ≥25 x 10^9/L at baseline.

The percentage of all subjects with baseline blood blasts ≥1% was 54.5%.

Numbers analysed

Analysis Populations

The analysis populations are described in the Section Statistical Methods and the numbers of patients per analysis population are shown in Table 29.

Table 29: Analysis populations (Intent-to-treat Population)

	Placebo (N = 96) n (%)	Fedratinib 400 mg (N = 96) n (%)	Fedratinib 500 mg (N = 97) n (%)	Total (N = 289) n (%)
ITT Population[a]	96 (100.0)	96 (100.0)	97 (100.0)	289 (100.0)
All Treated Population[b]	95 (99.0)	96 (100.0)	97 (100.0)	288 (99.7)
Crossover Safety Population[c]	71 (74.0)	NA	NA	71 (24.6)
Evaluable Subjects (EP) Population[d]	82 (85.4)	88 (91.7)	76 (78.4)	246 (85.1)
Symptom Analysis Population[e]	81 (84.4)	89 (92.7)	89 (91.8)	259 (89.6)
PK Population[f]	NA	95 (99.0)	96 (99.0)	191 (99.0)[g]
PK/PD-ECG Population[h]	NA	96 (100.0)	97 (100.0)	193 (100.0)[g]
Bone Marrow Fibrosis Population[i]	33 (34.4)	35 (36.5)	32 (33.0)	100 (34.6)
Follow-up Population[j]	63 (65.6)	71 (74.0)	70 (72.2)	204 (70.6)

ECG = electrocardiogram; EP = evaluable subjects; ITT = intent to treat; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic.

Outcomes and estimation

Primary Efficacy Endpoint - Spleen Response Rate

The Primary Efficacy Endpoint was spleen response rate (RR) which was defined as the proportion of subjects with ≥35% SVR at the End of Cycle 6 (EOC6). A confirmatory MRI/CT was required 4 weeks later. The IRC reviewed the MRI/CT images in a blinded manner.

The study met the primary endpoint. For the ITT Population, the spleen RR at the End of Cycle 6 confirmed 4 weeks later was 36.5% in the 400 mg arm and 40.2% in the 500 mg arm compared with 1.0% in the placebo arm (Table 30). Both active treatment arms showed clinically meaningful and statistically significant differences compared with placebo ($p < 0.0001$, 2-sided at a significance level = 0.025 for each comparison).

Table 30: Spleen response rate (⩾35% SVR) at the EOC6 confirmed 4 Weeks later (primary endpoint) and at the EOC6 (ITT Population) Study EFC12153

End of Cycle 6, confirmed 4 weeks later (Primary Endpoint)

	Placebo (N = 96)	Fedratinib 400 mg (N = 96)	Fedratinib 500 mg (N = 97)
EOC6			
n (%)	1 (1.0)	35 (36.5)	39 (40.2)
(95% CI)	(0, 3.1)	(26.8, 46.1)	(30.4, 50.0)
Difference	—	35.42	39.16
P-value[a]	—	< 0.0001	< 0.0001
(97.5% CI of difference)	—	(24.2, 46.7)	(27.8, 50.6)

End of Cycle 6

	Placebo (N = 96)	Fedratinib 400 mg (N = 96)	Fedratinib 500 mg (N = 97)
EOC6			
n (%)	1 (1.0)	45 (46.9)	48 (49.5)
(95% CI)	(0, 3.1)	(36.9, 56.9)	(39.5, 59.4)
Difference	—	45.83	48.44
P-value[a]	—	< 0.0001	< 0.0001
(97.5% CI of difference)	—	(34.2, 57.5)	(36.8, 60.1)

a **P-values were calculated based on the chi-square test comparing each fedratinib arm to the placebo arm; CIs were calculated using normal approximation.**
Sources: CSR EFC12153, Table 24 and Table 25.

When spleen volume reduction (SVR) was assessed without the requirement of confirmation 4 weeks later, the proportion of subjects who had ≥35% SVR was 46.9%, 49.5%, and 1.0% in the 400 mg, 500 mg and placebo arms, respectively. For 19 subjects without confirmation of SVR, 12 subjects had a SVR<35%, and for 5 subjects the confirmatory scan was not performed.

For the Evaluable Subjects Population (EP), the spleen RR at the End of Cycle 6 confirmed 4 weeks later was 1.2% (1/82) for the placebo arm, 39.8% (35/88) for the 400 mg arm, and 51.3% (39/76) for the 500 mg arm.

Spleen RR for Placebo Crossover Subjects After Fedratinib Treatment

For the placebo crossover subjects rerandomised to fedratinib after the initial randomisation period, the spleen RR at the End of Cycle 6 **after fedratinib treatment** was 28.6% (10/35) in the 400 mg arm and 44.4% (16/36) in the 500 mg arm.

Percentage Change in Spleen Volume at the End of Cycle 6

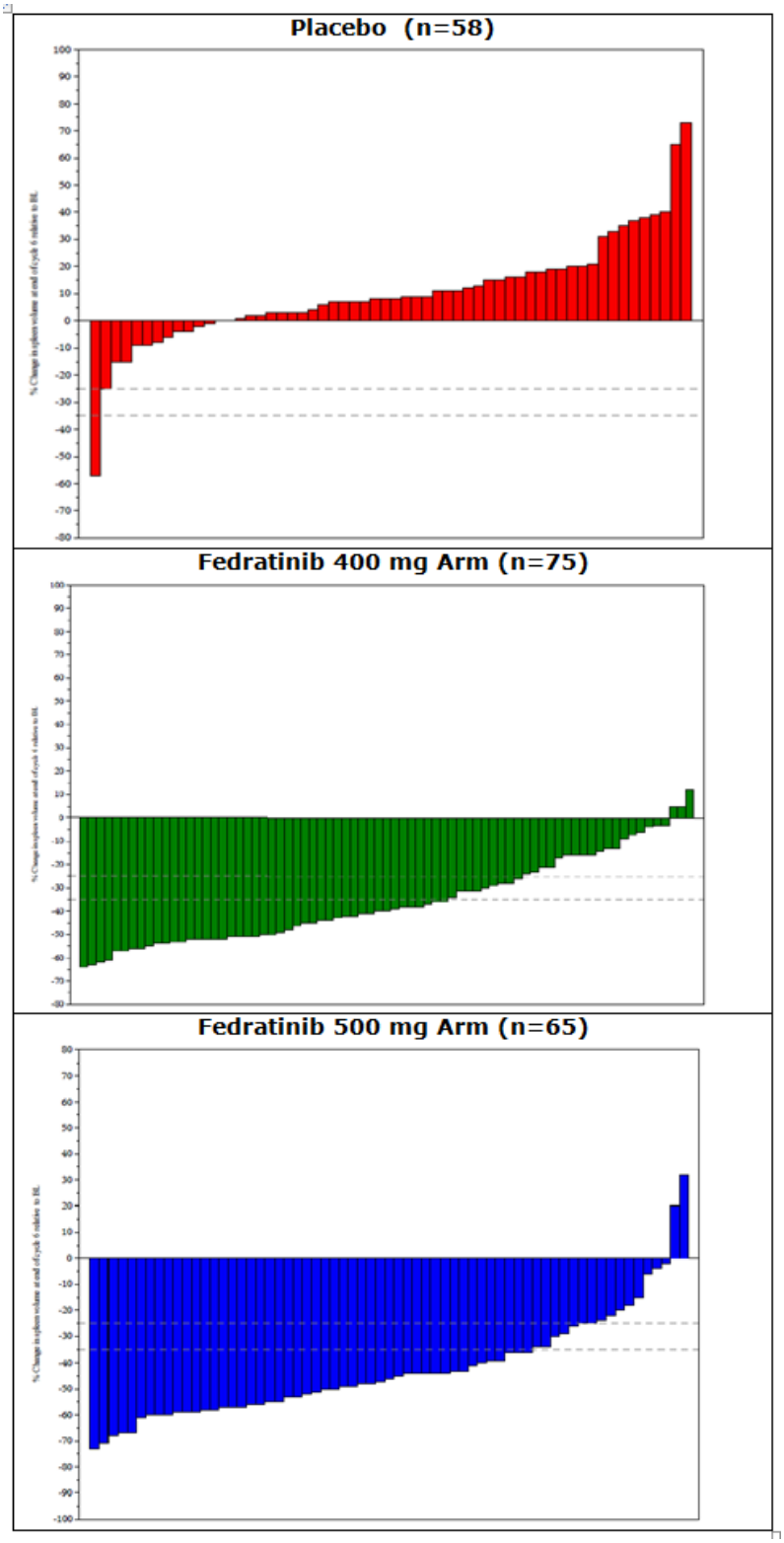
The mean percentage change in spleen volume at the End of Cycle 6 in the ITT Population with available baseline and EOC6 assessments were 10.3% in the placebo arm, -35.6% in the 400 mg arm, and -42.3% in the 500 mg arm. Each active treatment arm showed a significant SVR compared with placebo using a 2-sample t-test ($p < 0.001$) (Table 31). The results for percentage change in spleen volume at the End of Cycle 6 for the EP Population were similar to the corresponding results for the ITT Population.

Table 31: Percentage change in spleen volume at the EOC6 (ITT Population with available baseline and EOC6 assessments) Study EFC12153

	Placebo (N = 96)	Fedratinib	
		400 mg (N = 96)	500 mg (N = 97)
Spleen Volume (mL) at Baseline[a]			
n	91	94	92
Mean (SD)	2928 (1483.8)	2755 (1353.3)	2524 (1342.9)
Median	2660	2652	2366
Minimum, maximum	662, 7911	316, 6430	388, 8244
(95% CI)	(2619, 3237)	(2477, 3032)	(2246, 2802)
Spleen Volume (mL) at the EOC6			
n	58	75	65
Mean (SD)	3068 (1626.3)	1728 (1015.5)	1456 (879.7)
Median	2894	1536	1314
Minimum, maximum	571, 8097	284, 5530	313, 4443
(95% CI)	(2641, 3496)	(1494, 1961)	(1238, 1674)
% Change in Spleen Volume at the EOC6			
n	58	75	65
Mean (SD)	10.3 (19.74)	-35.6 (18.59)	-42.3 (20.24)
Median	8.0	-40.0	-46.0
Minimum, maximum	-57.0, 73.0	-64.0, 12.0	-73.0, 32.0
(95% CI)	(5.1, 15.5)	(-39.9, -31.3)	(-47.3, -37.3)
Difference in mean	—	-45.880	-52.585
(97.5% CI of the difference)	—	(-53.452, -38.307)	(-60.787, -44.383)
p-value	—	< 0.001	< 0.001

CI = confidence interval; EOC6 = End of Cycle 6; ITT = intent to treat; SD = standard deviation.
[a] Baseline spleen volume was defined as the last spleen volume measurement before the first dose of treatment.
Note: P-values and 97.5% CIs were calculated based on the t-test.
Source: Table 14.2.1.5.1

Waterfall plots showing the percentage change in spleen volume at the End of Cycle 6 are provided for the subjects in the ITT Population with available baseline and End-of-Cycle 6 assessments in Figure 16. At the End of Cycle 6, most subjects treated with fedratinib at either 400 mg (72/75; 96.0%) or 500 mg (63/65; 96.9%) had some degree of SVR. In contrast, a majority of subjects in the placebo arm (44/58; 75.9%) had an increase in spleen volume at the End of Cycle 6 (EOC6).



For each arm, the number of patients with available percentage change in spleen volume at the EOC6 is given.
Note: The dashed lines represent a spleen volume reduction at the EOC6 25% and 35%.

Figure 16: Waterfall plot of percentage change in spleen volume at the EOC6 relative to baseline: Subjects in the ITT population with available baseline and EOC6 assessments

Secondary Efficacy Endpoints

Symptom Response Rate using the modified MFSAF (Myelofibrosis Symptom Assessment Form)

The 6 key MF-associated symptoms were assessed using the modified MFSAF and measured on a scale from 0 (absent) to 10 (worst imaginable, TSS=60), thus reduction in TSS suggests improvement in symptom burden.

The compliance rate of the modified MFSAF (i.e., number of subjects with questionnaires completed) was ≥85.6% in each treatment arm at each cycle.

At baseline, 89.5% of subjects in the placebo arm, 94.8% of subjects in the 400 mg arm, and 93.8% of subjects in the 500 mg arm had evaluable data (at least 5 assessments available within the week before the next cycle).

At Cycle 6, the numbers of subjects evaluable at cycle 6 in the placebo, 400 mg and 500 mg arms were 56, 75 and 62 respectively.

The primary reasons for noncompliance (> 2 subjects at any assessment) were subject refusal, technical issues, failure to distribute the questionnaire, and "other" reason (not specified).

The requirements to have all of the symptoms scores for each day, and to have symptom scores from 5/7 days to calculate the weekly score, require high compliance and may exclude patients faring poorly, and thus unable or unwilling to complete the symptom scoring. The applicant provided data on excluded symptom evaluations, and presented the data based on all available assessments (as an average of the daily symptom scores), i.e., including data from patients from whom at least one complete symptom assessment is available from the given treatment cycle. Very few subjects (0 to 5 per treatment arm) had symptoms excluded from the CSR analyses of symptom RR. The differences in the number of symptom scores and proportion of responders was similar between the original analysis and the analysis utilizing all available symptoms scores. TSS was available from 82% of patients who had a baseline score available in the 400mg group at EOC6. As the results are consistent, and a low proportion of assessments are missing, the missing assessments are considered unlikely to significantly alter the reported results.

Symptom Response Rate – ITT Population With Non-missing Baseline TSS

The study met its key secondary endpoint, symptom RR (using the modified MFSAF). The proportion of subjects in the ITT Population with non-missing baseline TSS (including subjects with baseline TSS = 0) who had ≥50% reduction in the TSS from baseline to the End of Cycle 6 was 8.2% (7/85) in the placebo arm, 39.6% (36/91) in the 400 mg arm, and 34.1% (31/91) in the 500 mg arm (Table 32). Both active treatment arms showed clinically meaningful and statistically significant differences compared with placebo based on a step-down procedure for controlling multiplicity of the statistical comparison ($p < 0.0001$, 2-sided at a significance level = 0.025 for each comparison versus placebo).

Table 32: Symptom response rate (⩾50% reduction in total symptom score) at the EOC6 – Subjects in the ITT Population with non-missing baseline total symptom score Study EFC12153

	Placebo (N = 85)	Fedratinib	
		400 mg (N = 91)	500 mg (N = 91)
Response at the EOC6			
n (%)	7 (8.2)	36 (39.6)	31 (34.1)
(95% CI)	(2.4, 14.1)	(29.5, 49.6)	(24.3, 43.8)
Difference	—	31.33	25.83
P-value[a]	—	< 0.0001	< 0.0001
(95% CI of difference)	—	(18.0, 44.6)	(12.8, 38.8)

CI = confidence interval; EOC6 = End of Cycle 6; ITT = intent to treat; MFSAF = myelofibrosis symptom assessment form; TSS = total symptom score.

[a] P-values were calculated based on the chi-square test comparing each fedratinib arm to the placebo arm; CIs were calculated using normal approximation.

Note: The TSS was defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the MFSAF: night sweats, pruritus (itching), abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. Non-missing baseline TSS includes subjects with baseline TSS = 0.

Source: Table 14.2.12.6.2

Symptom Response Rate – Symptom Analysis Population

The Symptom Analysis Population (modified MFSAF) included ITT subjects evaluable at baseline (for symptom assessment) and Total Symptom Score >0 (Subjects without a baseline TSS > 0 were considered non-evaluable, due to no place for symptom reduction), in contrast to the ITT Population With Non-missing Baseline TSS which included subjects with baseline TSS = 0.).

At the End of Cycle 6, the symptom RR (≥50% reduction in TSS) for the Symptom Analysis Population was 8.6% (7/81) in the placebo arm, 40.4% (36/89) n the 400 mg arm, and 34.8% (31/89) in the 500 mg arm. These results are similar to those of the ITT Population.

Symptom improvement in the 400 and 500 mg arms was evident as early as the End of Cycle 1, and this improvement was maintained up to the End of Cycle 6 (Table 33). More than one quarter of fedratinib-treated subjects (30.3% in the 400 mg arm and 27.0% in the 500 mg arm) achieved ≥50% reduction in the TSS at the End of Cycle 1. From End of Cycle 2 onwards, the symptom RR did not increase appreciably and from Cycles 3 to 6, the symptom RR remained ≥38.2% for the 400 mg arm and ≥33.7% for the 500 mg arm.

Subjects without a baseline TSS > 0 were considered nonevaluable (due to no room for symptom reduction) for the symptom RR analysis. 4.2% and 2.1% of the patients had a baseline TSS of 0. Analysis excluding the patients with a TSS of 0 (symptom analysis population) showed a higher symptom response of 40.4% in fedratinib 400mg/day group. Two of the 4 subjects who were randomised to fedratinib and who had TSS = 0 at baseline had a spleen response (SVR ≥ 35%) at the EOC6, both treated with 500mg/day dose.

Of the 67 subjects in the fedratinib 400 mg arm who had data for spleen volume and TSS at baseline and at the EOC6, 24 (35.8%) subjects had both spleen and symptom response, 16 (23.9%) subjects had only spleen response, 11 (16.4%) subjects had only symptom response, and 16 (23.9%) subjects had neither spleen nor symptom response. However, most patients had some improvement in both endpoints, even if failing to meet the success criteria.

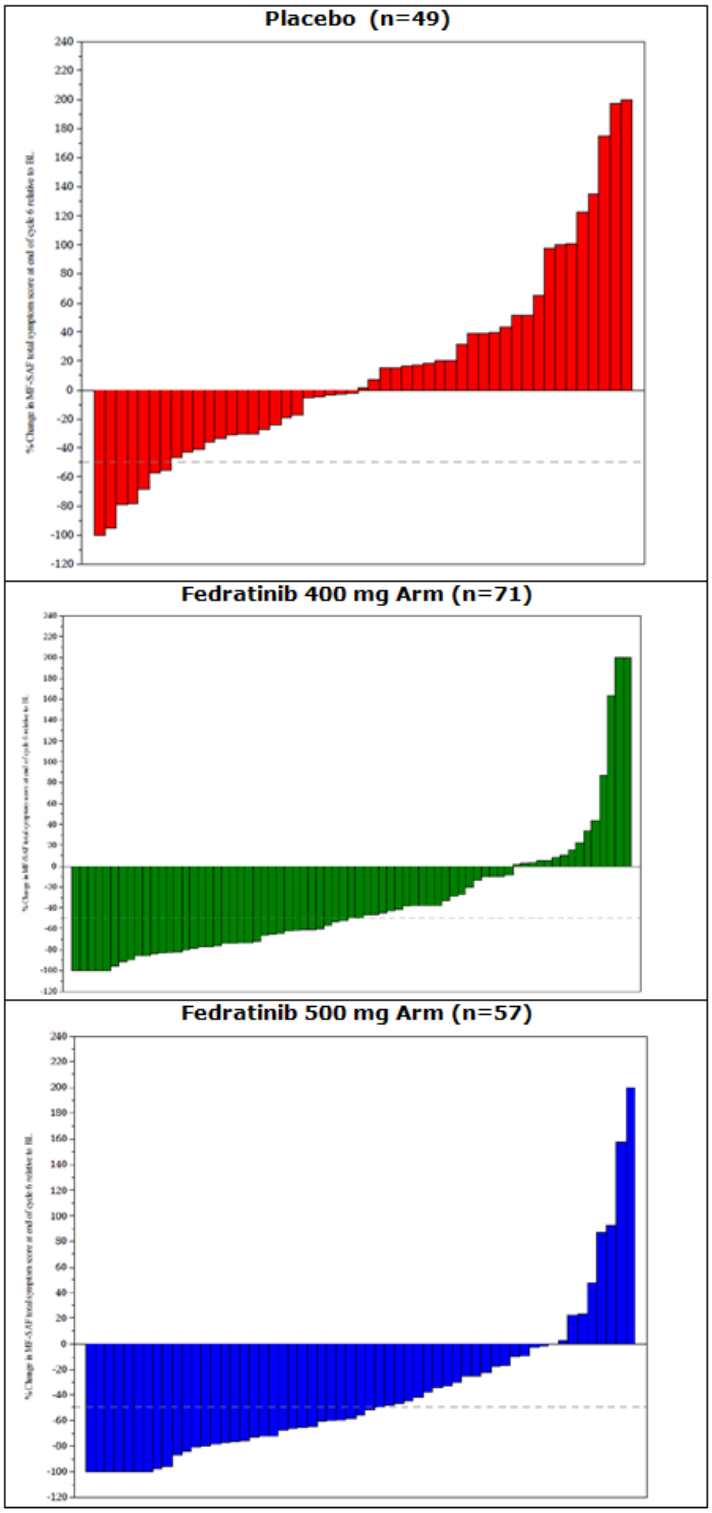
Table 33: Proportion of subjects with ⩾50% reduction from baseline in total symptom score by cycle - Symptom Analysis Population

		Fedratinib	
	Placebo (N=81)	400 mg (N=89)	500 mg (N=89)
Response at EOC 1			
n (%)	6 (7.4)	27 (30.3)	24 (27.0)
95% CI	1.7, 13.1	20.8, 39.9	17.7, 36.2
Response at EOC 2			
n (%)	11 (13.6)	34 (38.2)	26 (29.2)
95% CI	6.1, 21.0	28.1, 48.3	19.8, 38.7
Response at EOC 3			
n (%)	11 (13.6)	34 (38.2)	30 (33.7)
95% CI	6.1, 21.0	28.1, 48.3	23.9, 43.5
Response at EOC 4			
n (%)	9 (11.1)	40 (44.9)	30 (33.7)
95% CI	4.3, 18.0	34.6, 55.3	23.9, 43.5
Response at EOC 5			
n (%)	10 (12.3)	36 (40.4)	31 (34.8)
95% CI	5.2, 19.5	30.3, 50.6	24.9, 44.7
Response at EOC 6			
n (%)	7 (8.6)	36 (40.4)	31 (34.8)
95% CI	2.5, 14.8	30.3, 50.6	24.9, 44.7

Percent Change in Total Symptom Score

The waterfall plot for the Symptom Analysis Population (Figure 17) summarises the percentage change in modified MFSAF TSS at the End of Cycle 6 with available End-of-Cycle 6 assessment. The majority of subjects in the 400 mg (56/71; 78.9%) and 500 mg (48/57; 84.2%) arms had an improved TSS (ie, TSS percentage change <0) at the End of Cycle 6, whereas one half of the subjects in the placebo arm (25/49; 51.0%) had a worse TSS at the End of Cycle 6.

Comparison of symptom scores between groups was possible only in the placebo-controlled period of 6 cycles, and symptom assessment (TSS) was not evaluated after EOC6. While it is agreed that symptom evaluation has the highest value during the placebo-controlled phase of the study, durability of the symptom response is also of interest. Only EQ-5D1 data were collected after the EOC6 (at the End of Treatment (EOT), and at the 30-day Follow-up visit). EQ-5D utility index scores were similar at EOC6 and EOT. The number of patients with data from 30-day follow-up visit is too low to draw any conclusions, but overall, no dramatic changes were observed. Overall, the data presented suggest relatively stable QoL throughout the treatment period.



BL = baseline; EOC6 = End of Cycle 6; MFSAF or MF-SAF = myelofibrosis symptom assessment form; TSS = total symptom score.
Notes: The dashed line represents a 50% reduction in TSS. Subjects with TSS increased by at least 200% are plotted as 200% increase. The TSS was defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the MFSAF: night sweats, pruritus (itching), abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain.

Figure 17: Waterfall plot of percentage change in TSS at the EOC6 – Symptom Analysis Population with available EOC6 Study EFC12153

Individual Symptoms from Modified MFSAF

Reduction in Individual Symptom Scores is summarised below for the Symptom Analysis Population (ITT subjects with baseline Total Symptom Score > 0).

The 3 key individual symptoms tangential to the spleen: At the End of Cycle 6, subjects in the 400 and 500 mg arms respectively versus the placebo arm had **median percentage changes from baseline** of larger than -50.0%:

Abdominal discomfort: -50.0% and -52.4% versus +4.0%,

Early satiety: -66.6% and -67.4% versus +6.1%,

Pain under ribs on left side: -61.4% and -61.1% versus -7.0%.

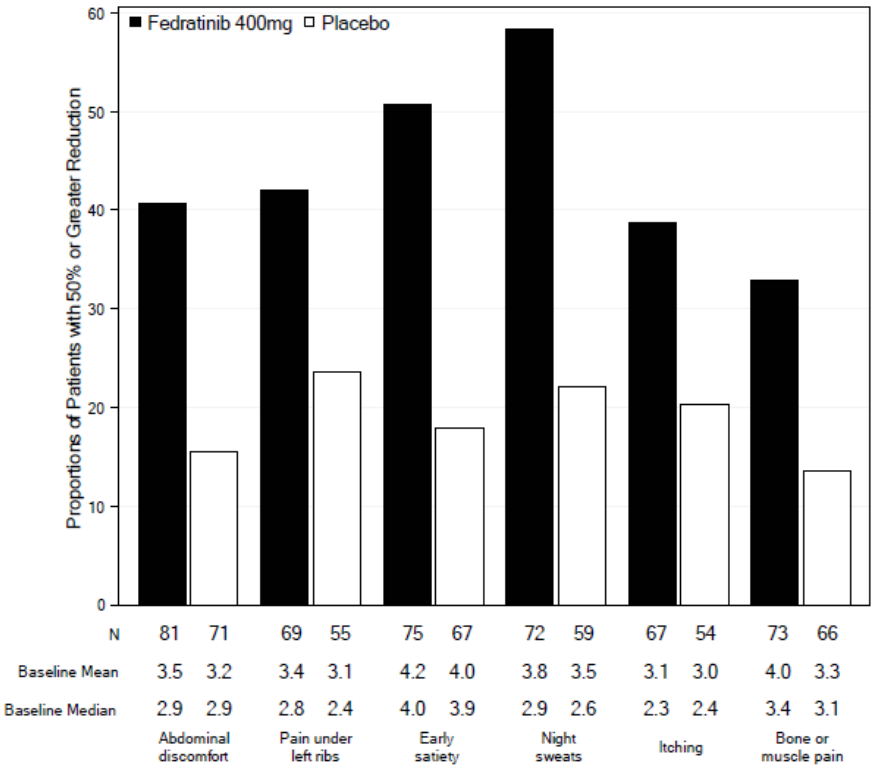
For subjects in the 400 and 500 mg arms versus the placebo arm the median percentage changes in the remaining symptom scores were:

Night sweats: -84.2% and -100.0% versus -13.5%,

Bone or muscle pain: -27.6% and -30.0% versus +6.5%,

Itching: -46.7% and -53.1% versus -35.6%.

The proportion of subjects in the Symptom Analysis Population with at least a 50% improvement in each of the individual symptoms that comprised the TSS (shown in Figure 18) indicate that all 6 of the symptoms contributed to the higher TSS response rate in the group treated with fedratinib 400 mg as compared to placebo.



Source: Figure 12 Summary of Clinical Efficacy

Figure 18: Proportions of subjects with ⩾ 50% reduction in individual scores at the end of cycle 6 – Study EFC12153 (Symptom Analysis Population)

Spleen Response Rate (≥25% SVR) at the End of Cycles 3 and 6

The RR25 (with 95% confidence intervals) for the ITT Population (n=96 in placebo and 400 mg arms and n=97 in the 500 mg arm) was for the placebo, 400mg and 500 mg arms respectively:

- at the End of Cycle 3: 1.0% (0, 3.1) in the placebo arm, 58.3% (48.5, 68.2) in the 400 mg arm, and 61.9% (52.2, 71.5) in the 500 mg arm respectively and

- at the End of Cycle 6: 2.1% (0, 4.9), 56.3% (46.3, 66.2), and 56.7% (46.8, 66.6), respectively.

Overall Survival and Progression-free Survival

No analyses were provided for the PFS or OS endpoints because of the short median follow-up time (i.e. due to the early termination of the study), which was approximately 575 days for each treatment arm (range = 568 to 580 days).

Duration of spleen response

The duration of spleen response (≥35% SVR) was defined as the time from the date of the first IRC-assessed response to the date of subsequent IRC-assessed PD or death, whichever was earlier. It was determined for subjects who achieved spleen response at any time during treatment or during the period before crossover for the placebo arm (i.e., responders).

Due to early termination of the study, and subsequent extensive censoring, Kaplan-Meier analysis was used to estimate duration of spleen response. Subjects without subsequent IRC-assessed PD or death were censored at the last assessment date.

The ITT Population included 54 and 57 IRC-assessed spleen responders in the 400 and 500 mg arms, respectively (Table 34). Based on Kaplan-Meier estimates, the median duration of spleen response in the fedratinib arms was 18.2 months in the 400 mg arm and 19.7 months in the 500 mg arm.
During the study, in 11.1% (6/54) and 14.0% (8/57) of responders in the 400 and 500 mg arms, respectively, the response ended due to PD or death.
One placebo subject had IRC-assessed spleen response before crossover at End of Cycle 3 and then crossed over to receive fedratinib 500 mg at End of Cycle 6 after which further SVR was observed. This placebo crossover subject did not have a PD/death event throughout the study, and thus was censored at 16.7 months.

Table 34: Kaplan-Meier analysis of duration of spleen response (ITT Population)

	Study EFC12153		
	Placebo [a] (N = 96)	Fedratinib 400 mg (N = 96)	Fedratinib 500 mg (N = 97)
Subjects with a Response	1	54	57
Duration of Response (months)			
Number of Ended Responses (%)	0	6 (11.1)	8 (14.0)
Number of Censored Subjects (%)	1 (100.0)	48 (88.9)	49 (86.0)
25% quantile (95% CI) [c]	NE (NE, NE)	18.2 (10.2, 18.2)	16.0 (11.7, 19.7)
Median (95% CI) [c]	NE (NE, NE)	18.2 (NE, NE)	19.7 (16.0, 19.7)
75% quantile (95% CI) [c]	NE (NE, NE)	18.2 (NE, NE)	19.7 (NE, NE)

Effect of fedratinib on the JAK2^{V617F} allele burden

In subjects who were determined to have the JAK2V617F mutant allele in peripheral blood granulocytes at baseline, the allele burden for this mutation was also measured on Day 1 of Cycle 4, at the End of Cycle 6, at the beginning of every third cycle thereafter (ie, Cycles 9, 12, etc) for 2 years, and at the End of Treatment.

Fifty-nine (61.5%), 62 (64.6%), and 72 (74.2%) subjects in the placebo, 400 mg, and 500 mg arms, respectively, had the JAK2V617F mutant allele at baseline. No significant changes in JAK2V617F allele burden were observed at Cycle 3 or Cycle 6 relative to the baseline in any of the treatment arms.

Health Related Quality of Life

Change in HRQOL and utility using the EQ-5D questionnaire were assessed at baseline and compared with the End of Cycle 6 and to the End of Treatment. The mean (SD) of the EQ-5D utility index score at baseline was 0.72 (0.256) in the placebo arm, 0.70 (0.245) in the 400 mg arm, and 0.67 (0.286) in the 500 mg arm. Mean change from baseline to the End of Cycle 6 was +0.05 (95% CI = 0 to 0.09) in the 400 mg arm and +0.04 (95% CI = -0.01 to 0.10) in the 500 mg arm versus -0.05 (95% CI = -0.11 to 0.01) in the placebo arm.

The visual analog scale (VAS) in EQ-5D recorded the respondent's self-rated health on a vertical scale with endpoints of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

Baseline health status measured by the (EQ-5D VAS) scores (ITT Population) was similar in the 3 arms: mean (SD) was 62.5 (21.2) in the placebo arm, 61.3 (22.2) in the 400 mg arm, and 60.1 (20.1) in the 500 mg arm. Subjects treated with fedratinib at both doses experienced improvement in HRQOL versus placebo at the End of Cycle 6, as measured by the EQ-5D. At the End of Cycle 6, there was a mean change of +6.2 (95% CI = 1.8 to 10.5) in the 400 mg arm and +3.6 (95% CI = -1.0 to 8.2) in the 500 mg arm, whereas placebo treatment led to slight worsening of HRQOL (mean change of -0.9 [95% CI = -7.7 to 5.8]).

A higher proportion of subjects in the 400 mg arm versus the placebo arm reported improvement for the EQ-5D dimensions especially for mobility (12.5% versus 4.3%), usual activities (11.5% versus

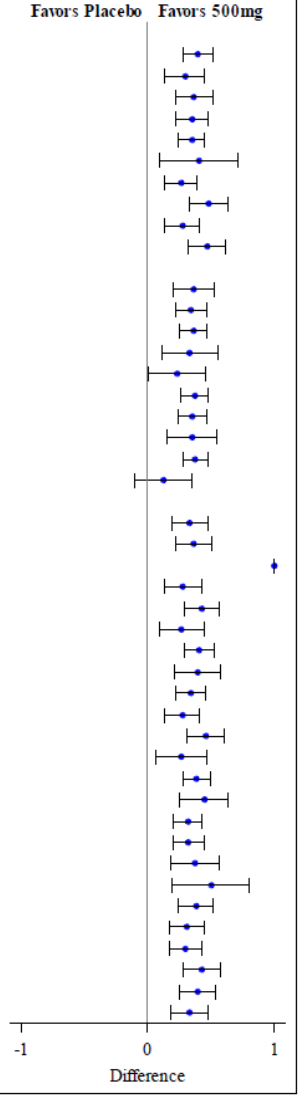
5.4%), and pain/discomfort (14.6% versus 3.2%). The percentages of subjects having reported worsening were comparable between treatment arms.

A higher proportion of subjects in the 500 mg arm versus the placebo arm reported improvement for the EQ-5D dimensions of usual activities (12.5% versus 5.4%) and pain/discomfort (14.5% versus 3.2%). The percentages of subjects having reported worsening were slightly lower in the 500 mg arm.

Ancillary analyses

Subgroup Analyses of Spleen Response Rate (≥ 35% SVR) Analyses by Baseline Factors
The consistency of the treatment effect on the primary endpoint of spleen RR at the End of Cycle 6 with confirmation 4 weeks later was further evaluated in subgroups defined according to clinically relevant demographic factors and baseline disease characteristics / prognostic factors. Forest plots showed a consistent benefit in spleen RR in favor of fedratinib over placebo for both tested doses (400 (Figure 19) and 500 mg *(Note assessor: Figure similar and not reproduced here)* for each of the evaluated subgroups of the ITT Population,

Subgroup	N	Response Rate	difference and 95% CI
Age: <=65 years old	105	(0 vs 39.3%)	39.3%(27.1%,51.6%)
Age: >65 years old	87	(1.9% vs 31.4%)	29.5%(13.7%,45.3%)
ECOG: 0	72	(0 vs 36.6%)	36.6%(21.8%,51.3%)
ECOG: >= 1	119	(1.6% vs 36.4%)	34.8%(21.7%,47.9%)
Race: White	176	(1.1% vs 36.0%)	34.9%(24.6%,45.3%)
Race: Non-White	16	(0 vs 40.0%)	40.0%(9.6%,70.4%)
Sex: Male	109	(1.8% vs 27.8%)	26.0%(13.5%,38.4%)
Sex: Female	83	(0 vs 47.6%)	47.6%(32.5%,62.7%)
Weight: >median	94	(2.3% vs 29.4%)	27.1%(13.8%,40.4%)
Weight: <=median	91	(0 vs 46.5%)	46.5%(31.6%,61.4%)
HGB >=10 g/dL: No	80	(0 vs 36.4%)	36.4%(20.0%,52.8%)
HGB >=10 g/dL: Yes	111	(2.1% vs 36.5%)	34.4%(21.9%,47.0%)
LDH >5 ULN: No	157	(1.3% vs 37.7%)	36.4%(25.3%,47.5%)
LDH >5 ULN: Yes	31	(0 vs 33.3%)	33.3%(11.6%,55.1%)
Platelet: <100 10^9/L	31	(0 vs 23.1%)	23.1%(0.2%,46.0%)
Platelet: >=100 10^9/L	159	(1.3% vs 39.0%)	37.7%(26.9%,48.6%)
WBC>=25 10^9/L: No	138	(1.5% vs 37.0%)	35.4%(24.0%,46.9%)
WBC>=25 10^9/L: Yes	53	(0 vs 34.8%)	34.8%(15.3%,54.2%)
RBC transfusion dependence: No	178	(1.1% vs 38.6%)	37.5%(27.1%,47.9%)
RBC transfusion dependence: Yes	14	(0 vs 12.5%)	12.5%(-10.4%,35.4%)
Blasts >=1%: No	85	(0 vs 33.3%)	33.3%(19.1%,47.6%)
Blasts >=1%: Yes	102	(2.0% vs 38.5%)	36.5%(22.7%,50.2%)
Fibrosis grade: 0	4	(0 vs 100.0%)	100.0%(100.0%,100.0%)
Fibrosis grade: 1 or 2	85	(2.4% vs 30.2%)	27.9%(13.4%,42.3%)
Fibrosis grade: 3	96	(0 vs 42.9%)	42.9%(29.0%,56.7%)
Baseline JAK-2 Status: Negative	62	(3.1% vs 30.0%)	26.9%(9.4%,44.3%)
Baseline JAK-2 Status: Positive	121	(0 vs 40.3%)	40.3%(28.1%,52.5%)
Spleen size >10cm: No	53	(0 vs 39.3%)	39.3%(21.2%,57.4%)
Spleen size >10cm: Yes	139	(1.4% vs 35.3%)	33.9%(22.2%,45.6%)
Spleen volume: >median	97	(2.0% vs 29.2%)	27.1%(13.7%,40.6%)
Spleen volume: <=median	88	(0 vs 45.7%)	45.7%(31.3%,60.0%)
Constitutional symptoms: No	49	(3.8% vs 30.4%)	26.6%(6.4%,46.8%)
Constitutional symptoms: Yes	143	(0 vs 38.4%)	38.4%(27.2%,49.5%)
Prior hydroxurea therapies: No	69	(0 vs 44.4%)	44.4%(25.7%,63.2%)
Prior hydroxurea therapies: Yes	123	(1.9% vs 33.3%)	31.5%(19.8%,43.2%)
Myelofibrosis type: Primary MF	120	(1.7% vs 33.9%)	32.1%(19.9%,44.4%)
Myelofibrosis type: Post-PV MF	51	(0 vs 37.5%)	37.5%(18.1%,56.9%)
Myelofibrosis type: Post-ET MF	21	(0 vs 50.0%)	50.0%(19.0%,81.0%)
Intermediate-2 risk	103	(2.2% vs 40.4%)	38.2%(24.8%,51.6%)
High risk MF	89	(0 vs 30.8%)	30.8%(16.3%,45.3%)
1st diagnosis time*: >median	103	(2.0% vs 31.5%)	29.4%(16.4%,42.4%)
1st diagnosis time*: <=median	89	(0 vs 42.9%)	42.9%(27.9%,57.8%)
Total symptom score: >median	85	(0 vs 39.6%)	39.6%(25.7%,53.4%)
Total symptom score: <=median	91	(2.1% vs 34.9%)	32.8%(18.0%,47.6%)



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EOC6 = End of Cycle 6; HGB = hemoglobin; ITT = intent to treat; JAK-2 = Janus kinase-2; LDH = lactate dehydrogenase; MF = myelofibrosis; post-ET MF = post-essential thrombocythemia myelofibrosis; post-PV MF = post-polycythemia vera myelofibrosis; RBC = red blood cell; SVR = spleen volume reduction; vs = versus; WBC = white blood cell.

Note: * First diagnosis time = time from first diagnosis of MF to randomisation.

Figure 19: Subgroup analyses by baseline factors of spleen RR (⩾ 35% SVR) at the EOC6 confirmed 4 weeks later – 400 mg compared with placebo (ITT Population)

Selection of Subgroups by Baseline Factors in the Fedratinib 400 mg Arm

For a number of subgroups, the Spleen Response Rate at the End of Cycle 6 confirmed 4 weeks later is given for the fedratinib 400 mg arm separately to facilitate comparison between contrasting subgroups e.g. Spleen RR per MF subtype (Table 35).

Table 35: Spleen RR (≥35% SVR) at the EOC6 confirmed 4 weeks later - Selection of subgroups by baseline factors (ITT Population)

			EFC12153 Fedratinib 400 mg (N = 96)
		N	**n** (%) (95 % CI)
Age Subgroup	**≤ 65**	**61**	**24 (39.3)** (27.1, 51.6)
	> 65	**35**	**11 (31.4)** (16.0, 46.8)
Sex	**Male**	**54**	**15 (27.8)** (15.8, 39.7)
	Female	**42**	**20 (47.6)** (32.5, 62.7)
Baseline ECOG PS	**ECOG 0**	**41**	**15 (36.6)** (21.8, 51.3)
	ECOG ≥1	**55**	**20 (36.4)** (23.7, 49.1)
MF Subtype:	**PMF**	**62**	**21 (33.9)** (22.1, 45.7)
	Post PV MF	**24**	**9 (37.5)** (18.1, 56.9)
	Post ET MF	**10**	**5 (50)** (19.0, 81.0)
Platelet Count:	**< 100x10^9/L**	**14**	**3 (21.4)** (0, 42.9)
	≥ 100x10^9/L	**82**	**32 (39.0)** (28.5, 49.6)
Spleen Volume	**≤ median**	**46**	**21 (45.7)** (31.3, 60.0)
	> median	**48**	**14 (29.2)** (16.3, 42.0)
MF risk category	**Intermediate-2**	**57**	**23 (40.4)** (27.6, 53.1)
	High-risk	**39**	**12 (30.8)** (16.3, 45.3)
JAK2 Mutational Status	**Mutated**	**62**	**25 (40.3)** (28.1, 52.5)

	Wild Type	**30**	**9 (30.0)** (13.6, 46.4)

Spleen Response Rate by Baseline Platelet Count

Due to the high unmet need for MF patients with a baseline platelet count <100 x 109/L, analyses were performed to evaluate spleen RR for the subgroups of subjects with a baseline platelet count <100 x 109/L versus ≥100 x 109/L. Subjects in both fedratinib arms showed a clinically meaningful spleen response compared with placebo, regardless of the baseline platelet count although in the fedratinib 400 mg arm, the rate was lower in patients with a baseline platelet count of $<100x10^9$/L versus ≥ $100x10^9$/L (21.4% versus 39.0%). However, it must be noted that a minority of patients in each arm had a platelet count of $<100x10^9$/L, with respectively 18, 14 and 15 subjects in the placebo, 400 mg and 500 mg arms and the 95% confidence intervals of the response rates were wide and overlapping.

Spleen Response Rate by other Baseline Subgroups of interest in relation to disease characteristics

Myelofibrosis Risk Category and JAK2V617F Mutational Status: In the analyses evaluating spleen RR based on the baseline MF risk category and baseline JAK2V617F mutational status, a clinically meaningful spleen RR compared with placebo was also seen for subjects in both fedratinib arms. In the fedratinib 400 mg arm, for the baseline Intermediate-2 risk and high-risk MF categories the spleen RRs were 40.4% and 30.8% respectively and for JAK2V617F mutational profile being mutant or wild type, the spleen RRs were 40.3% and 30.0% respectively. For both of these subgroups, taking the differences in patient numbers per category and the overlapping 95% confidence intervals, these rates can be regarded as being similar.

Myelofibrosis Subtype: For PMF (n=62), and Post PV MF (n=24), in the fedratinib 400 mg arm the Spleen RRs were practically the same at 33.9 and 37.5 respectively. Again, taking the differences in patient numbers per category and the overlapping 95% confidence intervals, these rates can be regarded as being similar. The Post ET MF subgroup (n=10) was too small to provide an estimate of the response rate which can be considered representative for Post ET MF patients.

Male vs Female Subjects: In the fedratinib 400 mg arm, for male subjects the Spleen RR was 15/54 (27.8%; 95% CI: 15.8, 39.7) and for females it was 20/42 (47.6%; 95% CI: 32.5, 62.7) with barely overlapping confidence intervals.
This was not seen in the fedratinib 500 mg arm, in which the Spleen RR was 26/61 (42.6%; 95% CI: 30.2, 55.0) in male subjects and in females it was 13/36 (36.1%; 95% CI: 20.4, 51.8). *(For Spleen RR in male and female patients please be also referred to the subgroup analyses in study ARD 12181 (JAKARTA2) where the rate (without LOCF) was also lower in males (13/53 (24.5%)) vs females 17/44 (38.6%) but the difference was less and with more overlap in the 95% confidence intervals.)*

Note on subgroups transfusion dependence/independence

For the subgroup of transfusion dependence/independence, the response rate in transfusion dependent patients was low (12.5%) in the 400 mg arm and high (60.0%) in the 500 mg arm. However, there were very few patients with transfusion dependence at baseline (n=14 for the fedratinib 400 mg vs placebo comparison and n=11 for the fedratinib 500 mg vs placebo comparison). Therefore, it is not possible to draw conclusions from this observation and it will not be pursued.

Results ARD12181 (JAKARTA2) / ARD12181 CSR Addendum

Participant flow

A total of 97 subjects were enrolled and treated in the study; of these 79 fulfilled the criteria of relapsed/refractory or intolerant based on post-hoc criteria (CSR Addendum cohort 1). Subject disposition is shown in Table 36 for the ITT population and cohort 1.

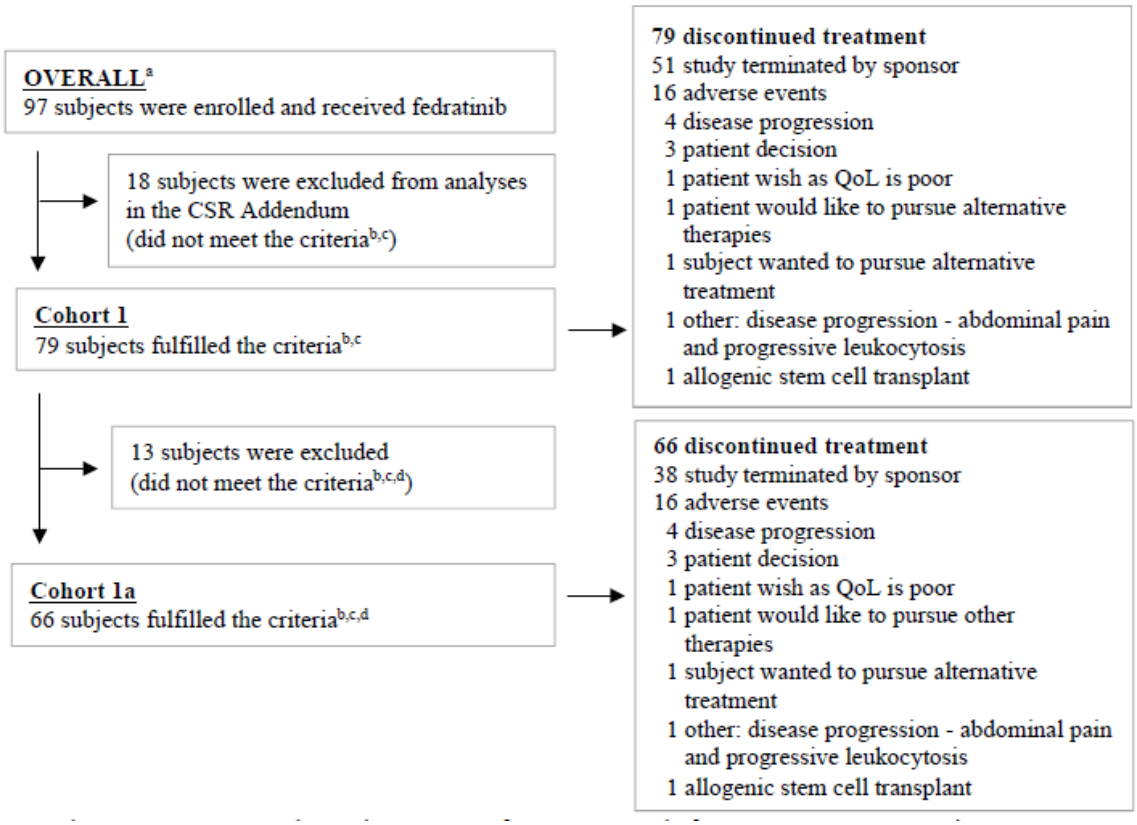
When the development of fedratinib was terminated on 18 Nov 2013, all subjects worldwide were permanently discontinued from fedratinib treatment. At the time of study termination, 63 subjects were still receiving fedratinib and study termination was the main reason for permanent treatment discontinuation (64.9%) followed by adverse events (18.6%) and to a lesser extent disease progression (6.2%). These frequencies were comparable for cohort 1 at 64.5%, 20.2% and 5.1% respectively and also for cohort 1a (Figure 20).

Of the 79 subjects that met the newly-defined criteria for R/R or intolerant to ruxolitinib treatment (Cohort 1), The criteria for Cohort 1a were met by 66 subjects and 13 subjects were excluded as they discontinued treatment prior to Cycle 6 due to termination of the study (Figure 20).

Table 36: Subject disposition - Study ARD12181 (ITT Population and Cohort 1)

	Fedratinib (N = 97) n (%)	**Cohort 1 (N=79) n (%)**
Enrolled but not treated	0	
Enrolled and treated	97 (100)	79 (100)
Discontinued study treatment	97 (100)	79 (100)
Reason for discontinuation		
Adverse event	18 (18.6)	16 (20.2)
Poor compliance to protocol	0	
Disease progression	6 (6.2)	4 (5.1)
Other	73 (75.3)	59 (74.7)
Study terminated by sponsor	63 (64.9)	51 (64.5)
Subject decision	3 (3.1)	3 (3.8)
Subject wish as the quality of life is poor	1 (1.0)	1 (1.3)
Subject withdraw consent, also no follow-up	1 (1.0)	
Subject would like to pursue alternative therapies	1 (1.0)	1 (1.3)
Subject wanted to pursue alternative treatment	1 (1.0)	1 (1.3)
Subject decided to withdraw due to lack of clinical benefit	1 (1.0)	
Allogenic stem-cell transplant	1 (1.0)	1 (1.3)
Disease progression - feeling abdominal pain and progressive leucocytosis	1 (1.0)	1 (1.3)

ITT = intent to treat.; cohort 1: relapsed/refractory or intolerant based on post-hoc criteria.



a: A total of 97 subjects were enrolled and treated in the study. b: Relapsed/refractory to ruxolitinib
c: Intolerant to ruxolitinib d: Had received Cycle 6 of fedratinib treatment or had discontinued fedratinib treatment before Cycle 6 due to reasons other than "Study terminated by the sponsor" (ie, had discontinued due to an "AE," "Withdrawal of consent," "Investigator decision," or "Progressive disease").

Figure 20: Subject disposition overall and by cohort – All Subjects (Post-hoc Analysis)

Recruitment

Patients were recruited from forty active sites in Canada, Austria, Belgium, France, Germany, Italy, Spain, Netherlands, United Kingdom, and the United States. Date first subject enrolled: 30 Apr 2012. Date last subject completed: 07 May 2014.

Conduct of the study

Protocol deviations
In the study, 4 subjects had important protocol deviations, all of which were related to the subjects not meeting inclusion/exclusion criteria. Protocol deviations were medically reviewed prior to database lock leading to no subjects being excluded from the efficacy analyses, as it was considered that none would affect the interpretation of results.

Baseline data

Demographic Characteristics

The ITT population consisted of 54.6% men and 45.4% women; subjects were mostly white (94.8%) and had a median age 67.0 years (Table 37). The proportion of subjects who were ≤65 years of age was 42.3% and 13.4% was older than 75 years Results were comparable between the ITT population and chort1 and cohort 1a.

Table 37: Demographic characteristics – ITT population ARD12181

	Study ARD12181 Fedratinib 400 mg		
	Overall N = 97	Cohort 1[a] N = 79	Cohort 1a [a] N = 66
Age (years)			
n	97	79	66
Mean (SD)	66.5 (8.14)	66.3 (8.43)	65.7 (8.64)
Median	67.0	66.0	66.0
Min, Max	38, 83	38, 83	38, 83
Age Group (≤ 65), n (%)	41 (42.3)	36 (45.6)	32 (48.5)
Age Group (> 65), n (%)	56 (57.7)	43 (54.4)	34 (51.5)
Age Group (≤ 75), n (%)	84 (86.6)	68 (86.1)	58 (87.9)
Age Group (> 75), n (%)	13 (13.4)	11 (13.9)	8 (12.1)
Sex, n (%)			
Male	53 (54.6)	41 (51.9)	35 (53.0)
Female	44 (45.4)	38 (48.1)	31 (47.0)
Race, n (%)			
White	92 (94.8)	74 (93.7)	63 (95.5)
Black	1 (1.0)	1 (1.3)	0 (0.0)
Asian	4 (4.1)	4 (5.1)	3 (4.5)
Other	0	0 (0.0)	0 (0.0)
Weight (kg)			
n	96	78	65
Mean (SD)	73.6 (12.89)	73.1 (13.58)	73.1 (12.84)
Median	73.0	72.2	73.0
Min, Max	47.0, 105.7	47.0, 105.7	47.0, 105.7
Region, n (%)			
Europe	63 (64.9)	NA	NA
North America	34 (35.1)	NA	NA
Other	0	NA	NA

cm = centimetre; NA = not available; SD = standard deviation

[a] Cohort 1 is a subset of the total population of the study based on the new definitions of R/R and intolerant to ruxolitinib that Celgene-Impact applied. Cohort 1a is a subset of Cohort 1 and includes subjects who either had the opportunity to receive a minimum of 6 cycles of fedratinib treatment or discontinued study treatment prior to Cycle 6 due to any reason other than the clinical hold/global termination of the programme.

Note: The denominator for percentages is the number of subjects in the ITT Population.

Baseline Myelofibrosis Disease Characteristics

Baseline disease characteristics are summarised in Table 38. In the overall ITT population (n=97), the largest proportion of subjects (54.6%) had PMF, followed by post-PV MF (25.8%) and post-ET MF (19.6%). The median time since diagnosis of MF was 4.0 years. The most frequent MF risk categories by the IPSS or the DIPSS were intermediate-2 risk (48.5%) and high risk (35.1%); 16.5% was intermediate- 1 risk with symptoms. Almost all subjects (95.9%) had constitutional symptoms (night sweats, itching, abdominal discomfort, abdominal pain, early satiety, or bone pain) prior to starting treatment with fedratinib. Most subjects had an ECOG PS of 0 (26.8%) or 1 (46.4%) and about 15% were RBC-transfusion dependent. Approximately 60% of subjects had a mutant JAK2. The median spleen volume at baseline was 2893.50 mL (range: 737.0 to 7815.0 mL), which is approximately 14 times the median normal spleen volume of about 215 mL (Prassopoulos, 1997). The median spleen size at baseline was 18.0 cm (range: 5.0 to 36.0 cm). Disease characteristics at baseline for subjects in Cohorts 1 and 1a were comparable to that of the overall ITT population.

Table 38: Baseline disease characteristics for ARD12181 (ITT Population)

	Study ARD12181 Fedratinib 400 mg		
	Overall N = 97	**Cohort 1[a] N = 79**	**Cohort 1a[a] N = 66**
Type of MF, n (%)			
Primary	53 (54.6)	47 (59.5)	38 (57.6)
Post-PV	25 (25.8)	18 (22.8)	17 (25.8)
Post-ET	19 (19.6)	14 (17.7)	11 (16.7)
Risk Status, n (%)			
Intermediate-1 with symptoms	16 (16.5)	11 (13.9)	6 (9.1)
Intermediate-2	47 (48.5)	41 (51.9)	35 (53.0)
High-risk MF	34 (35.1)	27 (34.2)	25 (37.9)
Time since diagnosis of myelofibrosis disease (years)			
Mean (SD)	6.15 (5.589)	6.58 (5.712)	6.84 (5.749)
Median	4.08	5.35	5.61
Min, Max	0.3, 24.5	0.4, 24.5	0.4, 24.5
RBC transfusion dependence status, n (%)			
Yes	14 (14.4)	13 (16.5)	12 (18.2)
No	83 (85.6)	66 (83.5)	54 (81.8)
JAK2 mutational profile, n (%)			
Wildtype	29 (29.9)	25 (31.6)	20 (30.3)
Mutant	61 (62.9)	48 (60.8)	41 (62.1)
Missing	7 (7.2)	6 (7.6)	5 (7.6)
ECOG PS, n (%)			
0	26 (26.8)	24 (30.4)	18 (27.3)
1	45 (46.4)	32 (40.5)	25 (37.9)
2	23 (23.7)	21 (26.6)	21 (31.8)
Missing	3 (3.1)	2 (2.5)	2 (3.0)
Constitutional symptoms[c]			
Yes	93 (95.9)	76 (96.2)	64 (97.0)
No	4 (4.1)	3 (3.8)	2 (3.0)
Spleen Volume (MRI) (mL)			
n	94	77	64
Mean (SD)	3094.8 (1458.73)	3149.6 (1470.26)	3245.5 (1482.59)
Median	2893.5	2946.0	2997.5
Min, Max	737, 7815	737.0, 7815.0	784.0, 7815.0
Spleen Size (palpation) (cm)			
n	97	79	66
Mean (SD)	18.08 (7.380)	18.47 (7.479)	18.75 (7.678)
Median	18.00	18.00	18.00
Min, Max	5.0, 36.0	5.0, 36.0	5.0, 36.0

ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; Max = maximum; MF = myelofibrosis; Min = minimum; MRI = magnetic resonance imaging; NA = not available; post-ET = post-essential thrombocythemia; post-PV = post-polycythemia vera; PS = performance status; SCE = Summary of Clinical Efficacy; SD = standard deviation.

[a] Cohort 1 includes subjects meeting newly defined criteria for relapsed/refractory or intolerant to ruxolitinib. Cohort 1a is a subgroup of Cohort 1 that includes subjects who initiated Cycle 6 of fedratinib treatment or who had discontinued fedratinib treatment for reasons other than "study terminated by sponsor."

[c] A subject had constitutional symptoms if any of the symptoms in the baseline MPN-SAF (night sweats, itching, abdominal discomfort, abdominal pain, early satiety, bone pain) had a value greater than zero.

Prior Anticancer Treatments

The majority (79.4%) of subjects had received ≥2 prior anticancer therapies, and 13.4% of subjects had received ⩾4 prior anticancer therapies. Per protocol, all 97 subjects enrolled in the study had received prior treatment with ruxolitinib. Besides ruxolitinib, the most common anticancer therapy was hydroxycarbamide, which was received by 68.0% of subjects.

Prior Treatment with Ruxolitinib and Subjects Resistant or Intolerant as per Investigator's Assessment

The initial daily dose of ruxolitinib which subjects had received was 30 mg or 40 mg (currently approved initial dose for Jakavi) in 71.1% (69/97) of the subjects and 20 mg in 18.6% (18/97). The median duration of exposure to ruxolitinib prior to enrollment was 10.68 months and exposure ranged from 1.0 to 62.4 months. Subjects were classified as resistant or intolerant to ruxolitinib as per investigators' assessment and of the 97 subjects enrolled and treated, 64 (66.0%) subjects were classified as resistant to ruxolitinib, 32 (33.0%) subjects were classified as intolerant and one subject was categorised as "Other: Lack of efficacy". However, as mentioned above under "Patient Disposition", 79 subjects fulfilled the criteria of relapsed/refractory or intolerant based on post-hoc criteria applied by MF experts and formed Cohort 1.

Numbers analysed

The analysis populations are described in the Section Statistical Methods and the numbers of patients per analysis population are shown in Table 39.

Of the 97 enrolled subjects, 14 were excluded from the PP Population because they either missed the baseline MRI/CT scan assessment of spleen volume or did not have a post-baseline assessment of spleen volume. There were 90 (92.8%) subjects in the MFSAF Analysis Population, and 90 (92.8%) in the EORTC QLQ-C30 Analysis Population. These proportions were the same in cohort1 and cohort 1a.

All 97 subjects enrolled were included in the PK Population.

The Thiamine Supplementation Follow-up Population included 81 (83.5%) subjects, of whom 65 subjects were adequately followed up. Sixteen subjects were not part of this population because they either died prior to the Thiamine Supplementation Period (11 subjects) or did not choose to take thiamine and refused follow-up (5 subjects).

Table 39: Analysis Populations - Study ARD12181 primary and post-hoc analysis

	Fedratinib 400 mg		
	All subjects (N = 97) n (%)	**Cohort 1 N = 79**	**Cohort 1a N = 66**
ITT Population	97 (100)	79 (100.0)	66 (100.0)
All Treated Population	97 (100)	79 (100.0)	66 (100.0)
Per-protocol Population[b]	83 (85.6)	70 (88.6)	58 (87.9)
MFSAF Analysis Population[c]	90 (92.8)	74 (93.7)	62 (93.9)
Thiamine Supplementation Follow-up Population[d]	81 (83.5)		

ITT = intent-to-treat; MFSAF = myelofibrosis symptom assessment form

Outcomes and estimation

Spleen Response Rate

The pre-defined primary endpoint spleen RR used the LOCF method performed for the Per-protocol Population (n=83). The proportion of the 83 evaluable subjects in the PP Population who had a spleen response (≥ 35% spleen volume reduction (SVR)) was 48.2% (95% CI: 37.1% to 59.4%). The lower

limit of the 95% CI for the spleen RR was above 10%, which was used in defining a null hypothesis of ≤10% RR for determining the sample size by the original Sponsor of the product.

To confirm the robustness of the results, Celgene-Impact conducted 3 additional supportive analyses which yielded the following spleen RRs (95% CI), in line with results of the primary analysis: PP Population without LOCF: 36.1% (25.9, 47.4) [*30/83]*
ITT Population with LOCF: 41.2% (31.3, 51.7) *[40/97]*
ITT Population without LOCF: 30.9 (21.9, 41.1) *[30/97]*

The spleen RRs for the Overall ITT Population with and without LOCF, for Cohort 1 ITT without LOCF and for Cohort 1a ITT without LOCF are shown in Table 40. For cohort 1, the results were comparable to that of the overall ITT population without LOCF.

Table 40: Proportion of subjects with ⩾ 35% reduction in spleen volume relative to baseline at the end of cycle 6 - Study ARD12181 / ARD12181 CSR Addendum ITT Populations with and without LOCF)

	Fedratinib 400 mg			
	Overall ITT Population with LOCF (N = 97)	**Overall ITT Population without LOCF (N = 97)**	**Cohort 1 ITT without LOCF (N=79)**	**Cohort 1a ITT without LOCF (N=66)**
End of Cycle 6				
n (%)	40 (41.2)	30 (30.9)	24 (30.4)	24 (36.4)
95% CI	31.3, 51.7	21.9, 41.1	20.5, 41.8	24.9, 49.1

CI = confidence interval; ITT = intent-to-treat; LOCF last observation carried forward
Confidence interval estimated by Clopper-Pearson Exact method.
Note: Results are presented by the starting dose, ie, 400 mg. Of the 97 enrolled subjects, the majority (n = 64; 65.9%) did not have a dose up-titration.
Note: Spleen volume was measured by MRI/CT and reviewed in a blinded fashion by a central imaging laboratory.

Given the single arm design and the additional uncertainty from missing data due to early study termination by the original sponsor, the most conservative approach is the one based on the ITT without LOCF (i.e. missing for whatever reason is considered a non-response). This also supported by the substantially lower point estimate (30.9% vs 48.2%). Therefore, the results of the ITT without LOCF are considered most relevant in this report.

Analyses by Maximum Fedratinib Dose Administered

In study ARD12182, up-titration to 500 mg or 600 mg was allowed if predefined efficacy and safety criteria were met (within the first 6 cycles of the treatment, if the subject's spleen response did not achieve a ≥50% reduction in spleen size by palpation and there was no unacceptable drug toxicity). Of the 97 enrolled subjects, the majority (n = 64; 66.0%) did not have dose up-titration and 33 (34%) had a dose up-titration; 17 (17.5%) received a maximum dose of 500 mg once daily; 15 (15.5%) received a maximum dose of 600 mg QD; and 1 subject received a maximum dose of 800 mg/day, which was noted as a protocol deviation (this subject is analysed with the subjects who received a maximum dose of 600 mg once daily).

The spleen volume response of subjects who had a dose up-titration are summarised below.

17 subjects received a maximum dose of 500 mg/day. Of these, 1 subject did not have an End-of-Cycle 3 assessment:

- 10/17 subjects had the dose up-titrated, but never achieved a ≥35% SVR; furthermore, 5 out of

the 10 subjects needed a dose reduction to 400 mg/day or lower due to toxicity.

- 3/17 subjects already had a ≥ 35% SVR at a dose of 400 mg/day, before the dose up-titration to 500 mg/day occurred.
- 4/17 subjects achieved a ≥ 35% SVR after the dose up-titration; however, 2 of the 4 subjects needed a dose reduction to 400 mg/day due to toxicity.

15 subjects received a maximum dose of 600 mg/day. One subject is also mentioned here who took 800 mg/day (on Cycle 4 Day 8 only) instead of the intended 400 mg/day:

- 9/16 subjects had the dose up-titrated, but never achieved a ≥ 35% SVR; furthermore, 6 out of the 9 subjects needed a dose reduction to 400 mg/day due to toxicity.
- 1/16 subjects already had a ≥ 35% SVR before the dose up-titration to 800 mg/day occurred.
- 6/16 patients achieved a ≥ 35% SVR after the dose up-titration; however, 5 of the 6 subjects needed a dose reduction to 400 mg/day due to toxicity.

Thus 4/17 patients who received up-titration to a maximum of 500 mg/day and 6/16 patients who were up-titrated to a maximum of 600 mg/day achieved a ≥35% SVR after the dose up-titration. However, 7 of these 10 patients who had achieved a ≥35% SVR after the dose up-titration needed a dose reduction to 400 mg/day due to toxicity. The applicant concludes that for these 10 patients it is difficult to determine if dose up-titration may have provided any additional clinical benefit.

Most of the other patients did not achieve a ⩾35% SVR and at least half of those patients needed a dose reduction due to toxicity and 3 of 17 patients who had up-titrated to 500 mg had achieved a ≥35% SVR before the dose increase.

As the patients who responded only after dose up-titration are also counted in the total number of responders in study ARD12181, there may be an overestimation of the spleen RR observed with a dose of 400 mg in the population studied. In response to the D120 LoQ, the applicant provided an analysis of spleen RR in the ITT Population without LOCF, counting patients who only achieved a response after dose increase above 400 mg as non-responders. The Spleen Response rate (without LOCF) for patients who received only 400 mg, thus counting 8 subjects with dose up-titration as non responders, was lower at 22/97 (22.7%; 14.8, 32.3) compared to 30/97 (30.9%; 21.9, 41.1) for those who had dose up-titration.

Percentage Change in spleen volume End of Cycle 6 Change in spleen volume from baseline to end of Cycle 6 was analysed for the subjects with available baseline and end of Cycle 6 assessments. Median percent changes in spleen volume were as follows:

Per-protocol Population with LOCF:
−34.0% at End of Cycle 6 (n=82; 95% CI: −36.0%, −24.8%; range: −73% to 115%).

Among the evaluable subjects for percent change in spleen volume at End of Cycle 6, the majority (77/82) of subjects had some degree of reduction in spleen volume when using the LOCF method.

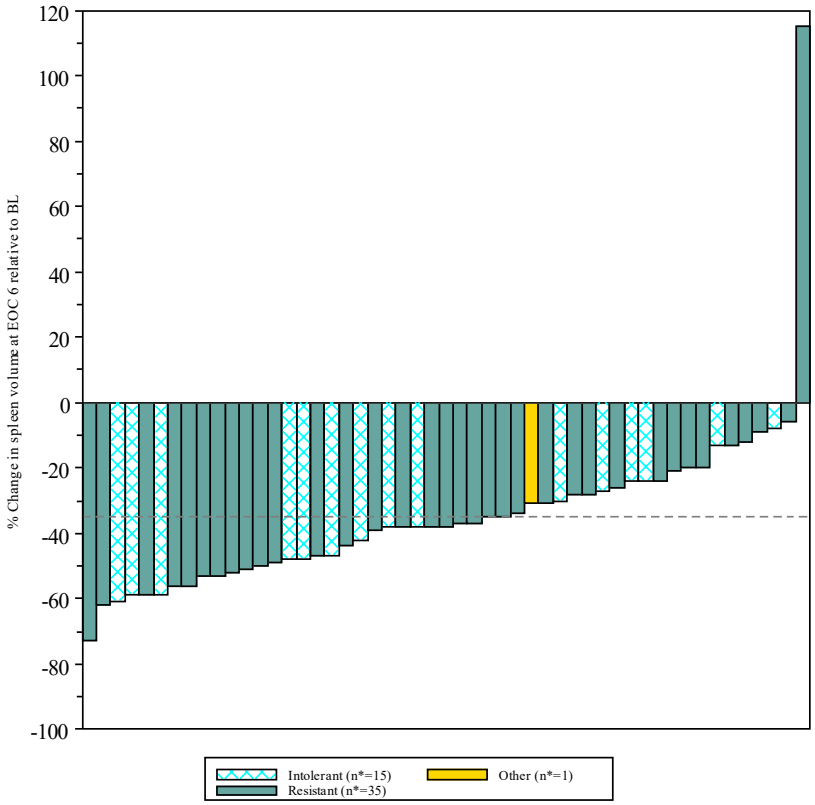
Per-protocol Population without LOCF:
-38.0% at End of Cycle 6 (n=51; 95% CI: −41.9%, −26.9%; range: −73% to 115%).

Among the evaluable subjects for percent change in spleen volume at End of Cycle 6, all but one subject had some degree of reduction in spleen volume (50/51) Figure 21.

ITT Population without LOCF: The median percent change of spleen volume was -38.0% at End of Cycle 6 (n=51; 95% CI: -41.9, -26.9; range: −73% to 115%).

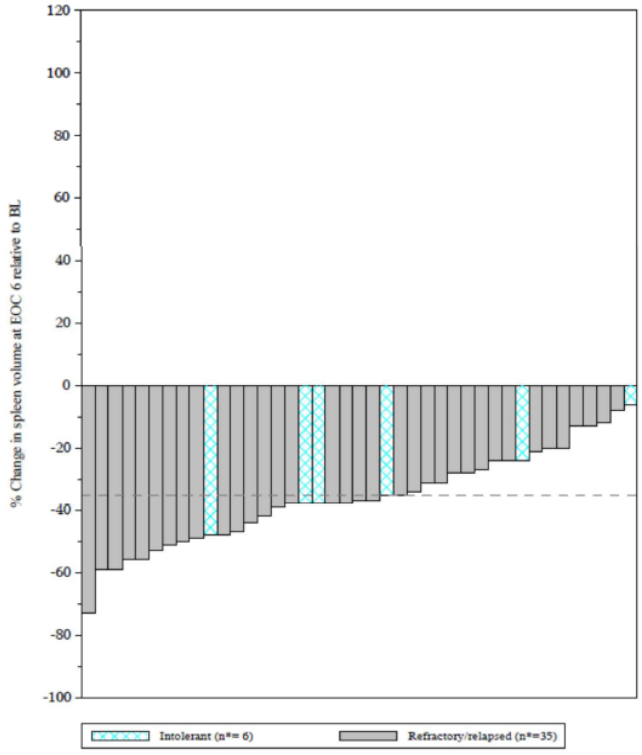
Note: The 51 (of 83) subjects who had both baseline and EOC6 spleen volume assessments were the same subjects in the ITT population (without LOCF) and the PP Population (without LOCF), which explains the identical results for the percent change in spleen volume at End of Cycle 6 (EOC6) in these 2 populations.

Cohort 1 (ITT Population without LOCF):
Among the 41 evaluable subjects for percent reduction in spleen volume, all subjects had some degree of reduction in spleen volume in both Cohorts 1 (Figure 22) and 1a (figure the same and not shown).



BL = baseline; CT = computed tomography; EOC6 = End of Cycle 6; MRI = magnetic resonance imaging; LOCF = last observation carried forward; n* = subjects with available percent change in spleen volume at EOC6.
Note: Spleen volume was measured by MRI/CT scan and reviewed in a blinded fashion by a central imaging laboratory. The analyses of percent reduction in spleen volume without LOCF did not impute the missing data.
Note: Subjects in this waterfall plot using ITT population is the same as subjects using per protocol population without LOCF in ARD12181

Figure 21: Waterfall plot of percent change in spleen volume from baseline to end of cycle 6 (without LOCF (n=51)) – Per Protocol Population



Footnote is the same as for the Watrefall Plot Per Protocol Population Figure 21

Figure 22: Waterfall plot of percent change in spleen volume from baseline to end of cycle 6 in Cohort 1 – Study ARD12181 (ITT population with available baseline and end of cycle 6 assessments (n=41)) (Post-hoc Analysis)

Secondary Efficacy endpoints

Symptom Response Rate using the modified MFSAF (Myelofibrosis Symptom Assessment Form)

The 6 key MF-associated symptoms were assessed using the modified MFSAF and measured on a scale from 0 (absent) to 10 (worst imaginable, TSS=60), thus reduction in TSS suggests improvement in symptom burden. Most (42/51) subjects in the MFSAF evaluable population with a TSS at End of Cycle 6 had a decrease in the modified MFSAF TSS at End of Cycle 6 (Figure 23).

The proportion of subjects with a ≥50% reduction in the TSS at End of Cycle 6 (the secondary endpoint Symptom RR) was 26.7% (Table 41). The proportion of subjects in the MFSAF Analysis Population achieving a ≥50% reduction in the TSS 31.1% at End of Cycle 3.

In the subset of subjects who were R/R or intolerant to ruxolitinib (Cohorts 1 and 1a, post-hoc analysis), symptom response rate was 27.0% and 32.3% respectively at the end of Cycle 6.

As for spleen RR, in response to the D120 LoQ, the applicant provided an analysis of response rate in the ITT Population, counting patients who only achieved a response after dose increase above 400 mg as non-responders. The Symptom Response rate for patients who received only 400 mg, thus counting 4 subjects with dose up-titration as non-responders, was lower at 20/93 (21.5%; 13.7, 31.2) for patients who received only 400 mg with 4 subjects considered non responders compared 24/90 (26.7%; 17.9, 37) for those who had dose up-titration.

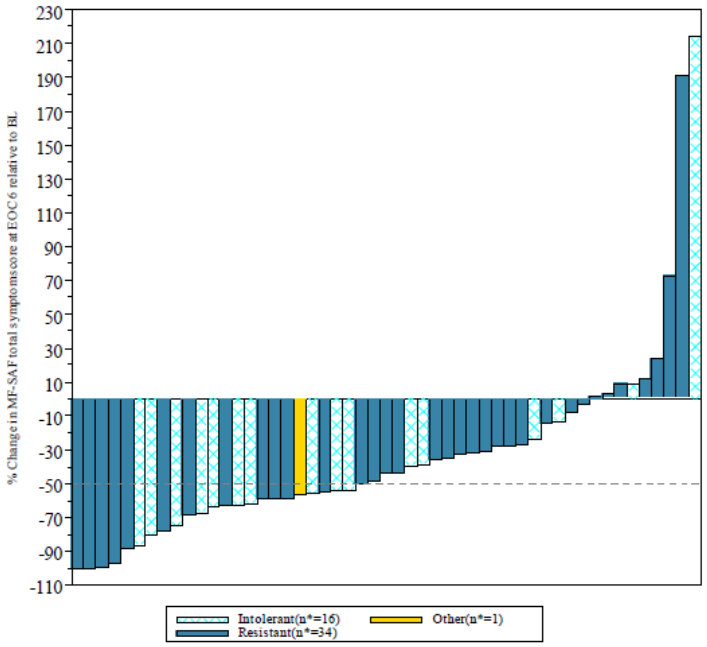
As for Study EFC12153, since the requirement to have all of the symptoms scores for each day, and to have symptom scores from 5/7 days to calculate the weekly score requires high compliance. In

response to D120 LoQ the applicant provided data on excluded symptom evaluations, demonstrating that symptom responses were similar also when all available symptom scores were included in the analyses.

Table 41: Symptom response rate – Study ARD12181 (ITT Population with non-zero baseline total symptom score)

Time Point	Study ARD12181 Fedratinib 400 mg		
	Overall N = 93	**Cohort 1 N = 74**	**Cohort 1a N = 62**
End of Cycle 3			
n (%)	28 (31.1)	22 (29.7)	18 (29.0)
95 % CI	21.8, 41.7	19.7, 41.5	18.2, 41.9
End of Cycle 6			
n (%)	24 (26.7)	20 (27.0)	20 (32.3)
95 % CI	17.9, 37	17.4, 38.6	20.9, 45.3

CI = confidence interval; ITT = intent-to-treat; MFSAF = Myelofibrosis Symptom Assessment Form; NA = not applicable
Confidence interval for response rate calculated using the Clopper-Pearson Exact method
Note: The denominator for percentages is the number of subjects in the ITT Population who have a non-zero Total Symptom Score at baseline. Subjects who were not assessed for symptom scores response are counted as non-responders.



BL = baseline; EOC 6 = End of Cycle 6; MFSAF = Myelofibrosis Symptom Assessment Form; n*= subjects with available percent change in total symptom score at EOC 6; TSS = total symptom score.

Figure 23: Waterfall plot of percent change from baseline to end of cycle 6 in modified MFSAF TSS in subjects resistant or intolerant to ruxolitinib per investigator's assessment – MFSAF Analysis Population

Median Percent Change in Total Symptom Score
The median percent change in TSS decreased over time, and the greatest reduction in TSS from baseline was observed at End of Cycle 6. For the 51 subjects in the MFSAF evaluable population with a TSS at End of Cycle 6, the median percent change was −44.33%.

All key symptoms assessed showed an improvement at End of Cycle 6 in half of the evaluable subjects, with median percent changes of:

- −83.33% in pain under ribs on left side
- −75.95% in night sweats
- −51.30% in early satiety
- −46.18% in abdominal discomfort
- −44.12% in pruritus
- −22.22% in bone or muscle pain

Spleen Response Rate at End of Cycle 3
In the overall ITT Population, the proportion of subjects with a ≥35% spleen volume reduction (SVR) at End of Cycle 3 was 40.2% (39/97 subjects). Comparable results were seen for Cohort 1 and 1a.

Table 42: Spleen response rate by MRI – Study ARD12181 (ITT Population)

	Fedratinib 400 mg		
Time Point	**Overall N = 97**	**Cohort 1 N = 79**	**Cohort 1a N = 66**
End of Cycle 3			
n (%)	39 (40.2)	34 (43.0)	27 (40.9)
95 % CI	30.4, 50.7	31.9, 54.7	29, 53.7

CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; MRI = magnetic resonance imaging; NA = not available
Cohort 1 and Cohort 1a: ITT Population without LOCF. For Overall ITT, it is not clear if this is also without LOCF.
Confidence intervals are calculated using Clopper-Pearson Exact method.

Duration of Spleen Response
For the duration of response analysis, responders were all subjects who at any time during treatment achieved a ≥ 35% reduction in spleen volume from baseline. The duration of spleen response was calculated from the first date of spleen response (i.e., ≥ 35% SVR from baseline) to the date of disease progression (i.e., ≥ 25% spleen volume increase from baseline) or death, whichever was earlier.

During the study, 2 responders had progressed or died prior to clinical hold.

The vast majority of responders, 45/47 subjects overall and 39/41 subjects in Cohort 1, were on treatment at the time of the clinical hold and the duration of response analysis was subject to extensive censoring.

Based on Kaplan-Meier estimates, 25% of patients had a duration of response of ≤ 9.4 months, the median duration was not estimable.

Effect of fedratinib on the JAK2^{V617F} allele burden and on bone marrow parameters

There were insufficient data to make statistically robust conclusions on changes in JAK2^{V617F} allele burden and bone marrow parameters during treatment. Data for both baseline and additional cycles of

treatment were collected from only 15 subjects for evaluation of effects on $JAK2^{V617F}$ allele burden and from only 13 subjects for bone marrow response assessment.

Exploratory Endpoint: Health-related Quality of Life

The EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 Analysis Population was used for the analysis of health-related QoL (HRQOL).

As one of the exploratory endpoints, scores in the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30), which is a cancer-specific instrument, were assessed at baseline and compared to those at the End of Cycle 6.

A high score for a functional scale or global health status/QoL represents a high/healthy level of functioning or a high QoL.

In half of the evaluable subjects, there was a post-baseline improvement at EOC6 for the following EORTC QLQ-C30 domains: global QoL, physical functioning, fatigue, pain, insomnia, and appetite loss. For all the other functional and symptom domains, level of QoL was overall maintained over the 6-cycle treatment period.

Ancillary analyses

The consistency of the treatment effect on the primary endpoint was further evaluated in subgroups defined according to clinically relevant demographic factors and baseline disease/prognosis characteristics. Regardless of the subgroups analysed fedratinib consistently showed clinical benefit in terms of spleen RR (≥ 35% SVR) at the end of Cycle 6 within the subsets of each subgroup and over the subgroups in the overall ITT population and in Cohort 1 (Table 43). In the various subgroups in Cohort 1a, the Spleen RRs were very similar to those in Cohort 1.

Spleen Response Rate by Baseline Platelet Count

Due to the limited number of treatment options for patients with MF and low platelet counts, spleen RR by baseline platelet count was also analysed. Irrespective of the baseline platelet count (< 100 x 10^9/L: Spleen RR 12/33 (36.4%) or ≥ 100 x 10^9/L: Spleen RR 18/64 (28.1%)), fedratinib showed clinical benefit for subjects in the ITT Population in terms of spleen RR (Table 43). The Spleen RR in patients with baseline platelet count < 100 x 10^9/L was 12/33 (36.4%) and in patients with baseline platelet count ≥ 100 x 10^9/L it was 18/64 (28.1%) and 95% confidence intervals for the rate were widely overlapping.

Spleen Response Rate by other Baseline Subgroups of interest in relation to disease characteristics

Myelofibrosis Risk Category and JAK2V617F Mutational Status: In the analyses evaluating spleen RR based on the baseline MF risk category and baseline JAK2V617F mutational status, a clinically meaningful spleen RR was seen in all subgroups.

For the baseline Intermediate risk and high-risk MF categories the spleen RRs were similar at 21/63 (33.3%) and 9/34 (26.5%) respectively with the same 95% confidence intervals.

For JAK2V617F mutational profile being mutant or wild type, the spleen RR was lower in the patients with wild type mutational profile being 5/29 (17.2%; 95% CI 3.5, 31.0) compared to 23/61 (37.7%; 95% CI 25.5, 49.9) in patients with the mutation, with 95% CIs which did not overlap. This is in contrast to study EFC12153 (JAKARTA) where this difference was not seen, although due to small patient numbers firm conclusions cannot be drawn.

Myelofibrosis Subtype
For PMF (n=53), and Post PV MF (n=25) and Post ET MF (n=19) the Spleen RRs were 28.3%, 44.0% and 21.1% respectively. Although the rate was lower in patients with Post ET MF, taking the differences in patient numbers per category and the 95% confidence intervals, which overlap but less so in the case of Post ET MF, it cannot be concluded that there is evidence of major differences in the Spleen RR between the three myelofibrosis subtypes.

Male vs Female Subjects
For male subjects the Spleen RR (without LOCF) was 13/53 (24.5%; 95% CI 12.9, 36.1) and for females it was 17/44 (38.6%; 95% CI 24.2, 53.0) with barely overlapping confidence intervals.

(For Spleen RR in male and female patients please be also referred to the subgroup analyses in study EFC12153 (JAKARTA) where the rate was also lower in males vs females but with a larger difference (27.8% vs 47.6%)).

Table 43: Subgroup analyses of spleen response rate (≥ 35% SVR) at the end of cycle 6 for demographic factors and baseline disease characteristics– Study ARD12181 (ITT Population without LOCF)

	Overall (N = 97)	**Cohort 1 N = 79**
Age (≤ 65, > 65 years)		
Age Subgroup: ≤ 65	**41**	**36**
n (%)	14 (34.1)	12 (33.3)
95 % CI	19.6, 48.7	18.6, 51.0
Age Subgroup: > 65	**56**	**43**
n (%)	16 (28.6)	12 (27.9)
95 % CI	16.7, 40.4	15.3, 43.7
Age (≤ 75, > 75 years)		
Age Subgroup: ≤75	**84**	**68**
n (%)	27 (32.1)	21 (30.9)
95 % CI	22.2, 42.1	20.2, 43.3
Age Subgroup: > 75	**13**	**11**
n (%)	3 (23.1)	3 (27.3)
95 % CI	0.2, 46.0	6.0, 61.0
Sex		
Male	**53**	**41**
n (%)	13 (24.5)	11 (26.8)
95 % CI	12.9, 36.1	14.2, 42.9
Female	**44**	**38**
n (%)	17 (38.6)	13 (34.2)
95 % CI	24.2, 53.0	19.6, 51.4
Baseline ECOG Performance Status (0, 1, 2)		
Baseline ECOG PS Subgroup: 0	**26**	**24**
n (%)	13 (50.0)	11 (45.8)
95 % CI	30.8, 69.2	25.6, 67.2
Baseline ECOG PS Subgroup: 1	**45**	**32**

n (%)	13 (28.9)	9 (28.1)
95 % CI	15.6, 42.1	13.7, 46.7
Baseline ECOG PS Subgroup: 2	**23**	**21**
n (%)	4 (17.4)	4 (19.0)
95 % CI	1.9, 32.9	5.4, 41.9
Myelofibrosis Subtype (PMF, Post PV MF, Post ET MF)		
MF Subtype: PMF	**53**	**47**
n (%)	15 (28.3)	13 (27.7)
95 % CI	16.2, 40.4	15.6, 42.6
MF Subtype: Post PV MF	**25**	**18**
n (%)	11 (44.0)	7 (38.9)
95 % CI	24.5, 63.5	17.3, 64.3
MF Subtype: Post ET MF	**19**	**14**
n (%)	4 (21.1)	4 (28.6)
95 % CI	2.7, 39.4	8.4, 58.1
Baseline Haemoglobin (< 10 g/dL, ⩾ 10 g/dL)		
Baseline Hgb < 10 g/dL	**51**	**46**
n (%)	14 (27.5)	12 (26.1)
95 % CI	15.2, 39.7	14.3, 41.1
Baseline Hgb ≥ 10 g/dL	**46**	**33**
n (%)	16 (34.8)	12 (36.4)
95 % CI	21.0, 48.5	20.4, 54.9
Baseline Platelet Count (< 100 x 10^9 L, ≥ 100 x 10^9 L)		
Baseline Platelet Count: < 100x10^9/L	**33**	**28**
n (%)	12 (36.4)	11 (39.3)
95 % CI	20.0, 52.8	21.5, 59.4
Baseline Platelet Count: ≥ 100x10^9/L	**64**	**51**
n (%)	18 (28.1)	13 (25.5)
95 % CI	17.1, 39.1	14.3, 39.6
Baseline Spleen Volume (≤ Median, >Median)		
Baseline Spleen Volume: ≤ median	**47**	**41**
n (%)	18 (38.3)	15 (36.6)
95 % CI	24.4, 52.2	22.1, 53.1
Baseline Spleen Volume: > median	**47**	**38**
n (%)	12 (25.5)	9 (23.7)
95 % CI	13.1, 38.0	11.4, 40.2
Baseline Spleen Size (≤ 10 cm, > 10 cm)		
Baseline Spleen Size: ≤ 10 cm	**12**	**12**
n (%)	7 (58.3)	7 (58.3)
95 % CI	30.4, 86.2	27.7, 84.8
Baseline Spleen Size: > 10 cm	**85**	**67**

n (%)	23 (27.1)	17 (25.4)
95 % CI	17.6, 36.5	15.5, 37.5
Risk Category (Intermediate, High-risk)		
Intermediate-1 (n=16) + Intermediate-2 (n=47)	**63**	**-**
n (%)	21 (33.3)	-
95 % CI	21.7, 45.0	-
Intermediate-1 with symptoms	**16**	**11**
n (%)	3 (18.8)	2 (18.2)
95 % CI	4.0,45.6	2.3, 51.8
Intermediate-2	**47**	**41**
n (%)	18 (38.3)	15 (36.6)
95 % CI	24.5, 53.6	22.1, 53.1
High-risk	**34**	**27**
n (%)	9 (26.5)	7 (25.9)
95 % CI	12.9, 44.4	11.1, 46.3
JAK2 Mutational Status (Mutated, Wild Type)		
Mutated	**61**	**48**
n (%)	23 (37.7)	17 (35.4)
95 % CI	25.5, 49.9	22.2, 50.5
Wild Type	**29**	**25**
n (%)	5 (17.2)	5 (20.0)
95 % CI	3.5, 31.0	6.8, 40.7

Confidence interval calculated using the Clopper-Pearson Exact method.

Subgroup analyses by the subgroups ruxolitinib R/R vs intolerant

Analyses were performed on subjects enrolled in the study and determined to be relapsed/refractory (R/R) or intolerant to ruxolitinib based on criteria recommended by MF experts from the US and EU

Spleen RR were 30.8% (20/65 subjects) for subjects R/R to ruxolitinib and 28.6% (4/14) for subjects intolerant to ruxolitinib in Cohort 1; in Cohort 1a, the spleen RRs were 35.7% (20/56) and 40.0% (4/10), respectively (Table 44).

Spleen RRs are consistent with the overall ITT study population (N = 97), although the number of ruxolitinib intolerant patients is too low to make conclusions about this subgroup.

Table 44: Subjects R/R or intolerant to ruxolitinib with ≥35% reduction in spleen volume at end of cycle 6 – ITT Population (Post-hoc Analysis)

	Fedratinib 400 mg			
	Cohort 1		Cohort 1a	
	R/R[a] N = 65	Intolerant[b] N = 14	R/R[a] N = 56	Intolerant[b] N = 10
End of Cycle 6				
n (%)	20 (30.8)	4 (28.6)	20 (35.7)	4 (40.0)
95% CI[c]	19.9, 43.4	8.4, 58.1	23.4, 49.6	12.2, 73.8

Efficacy Data following discontinuation

In study EFC12153, as mentioned under "*Disposition of Subjects"* at the time of study termination, all subjects had either completed the first 6 cycles or had previously permanently discontinued treatment.

Before EOC6: The numbers of patients who discontinued treatment permanently before end of Cycle 6 (EOC6) were 24, 21 and 31 patients in the placebo, 400 mg and 500 mg arms respectively. Among those who discontinued before EOC6, the most frequent reason was adverse event at 33.3%, 16.9% and 77.4% in the placebo, 400 mg and 500 mg arms respectively. For discontinuation due to PD, 16.7% discontinued in placebo arm and one patient in each of the fedratinib arms.

After EOC6: The most common reason for discontinuation after EOC6 was study termination by Sanofi at 68% of patients from the fedratinib arms who were continuing to receive fedratinib (51/75 from the 400 mg arm and 45/66 from the 500 mg arm (a*pplicant response to LoQ*) and 68% (49/71) of patients who had crossed from placebo to fedratinib (placebo number from EFC12153 CSR).

According to the EFC12153 study protocol, spleen size by palpation, ECOG Performance status and safety assessments were to be performed following permanent fedratinib treatment discontinuation. The applicant provided information *(post-hoc in response to Q129 in D120 LoQ)* on spleen size/volume and symptom score (TSS) (also on safety) in patients who permanently discontinued before EOC6 and in patients who permanently discontinued after EOC6. The aim was to gain more insight into the further course of the disease after treatment discontinuation.

Spleen volume reduction after treatment discontinuation
Very limited data were available on spleen volume reduction after treatment discontinuation. One of the subjects (from the fedratinib 500 mg arm) who discontinued before EOC6 had a ≥ 35% spleen volume reduction at EOT.
Considering **only patients from the fedratinib arms**, with available spleen volume assessments**,** of the 41 subjects who permanently discontinued treatment **after the EOC6**, 14.3% (3/21) of subjects in the 400 mg arm and 20.0% (4/20) in the 500 mg arm had a ≥ 35% spleen volume reduction at EOT.

Change in Spleen Size after treatment discontinuation
For subjects in the All Treated Population who permanently discontinued treatment **before the EOC6**, the mean percentage change in spleen size (by palpation) at the EOT for subjects with baseline assessments was -5.8% in the placebo arm, -12.1% in the 400 mg arm, and -21.8% in the 500 mg arm.
Considering **only patients from the fedratinib arms,** for subjects who permanently discontinued treatment **after the EOC6**, the mean percentage change in spleen size at the EOT for subjects with baseline assessments was -45.0% in the 400 mg arm (assessment in 67 of 75 subjects) and -54.3% in the 500 mg arm (assessment in 52 of 66 subjects).
It can be noted that the EOT (End of Treatment) was to be performed at least 30 days following last administration of fedratinib or placebo.

Spleen response Per Modified IWG-MRT Criteria
Best response (spleen size reduction [by palpation]) **after** permanent treatment discontinuation based on all available spleen size assessments was assessed in all patients who had received fedratinib using the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria.
Patients originally in the placebo arm, who received treatment with fedratinib, consisted of those who had progressive disease before EOC6 (n=10) and those who crossed over at EOC6 (n=61). These, added to the 96 patients in the fedratinib 400 mg arm and 97 in the 500 mg arm, account for the total number of 264 patients who had received treatment with fedratinib.

For 152 of these 264 subjects, a spleen assessment was available, 84 subjects treated with fedratinib 400 mg and 68 subjects treated with fedratinib 500 mg.

[Spleen response Per Modified IWG-MRT Criteria: a baseline splenomegaly that was palpable at 5 to 10 cm, below the LCM, became not palpable; or a baseline splenomegaly that was palpable at > 10 cm, below the LCM, decreased by ≥ 50%. A baseline splenomegaly that was palpable at < 5 cm, below the LCM (left costal margin), was not eligible for spleen response.
Stable disease: a response not belonging to the spleen response or PD response categories.]

It is understood that for this assessment of Spleen response Per Modified IWG-MRT Criteria, baseline assessment refers to an assessment prior to or at the EOT.

Regardless of subsequent anticancer therapy, 79.6% (121/152) of subjects who had available spleen size assessments had a best response of stable disease **after** permanent treatment discontinuation.

The RR (spleen size reduction of 50%) was 2.6% (4/152) and the rate of PD was 17.8% (27/152)

Note that subjects who crossed over to fedratinib from placebo are counted in the corresponding 400 or 500 mg fedratinib arm.

Among subjects who received further anticancer therapy after permanent treatment discontinuation, the rate of stable disease was 73% (54/74) over both arms, the RR was 4.1% (3/74) and the rate of PD was 23.0% (17/74)

Among subjects who did **not** receive further anticancer therapy after permanent treatment discontinuation, the rate of stable disease was 85.9% (67/78) over both arms, only one subject (500 mg arm) had a response and the rate of PD was12.8% (10/78)

According to the study design, the modified Myelofibrosis Symptom Assessment Form (MFSAF) was not completed after the EOC6 thus no relevant data on TSS are available.

Efficacy Data in Subjects Who Received Ruxolitinib or Hydroxyurea After Permanently Discontinuing Fedratinib
Per protocol, in Study EFC12153 subjects were followed for survival, progression (as assessed by spleen size), and further anticancer therapy every 3 months from the date of treatment discontinuation until death. Additionally, for subjects who had previously discontinued fedratinib, spleen size by palpation was also assessed at a Follow-up visit (14 to 33 days after thiamine supplementation) during the Thiamine Supplementation Period. The planned follow-up for survival and IWG-MRT assessment of clinical response did not occur after the clinical hold/study termination.

In response to the D120 LoQ, the applicant has provided information showing that, after discontinuation the proportions of subjects (ITT population) who received ruxolitinib (62/289 (21.5%)) or hydroxyurea (56/289 (19.4%)) as further anticancer therapy were similar. In the 145 subjects with permanent treatment discontinuation due to early study termination by Sanofi, and the 144 subjects without early study termination (further treatment in these latter cases was considered as second line therapy), the proportions of subjects who received ruxolitinib were approximately the same at 22.1 % and 20.8% respectively. The proportions of subjects who received hydroxyurea were fairly similar at 15.2% and 23.6% respectively.

Investigator Assessment of Clinical Response per Modified IWG-MRT Criteria
Information regarding the investigator IWG-MRT assessment of efficacy was available for 15 subjects who received ruxolitinib or hydroxyurea after permanently discontinuing fedratinib 400 mg or 500 mg. 13 of these subjects were fedratinib-treated, including 4 subjects who received fedratinib after crossover from placebo. From the short narratives provided, among the 13 fedratinib treated subjects, 4 had received ruxolitinib and 9 had received hydroxyurea.

The best response after subsequent therapy with ruxolitinib or hydroxyurea was PR for 1 subject (ruxolitinib treated), stable disease for 8 subjects, and PD for 4 subjects (all treated with hydroxyurea). The duration of treatment with ruxolitinib or hydroxyurea was not reported in most cases and varied considerably e.g. from several days to almost one year, in the rest.

Applicant's Assessment of Best Response in Spleen Size Reduction Per Modified IWG-MRT Criteria
Data were available for applying the IWG-MRT criteria to assess best response (spleen size reduction) after initiation of follow-up therapy with ruxolitinib or hydroxyurea, for 41 subjects who had received treatment with fedratinib (23/52 subjects who had received fedratinib 400 mg and 18/47 who had received fedratinib 500 mg). These 41 subjects included 7 of the 9 subjects who had crossed over from placebo to fedratinib 400 mg or 500 mg.
Best spleen response (spleen size was measured by palpation) was evaluated per the modified IWG-MRT criteria (Tefferi, 2013 - see above for definitions of response and stable disease).
The response rates were: Response 14.6% (6/41); Stable disease 80.5% (33/41); PD 4.9% (2/41).
No information is given on the duration of treatment with ruxolitinib or hydroxyurea.

Analysis of survival after initiation of ruxolitinib or hydroxyurea was not performed due to the very limited numbers of subjects who died. Altogether 13 subjects died after receiving ruxolitinib (N = 2) or hydroxyurea (N = 12 (one subject received both ruxolitinib and hydroxyurea)) as follow-up anticancer therapy. Eleven patients who had been treated with fedratinib died, 10 of whom had received hydroxyurea and one had received ruxolitinib.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 45: Summary of efficacy for trial ECF12153

Title: A Phase 3, Multicenter, Randomized, Double blind, Placebo-Controlled, 3-arm Study of SAR302503 in Patients with Intermediate-2 or High-risk Primary Myelofibrosis, Post polycythemia Vera Myelofibrosis, or Post essential Thrombocythemia Myelofibrosis with Splenomegaly		
Study identifier	ECF12153 (JAKARTA)	
Design	The study was a phase 3 multicentre, randomised, double-blind, placebo-controlled, 3-arm study. Patients were randomised (1:1:1) to 400 mg or 500 mg fedratinib, or placebo, once daily. Eligible patients on placebo could cross-over to fedratinib at the end of cycle 6 and were re-randomised to 400 mg or 500 mg fedratinib.	
	Duration of main phase:	Fedratinib (400 or 500 mg) or placebo was taken orally once daily for at least 6 consecutive 28-day cycles. Fedratinib treatment was continued as long as patients benefitted from therapy. Eligible patients on placebo could cross-over to fedratinib at the end of cycle 6 and were re-randomised to 400 mg or 500 mg fedratinib.
	Duration of Run-in phase:	N/A

Hypothesis	Superiority		
Treatments groups	Fedratinib 400 mg (N=97)		Taken on an empty stomach. Dose increases were not allowed. Dose reduction because of toxicity until 200 mg/day. CYP3A4 inhibitors or inducers were not allowed.
	Fedratinib 500 mg (N=97)		
	Placebo (N=96)		
Endpoints and definitions	Primary endpoint	Spleen RR	Spleen response rate, defined as a proportion of subjects with ≥35% spleen volume reduction (SRV) at the end of cycle 6 (EOC6). Confirmation of Spleen RR was required 4 weeks later.
	Secondary endpoint	Symptom RR	Symptom response rate using the modified MFSAF was defined as the proportion of subjects with ≥50% reduction in total symptom score (TSS) from baseline to EOC6. The TSS was defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified MFSAF.
		Change in spleen volume	
Database lock	01 May 2013		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT population, defined as all patients who were randomised. End of Cycle 6 with confirmation 4 weeks later.			
Descriptive statistics and estimate variability	Treatment group	Fedratinib 400 mg	Fedratinib 500 mg	Placebo
	Number of subjects	N=97	N=97	N=96
	Spleen RR (%)	36.5	40.2	1.0
	95% CI	26.8, 46.1	30.4, 50.0	0, 3.1
	Symptom RR (%)	39.6	34.1	8.2
	95% CI	29.5, 49.6	24.3, 43.8	2.4, 14.1
	Change in spleen volume (%)	N=75 -35.6	N=65 -42.3	N=58 10.3
	95% CI	5.1, 15.5	-39.9, -31.3	-47.3, -37.3
Effect estimates per comparison	Primary endpoint **Spleen RR**	Comparison groups		**Fedratinib 400 mg vs placebo**
		Difference		35.42
		97.5% CI		24.4, 46.7

		P-value Chi-square test	<0.0001
			Fedratinib 500 mg vs placebo
		Difference	39.16
		97.5% CI	27.8, 50.6
		P-value Chi-square test	<0.0001
	Secondary endpoint **Symptom RR**	Comparison groups	**Fedratinib 400 mg vs placebo**
		Difference	31.33
		95% CI	18.0, 44.6
		P-value Chi-square test	<0.0001
			Fedratinib 500 mg vs placebo
		Difference	25.83
		95% CI	12.8, 38.8
		P-value Chi-square test	<0.0001
	Change in spleen volume	Comparison groups	**Fedratinib 400 mg vs placebo**
		Difference	-45.9
		97.5% CI	-53.5, -38.8
		P-value t-test	<0.0001
		Comparison groups	**Fedratinib 500 mg vs placebo**
		Difference	-52.6
		97.5% CI	-60.8, -44.4
		P-value t-test	<0.0001
Notes	Within the fedratinib arms, 21 and 31 patients discontinued treatment before EOC6 in the 400 mg and 500 mg group, respectively, mostly due to adverse events (400 mg: n=13, 500 mg: n=24). Over the entire treatment duration, most patients discontinued due to early study termination (400m: n=61, 500 mg: n=52) and due to adverse events (400 mg: n=26, 500 mg: n=35). Study discontinuation due to disease progression was observed in 6 and 3 patients in the 400 mg and 500 mg group, respectively. Placebo group: All patients discontinued at EOC6 in line with protocol, and n=24 before EOC6. Main reasons are adverse events (n=8), consent withdrawn (n=5) and disease progression or subject request (both n=4).		

Table 46: Summary of efficacy for trial ARD12181

Title: A Phase 2, Multicenter, Open-label, Single-arm Study of SAR302503 in Subjects Previously Treated With Ruxolitinib and With a Current Diagnosis of Intermediate or High-risk Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis				
Study identifier	ARD12181 (JAKARTA2)			
Design	The study was a nonrandomised, open-label, single-arm, multicentre study of fedratinib in which all patients received 400 mg fedratinib.			
	Duration of main phase:		Fedratinib 400 mg was taken orally once daily for 6 consecutive 28-day cycles. Fedratinib treatment could be continued as long as patients benefitted from therapy.	
	Duration of Run-in phase:		N/A	
Hypothesis	N/A. The initial chi square test for testing whether the primary endpoint was > 10% was omitted due to early study termination.			
Treatments groups	Fedratinib 400 mg (N=97)		Taken on an empty stomach. Dose increases up to 600 mg/day were allowed. Dose reduction because of toxicity until 200 mg/day. CYP3A4 inhibitors or inducers were not allowed.	
Endpoints and definitions	Primary endpoint	Spleen RR	Spleen response rate, defined as a proportion of subjects with ≥35% spleen volume reduction (SRV) at the end of cycle 6 (EOC6).	
	Secondary endpoint	Symptom RR	Symptom response rate using the modified MFSAF was defined as the proportion of subjects with ≥50% reduction in total symptom score (TSS) from baseline to EOC6. The TSS was defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified MFSAF.	
Database lock	12 Jun 2014.			
Results and Analysis				
Analysis description	**Primary Analysis Sanofi**			
Analysis population and time point description	Primary endpoint: Per Protocol population with LOCF end of cycle 6			
Descriptive statistics and estimate variability	Treatment group	All patients		
	Number of subjects	N=83		
	Primary endpoint spleen RR (%)	48.2		
	95% CI	37.1, 59.4		
Notes	Within the initial SAP by Sanofi, the primary analysis was based on the per protocol population with LOCF. A total of 83/97 patients were included in the PPS. R/R or intolerant was assessed by the investigator without predefined criteria			
Analysis description	**Post-hoc analyses by Celgene**			

Analysis population and time point description	Primary endpoint: ITT with non-responder imputation at EOC6 *Post-hoc analysis by Celgene to address potential bias due to administrative early closure of the study, most conservative approach* Secondary endpoint symptom score: MSAF analysis population with a baseline TSS>0 at EOC6 Additional cohorts were identified retrospectively based on expert meeting Cohort 1: R/R and intolerance to ruxolitinib Cohort1a: Subgroup of cohort 1, primary endpoint measurement not affected by early study termination			
Descriptive statistics and estimate variability	Treatment group	All patients	Cohort 1	Cohort1a
	Number of subjects	N=97	N=79	N=66
	Primary endpoint spleen RR (%)	30.9 *Only dose 400 mg: 22.7*	30.4	36.4
	95% CI	21.9, 41.1	20.5, 41.8	24.9, 49.1
	Secondary endpoint Symptom RR (%)	N=93 25.8 *Only dose 400 mg: 21.5*	N=74 27.0	N=62 32.3
	95% CI	16.9, 34.7	17.4, 38.6	20.9, 45.3
	Spleen RR (%) end of cycle 3	40.2	43.0	40.9
	95% CI	30.4, 50.0	31.9, 54.7	29.0, 53.7
Notes	A total of 97 patients were enrolled. Thirty-nine patients discontinued before end of cycle 6, n=17 due to early study termination and n=14 due to adverse events. Post-hoc, several amendments were made by the applicant Celgene resulting in new cohorts based on criteria set by experts and in more conservative analyses given the single arm study design and potential bias by study termination.			

Clinical studies in special populations

Table 47: Clinical studies in special populations – age ⩾ 65 years

ITT Population	**Age 65-74 (Older subjects number /total number)**	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials EFC12153 (JAKARTA) All Subjects	116/289	31/289	2/289
Non Controlled trials ARD12181 (JAKARTA2)	45/97	16/97	0/97

Study EFC12153

The proportions of subjects with ≥ 35% spleen volume reduction (SVR) at the EOC6 **confirmed 4 weeks later** were 27.6% (8/29) in the 400 mg arm and 46.5% (20/43) in the 500 mg arm compared with 0% (0/44) in the placebo arm. The proportions of subjects with ≥ 35% at the EOC6 were 41.4% (12/29) in the 400 mg arm and 55.8% (24/43) in the 500 mg arm compared with 0% (0/44) in the placebo arm. For both analyses, the active treatment arms showed clinically meaningful and statistically significant differences compared with placebo ($p \leq 0.0002$).

In the smaller subgroup of subjects 75 to 84 years (N = 31), a benefit in spleen RR at the EOC6 was observed in favor of fedratinib over placebo for both doses (400 and 500 mg) but the differences were not statistically significant. The proportions of subjects with ≥ 35% SVR at the EOC6 **confirmed 4 weeks later** were 33.3% (3/9) in the 400 mg arm and 33.3% (4/12) in the 500 mg arm compared with 10.0% (1/10) in the placebo arm. The proportions of subjects with ≥ 35% SVR at the EOC6 were 44.4% (4/9) in the 400 mg arm and 33.3% (4/12) in the 500 mg arm compared with 10.0% (1/10) in the placebo arm.

Table 48: Spleen response rate (⩾ 35% SVR) by MRI/CT at the EOC6, confirmed 4 weeks later, for elderly subjects by age group – Study EFC12153 (ITT Population)

	Age 65-74 years			Age 75-84 years			Age 85+ years		
		Fedratinib			Fedratinib			Fedratinib	
	Placebo[a] (N = 44)	400 mg (N = 29)	500 mg (N = 43)	Placebo[a] (N = 10)	400 mg (N = 9)	500 mg (N = 12)	Placebo[a] (N = 1)	400 mg (N = 1)	500 mg (N = 0)
n (%)	0	8 (27.6)	20 (46.5)	1 (10.0)	3 (33.3)	4 (33.3)	0	1 (100)	0
95% CI[b]	—	11.3, 43.9	31.6, 61.4	0.0, 28.6	2.5, 64.1	6.7, 60.0	—	100.0, 100.0	—
Difference from Placebo (%)	—	27.59	46.51	—	23.33	23.33	—	—	—
p-value[c]	—	0.0002	< 0.0001	—	0.2129	0.1935	—	—	—
95% CI for difference[b]	—	11.3, 43.9	31.6, 61.4	—	-12.6, 59.3	-9.2, 55.8	—	—	—

CI = confidence interval; CT = computed tomography; EOC6 = End of Cycle 6; ITT = intent to treat; MRI = magnetic resonance imaging; SVR = spleen volume reduction. a: Data for placebo subjects who crossed over to fedratinib treatment were not counted after the date of crossover. b: Confidence intervals were calculated using the normal approximation. c: P-values were calculated based on the chi-square test comparing each fedratinib arm to the placebo arm. *Notes:* Subjects who were not assessed for spleen response were counted as nonresponders.

Study ARD12181

In the ITT Population, the spleen RR at the EOC6 (without LOCF) was 24.4% (11/45) in subjects in the 65 to 74 years age group and 31.3% (5/16) in subjects in the 75 to 84 years age group.

Table 49: Spleen response rate (≥ 35% SVR) by MRI/CT at the EOC6 for elderly subjects by age group – Study ARD12181 (ITT Population without LOCF)

	Fedratinib 400 mg		
	Age 65-74 years (N = 45)	Age 75-84 years (N = 16)	Age 85+ years (N = 0)
EOC6			
n (%)	11 (24.4)	5 (31.3)	0
95% CI	12.9, 39.5	11.0, 58.7	—

Confidence intervals were calculated using the Clopper-Pearson Exact method.
Notes: Subjects who were not assessed for spleen response were counted as nonresponders.

In the Per-protocol Population the spleen RR at the EOC6 using the LOCF method (which imputed the missing spleen volume at the EOC6 with the last spleen volume measurement before the EOC6) was

50.0% (18/36) in subjects in the 65 to 74 years age group and 40.0% (6/15) in subjects in the 75 to 84 years age group

Comparing the spleen RR at the EOC6 for the elderly subgroups who received fedratinib 400 mg in each study to the corresponding overall study population:

- Study EFC12153

EOC6: 41.4% (65 to 74 years) and 44.4% (75 to 84 years) versus 46.9% (overall)
EOC6 (confirmed 4 weeks later): 27.6% (65 to 74 years) and 33.3% (75 to 84 years) versus 36.5% (overall)

- Study ARD12181

24.4% (65 to 74 years) and 31.3% (75 to 84 years) versus 30.9% (overall).

Supportive study(ies)

The possibility to predict the time course of spleen volume in patients using fedratinib after ruxolitinib in study ARD12181 (JAKARTA2) based on the time course observed in the ruxolitinib-naïve patients in the 400 mg arm of EFC12153 (JAKARTA) was investigated on request of the Medicines Evaluation Board. Visually, the time profiles of those patients in ARD12181 (JAKARTA2) with follow-up available beyond end of cycle 3 are similar to that patients in EFC12153 (JAKARTA). Prediction of a future value of a JAKARTA-2 patient was based on either a) all JAKARTA and JAKARTA-2 data, b) all JAKARTA data and the history of the JAKARTA-2 patients up to the point to predict, c) only the JAKARTA data. The fit and prediction accuracy of all models was reasonably to well, and all models showed on average a further reduction in spleen volume. By construction, these predictions are for patients that stay on treatment.

On request of the applicant, an external outcome research consultancy company performed a systematic literature review of all studies with treatments applied after ruxolitinib. Subsequently an indirect comparison was conducted of fedratinib after ruxolitinib versus best supportive care after ruxolinitib. The search and modeling were performed adequately. Only three studies could be used for indirect treatment comparison (JAKARTA-2: 97 patients, SIMPLIFY-2: 52, PERSIST-2: 72). Best available (BAT) therapy was mostly ruxolitinib (SIMPLIFY-2: 89%, PERSIST-2: 45%). The comparisons were conducted with matching adjusted indirect comparison (MAIC) and simulated treatment comparison methodology. These suggested that fedratinib could have a potential clinical benefit superior to best available care after ruxolitinib in terms of spleen RR and total symptom score. However, several limitations are present including: lack of a common comparator (JAKARTA-2 is a single arm trial); the strong assumptions that every prognostic variable and every treatment effect modifier that is imbalanced between JAKARTA-2 and one of the other studies as to be available; in/exclusion criteria and outcome measurement are not fully comparable between studies. In particular, PERSIST-2 included both ruxolitinib naive patients and ruxolitinib pretreated patients and outcomes of these could not be separated.

2.5.3. Discussion on clinical efficacy

The claimed indication for Inrebic in the treatment of patients with myelofibrosis is as follows:

Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are JAK inhibitor naïve or who have been treated with ruxolitinib.

Design and conduct of clinical studies

Study Design

In order to support the claimed indication, the applicant has submitted 2 pivotal studies:

- EFC12153 (JAKARTA) to support an indication in JAK inhibitor naïve patients
- ARD12181 (JAKARTA2) to support an indication in patients who have been treated with ruxolitinib.

For study ARD12181 (JAKARTA2) the applicant also submitted a **CSR Addendum** *(see below under Study conduct, analysis and reporting of results)*, which covers only a sub-population (Cohort 1, n=79) of the total study population (n=97). Cohort 1 consisted of all subjects enrolled in the study who met the post-hoc expert criteria for either R/R or intolerant to ruxolitinib.

EFC12153 (JAKARTA) was a randomised, controlled trial with 3 arms, in which the efficacy and safety of 2 doses of fedratinib (400 mg and 500 mg) were compared to placebo.
Comparison against placebo provides a measure of absolute efficacy for this new drug and in this regard this placebo-controlled study is suitable and of value. However, fedratinib is not the first of its kind in this class since the JAK kinase inhibitor ruxolitinib (Jakafi approved in the US in November 2011; Jakavi, approved in the EU in August 2012) has become standard of care in patients with primary myelofibrosis (PMF) who have PMF related symptoms or who develop splenomegaly or PMF related symptoms while on other treatment. Nevertheless, it can be taken into consideration that study EFC12153 (JAKARTA) was designed and initiated (first patient enrolled in December 2011) before ruxolitinib was widely available or approved in the EU.

The applicant's justification for the design of study ARD12181 (JAKARTA2) (first patient enrolled in April 2012) as an open-label, single-arm trial is that the study investigated fedratinib in a population with an unmet medical need, such as subjects who have failed treatment with ruxolitinib and have no other options. It can be argued that a comparator arm offering best treatment options available at that time could have been used. Indeed, the applicant has recently initiated a Phase 3 open-label, RCT (FEDR-MF-002, NCT03952039) in this population with current best available therapy as comparator.

As study ARD12181 (JAKARTA2) did not have a comparator arm, for assessing the relevance of the data in relation to treatments which might otherwise have been given, one has to rely on external control data with the limitations of such a comparison. However, the uncertainty which this brings is alleviated by the fact that fedratinib showed a large effect in the placebo-controlled trial and the disease myelofibrosis does not show spontaneous remission.

Patient population - inclusion requirements
Both pivotal studies included only adults and with regard to patient and disease characteristics, the inclusion and exclusion criteria were similar in these studies with the important exception that in study EFC12153 (JAKARTA) patients had not previously been treated with a JAK inhibitor whereas in study ARD12181 (JAKARTA2) only patients who had previously been exposed to ruxolitinib were included.

Principal inclusion requirements of relevance to the expected benefits and proposed indication were almost the same in both trials i.e. MF classified as high-risk or intermediate-risk level 2, as defined by modified IWG-MRT criteria (which include constitutional symptoms) at screening and with an enlarged spleen, palpable ≥5 cm below the costal margin. In study ARD12181 (JAKARTA2), patients with MF classified as intermediate-1 with symptoms and with splenomegaly ≥5 cm below the costal margin could also be included.

In both studies, presence of mutations in JAK2 was not required for inclusion which is understood as the JAK2 inhibitor ruxolitinib has been found to have efficacy in reduction of spleen volume and MF symptoms regardless of the presence or not of the $JAK2^{V617F}$ mutation.

Patient population patients included

In study EFC12153 (JAKARTA) the overall frequency of subjects with intermediate-2 or high-risk status was 51.9% and 48.1%, respectively, and in the 400 mg arm (the dose also used in ARD12181 (JAKARTA2)) these frequencies were 59.4% and 40.6% respectively.

In study ARD12181 (JAKARTA2) the most frequent MF risk categories by the IPSS or the DIPSS were intermediate-2 risk (48.5%) and high risk (35.1%), while intermediate- 1 risk with symptoms (16.5%) was less frequent.

Fairly similar proportions of patients with intermediate risk and high risk patients were thus included in study EFC12153 (JAKARTA), in particular in the 400 mg arm, and in study ARD12181 (JAKARTA2). Although study ARD12181 included a small proportion of Intermediate-1 risk patients (16 of 97 patients), inclusion of these patients with a lower risk category is considered acceptable as they also had to fulfil the same inclusion criteria of spleen ≥5 cm below costal margin by palpation and presence of MF symptoms as the Intermediate-2 risk patients in study EFC12153 (JAKARTA), criteria which are relevant to the claimed therapeutic value of this JAK2 inhibitor. Additionally, in study ARD12181 patients were required to be resistant or intolerant to ruxolitinib as per investigators' assessment.

In study EFC12153 (JAKARTA) the largest proportion of subjects in the ITT Population had PMF (63.3%), followed by post-PV MF (26.3%) and post-ET MF (10.4%).

In study ARD12181 (JAKARTA2) these distributions were quite similar with most subjects (54.6%) having a diagnosis of PMF, followed by post-PV MF (25.8%) and post-ET MF (19.6%).

These proportions are very similar to those investigated in the ruxolitinib pivotal studies in which patients with PMF, post-PV MF and post-ET MF represented approximately 50%, 30% and 20% respectively of the population (Jakavi EPAR).

Dose justification and doses used

With respect to exposure-efficacy relationships, significant relationships were established between the cumulative AUC from cycle 1 to cycle 6 (AUCC1-C6) and percent change in spleen volume at the end of cycle 6, spleen volume response rate (RR, percentage of patients with >35% reduction at the end of cycle 6), and total symptom score response (TSSR). In general, the increase in effect on these efficacy parameters going from the 400 to the 500 mg dose was found to be limited which may be attributable to the dose reductions and dose interruptions, resulting in significantly overlapping cumulative AUCC1-C6 for the 400 mg and 500 mg dose cohorts.

In Study TED12037, doses from 30 mg to 800 mg per day in consecutive 28-day cycles were tested and 680 mg/day was determined to be the MTD.

Study ARD11936 further evaluated the doses of 300 mg, 400 mg and 500 mg QD and generated additional PK and PD data. In that study, spleen RR (defined as ≥35% SVR at End of Cycle 6) was 60.0% and 63.6% in the 400 mg and 500 mg group respectively, compared to 30% in the 300 mg group. Symptom response rates of ≥50% reduction in TTS at End of Cycle 6 were 33.3% in the 300 mg group, 60.0% in the 400 mg group, and 37.5% in the 500 mg group.

In Study EFC12153 (JAKARTA) there was a trend for better spleen and symptom response in the 500 mg arm than in the 400 mg arm. However, with the 400 mg dose, Grade 3 or 4 TEAEs including Grade 3 or 4 thrombocytopenia and TEAEs leading to dose interruption or dose reduction or to permanent treatment discontinuation were less frequent.

Overall, the findings supported the investigation of the 400 mg/day and 500 mg day doses in the pivotal studies and subsequently the choice of 400 mg/day as the dose proposed for approval. Dose titration has not been studied in JAK inhibitor naïve patients, apart from allowing dose up-titration in the dose escalation study, and in the 300mg group in the dose ranging study. Dose up-titration up to 600mg/day was allowed based on response in study ARD12181 (JAKARTA2), as it was hypothesised that higher doses may be required in ruxolitinib-treated patients. The dose subgroups are too small to draw conclusions on role of dose up-titration in efficacy.

Endpoints

The primary endpoint of Spleen response rate (RR), defined as the proportion of subjects with ≥35% Spleen volume reduction (SVR) at the End of Cycle 6 (EOC6) was similar in both studies but was more stringent in study EFC12153 (JAKARTA) by requiring confirmation 4 weeks after EOC6 which was not required in study ARD12181 (JAKARTA2).

The Spleen RR based on ≥35% Spleen volume reduction is agreed as a criterion of spleen response by the Revised IWG-MRT (International Working Group-Myeloproliferative Neoplasms Research and Treatment) and is considered appropriate.

The important secondary endpoint of Symptom RR was the same in both pivotal studies. It was defined as the proportion of subjects with ≥50% reduction in the total symptom score (TSS) *(defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified MFSAF)* from baseline to the End of Cycle 6.

The modified MFSAF includes 6 key response elements of the MPN-SAF (Myeloproliferative Neoplasm (MPN)-associated symptoms, as measured by the Myeloproliferative Neoplasm Symptom Assessment Form). These key symptoms are night sweats, itching, abdominal discomfort, filling early satiety, pain under ribs on left side, and bone or muscle pain and are recognised as being important as determining the symptom burden for the patient although fatigue which is common in patients with MF was not included.

Study conduct, analysis and reporting of results

There were 4 protocol amendments in Study EFC12153 (JAKARTA) none of which are considered likely to have negatively impacted the conduct of the study or the data obtained. They concerned a more rigorous endpoint on symptom score i.e a ≥50% reduction in the total symptom score (TSS) instead of ≥40% reduction in any of the 6 symptoms, introduced before the first patient first visit (22 Dec 2011). Amendments also improved safety monitoring and central review of bone marrow biopsy samples.

Several important protocol deviations were identified in Study (JAKARTA) and in response to the D120 LoQ, the applicant provided further information and clarification on these deviations, the most common of which involved a rerandomisation issue. At re-randomisation, to protect the blinding, subjects previously randomised to either 400 or 500 mg of fedratinib maintained the same dose level in a blinded fashion and were not permitted to cross over to a different dose level. Thus, re-randomisation deviations would have only been expected to have an impact on subjects who received placebo past Cycle 6, which occurred for 3 subjects. One subject who had approximately a half-cycle (15 days) longer treatment with placebo than planned per protocol, showed response to fedratinib and another for whom there was a delay of 7 days before starting fedratinib discontinued treatment in Cycle 8 due to PD. A third subject responded very well to fedratinib (reduction from baseline in spleen volume of 58% at EOC12) and might have benefitted even more if the two cycles of treatment with fedratinib had not been missed. Overall the outcome for these 3 subjects does not seem to have been adversely affected by receiving placebo past Cycle 6. The argumentation of the applicant is accepted, that the rerandomisation deviations did not affect interpretation of the data for subjects who received placebo

past Cycle 6 (i.e. after assessment of the primary and other key efficacy endpoints) due to re-randomisation deviations.

For 8 (2.8%) subjects, 2 subjects in the placebo arm and 6 subjects in the 500 mg arm, the treatment kit dispensed was not the same as the treatment kit authorised by IVRS. Deviations which consisted of a subject receiving the correct treatment per protocol but from a wrong kit that was dispensed instead of the allocated treatment kit are considered to be of a minor nature (3 subjects). Incorrect treatment with placebo (one cycle and one day) in 2 subjects while on treatment with fedratinib, and early start with fedratinib in Cycle 6 instead of Cycle 7 after crossover from placebo (1 subject) are not expected to have had adverse consequences for the subjects involved.

Two subjects in the placebo arm, who should have switched to active treatment per protocol, continued to receive placebo. One subject did not crossover to fedratinib at Cycle 4 when MRI indicated PD and continued to receive placebo for a further 2 cycles followed by fedratinib or Cycles 7 through 17. The other continued to receive placebo for 5 cycles after EOC6 and thereafter fedratinib 400 mg from Cycles 12 into Cycle 18.

At one site no source documentation for study drug administration could be verified or was not recorded for 2 subjects which are considered to be serious issues concerning study conduct. The site was closed and persistent GCP issues at that site were appropriately addressed by Sanofi.

The deviations concerning treatment administered which are considered most likely to have had the potential to negatively impact the outcome for 2 of the 3 subjects to whom it happened, concerned failure of timely crossover to active treatment from placebo. As these deviations occurred at 3 different sites, the study is long since closed and Sanofi is no longer the sponsor for this product it is not considered necessary to pursue these deviations further.

All the deviations described are not considered to have affected the interpretation of the data relevant to the primary endpoint or to have influenced the outcome in favour of fedratinib.

In study ARD12181 (JAKARTA2) there were similar protocol amendments as in study EFC12153 (JAKARTA) to improve safety monitoring. Notable protocol amendments in study ARD12181 were aimed at expanding the population. In Amendment 3 (28 Nov 2012 - first subject was enrolled on 30 Apr 2012) the sample size was increased to 70 subjects in order to provide sufficient statistical power. Additionally, subjects who were intolerant to or allergic to ruxolitinib after receiving ruxolitinib treatment for less than 14 days were included as well as subjects categorised as intermediate-1 with symptoms. Nevertheless, a significantly higher number of patients was enrolled (97). In response to D120 LoQ the applicant provided a rationale for sample size increase and a sensitivity analysis based on first 70 evaluable patients, indicating that the Amendment did not appear to have a significant effect on efficacy analyses.

Inclusion of patients with a lower risk category is not seen as likely to impact the primary (spleen response rate and main secondary endpoint (reduction in total symptom score (TSS)) as such subjects were also required to have spleen ≥5 cm below costal margin as measured by palpation and to have MF symptoms.

The same applies to subjects included because of being intolerant to or allergic to ruxolitinib after receiving ruxolitinib treatment for less than 14 days and also allows collection of data from additional patients who may be in need of an alternative to ruxolitinib.

CSR Addendum Study ARD1218

In the CSR Addendum submitted by the applicant for study ARD12181, Cohort 1 consisted of all subjects enrolled in the study who met the post-hoc expert criteria for either R/R or intolerant to

ruxolitinib. **All analyses in the CSR Addendum were done on this ITT population** *(some supportive analyses were also done on the PP Population.*)

The LOCF method which imputed a missing spleen volume measurement at the End of Cycle 6 with an End of Cycle 3 measurement, if available (and which had been pre-specified in the study ARD12181 SAP) **was not applied** in the CSR Addendum. It is agreed with the applicant that not applying LOCF may have provided a more objective and conservative estimation of the spleen RR at End of Cycle 6 in patients who may be R/R or intolerant to ruxolitinib.

In contrast use of LOCF and the per protocol population for the primary analyses of efficacy endpoint were pre-specified per the SAP for study ARD12181 and reported in the main CSR.

Statistical analyses

Statistical tests and regression models were adequate in both studies. The early study termination due to the FDA clinical hold did not influence the assessment of the spleen RR at end of cycle 6 (the primary endpoint) in study EFC12153 (JAKARTA) but did limit the long-term follow-up. In particular, OS and PFS were not analysed. The analysis in study ARD12181 (JAKARTA2) was impacted more severely, as for 21/97 patients the primary endpoint was missing by early study termination only (i.e., not due to having, before the end of cycle 6 or before early study termination: a progression, adverse event, patient withdrawal, or non-evaluable scans). The original Sponsor (Sanofi) only analysed a selection of the originally protocol preplanned endpoints. Moreover, the primary analysis of spleen RR was on the Per Protocol set (i.e., patients needed to have an end of cycle 3 assessment) and missing end of cycle 6 assessment was imputed by the end of cycle 3 assessment (LOCF-imputation). It is not clear to which patient population this effect would apply and/or whether it would be a too optimistic or pessimistic estimate for the ITT population. Problems are for instance that patients may drop-out before the end of cycle 3, and also the end of cycle 3 assessment may not be representative for what is observed at the end of cycle 6. Moreover, the Sanofi inclusion was based on investigators' judgement of patients being R/R or intolerant to ruxolitinib. The applicant performed additional post-hoc analyses addressing these issues. Cohort 1 and 1a were based on criteria for R/R or intolerance to ruxolitinib. However, applying these new criteria to patients preselected by investigators' judgement does not necessarily represent the situation of recruiting patients based on these new criteria from the start. Analyses in the ITT sets (ITT, Cohort 1 ITT, Cohort 1a ITT) were applied using not only LOCF, but also non-responder imputation. The ITT analysis with non-responder imputation is at least interpretable as a conservative estimate for the spleen RR in the population satisfying the in/exclusion criteria regardless of intercurrent events leading to treatment discontinuation and lost-to-follow-up (a treatment policy estimand). Due to the early study discontinuation, missing data at cycle 6 only due to study termination is not informative for the outcome of these patients (missing-completely-at-random). Leaving these patients out could be used to obtain another, more unbiased estimate in the ITT population.

Efficacy data and additional analyses

The principal efficacy data have been obtained by means of endpoints related to reduction in the size of the of the spleen and decrease in myelofibrosis related symptoms, in particular Spleen Response Rate and Symptom Response Rate in the 2 pivotal studies EFC12153 (JAKARTA), and ARD12181 (JAKARTA2).

Primary endpoint Spleen Response Rate (RR)

Note that ≥ 35% spleen volume reduction (SVR) was the definition of Spleen response.

In study EFC12153 (JAKARTA), for the ITT Population, the primary endpoint of Spleen RR at the End of Cycle 6 confirmed 4 weeks later (rate and 95% CI) was:

400 mg arm: 35/96 (36.5%; 26.8, 46.1); **500 mg arm:** 39/97 (40.2%; 30.4, 50.0). Placebo n=1.

For 12 subjects a spleen volume reduction of ≥35% at EOC6 was not confirmed in the confirmatory MRI/CT 4 weeks later (10 subjects with SVR 25% to 35% at 4 weeks later and 2 with SVR <25% at 2 months later),for 6 subjects there were no confirmatory scan data and for one subject the confirmatory scan was done approximately 2 weeks after End of Cycle 6 instead of at 4 weeks after EOC6.

The lack of confirmation of response 4 weeks later due either to non-confirmation or lack of data resulted in similarly lower response rates in both of the fedratinib arms, with 10 fewer responders in the 400 mg arm and 9 fewer in the 500 mg arm.

The Spleen RR at EOC6 without confirmatory MRI/CT (rate and 95% CI) was:

400 mg arm: 45/96 (46.9%; 36.9, 56.9); **500 mg arm:** 48/97 (49.5%; 39.5, 59.4). Placebo n=1.

Thus, without confirmation there was also a large difference in Spleen RR at EOC6 in both fedratinib arms compared to the placebo arm but the Spleen RRs obtained at EOC6 according to the primary endpoint with confirmed 4 weeks MRI/CT can be considered more conservative.

Clear efficacy has been observed in terms of spleen volume reduction has been observed. Of the 67 subjects in the fedratinib 400 mg arm who had data for spleen volume and TSS at baseline and at the EOC6, 24 (35.8%) subjects had both spleen and symptom response, 16 (23.9%) subjects had only spleen response, 11 (16.4%) subjects had only symptom response, and 16 (23.9%) subjects had neither spleen nor symptom response. However, most patients had some improvement in both endpoints, even if failing to meet the success criteria.

For the placebo crossover subjects rerandomised to fedratinib after the initial randomisation period, the spleen RR at the End of Cycle 6 **after fedratinib treatment** was similar to that 28.6% (10/35) in the 400 mg arm and 44.4% (16/36) in the 500 mg arm although the small numbers of such patients precludes making firm conclusions.

In study EFC12153 a considerable number of patients discontinued treatment permanently before end of Cycle 6 (24, 21 and 31 patients in the placebo, 400 mg and 500 mg arms respectively. The applicant was asked to provide and discuss available parameters of efficacy, in particular spleen size/volume (also symptom score (TSS) and safety) in patients who permanently discontinued before end of Cycle 6 and in patients who permanently discontinued after EOC6 in order to gain more insight into the further course of the disease after discontinuation.

For patients who permanently discontinued, information regarding spleen volume reduction and on the applicant's assessment of best response in Spleen Size Reduction per modified IWG-MRT criteria was available in the applicant's response to the D120 LoQ.

Very limited data were available on spleen volume reduction and the most relevant information is considered to come from patients who permanently discontinued treatment after the EOC6. Data were available from only 41 fedratinib treated patients (not counting patients who crossed over from the placebo arm) of whom 14.3% (3/21) of subjects in the 400 mg arm and 20.0% (4/20) in the 500 mg arm had a ≥ 35% spleen volume reduction **at EOT**. The mean percentage change in spleen size by palpation at the EOT for subjects with baseline assessments was -45.0% in the fedratinib 400 mg arm (in 67/75 subjects) and -54.3% in the 500 mg arm (in 52/66 subjects).

Best response (spleen size reduction by palpation) **after** permanent treatment discontinuation based on all available spleen size assessments was assessed in all patients who had received fedratinib using

the (IWG-MRT) criteria. It is understood that for this assessment, baseline assessment refers to an assessment prior to or at the EOT.

Regardless of subsequent anticancer therapy, 79.6% (121/152) of subjects who had available spleen size assessments had a best response of stable disease after permanent treatment discontinuation. The RR (spleen size reduction of 50%) was 2.6% (4/152) and the rate of PD was 17.8% (27/152). Note that subjects who crossed over to fedratinib from placebo are counted for this analysis in the corresponding 400 or 500 mg fedratinib arm. Among subjects who received further anticancer therapy after permanent treatment discontinuation, the rate of stable disease was 73% (54/74) over both arms, the RR was 4.1% and the rate of PD was 23%.

Among subjects who did **not** receive further anticancer therapy after permanent treatment discontinuation, the rate of stable disease was 85.9% (67/78) over both arms and only one subject (500 mg arm) had a response and the rate of PD was 12.8%.Available data on spleen size reduction by palpation are from EOT assessments which were to be performed at least 30 days following the last administration of fedratinib or placebo. These assessments have been performed soon after treatment/study discontinuation and therefore have limited potential to be informative about the ongoing status of the disease.

According to the study design, the modified Myelofibrosis Symptom Assessment Form (MFSAF) was not completed after the EOC6 thus no relevant data on TSS are available.

The primary endpoint in study EFC12153 (JAKARTA) was based on a ≥ 35% reduction in spleen volume by MRI for which there are few data after treatment discontinuation with most available data on spleen size post-discontinuation based on size by palpation, although it is reassuring that the mean percentage change in spleen size by palpation at the EOT was 45% to 50% (not including patients who crossed over from placebo).
It is also somewhat reassuring that evaluated from a "baseline" point at or before EOT, approximately 80% of patient were assessed as having a response corresponding to stable disease per modified IWG-MRT criteria which is based on an assessment (by palpation) of spleen size reduction, although it can also be noted that the rate of PD was 17.8% in the 152 fedratinib patients for whom there were post-discontinuation data.

Overall, the additional information submitted does not suggest a high rate of loss of response but also does not provide a great amount of insight into the further course of the disease after discontinuation.

Concerning patients who received ruxolitinib or hydroxyurea post-discontinuation as anticancer therapy, information regarding the applicant's assessment of best response in Spleen Size Reduction per modified IWG-MRT criteria was available in the applicant's response to the D120 LoQ for 41 fedratinib treated subjects (7 of whom had crossed to fedratinib treatment). The majority of these patients (80%) were assessed as having stable disease based on spleen response. Unfortunately the information on efficacy of post-discontinuation anticancer therapy has not been separately evaluated in patients who received ruxolitinib and in patients who received hydroxyurea, nor in patients who received these treatments as a second line therapy or due to discontinuation of the study by Sanofi. There is also very little information on the duration of treatment with ruxolitinib or hydroxyurea. There is no analysis of survival and data on survival are extremely limited but it can be noted that 10 of the 11 fedratinib treated patients who died had received hydroxyurea and 2 had received ruxolitinib (one subject had received both). Overall the numbers of patients are too low to draw any conclusions on efficacy of ruxolitinib compared to hydroxyurea following treatment with fedratinib or on response to ruxolitinib in patients previously treated with fedratinib.

In ARD12181 (JAKARTA2), the effect in the ITT population with non-responder imputation (subjects with missing data on response status at EOC6 being counted as non-responders) is 30/97 responders

i.e. 30.9%. This estimate is likely to be conservative, but is less conservative than the estimate counting subjects with dose up-titration as non responders (please see below). Twenty one of 97 patients had an early study termination before EOC6 purely due to early termination, i.e., not related to efficacy outcome, that is without any of the following: progression, AE, reaching end of cycle 6 with a reduction <35%, patient withdrawal, or unevaluable measurement, so these 21 may be regarded as missing completely at random. Using this a more unbiased estimate would be 30/(97-21)=39.5%.

Efficacy with up-titration of dose in study ARD12181 (JAKARTA2)

In study ARD12182, up-titration to 500 mg or 600 mg was allowed if predefined efficacy and safety criteria were met: 33 patients had a dose up-titration, 17 up to a maximum dose of 500 mg once daily and 15 up to a maximum dose of 600 mg daily, and 1 patient received a single maximum dose of 800 mg/day.

Four of the 17 patients (4/17) who received up-titration to a maximum of 500 mg/day and 6/16 patients who were up-titrated to a maximum of 600 mg/day achieved a ≥35% SVR (spleen volume reduction) after the dose up-titration. However, 7 of these 10 patients who had achieved a ≥35% SVR after the dose up-titration needed a dose reduction to 400 mg/day due to toxicity. For these 10 patients, it is not clear if dose up-titration may have provided any additional clinical benefit. Most of the other patients did not achieve a ≥35% SVR and at least half of those patients needed a dose reduction due to toxicity and 3 of 17 patients who had up-titrated to 500 mg had achieved a ≥35% SVR before the dose increase.

All in all, it is not evident that up-titration of the dose was of benefit to the patients.

As the patients who responded only after dose up-titration are also counted in the total number of responders in study ARD12181, there may be an overestimation of the spleen RR observed with a dose of 400 mg in the population studied. The applicant provided an analysis of spleen RR in the ITT Population without LOCF, counting patients who only achieved a response after dose increase above 400 mg as non-responders. The Spleen Response rate (without LOCF) for patients who received only 400 mg, thus counting 8 subjects with dose up-titration as non responders, was lower at 22/97 (22.7%; 14.8, 32.3) compared to 30/97 (30.9%; 21.9, 41.1) for those who had dose up-titration. The response rates are clearly lower when patients with dose up-titration are excluded. However, the 95% confidence intervals for the response rates with and without exclusion of patients who had dose up-titration overlap almost fully in the analyses for both Spleen Response and Symptom Response. It can also be taken into account that 21 subjects did not have response assessments at EOC6 due to the clinical hold, and, because this event is unrelated to patient's characteristics or outcome, distribution of responses would therefore be expected to be the same as in those in that were measured before the clinical hold (i.e. the denominator could be taken as 97-21 = 76, which would give a response rate of 28.9%). Overall it is still considered that clinically relevant response rates were achieved in study ARD12181.

Subgroup Analyses of the Primary Endpoint Spleen Response Rate

In study ECF12153 (JAKARTA), the Spleen RR (*at the End of Cycle 6 With Confirmation 4 Weeks Later)* was evaluated according to several subgroups defined according to baseline patient and disease characteristics. Taking into account the wide, overlapping confidence intervals for the difference in spleen RR between fedratinib and placebo in the various subgroups for both the 400 mg and 500 mg fedratinib arms it can be concluded that overall a fairly consistent picture of similar Spleen RR across subgroups was seen. This was also the case for comparisons between contrasting subsets of each subgroup e.g. age ≤65 years vs age >65 years, and importantly also for subgroups of interest in relation to disease characteristics such as myelofibrosis risk category and $JAK2^{V617F}$ mutational status.

Similar Spleen RRs were observed between subjects in the 65 to 74 years age group and the smaller subgroup of subjects 75 to 84 years who received fedratinib 400 mg in Studies ECF12153 (JAKARTA) and ARD12181 (JAKARTA2) and these rates were consistent with those in the overall population.

However, it must be noted that in the fedratinib 400 mg arm, for male subjects the Spleen RR at 27.8% (95% CI:15.8, 39.7) was lower than for females in whom it was 47.6% (95% CI: 32.5, 62.7), with barely overlapping confidence intervals, which was not seen in the fedratinib 500 mg arm, in which the Spleen RR was 42.6% in male subjects and 36.1% in females.

In Study ARD12181 (JAKARTA2), as for ECF12153 (JAKARTA), regardless of the subgroups analysed fedratinib consistently showed clinical benefit in terms of spleen RR at the end of Cycle 6 within the subsets of each subgroup and over the subgroups in the overall ITT population and in Cohort 1.

Notably, in study ARD 12181 (JAKARTA2) the spleen RR was also lower in males at 24.5% (95% CI 12.9, 36.1) than in females in whom it was 38.6% (95% CI 24.2, 53.0) although the difference between males and females was less than in study ECF12153 (JAKARTA) and with more overlap in the 95% confidence intervals.
In response to a request to discuss the observed lower Spleen RR in males, the applicant mentions the larger spleen volume in males as one possible factor. In the information provided, the percentage reduction in spleen volume from baseline to EOC6 for males and females respectively in the 2 studies was: EFC12153 Fedratinib 500 mg: 42% and 46%; EFC12153 Fedratinib 400 mg: 26% and 42%; ARD12181: 33% and 33% (apparently without exclusion of patients who had had dose up-titration). While suggestive of a lower effect in males with fedratinib 400 mg in study EFC12153, this was not consistent with the observation of the same percentage reduction in spleen volume in males and females in study ARD12181, in which the majority of patients received a dose of 400 mg (although a different study population having had prior ruxolitinib treatment). In popPK analysis FEDR-MPK-001, gender was not a statistically significant covariates affecting fedratinib PK exposure. The applicant has conducted, separately for each study, a logistic regression of modelling the primary efficacy endpoint and concludes that results show that sex is not a significant factor in predicting the outcome, after adjustment for selected baseline factors including spleen volume, body weight, ECOG PS. Overall, it is not established that males will have a lower response to fedratinib in terms of spleen volume reduction than females.

In Study ARD12181 (JAKARTA2), in subgroup analyses of Spleen RR by the subgroups ruxolitinib relapsed/refractory (n=65) and intolerant (n=14) based on criteria recommended by MF experts (Cohort 1) revealed a rate of approximately 30% in both subgroups. This is consistent with the overall ITT study population (N = 97), although the number of ruxolitinib intolerant patients is too low to make conclusions about this subgroup.

Overall the subgroup analyses have not revealed issues which are considered to require modifications to key sections of the SmPC.

Secondary endpoint of Symptom Response Rate (RR)

In study ECF12153 (JAKARTA), the Symptom RR (≥50% reduction in the total symptom score (TSS)) was 39.6% in the fedratinib 400 mg arm, 34.1% in the fedratinib 500 mg arm compared to 8.2% in the placebo arm, clearly showing a benefit compared to placebo.

In study ARD12181 (JAKARTA2), the Symptom RR was 25.8%, somewhat lower than in the 400 mg arm of study ECF12153 (JAKARTA) but nevertheless clinically relevant. However, there is uncertainty concerning response rates in study ARD12181 (JAKARTA2) as dose up-titration was permitted. As for spleen RR, the applicant provided an analysis of symptom response rate in the ITT population counting patients who only achieved a response after dose increase above 400 mg as non-responders.
The Symptom Response rate for patients who received only 400 mg, thus counting 4 subjects with

dose up-titration as non responders, was lower at 20/93 (21.5%; 13.7, 31.2) for patients who received only 400 mg with 4 subjects considered non responders compared to 24/90 (26.7%; 17.9, 37) for those who had dose up-titration. Although lower in this analysis, it is still considered that clinically relevant response rates were achieved in study ARD12181.

The requirements to have all of the symptoms scores for each day, and to have symptom scores from 5/7 days to calculate the weekly score, require high compliance and may exclude patients faring poorly, and thus unable or unwilling to complete the symptom scoring. In response to D120 LoQ the applicant provided data on excluded symptom evaluations, demonstrating that symptom responses were similar also when all availbale symptom scores were included in the analyses.

For individual symptom scores, in both pivotal studies (in both arms of ECF12153 (JAKARTA), the largest reductions in scores were recorded for pain under ribs on left side, night sweats and early satiety with median percent of changes (reduction) of approximately 50% to 80% with night sweats close to 80% in both studies. For abdominal discomfort and itching the median percent of changes were approximately in the range 44% to 50% and lowest for bone or muscle pain at approximately 22% to 30%. These percent changes over the range of symptoms show that improvement in all symptoms contributed to the reduction to TSS, some more than others. Notably, reduction in night sweats which may be attributable to reduced cytokine activity and reduction in symptoms which could be attributed to reduction in spleen volume, both of which are characteristically increased in myelofibrosis, showed the greatest reduction.

Duration of Spleen response

Median duration of Spleen response could not be fully assessed in either pivotal study due to the early termination of the studies. Assessment of overall Survival within either study was not feasible once the studies had been terminated.
The lack of information on duration of the beneficial effects observed is likely to be met by the ongoing Phase 3 study FEDR-MF-002.

Health-related quality of life

HRQOL was assessed using different tools in the pivotal studies, EuroQol-5D (EQ-5D™) questionnaire in study ECF12153 (JAKARTA) and the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) in study ARD12181 (JAKARTA2). Using these tools there was an improvement from baseline in both studies. In study ARD12181 (JAKARTA2) the improvement seems to have been moderate although there was no dis-improvement from baseline and the evaluation is hampered by the lack of a comparator arm for such a subjective assessment. In study ECF12153 (JAKARTA), improvements relative to baseline were reported for both fedratinib arms compared to dis-improvement in the placebo arm, but the improvement tended to be less in the fedratinib 500 mg arm. These improvements in HRQOL seem to be in contrast with the quite large improvements in myelofibrosis related symptoms recorded by the MFSAF which one would expect to have had a greater impact on QOL although it is not clear that the QOL tools were adequate for capturing reduced burden of myelofibrosis related symptoms. In response to D120 LoQ the applicant provided available follow-up data collected at EOC and day 30 visits. Only EQ-5D1 data were collected after the EOC6. EQ-5D utility index scores were similar at EOC6 and EOT. The number of patients with data from 30-day follow-up visit is too low to draw any conclusions, but overall, no dramatic changes were observed. Overall, the data presented suggest relatively stable QoL throughout the treatment period.

Supportive studies

The dose-finding studies provided support the proposed posology of 400 mg/day.

2.5.4. Conclusions on the clinical efficacy

In both pivotal studies the efficacy data robustly show a clinically relevant reduction in spleen volume with a spleen response rate, using a dose of 400 mg which is the intended dose for approval. In the fedratinib 400 mg arm of study ECF12153 (JAKARTA) which included JAK inhibitor naïve patients, the spleen response rate was 36.5%. In the single arm study ARD12181 (JAKARTA2), in which fedratinib was investigated in patients who had previously received ruxolitinib, of whom the majority (79/97) were relapsed/refractory to or intolerant to ruxolitinib, using a non-responder imputation for missing data, a conservative estimate of the spleen response rate was 30.9% with the most conservative estimate being 22.7% if 8 subjects with dose up-titration are also counted as non-responders.

For the 400 mg dose, the median reduction in spleen volume at the End of Cycle 6 was approximately 40% in both studies and in study ECF12153 (JAKARTA) it was confirmed 4 weeks after EOC6. In both studies, MRI/CT scans were reviewed by an independent central imaging laboratory.

In study ECF12153 (JAKARTA), the secondary endpoint of symptom response rate (RR) using the modified MFSAF was 39.6% in the fedratinib 400 mg arm, 34.1% in the fedratinib 500 mg arm compared to 8.2% in the placebo arm. In study ARD12181 (JAKARTA2), the Symptom RR was 25.8%. The observed reduction in the total symptom score symptom burden is also considered to be of clinical relevance.

While there is uncertainty in how to evaluate the benefit of fedratinib in patients with prior treatment with ruxolitinib (study ARD12181 (JAKARTA2), in relation to available treatment options, this can be mitigated by the ongoing RCT study FEDR-MF-002 in which fedratinib is being compared to Best Available Therapy and which will be considered in the RMP as category 3 PASS.

2.6. Clinical safety

2.6.1. Patient exposure

A total of 807 subjects (193 healthy volunteers, 75 subjects with solid tumours, and 539 subjects with MF, PV, or ET, of whom 459 were subjects with MF) received at least one dose of fedratinib in the clinical development programme. Of these, 608 patients received continuous doses of fedratinib for the treatment of myeloproliferative neoplasm (MPN, n=539, dose range 30-800 mg/day) or solid tumours (n=69, all 500 mg dose) which were included in Safety Analysis Pool #2. This included 1 phase 3 placebo-controlled trial, 4 uncontrolled phase 2 trials and 4 phase 1 or phase 1/2 studies.

In the 300 to < 450 mg group (n=299), the median average daily dose was 394.6 mg (range: 142.4 to 554.9 mg), and the median duration of exposure was 40.6 weeks (range 0.7 to 281.0 weeks). A total of 199 subjects were exposed for ≥6 months or longer and 120 subjects were exposed for ≥12 months or longer. In the 450 to < 550 mg group (n=237), the median average daily dose was 481.8 mg (range: 96.0 to 538.5 mg) and the median duration of exposure was 31.0 weeks (range 0.1 to 290.6 weeks). A total of 123 subjects were exposed for ≥6 months and 84 subjects were exposed for ≥12 months.

The primary focus of the safety analysis is on the data from the 2 key clinical studies EFC1253 (JAK-naïve population, 400 and 500 mg) and ARD12181 (previously treated with ruxolitinib, 400 mg) and the Safety Pool #1 including these key clinical studies and study ARD11936 (JAK-naïve population, n=31, phase 2 dose-ranging 300-550 mg). Placebo treatment was restricted to up to 6 cycles of treatment. Safety data from the placebo patients who were randomised for cross-over were not included but are part of Safety Pool #2. This concerned 71 placebo subjects of which 35 received 400

mg and 36 received 500 mg fedratinib with a median duration of fedratinib exposure of 44 weeks in each fedratinib arm.

Disposition of subjects in the key studies and Safety Pool #1 is shown in Table 50.
A total of 17.7% and 28.9% patients in the 400 mg and 500 mg arm, respectively, discontinued before end of cycle 6 compared to 34.4% in the placebo group in study EFC12153. In study ARD12181, 40.2% of patients discontinued before cycle 6. Overall, all patients discontinued treatment, mainly due to early study termination (about 45% to 65% in individual studies). The second most frequently reported reason for treatment discontinuation was adverse events (18.6% to 36.1% for fedratinib-treated patients in individual studies). More patients in the 500 mg group discontinued treatment due to adverse events compared to the 400 mg group in study EFC12153. The main reason in the placebo group for treatment discontinuation was crossover to fedratinib after 6 cycles of treatment, according to protocol. The median duration of exposure in study ARD11936 was 54.0 weeks in the 300 mg treatment group, 87.8 weeks in the 400 mg treatment group, and 101.4 weeks in the 500 mg treatment group.

Table 50: Disposition of subjects: Study EFC12153, Study ARD12181, and Safety Pool #1 (All Subjects)

	Study EFC12153			Study ARD12181	Safety Pool #1			
		Fedratinib		Fedratinib	Fedratinib Pool			
	Placebo (N = 96) n (%)	400 mg (N = 96) n (%)	500 mg (N = 97) n (%)	400 mg (N = 97) n (%)	300 mg (N = 10) n (%)	400 mg (N = 203) n (%)	500 mg (N = 108) n (%)	Total Fed (N = 321) n (%)
ITT Population[a]	96 (100.0)	96 (100.0)	97 (100.0)	97 (100.0)	10 (100.0)	203 (100.0)	108 (100.0)	321 (100.0)
Safety Population[b]	95 (99.0)	96 (100.0)	97 (100.0)	97 (100.0)	10 (100.0)	203 (100.0)	108 (100.0)	321 (100.0)
Subjects discontinuing treatment before end of Cycle 6[c]	33 (34.4)	17 (17.7)	28 (28.9)	39 (40.2)	3 (30.0)	56 (27.6)	28 (25.9)	87 (27.1)
Subjects discontinuing treatment[c]	95 (99.0)	96 (100.0)	97 (100.0)	97 (100.0)	10 (100.0)	203 (100.0)	108 (100.0)	321 (100.0)
Reason for treatment discontinuation before end of Cycle 6								
Placebo crossover (EFC12153)[c]	10 (10.4)							
Adverse event	8 (8.3)	10 (10.4)	23 (23.7)	14 (14.4)	2 (20.0)	24 (11.8)	23 (21.3)	49 (15.3)
Progressive disease	4 (4.2)	1 (1.0)	1 (1.0)	3 (3.1)	0	4 (2.0)	1 (0.9)	5 (1.6)
Protocol deviation	0	1 (1.0)	0	0	0	1 (0.5)	0	1 (0.3)
Study early termination	0	0	0	17 (17.5)	0	17 (8.4)	0	17 (5.3)
Withdrawal by subject	5 (5.2)	0	3 (3.1)	2 (2.1)	0	2 (1.0)	3 (2.8)	5 (1.6)
Other	6 (6.3)	5 (5.2)	1 (1.0)	3 (3.1)	1 (10.0)	8 (3.9)	1 (0.9)	10 (3.1)
Reason for treatment discontinuation								
Placebo crossover (EFC12153)[c]	71 (74.0)							
Adverse event	8 (8.3)	26 (27.1)	35 (36.1)	18 (18.6)	2 (20.0)	48 (23.6)	36 (33.3)	86 (26.8)
Lack of efficacy	0	0	2 (2.1)	0	0	0	2 (1.9)	2 (0.6)
Progressive disease	4 (4.2)	6 (6.3)	3 (3.1)	7 (7.2)	0	13 (6.4)	3 (2.8)	16 (5.0)
Protocol deviation	0	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.9)	2 (0.6)
Study early termination	0	51 (53.1)	45 (46.4)	63 (64.9)	4 (40.0)	118 (58.1)	52 (48.1)	174 (54.2)
Withdrawal by subject	6 (6.3)	1 (1.0)	3 (3.1)	2 (2.1)	2 (20.0)	3 (1.5)	3 (2.8)	8 (2.5)
Other	6 (6.3)	11 (11.5)	8 (8.2)	7 (7.2)	2 (20.0)	20 (9.9)	11 (10.2)	33 (10.3)

ITT = intention to treat.
[a] The ITT Population consists of all subjects randomized (or enrolled for nonrandomized studies). One subject in Study EFC12153 was randomized but died before treatment.
[b] The Safety Population consists of subjects who received at least 1 dose of study treatment (even if partial) for randomized studies or all treated subjects for nonrandomized studies.
[c] Placebo subjects in Study EFC12153 who crossed over to fedratinib treatment are counted as discontinued on the date of crossover. Discontinuation after crossover is not accounted for in this table.
Note: The denominator for percentages is the number of subjects in the ITT Population. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.
Source: ISS Table 1.1.1 and ISS Table 1.1.4

The extent of exposure is shown in Table 51. The median duration of exposure was 62.1 weeks for the 400 mg arm, 59.7 weeks for the 500 mg arm and 24 weeks for the placebo arm in study EFC12153 and 24.4 weeks for fedratinib 400 mg in study ARD12181. The mean relative dose intensity varied between 85.9% (500 mg dose study EFC12153) and 96.1% (study ARD12181) in the individual studies. At termination of studies, 62 and 57 subjects in the 400 and 500 mg arms, respectively, had received ≥ 12 treatment cycles in study EFC12153 and 14 subjects received ≥12 cycles of treatment in study ARD12181.

Overall for Safety Pool #1, a total of 203 subjects across the 3 studies were assigned to treatment with the recommended dose of 400 mg fedratinib; median duration of exposure was 35.6 weeks and median number of cycles initiated was 9. The duration of exposure was ≥ 6 months for 128 (63.1%) patients and ≥ 12 months for 77 (37.9%) patients. A total of 108 patients received 500 mg, median duration of exposure was 60.6 weeks and median number of cycles initiated was 15. The duration of exposure was ≥ 6 months for 77 (71.3%) patients and ≥ 12 months for 61 (56.5%) patients. The median age was 65.0 years (range: 36 to 86 years); 47.0% of subjects were > 65 years of age and 11.8% were > 75 years of age. The percentage of male subjects varied between 40.0%-62% in the different dose groups. Most subjects (89.1%) were Caucasian/White. Demographic and baseline disease characteristics of the patients in the pivotal studies are described in the efficacy section. Study ARD12181 included a more severe patient population with more advanced disease compared to subjects treated in first line in study EFC12153. More specifically, the ARD12181 study population had higher median baseline spleen volumes and median TSS. In addition, a higher number of subjects at baseline had low platelet counts and low haemoglobin.

Table 51: Extent of exposure during the entire treatment-duration: Study EFC12153, Study ARD12181, and Safety Pool #1 (Safety Population)

	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
	Placebo[a] (N = 95)	400 mg (N = 96)	500 mg (N = 97)	400 mg (N = 97)	300 mg (N = 10)	400 mg (N = 203)	500 mg (N = 108)
Number of Cycles Initiated							
Mean (SD)	5.0 (1.80)	13.2 (6.38)	11.6 (6.99)	7.3 (4.43)	15.2 (10.73)	10.8 (6.70)	12.7 (7.70)
Median	6.0	16.0	14.0	6.0	13.5	9.0	15.0
Minimum, Maximum	1.0, 11.0	1.0, 23.0	1.0, 22.0	1.0, 20.0	2.0, 28.0	1.0, 29.0	1.0, 29.0
Duration of Exposure[b] (weeks)							
Mean (SD)	19.8 (7.91)	52.0 (25.84)	46.4 (28.90)	28.1 (17.80)	60.5 (43.22)	42.2 (27.01)	50.9 (31.66)
Median	24.0	62.1	59.7	24.4	54.0	35.6	60.6
Minimum, Maximum	1.7, 43.7	1.00, 91.86	0.86, 89.00	0.7, 79.4	4.7, 109.3	0.7, 114.6	0.9, 113.6
Cumulative Dose (mg)							
Mean (SD)	NA	134610 (69822.5)	139695 (91943.4)	77915 (56648.3)	121260 (97351.75)	110612 (72817.4)	153042 (100452.9)
Median	NA	153050	152400	59600	108650	93200	161650
Minimum, Maximum	NA	2800, 257200	2400, 294400	2000, 251300	4700, 283700	2000, 320800	2400, 364800
Average Daily Dose (mg)							
Mean (SD)	NA	371.3 (44.70)	429.6 (84.23)	384.5 (82.55)	258.2 (69.34)	375.7 (66.81)	428.7 (81.20)
Median	NA	395.1	464.9	400.0	276.4	397.7	457.2
Minimum, Maximum	NA	202.9, 400.0	96.0, 500.0	158.5, 554.9	142.4, 381.3	158.5, 554.9	96.0, 500.0
Relative Dose Intensity (%)[c]							
Mean (SD)	NA	92.8 (11.17)	85.9 (16.85)	96.1 (20.64)	86.1 (23.11)	93.9 (16.7)	85.7 (16.24)
Median	NA	98.8	93.0	100.0	92.1	99.4	91.4
Minimum, Maximum	NA	50.7, 100.0	19.2, 100.0	39.6, 138.7	47.5, 127.1	39.6, 138.7	19.2, 100.0

NA = not applicable; SD = standard deviation.

[a] Data for placebo subjects in Study EFC12153 who crossed over to fedratinib treatment are not counted after the date of crossover.

[b] Duration of exposure was calculated as [(last dose date – first dose date + 1 day)/7]. Last dose date was taken as the last dose date at the end of Cycle 6 or last dose date if before Cycle 6 for the first 6 cycle summary (or the day before the crossover date for Study EFC12153) and the actual last dose date for the full treatment period summary.

[c] Relative dose intensity was calculated as (cumulative dose in mg) / ([duration of exposure in weeks] ×[planned dose intensity in mg/4 weeks]). Planned dose intensity was 8400 mg/4 weeks for the 300 mg pool, 11200 mg/4 weeks for the 400 mg pool, and 14000 mg/4 weeks for the 500 mg pool.

Note: Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.

2.6.2. Adverse events

An overview of the treatment-emergent adverse events (TEAEs) reported at any time for study EFC12153, study ARD12181, and Safety Pool #1 for the entire treatment duration is shown in Table 52. Most patients had any TEAE and ≥90% had fedratinib treatment-related TEAEs. For the pooled 400 mg dose, Grade 3 or 4 TEAEs occurred in 68.0% and treatment-related Grade 3 or 4 TEAEs in 49.8% of patients. Treatment-related serious adverse events (SAEs) occurred in 11.3% of patients. About a

quarter of patients had TEAEs leading to permanent treatment discontinuation, and over 30% had TEAEs leading to dose interruptions and dose reductions. Any type of TEAE was more common in the 500 mg arm compared to the 400 mg arm, except for death and treatment-related SAE (study EFC12153). Any type of TEAE was more common in the fedratinib-treated groups compared to placebo, except for death and treatment-emergent SAE when comparing data up to 6 cycles (data not shown).

Within the pretreated patients (study ARD12181), TEAEs in all categories for fedratinib 400 mg were in general observed in the same order of magnitude as for the naïve population (study EFC12153), despite a shorter follow-up period. TEAEs were reported more frequently when comparing data up to 6 cycles, the largest differences based on an indirect comparison were seen for grade 3 or 4 treatment-related TEAEs (51.5% vs 37.5%) and TEAEs leading to dose reduction (36.1% vs 18.8%).

Table 52: Overview of treatment-emergent adverse events during entire treatment duration in subjects with PMF, Post-PV MF, or Post-ET MF: Studies EFC12153, and ARD12181 and Safety Pool #1

	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
Subjects with ≥ 1:	Placebo[a] (N = 95) n (%)	400 mg (N = 96) n (%)	500 mg (N = 97) n (%)	400 mg (N = 97) n (%)	300 mg (N = 10) n (%)	400 mg (N = 203) n (%)	500 mg (N = 108) n (%)
Any TEAE	89 (93.7)	96 (100.0)	95 (97.9)	97 (100.0)	10 (100.0)	203 (100.0)	106 (98.1)
Treatment-related TEAE	37 (38.9)	86 (89.6)	92 (94.8)	88 (90.7)	9 (90.0)	184 (90.6)	103 (95.4)
Grade 3 or 4 TEAE	29 (30.5)	68 (70.8)	76 (78.4)	61 (62.9)	8 (80.0)	138 (68.0)	87 (80.6)
Treatment-related Grade 3 or 4 TEAE	9 (9.5)	46 (47.9)	64 (66.0)	50 (51.5)	5 (50.0)	101 (49.8)	75 (69.4)
TEAE leading to death	6 (6.3)	5 (5.2)	8 (8.2)	7 (7.2)	0	12 (5.9)	8 (7.4)
Treatment-emergent SAE	22 (23.2)	37 (38.5)	43 (44.3)	33 (34.0)	7 (70.0)	74 (36.5)	49 (45.4)
Treatment-related treatment-emergent SAE	1 (1.1)	11 (11.5)	12 (12.4)	11 (11.3)	2 (20.0)	23 (11.3)	14 (13.0)
TEAE leading to permanent treatment discontinuation	8 (8.4)	26 (27.1)	35 (36.1)	19 (19.6)	2 (20.0)	49 (24.1)	36 (33.3)
TEAE leading to dose interruption	10 (10.5)	32 (33.3)	45 (46.4)	26 (26.8)	6 (60.0)	65 (32.0)	52 (48.1)
TEAE leading to dose reduction	7 (7.4)	24 (25.0)	44 (45.4)	35 (36.1)	5 (50.0)	67 (33.0)	54 (50.0)

SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] Adverse events for placebo subjects who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.
Note: A TEAE is defined as an adverse event that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of study drug. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.

Common AEs

The most commonly reported TEAEs (≥20%) in the pooled 400 mg group were diarrhoea (67.5%), nausea (61.6%), anaemia (51.7%), vomiting (44.8%), thrombocytopenia (21.7%), and fatigue (20.7%) (Table 53). The pattern of common AEs was comparable between the pretreated (study ARD12181) and naïve population (study EFC12153). Frequencies of TEAEs were in the same order of magnitude for the 400 mg and 500 mg group (study EFC12153). TEAEs reported with a ≥ 10% difference between the fedratinib arms were diarrhoea and fatigue (higher in the 400 mg group) and vomiting (higher in the 500 mg group).

In general, the frequencies of all TEAEs (all grades) reported for subjects in the fedratinib groups were greater than or similar to the corresponding frequencies up to 6 cycles (study EFC12153). TEAEs reported with a ≥ 10% difference between analysis periods were anaemia (400 mg and 500 mg group) and fatigue (500 mg only).

Table 53: Treatment emergent adverse events reported in ⩾ 10% of subjects in any 400 mg or 500 mg fedratinib treatment group during entire treatment duration in Studies EFC12153, Study ARD12181, and Safety Pool #1 (Safety Population)

	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
Preferred Term	Placebo[a] (N = 95) n (%)	400 mg (N = 96) n (%)	500 mg (N = 97) n (%)	400 mg (N = 97) n (%)	300 mg (N = 10) n (%)	400 mg (N = 203) n (%)	500 mg (N = 108) n (%)
Subjects with ≥ 1 TEAE	89 (93.7)	96 (100.0)	95 (97.9)	97 (100.0)	10 (100.0)	203 (100.0)	106 (98.1)
Diarrhoea	15 (15.8)	68 (70.8)	58 (59.8)	60 (61.9)	7 (70.0)	137 (67.5)	67 (62.0)
Nausea	15 (15.8)	64 (66.7)	51 (52.6)	54 (55.7)	8 (80.0)	125 (61.6)	61 (56.5)
Anaemia	13 (13.7)	53 (55.2)	47 (48.5)	47 (48.5)	4 (40.0)	105 (51.7)	53 (49.1)
Vomiting	5 (5.3)	44 (45.8)	54 (55.7)	40 (41.2)	6 (60.0)	91 (44.8)	62 (57.4)
Thrombocytopenia	8 (8.4)	16 (16.7)	22 (22.7)	26 (26.8)	1 (10.0)	44 (21.7)	24 (22.2)
Fatigue	9 (9.5)	24 (25.0)	14 (14.4)	15 (15.5)	6 (60.0)	42 (20.7)	21 (19.4)
Constipation	7 (7.4)	12 (12.5)	19 (19.6)	20 (20.6)	3 (30.0)	36 (17.7)	23 (21.3)
Abdominal pain	14 (14.7)	15 (15.6)	14 (14.4)	12 (12.4)	1 (10.0)	31 (15.3)	18 (16.7)
Cough	6 (6.3)	13 (13.5)	14 (14.4)	13 (13.4)	2 (20.0)	30 (14.8)	18 (16.7)
Dizziness	3 (3.2)	13 (13.5)	10 (10.3)	11 (11.3)	1 (10.0)	29 (14.3)	12 (11.1)
Headache	1 (1.1)	13 (13.5)	6 (6.2)	13 (13.4)	3 (30.0)	29 (14.3)	8 (7.4)
Dyspnoea	6 (6.3)	11 (11.5)	12 (12.4)	12 (12.4)	2 (20.0)	28 (13.8)	16 (14.8)
Asthenia	6 (6.3)	13 (13.5)	16 (16.5)	11 (11.3)	0	27 (13.3)	18 (16.7)
Pruritus	3 (3.2)	6 (6.3)	7 (7.2)	17 (17.5)	2 (20.0)	26 (12.8)	10 (9.3)
Oedema peripheral	8 (8.4)	14 (14.6)	9 (9.3)	6 (6.2)	5 (50.0)	25 (12.3)	13 (12.0)
Muscle spasms	1 (1.1)	15 (15.6)	8 (8.2)	7 (7.2)	0	24 (11.8)	10 (9.3)
Urinary tract infection	1 (1.1)	9 (9.4)	10 (10.3)	12 (12.4)	0	22 (10.8)	13 (12.0)
Pyrexia	3 (3.2)	7 (7.3)	6 (6.2)	11 (11.3)	2 (20.0)	21 (10.3)	8 (7.4)
Blood creatinine increased	1 (1.1)	11 (11.5)	17 (17.5)	8 (8.2)	0	20 (9.9)	20 (18.5)
Bone pain	2 (2.1)	12 (12.5)	8 (8.2)	7 (7.2)	2 (20.0)	20 (9.9)	11 (10.2)
Pain in extremity	4 (4.2)	12 (12.5)	3 (3.1)	6 (6.2)	3 (30.0)	20 (9.9)	6 (5.6)
Alanine aminotransferase increased	1 (1.1)	12 (12.5)	9 (9.3)	6 (6.2)	1 (10.0)	18 (8.9)	12 (11.1)
Blood product transfusion dependent[b]	2 (2.1)	10 (10.4)	12 (12.4)	8 (8.2)	0	18 (8.9)	12 (11.1)
Decreased appetite	3 (3.2)	6 (6.3)	9 (9.3)	9 (9.3)	0	17 (8.4)	12 (11.1)
Weight decreased	5 (5.3)	5 (5.2)	12 (12.4)	9 (9.3)	1 (10.0)	14 (6.9)	16 (14.8)
Weight increased	4 (4.2)	12 (12.5)	8 (8.2)	1 (1.0)	3 (30.0)	13 (6.4)	9 (8.3)
Aspartate aminotransferase increased	0	6 (6.3)	10 (10.3)	6 (6.2)	1 (10.0)	12 (5.9)	12 (11.1)
Hyperkalaemia	2 (2.1)	6 (6.3)	10 (10.3)	3 (3.1)	2 (20.0)	10 (4.9)	13 (12.0)
Neutropenia	0	6 (6.3)	12 (12.4)	1 (1.0)	0	8 (3.9)	12 (11.1)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a] Adverse events for placebo subjects who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

[b] The AE of blood product transfusion dependent is based on investigator reporting, not by calculation of the number of red blood cell transfusions per month based on the Gale, 2011 definition.

Note: Adverse events are coded using MedDRA Version 20.1. A TEAE is defined as an adverse event that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of study drug. Table is sorted by descending frequency on the 400 mg Any Grade column of Safety Pool #1. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.

Source: CSR EFC12153 Table 14.3.1.3.2, CSR ARD12181 Table 14.3.1.3, and ISS Table 3.4.4.1

Up to 6 cycles

For the naïve population (study EFC12153), the most commonly reported TEAE in the placebo group was diarrhoea (15.8%). The TEAEs reported with a ≥ 5% difference in the 400 mg group versus the placebo group were diarrhoea (65.6% versus 15.8%), nausea (61.5% versus 14.7%), anaemia (39.6% versus 13.7%), vomiting (38.5% versus 5.3%), muscle spasms (11.5% versus 1.1%), blood creatinine increased (10.4% versus 1.1%), pain in extremity (10.4% versus 4.2%), alanine aminotransferase (ALT) increased and headache (each 9.4% versus 1.1%), weight increased (9.4% versus 4.2%), dizziness (8.3% versus 3.2%), bone pain (8.3% versus 2.1%), dysuria (6.3% versus 0%), urinary tract infection (6.3% versus 1.1%), and aspartate aminotransferase (AST) increased

(5.2% versus 0%). Additional TEAEs reported with a ≥ 5% difference in the 500 mg group versus the placebo group and not in the 400 mg were thrombocytopenia (18.6% vs 8.4%), constipation (16.5% vs 7.4%), asthenia (13.4% vs 6.3%), blood product transfusion dependent and hyperkalemia (each 9.3% vs 2.1%), neutropenia (9.3% vs 0%), and lipase increased (8.2% vs 1.1%).

TEAEs in the pretreated patients (study ARD12181) were in general reported in the same order of magnitude as those observed in the naïve population. TEAEs reported with a ≥10% difference between study ARD12181 and study EFC12153 were constipation (20.6% vs 9.4%), thrombocytopenia (26.8% vs 10.4%), pyrexia (11.3% vs 1.0%) and pruritis (17.5% vs 3.1%), all observed at higher frequencies in the pre-treated population.

AE with toxicity ≥ Grade 3

Overall, 68.0% of patients receiving 400 mg fedratinib reported grade 3 or 4 TEAEs (Safety Pool #1); most commonly reported (≥5%) Grade 3 or 4 TEAEs were anaemia (41.4%), thrombocytopenia (16.7%), lipase increased (5.9%), and diarrhoea (5.4%) (Table 54). The rate of Grade ≥ 3 fatigue/asthenia for the entire treatment duration in the 400 mg was 5.9%. The pattern was comparable for the pretreated (study ARD12181) and naïve population (study EFC12153). Common (≥5%) grade 3 or 4 TEAEs for the 500 mg dose and with a ≥5% difference compared to the 400 mg dose were thrombocytopenia, neutropenia, vomiting, nausea, and blood product transfusion dependent (Study EFC12153).

Up to 6 cycles

Grade 3 or 4 TEAEs ≥5% difference compared to placebo for the 400 mg group were anaemia and diarrhoea (study EFC12153) Grade 3 or 4 TEAEs of thrombocytopenia were comparable for the 400 mg group and placebo (5.2% vs 6.3%). For the 500 mg group these were besides anaemia and diarrhoea, thrombocytopenia, neutropenia, lipase increased, vomiting, nausea, and blood product transfusion dependent. Grade 3 or 4 TEAEs ≥ 5% difference (increase) in the pretreated patients (study ARD12181) compared to study EFC1253 up to 6 cycles for 400 mg were anaemia (38.1% vs 30.2%) and thrombocytopenia (21.6% vs 5.2%).

Table 54: Grade 3 or 4 treatment-emergent adverse events reported in ⩾ 5% of subjects in any 400 mg or 500 mg fedratinib group during entire treatment duration in Study EFC12153, Study ARD12181, and Safety Pool #1 (Safety Population)

	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
MedDRA System Organ Class Preferred Term	Placebo[a] (N = 95) n (%)	400 mg (N = 96) n (%)	500 mg (N = 97) n (%)	400 mg (N = 97) n (%)	300 mg (N = 10) n (%)	400 mg (N = 203) n (%)	500 mg (N = 108) n (%)
Subjects with ⩾ 1 Grade 3 or 4 TEAE	29 (30.5)	68 (70.8)	76 (78.4)	61 (62.9)	8 (80.0)	138 (68.0)	87 (80.6)
Blood and lymphatic system disorders	**14 (14.7)**	**49 (51.0)**	**50 (51.5)**	**45 (46.4)**	**5 (50.0)**	**98 (48.3)**	**57 (52.8)**
Anaemia	7 (7.4)	43 (44.8)	40 (41.2)	37 (38.1)	4 (40.0)	84 (41.4)	46 (42.6)
Thrombocytopenia	6 (6.3)	11 (11.5)	18 (18.6)	21 (21.6)	1 (10.0)	34 (16.7)	20 (18.5)
Neutropenia	0	4 (4.2)	10 (10.3)	1 (1.0)	0	6 (3.0)	10 (9.3)
Investigations	**1 (1.1)**	**12 (12.5)**	**19 (19.6)**	**20 (20.6)**	**5 (50.0)**	**37 (18.2)**	**25 (23.1)**
Lipase increased	1 (1.1)	4 (4.2)	7 (7.2)	6 (6.2)	2 (20.0)	12 (5.9)	8 (7.4)
Gastrointestinal disorders	**5 (5.3)**	**11 (11.5)**	**24 (24.7)**	**10 (10.3)**	**2 (20.0)**	**23 (11.3)**	**27 (25.0)**
Diarrhoea	0	5 (5.2)	5 (5.2)	4 (4.1)	1 (10.0)	11 (5.4)	6 (5.6)
Vomiting	0	3 (3.1)	9 (9.3)	0	2 (20.0)	4 (2.0)	9 (8.3)
Nausea	0	0	6 (6.2)	0	1 (10.0)	1 (0.5)	6 (5.6)
Metabolism and nutrition disorders	**5 (5.3)**	**9 (9.4)**	**11 (11.3)**	**11 (11.3)**	**3 (30.0)**	**23 (11.3)**	**15 (13.9)**
Hyperkalaemia	2 (2.1)	2 (2.1)	6 (6.2)	1 (1.0)	1 (10.0)	4 (2.0)	9 (8.3)
Cardiac disorders	**5 (5.3)**	**13 (13.5)**	**8 (8.2)**	**6 (6.2)**	**0**	**19 (9.4)**	**9 (8.3)**
Cardiac failure	2 (2.1)	6 (6.3)	2 (2.1)	2 (2.1)	0	8 (3.9)	3 (2.8)
Infections and infestations	**4 (4.2)**	**7 (7.3)**	**18 (18.6)**	**6 (6.2)**	**0**	**16 (7.9)**	**22 (20.4)**
Pneumonia	1 (1.1)	2 (2.1)	5 (5.2)	2 (2.1)	0	5 (2.5)	6 (5.6)
General disorders and administration site conditions	**3 (3.2)**	**8 (8.3)**	**12 (12.4)**	**3 (3.1)**	**3 (30.0)**	**12 (5.9)**	**12 (11.1)**
Fatigue	0	7 (7.3)	7 (7.2)	2 (2.1)	3 (30.0)	9 (4.4)	7 (6.5)
Social circumstances	**0**	**3 (3.1)**	**8 (8.2)**	**2 (2.1)**	**0**	**5 (2.5)**	**8 (7.4)**
Blood product transfusion dependent[b]	0	3 (3.1)	8 (8.2)	2 (2.1)	0	5 (2.5)	8 (7.4)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; TEAE = treatment-emergent adverse event.

[a] Adverse events for placebo subjects who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

[b] The adverse event of blood product transfusion dependent is based on investigator reporting, not by calculation of the number of red blood cell transfusions per month based on the Gale, 2011 definition.

Note: Adverse events are coded using MedDRA Version 20.11 and were graded using NCI CTCAE Version 4.03. A TEAE is defined as an adverse event that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of study drug. Table is sorted by descending frequency on the 400 mg Grade 3/4 column of Safety Pool #1. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.

Source: CSR EFC12153 Table 14.3.1.3.2, CSR ARD12181 Table 14.3.1.3, and ISS Table 3.2.4.1

Treatment-related TEAEs

Overall in Safety Pool #1, treatment-related TEAEs (all grades) reported for the entire treatment duration in ≥ 10% of fedratinib-treated subjects for the pooled 400 mg group were diarrhoea (56.7%), nausea (56.2%), vomiting (40.4%), anaemia (33.0%), and thrombocytopenia (16.7%) (Table 55). Neutropenia was the only additional treatment-related TEAE ≥ 10% in patients receiving 500 mg dose.

Table 55: Treatment-related treatment-emergent adverse events reported in ⩾ 10% of subjects in any 400 mg or 500 mg fedratinib treatment group during entire study duration in studies EFC12153, study ARD12181, and safety pool #1 (safety population).

	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
Preferred Term	**Placebo[a] (N = 95) n (%)**	**400 mg (N = 96) n (%)**	**500 mg (N = 97) n (%)**	**400 mg (N = 97) n (%)**	**300 mg (N = 10) n (%)**	**400 mg (N = 203) n (%)**	**500 mg (N = 108) n (%)**
Subjects with ≥ 1 treatment-related TEAE	**37 (38.9)**	**86 (89.6)**	**92 (94.8)**	**88 (90.7)**	**9 (90.0)**	**184 (90.6)**	**103 (95.4)**
Diarrhoea	10 (10.5)	56 (58.3)	53 (54.6)	50 (51.5)	4 (40.0)	115 (56.7)	61 (56.5)
Nausea	11 (11.6)	56 (58.3)	46 (47.4)	51 (52.6)	6 (60.0)	114 (56.2)	56 (51.9)
Vomiting	4 (4.2)	39 (40.6)	49 (50.5)	36 (37.1)	4 (40.0)	82 (40.4)	57 (52.8)
Anaemia	5 (5.3)	33 (34.4)	30 (30.9)	29 (29.9)	1 (10.0)	67 (33.0)	35 (32.4)
Thrombocytopenia	6 (6.3)	12 (12.5)	18 (18.6)	20 (20.6)	0	34 (16.7)	20 (18.5)
Fatigue	4 (4.2)	9 (9.4)	9 (9.3)	6 (6.2)	1 (10.0)	16 (7.9)	12 (11.1)
Alanine aminotransferase increased	1 (1.1)	10 (10.4)	6 (6.2)	4 (4.1)	1 (10.0)	14 (6.9)	7 (6.5)
Neutropenia	0	5 (5.2)	11 (11.3)	1 (1.0)	0	7 (3.4)	11 (10.2)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event. [a] Adverse events for placebo subjects who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover. Note: Adverse events are coded using MedDRA Version 20.1. A TEAE is defined as an adverse event that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of study drug. Table is sorted by descending frequency on the 400 mg Any Grade column of Safety Pool #1. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936. Source: CSR EFC12153 Table 14.3.1.9.2, CSR ARD12181 Table 14.3.1.6, and ISS Table 3.6.2.1.

Treatment-related Grade 3 or 4 TEAEs reported for the entire treatment duration in ≥5% of fedratinib-treated subjects in the pooled 400 mg group were anemia (26.1%), and thrombocytopenia (11.8%) (Table 56). Two subjects in the 400 mg dose group had a Grade 5 treatment-related TEAE reported during the entire treatment duration: acute leukaemia in 1 subject and cardiogenic shock in 1 subject. Additional treatment-related TAEs in the 500 mg group in ≥5% of patients were neutropenia, vomiting, lipase increased and nausea.

Table 56: Treatment-related Grade 3 or 4 treatment-emergent adverse events reported in ⩾ 5% of subjects in any 400 mg or 500 mg fedratinib group during entire treatment duration in study EFC12153, study ARD12181, and safety pool #1 (Safety Population)

	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
MedDRA System Organ Class Preferred Term	Placebo[a] (N = 95) n (%)	400 mg (N = 96) n (%)	500 mg (N = 97) n (%)	400 mg (N = 97) n (%)	300 mg (N = 10) n (%)	400 mg (N = 203) n (%)	500 mg (N = 108) n (%)
Subjects with ≥ 1 treatment-related Grade 3 or 4 TEAE	**9 (9.5)**	**46 (47.9)**	**64 (66.0)**	**50 (51.5)**	**5 (50.0)**	**101 (49.8)**	**75 (69.4)**
Blood and lymphatic system disorders	**6 (6.3)**	**31 (32.3)**	**35 (36.1)**	**29 (29.9)**	**1 (10.0)**	**64 (31.5)**	**41 (38.0)**
Anaemia	3 (3.2)	26 (27.1)	25 (25.8)	23 (23.7)	1 (10.0)	53 (26.1)	30 (27.8)
Thrombocytopenia	4 (4.2)	7 (7.3)	14 (14.4)	15 (15.5)	0	24 (11.8)	16 (14.8)
Neutropenia	0	3 (3.1)	9 (9.3)	1 (1.0)	0	5 (2.5)	9 (8.3)
Investigations	**0**	**9 (9.4)**	**10 (10.3)**	**14 (14.4)**	**4 (40.0)**	**25 (12.3)**	**15 (13.9)**
Lipase increased	0	4 (4.2)	6 (6.2)	4 (4.1)	2 (20.0)	10 (4.9)	7 (6.5)
Gastrointestinal disorders	**0**	**7 (7.3)**	**16 (16.5)**	**7 (7.2)**	**2 (20.0)**	**15 (7.4)**	**16 (14.8)**
Diarrhoea	0	4 (4.2)	5 (5.2)	4 (4.1)	1 (10.0)	9 (4.4)	5 (4.6)
Vomiting	0	3 (3.1)	9 (9.3)	0	2 (20.0)	3 (1.5)	9 (8.3)
Nausea	0	0	6 (6.2)	0	1 (10.0)	1 (0.5)	6 (5.6)
General disorders and administration site conditions	**0**	**5 (5.2)**	**8 (8.2)**	**1 (1.0)**	**0**	**6 (3.0)**	**8 (7.4)**
Fatigue	0	4 (4.2)	5 (5.2)	0	0	4 (2.0)	5 (4.6)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; TEAE = treatment-emergent adverse event. [a] Adverse events for placebo subjects who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover. Note: Adverse events are coded using MedDRA Version 20.11 and were graded using NCI CTCAE Version 4.03. A TEAE is defined as an adverse event that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of study drug. Table is sorted by descending frequency on the 400 mg Grade 3/4 column of Safety Pool #1. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.

Frequencies of treatment-related TEAEs were reported in the same order of magnitude for the pretreated and naïve population except for thrombocytopenia which was more frequently reported in the pretreated patients (20.6% vs 8.3%, up to 6 cycles). Frequencies of treatment-related TEAEs for the entire treatment duration were largely similar but reported at somewhat higher frequencies than those reported up to 6 cycles.

Serious adverse event/deaths/other significant events

Deaths

Overall, 5.9% and 5.6% of patients died on treatment in the 400 mg and 500 mg group, respectively (Table 57). There was no trend compared to placebo or for dose based on study EFC12153. Main cause of death was disease progression in the 400 mg group and adverse events in the 500 mg group. Most deaths post-treatment were due to progressive disease.

Table 57: Death rate and reasons for death in subjects in Study EFC12153, Study ARD12181, and Safety Pool #1 (Safety Population)

	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
	Placebo[a] (N = 95) n (%)	400 mg (N = 96) n (%)	500 mg (N = 97) n (%)	400 mg (N = 97) n (%)	300 mg (N = 10) n (%)	400 mg (N = 203) n (%)	500 mg (N = 108) n (%)
Deaths during on-treatment period	**6 (6.3)**	**5 (5.2)**	**6 (6.2)**	**7 (7.2)**	**0**	**12 (5.9)**	**6 (5.6)**
Reason for death during on-treatment period							
Disease progression	2 (2.1)	3 (3.1)	1 (1.0)	4 (4.1)	0	7 (3.4)	1 (0.9)
Adverse event	4 (4.2)	2 (2.1)	5 (5.2)	3 (3.1)	0	5 (2.5)	5 (4.6)
Other	0	0	0	0	0	0	0
Deaths post treatment	**6 (6.3)**	**10 (10.4)**	**18 (18.6)**	**11 (11.3)**	**4 (40.0)**	**24 (11.8)**	**20 (18.5)**
Reason for death post-treatment							
Disease progression	4 (4.2)	6 (6.3)	10 (10.3)	9 (9.3)	1 (10.0)	16 (7.9)	11 (10.2)
Adverse event	0	0	2 (2.1)	0	0	0	2 (1.9)
Other	2 (2.1)	4 (4.2)	6 (6.2)[b]	2 (2.1)	3 (30.0)	8 (3.9)	7 (6.5)

[a] Deaths for placebo subjects who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.
[b] One additional death was reported by the investigator on the Vital Status electronic case report form (e-CRF) but not on the Death e-CRF, and is included as "Other" in this table. This death occurred > 30 days after the last dose of fedratinib 500 mg; the cause of death in CSR EFC12153 Listing 16.2.7.4 is "not collected." The death was queried, and no further information was available from the site.
Note: The on-treatment period is the period from first dose of any study treatment up to 30 days after the last dose of any study drug. The post-treatment period is the period starting from 31 days after last dose (after the on-treatment period or the post-crossover on-treatment period) until the end of the follow-up period. The denominator for percentages is the number of subjects in the Safety Population. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.
Source: CSR EFC12153 Table14.3.2.1.2, CSR ARD12181 Table 14.3.2.6, CSR ARD12181 Listing 16.2.7.8, and ISS Table 3.14.4

Treatment-emergent AEs leading to death during the entire treatment duration are presented in Table 58. Thirteen subjects (6.4%) in the pooled 400 mg group and 8 subjects (7.4%) in the pooled 500 mg group reported TEAEs leading to death. Disease progression, acute myeloid leukaemia, cardiorespiratory arrest, and sepsis were each reported in 2 subjects (1.0%) in the 400 mg group, all other TEAEs leading to death were reported in 1 subject in either or both pooled groups. Cardiogenic shock and acute leukaemia in 1 subject each in the pooled 400 mg group from Study EFC12153 were treatment-related; all other TEAEs leading to death during the entire treatment duration in Safety Pool #1 were not treatment-related. The subject with cardiogenic shock had multiple underlying factors considered unrelated to fedratinib by the investigator, that triggered the subsequent events. The subject who died from acute leukaemia had a history of high-risk MF diagnosed 3 years before starting treatment and continued fedratinib until Cycle 16, when transformation to acute leukaemia occurred.

Table 58: Treatment-emergent adverse events leading to death reported in any treatment group during entire treatment duration in Study EFC12153, Study ARD12181, and Safety Pool #1 (Safety Population)

MedDRA System Organ Class Preferred Term	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
	Placebo[a] (N = 95) n (%)	400 mg (N = 96) n (%)	500 mg (N = 97) n (%)	400 mg (N = 97) n (%)	300 mg (N = 10) n (%)	400 mg (N = 203) n (%)	500 mg (N = 108) n (%)
Subjects with ≥ 1 TEAE leading to death	6 (6.3)	5 (5.2)	8 (8.2)	7 (7.2)	0	13 (6.4)	8 (7.4)
General disorders and administration site conditions	**1 (1.1)**	**1 (1.0)**	**1 (1.0)**	**2 (2.1)**	**0**	**4 (2.0)**	**1 (0.9)**
Disease progression	1 (1.1)	0	1 (1.0)	1 (1.0)	0	2 (1.0)	1 (0.9)
General physical health deterioration	0	0	0	1 (1.0)	0	1 (0.5)	0
Multiple organ dysfunction syndrome	0	1 (1.0)	0	0	0	1 (0.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.1)**	**3 (3.1)**	**0**	**1 (1.0)**	**0**	**4 (2.0)**	**0**
Acute myeloid leukaemia	0	1 (1.0)	0	1 (1.0)	0	2 (1.0)	0
Acute leukaemia	0	1 (1.0)	0	0	0	1 (0.5)	0
Myelofibrosis	0	1 (1.0)	0	0	0	1 (0.5)	0
Transformation to acute myeloid leukaemia	1 (1.1)	0	0	0	0	0	0
Cardiac disorders	**1 (1.1)**	**2 (2.1)**	**2 (2.1)**	**1 (1.0)**	**0**	**3 (1.5)**	**2 (1.9)**
Cardio-respiratory arrest	0	1 (1.0)	0	1 (1.0)	0	2 (1.0)	0
Cardiogenic shock	0	1 (1.0)	0	0	0	1 (0.5)	0
Cardiac arrest	0	0	1 (1.0)	0	0	0	1 (0.9)
Cardiac failure	0	0	1 (1.0)	0	0	0	1 (0.9)
Myocardial ischaemia	1 (1.1)	0	0	0	0	0	0
Infections and infestations	**2 (2.1)**	**1 (1.0)**	**1 (1.0)**	**2 (2.1)**	**0**	**3 (1.5)**	**1 (0.9)**
Sepsis	1 (1.1)	1 (1.0)	0	1 (1.0)	0	2 (1.0)	0
Pneumonia	1 (1.1)	0	0	1 (1.0)	0	1 (0.5)	0
Pyelonephritis	0	0	1 (1.0)	0	0	0	1 (0.9)
Vascular disorders	**0**	**1 (1.0)**	**0**	**1 (1.0)**	**0**	**2 (1.0)**	**0**
Shock	0	0	0	1 (1.0)	0	1 (0.5)	0
Shock haemorrhagic	0	1 (1.0)	0	0	0	1 (0.5)	0
Blood and lymphatic system disorders	**0**	**1 (1.0)**	**1 (1.0)**	**0**	**0**	**1 (0.5)**	**1 (0.9)**
Disseminated intravascular coagulation	0	1 (1.0)	0	0	0	1 (0.5)	0
Leukocytosis	0	0	1 (1.0)	0	0	0	1 (0.9)
Injury, poisoning and procedural complications	**1 (1.1)**	**1 (1.0)**	**0**	**0**	**0**	**1 (0.5)**	**0**
Muscle rupture	0	1 (1.0)	0	0	0	1 (0.5)	0
Transfusion-related acute lung injury	1 (1.1)	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**3 (3.1)**	**1 (1.0)**	**0**	**1 (0.5)**	**3 (2.8)**
Respiratory failure	0	0	1 (1.0)	1 (1.0)	0	1 (0.5)	1 (0.9)
Pneumonitis	0	0	1 (1.0)	0	0	0	1 (0.9)
Pulmonary embolism	0	0	1 (1.0)	0	0	0	1 (0.9)
Gastrointestinal disorders	**1 (1.1)**	**0**	**1 (1.0)**	**0**	**0**	**0**	**1 (0.9)**
Ascites	1 (1.1)	0	0	0	0	0	0
Haematemesis	0	0	1 (1.0)	0	0	0	1 (0.9)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] Adverse events for placebo subjects who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

Note: Adverse events are coded using MedDRA Version 20.1. A TEAE is defined as an adverse event that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of study drug. Multiple TEAEs leading to death could have been reported in a given subject. Table is sorted by the 400-mg column of Safety Pool #1 by descending AE frequency for SOC and within each SOC, sorting is done by descending AE frequency of PT. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.

Source: CSR EFC12153 Table 14.3.2.4.2, CSR ARD12181 Table 14.3.2.5, and ISS Table 3.12.4.1

Serious adverse events

Treatment-emergent SAEs reported in ≥2% of subjects in any 400 mg or 500 mg treatment group during the entire treatment duration in Safety Pool #1 are presented in Table 59. Most treatment-emergent SAEs (Preferred Term (PTs)) were reported in 1 subject in a given pooled fedratinib treatment group. SAEs reported in ≥5 subjects in the 400 mg group were pneumonia (4.4%), anaemia

(2.5%) and cardiac failure (3.0%). Within study EFC12153, SAEs were in general comparable between 400 mg and 500 mg group. AST and ALT increased was only reported in the 500 mg group.

Up to 6 cycles

Up to 6 cycles, the frequency of subjects with treatment-emergent SAEs up was comparable between treatment groups in study EFC12153 (23.2%, 20.8%, and 26.8% in the placebo, 400 mg and 500 mg group, respectively). A higher frequency (34.0%) was observed in the pretreated population (study ARD12181).

Table 59: Treatment-emergent serious adverse events reported in ⩾ 2% of subjects in any 400 mg or 500 mg fedratinib treatment group during entire treatment duration in Study EFC12153, Study ARD12181, and Safety Pool #1 (Safety Population)

	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
MedDRA System Organ Class Preferred Term	Placebo[a] (N = 95) n (%)	Fed 400 mg (N = 96) n (%)	Fed 500 mg (N = 97) n (%)	Fed 400 mg (N = 97) n (%)	Fed 300 mg (N = 10) n (%)	Fed 400 mg (N = 203) n (%)	Fed 500 mg (N = 108) n (%)
Subjects with ≥ 1 treatment-emergent SAE	22 (23.2)	37 (38.5)	43 (44.3)	33 (34.0)	7 (70.0)	74 (36.5)	49 (45.4)
Infections and infestations	**5 (5.3)**	**11 (11.5)**	**15 (15.5)**	**8 (8.2)**	**0**	**21 (10.3)**	**18 (16.7)**
Pneumonia	2 (2.1)	4 (4.2)	4 (4.1)	4 (4.1)	0	9 (4.4)	5 (4.6)
Sepsis	1 (1.1)	2 (2.1)	1 (1.0)	1 (1.0)	0	3 (1.5)	1 (0.9)
Lung infection	0	0	2 (2.1)	1 (1.0)	0	1 (0.5)	2 (1.9)
Cardiac disorders	**5 (5.3)**	**11 (11.5)**	**9 (9.3)**	**6 (6.2)**	**0**	**17 (8.4)**	**9 (8.3)**
Cardiac failure	3 (3.2)	5 (5.2)	3 (3.1)	1 (1.0)	0	6 (3.0)	3 (2.8)
Atrial fibrillation	0	2 (2.1)	1 (1.0)	1 (1.0)	0	3 (1.5)	1 (0.9)
Acute myocardial infarction	1 (1.1)	0	2 (2.1)	0	0	0	2 (1.9)
Cardiac failure congestive	0	0	2 (2.1)	0	0	0	2 (1.9)
Blood and lymphatic system disorders	**4 (4.2)**	**8 (8.3)**	**11 (11.3)**	**4 (4.1)**	**1 (10.0)**	**13 (6.4)**	**13 (12.0)**
Anaemia	1 (1.1)	4 (4.2)	5 (5.2)	1 (1.0)	1 (10.0)	5 (2.5)	7 (6.5)
Disseminated intravascular coagulation	0	2 (2.1)	0	0	0	2 (1.0)	0
Thrombocytopenia	0	1 (1.0)	2 (2.1)	0	0	1 (0.5)	3 (2.8)
Splenic infarction	2 (2.1)	0	2 (2.1)	0	0	0	2 (1.9)
Respiratory, thoracic and mediastinal disorders	**3 (3.2)**	**3 (3.1)**	**4 (4.1)**	**7 (7.2)**	**0**	**11 (5.4)**	**5 (4.6)**
Pleural effusion	1 (1.1)	0	0	3 (3.1)	0	3 (1.5)	1 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (3.2)**	**6 (6.3)**	**5 (5.2)**	**3 (3.1)**	**0**	**9 (4.4)**	**5 (4.6)**
Acute myeloid leukaemia	0	2 (2.1)	0	1 (1.0)	0	3 (1.5)	0
Injury, poisoning and procedural complications	**2 (2.1)**	**2 (2.1)**	**1 (1.0)**	**4 (4.1)**	**0**	**6 (3.0)**	**1 (0.9)**
Fall	0	0	0	2 (2.1)	0	2 (1.0)	0
Metabolism and nutrition disorders	**2 (2.1)**	**2 (2.1)**	**4 (4.1)**	**3 (3.1)**	**0**	**5 (2.5)**	**4 (3.7)**
Hyperkalaemia	1 (1.1)	1 (1.0)	2 (2.1)	1 (1.0)	0	2 (1.0)	2 (1.9)
Hyponatraemia	0	0	2 (2.1)	0	0	0	2 (1.9)
Investigations	**0**	**1 (1.0)**	**4 (4.1)**	**1 (1.0)**	**1 (10.0)**	**2 (1.0)**	**4 (3.7)**
Alanine aminotransferase increased	0	0	2 (2.1)	0	1 (10.0)	0	2 (1.9)
Aspartate aminotransferase increased	0	0	2 (2.1)	0	1 (10.0)	0	2 (1.9)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] Adverse events for placebo subjects who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

Note: Adverse events are coded using MedDRA Version 20.1. A TEAE is defined as an adverse event that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of study drug. Table is sorted by the 400-mg of Safety Pool #1 column by descending AE frequency for SOC and within each SOC, sorting is done by descending AE frequency of PT. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.

Source: CSR EFC12153 Table 14.3.2.6.2, CSR ARD12181 Table 14.3.2.1, and ISS Table 3.7.4.1

Treatment-related SAEs

Safety Pool #1: The frequency of subjects with treatment-related treatment-emergent SAEs reported were similar in the 400 mg and 500 mg groups (11.3% and 13.0%). Treatment-related SAEs reported in ≥ 2 subjects in any pooled dose group were anemia , pneumonia, diarrhoea, and acute kidney injury in the 400 mg group, and anaemia and WE in the 500 mg group (Table 60).

The frequencies of subjects with treatment-related treatment-emergent SAEs reported during the entire treatment duration were similar in the 400 mg and 500 mg groups (11.5% and 12.4%, respectively) (study EFC12153). Anaemia (2 subjects each in the 400 mg and 500 mg groups) was the only treatment-related treatment-emergent SAE reported during the entire treatment duration in >1 subject in any treatment group.

Treatment-related treatment-emergent SAEs occurred in 11.3% in the pretreated population and was numerically higher than for the naïve population (6.3% at 400 mg up to 6 cycles). Pneumonia was the only treatment-related treatment-emergent SAE reported in > 1 subject and occurred in 2 subjects (study ARD12181).

Table 60 Treatment-related Serious adverse events reported in more than 1 subject in any treatment group during the entire treatment duration of Study EFC12153, Study ARD12181, and Safety Pool #1 (Safety Population)

	EFC12153		ARD12181	Safety Pool #1			
Preferred Term	Fedratinib 400 mg N = 96 n (%)	Fedratinib 500 mg N = 97 n (%)	Fedratinib 400 mg N = 97 n (%)	Fedratinib 300 mg[a] N = 10 n (%)	Fedratinib 400 mg[b] N = 203 n (%)	Fedratinib 500 mg[c] N = 108 n (%)	Total Fedratinib N = 321 n (%)
Any treatment-related SAE	11 (11.5)	12 (12.4)	11 (11.3)	2 (20.0)	23 (11.3)	14 (13.0)	39 (12.1)
Anaemia	2 (2.1)	2 (2.1)	1 (1.0)	0	3 (1.5)	3 (2.8)	6 (1.9)
Acute kidney injury	1 (1.0)	1 (1.0)	1 (1.0)	0	2 (1.0)	1 (0.9)	3 (0.9)
Diarrhoea	0	1 (1.0)	1 (1.0)	0	2 (1.0)	1 (0.9)	3 (0.9)
Pneumonia	1 (1.0)	0	2 (2.1)	0	3 (1.5)	0	3 (0.9)
Alanine aminotransferase increased	0	1 (1.0)	0	1 (10.0)	0	1 (0.9)	2 (0.6)
Amylase increased	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.9)	2 (0.6)
Aspartate aminotransferase increased	0	1 (1.0)	0	1 (10.0)	0	1 (0.9)	2 (0.6)
Encephalopathy	0	1 (1.0)	1 (1.0)	0	1 (0.5)	1 (0.9)	2 (0.6)
Lipase increased	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.9)	2 (0.6)
Nausea	0	0	0	1 (10.0)	1 (0.5)	0	2 (0.6)
Vomiting	0	1 (1.0)	0	1 (10.0)	0	1 (0.9)	2 (0.6)
Wernicke's encephalopathy	0	1 (1.0)	0	0	0	2 (1.9)	2 (0.6)

SAE = serious adverse event.
[a] Data for fedratinib 300 mg dose is from Study ARD11936.
[b] Includes data for 10 subjects who received fedratinib 400 mg in Study ARD11936.
[c] Includes data for 11 subjects who received fedratinib 500 mg in Study ARD11936.
Note: Preferred terms are in order of descending frequency, and then alphabetical order based on the total fedratinib column.
Note: Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.
Sources: CSR EFC12153 Table 14.3.2.15.2; CSR ARD12181 Table 14.3.2.3; ISS Table 3.8.2.1.

Other AEs of special interest (AESI)

- Grade 3 or 4 anaemia and RBC transfusion dependence

Grade 3 or 4 anaemia was common, with low frequencies of serious Grade 3 or 4 anaemia (2.5% for the 400 mg dose Safety Pool #1). Overall, in Safety Pool #1 400 mg, permanent treatment discontinuation was infrequently seen (1.5%) and dose modifications were limited (6.4% reported dose reductions and 3.0% reported dose interruptions due to anemia. About 58.1% of patients received transfusions. The median time to onset of new or worsened ≥ Grade 3 anaemia was 60.0 days with 75% of cases occurring within 114.0 days in the 400 mg. Frequencies were comparable or somewhat higher for the 500 mg dose group and median time to onset was somewhat earlier.

Among the subjects who were RBC transfusion independent at baseline, 12.2%, 25.0% and 26.1% of subjects in the placebo, 400 mg and 500 mg group respectively became RBC transfusion dependent over the entire treatment duration (EFC12153). The number of RBC transfusions and rates of RBC transfusion dependency between the placebo and the 400 or 500 mg arms were comparable when

taking into account the difference in follow-up. Within study ARD12181, 27.7% of patients became RBC transfusion dependent.

- Grade 3 or 4 Thrombocytopenia and Platelet Transfusion

Grade 3 or 4 thrombocytopenia was common, with low frequencies of serious Grade 3 or 4 thrombocytopenia (1.5% for the 400 mg dose Safety Pool #1). Grade 3 or 4 bleeding events were reported in 4.4% in the 400 mg group. About 10% of patients had bleeding events associated with thrombocytopenia that required clinical intervention. The frequency of subjects with platelet transfusions was 8.9% in the 400 mg. Permanent treatment discontinuation due to thrombocytopenia was reported in 3.0% of patients and dose modifications were reported in the same order of magnitude. The median time to onset of new or worsened ≥ Grade 3 thrombocytopenia was 69.5 days with 75% of cases occurring within 200.0 days in the 400 mg group. Frequencies for the 500 mg were largely comparable or somewhat higher.

- Cases of encephalopathy, including Wernicke's

Within Safety Pool #2, eight fedratinib-treated subjects with neurological signs or symptoms suggesting the diagnosis of potential WE or other encephalopathy were identified. The time on fedratinib until symptoms were described was between two and thirteen 28-day cycles. Seven out of the 8 subjects were taking fedratinib at 500 mg prior to the onset of the neurologic findings (doses were escalated in certain studies). Most events resolved with some residual neurological symptoms including memory loss, cognitive impairment and dizziness except for 1 subject with head and neck cancer, brain metastasis, difficulty eating, and weight loss who had a fatal outcome. The 1 male subject on 400 mg had findings most likely associated with hepatic encephalopathy and therefore the experts agreed that this was not WE. For one subject, consensus was reached on the diagnosis of WE whereas for the remaining 6 cases there was no consensus between experts. All 7 of these potential cases had pre-existing malnutrition, weight loss, significant GI AEs that were not adequately controlled, or other risk factors that may have contributed to thiamine deficiency. Except for one patient, (potential) cases of WE were amongst others treated with thiamine supplementation.

- Grade 3 or 4 ALT, AST, or Total Bilirubin (TBL) Elevation

In Safety Pool #1, the frequencies of subjects with Grade 3 or 4 ALT, AST, or TBL elevation based on laboratory values were 6.4% in the 400 mg. The frequencies of subjects with Grade 3 or 4 ALT, AST, or TBL elevation (by PTs) and serious Grade 3 or 4 ALT, AST, or TBL elevation were 6.4% and 1.0%, respectively in the 400 mg. TE Grade 3 or 4 ALT, AST, or TBL elevation (by PTs) infrequently led to permanent treatment discontinuation or dose modifications. The median time to onset of any grade new or worsened transaminase (ALT or AST) elevation was 29.0 days for the 400 mg with 75% of cases occurring within 71.0 days. The median time to onset of Grade 3 or 4 ALT was 168.0 days and the median time to onset of Grade 3 or 4 AST was 192.0 days. Within the 500 mg group, grade 3 or 4 AEs and SAEs were reported more frequently. Time to onset was comparable or slightly longer in the 500 mg group compared to the 400 mg group.

Within Safety Pool #2, there was 1 subject (study ARD11936) in the fedratinib 300 mg group who had Grade 4 elevations of ALT, AST, and bilirubin, meeting Hy's law criteria, and reported as hepatic failure that resolved following treatment discontinuation.

- Cardiac failure/Cardiomyopathy

In Safety Pool #1, the frequency of cardiac failure/cardiomyopathy TEAEs (any grade) was 22.7% in the 400 mg. The frequency of Grade 3 or 4 cardiac failure/cardiomyopathy AEs was 6.4% and the frequency of cardiac failure/cardiomyopathy AEs reported as an SAE was 6.9%. The frequencies of

subjects with peripheral oedema (PT; any grade) and cardiac failure (PT; any grade) were 12.3% and 4.4%, respectively. In general, frequencies were in the same order of magnitude for the 500 mg dose group. Cardiac failure was considered treatment-related by the investigator for only 1 subject in the 400 mg group (Study EFC12153) and there was only one report of Grade 5 cardiac failure in the 500 mg group, which was not considered treatment related. Both subjects also had oedema peripheral.

There was no consistent signal of cardiac failure in fedratinib-treated subjects compared with placebo up to 6 cycles (study EFC12153).

- Grade 3 or 4 Hyperamylasaemia or Hyperlipasaemia

In Safety Pool #1, the frequencies of subjects with treatment-emergent Grade 3 or 4 hyperamylasaemia or hyperlipasaemia based on laboratory values were 13.3% in the 400 mg. The frequency of subjects with Grade 3 or 4 hyperamylasaemia or hyperlipasaemia (AESI risk category based on TEAEs by PTs) was 8.9% in the 400 mg group and the frequencies of serious Grade 3 or 4 events were 1.0%. According to protocol, Grade 3 or 4 hyperamylasaemia or hyperlipasaemia was treated with dose interruption and dose reduction and led to permanent treatment discontinuation in 2.0% of patients. Grade 3 pancreatitis was reported for 1 subject in the 400 mg group in study EFC12153 and considered treatment-related. The event resolved after treatment discontinuation. The median time to onset of Grade 3 or 4 lipase (laboratory value) was 60.0 days and the median time to onset of any grade new or worsened amylase/lipase elevation was 16.0 days in the 400 mg group; 75% of cases occurred within 85.0 days. Results for the 500 mg were in general comparable.

- Secondary malignancies

In Safety Pool #1, the frequency of treatment-emergent secondary malignancies was similar in the 400 mg and 500 mg groups (5.4% and 4.6%, respectively). Neoplastic events primarily consisted of progression to AML, basal cell carcinoma, and squamous cell carcinoma.

- Gastrointestinal TEAEs

TEAEs were most frequently reported in the gastrointestinal (GI) disorders system order class (SOC), and nausea, vomiting and diarrhoea were the most frequently reported PTs in the SOC. These events were primarily Grade 1 and 2, frequency of subjects with grade 3 or 4 TEAEs were limited as discussed previously in the section on Grade 3 or 4 TEAEs. Dose reductions or interruptions were reported in <10% of patients and treatment discontinuation occurred infrequently. Symptoms were commonly treated with antidiarrhoeals/intestinal anti-inflammatory agents, anti-emetics and antinauseants.

For Safety Pool #1, the median time to onset of nausea (any grade) was 5.0 – 6.0 days in the fedrainib treated groups. Most events resolved and median time to resolution was 45.5 -52.5 days. The median time to onset of diarrhoea (any grade) was 6.0 days in the 400 mg and the median time to resolution was 16.5 days. The median time to onset of vomiting (any grade) was 2.0 days and the median time to resolution was 9.0 -11.0 days. In general for these GI TEAEs, the pattern of early onset and high frequency in the first cycle was followed by a steady decrease in the subsequent 2 cycles with stabilisation with some variability was commonly observed up to Cycle 6.

- Severe infection

Safety Pool #1: The frequency of subjects with severe infection (any grade, applicant-based definition including opportunistic and viral infections) during the entire treatment duration was 5.4% in the 400 mg group and 5.6% in the 500 mg group. The frequency of subjects with severe infection (any grade) up to 6 cycles was 3.2% in the placebo group, 3.0% in the 400 mg group, and 2.8% in the 500 mg group.

The frequency of subjects with TEAEs (all grades and SAEs) in the infections and infestations SOC was comparable between fedratinib arms and placebo (study EFC12153 up to 6 cycles).

- Blood creatinine increased

In Safety Pool #1, increased blood creatinine by laboratory values (all grades) was reported in 73.9% in the 400 mg group, Grade 3 events were reported in 3% of subjects. Dose modifications and treatment discontinuation were low. The median time to onset of any grade creatinine increased in occurred in Cycle 1 at 27.0 days, with 75% of cases occurring within 82.0 days. Treatment-emergent renal failure was reported in 2.0% of patients and treatment-emergent chronic kidney disease was reported in 0.5%. Acute kidney injury was reported in 1.0% of patients and treatment-emergent dehydration in 2.5% of patients.

2.6.3. Laboratory findings

Haematology

Safety Pool #1: Shifts in the severity of anaemia and white blood cell counts from baseline Grade 0 to 2 to Grade 3 (worst grade) on treatment up to 6 cycles occurred more frequently in the fedratinib groups compared with the placebo group. Shifts in the severity of platelet, neutrophil, and lymphocyte counts were comparable for the 400 mg and placebo group and higher for the 500 mg group for platelet counts and neutrophil counts compared to placebo.

In general, haematology values across analytes remained stable in the placebo group (up to 6 cycles), while fedratinib treatment was associated with decreasing values through 12 cycles, with the largest decrease occurring between baseline and the first on-treatment data point (Cycle 2) for haemoglobin, leukocytes (WBC), neutrophils, and platelets. For leukocytes and neutrophils, this early drop in values was substantial, with values decreasing nearly 50% in both the 400 and 500 mg groups. Following nadir, there was a partial recovery in mean haemoglobin levels though 12 cycles, but mean platelet counts remained lower.

Serum chemistry

The largest changes in mean serum chemistry values typically occurred between baseline and the first on-treatment data point (Cycle 2). Overall, shifts in clinical chemistry parameters were observed infrequently among subjects in both pivotal studies and the safety pool #1, and even fewer subjects in either group had shifts to values Grade ≥3. Larger mean change increases from baseline to Cycle 12 (approximately 10% to 33%) were noted for ALT, amylase, creatinine, and lipase; larger decreases were noted for ALP, LDH, and urate. The frequencies of subjects with electrolyte or metabolic laboratory abnormalities were generally similar among the treatment groups in study EFC12153.

Mean prothrombin time (in Safety Pools #1) and mean activated partial thromboplastin time (in Safety Pool #2) decreased over time in fedratinib-treated subjects, however these changes were not clinically meaningful.

Vital signs

No clinically relevant changes in vital signs were reported across the safety population in Safety Pool #1 and #2 and there was no sign of prolongation of QTc.

2.6.4. Safety in special populations

- **Age**

Within the Safety Pool #1, 151 (47%) were >65 years and 38 (12%) were >75 years of age. In general, the frequency and distribution of TEAEs was similar in subjects ≤ 65 versus > 65 years of age and similar relationships were observed when comparing the placebo and fedratinib treated groups. In subjects > 65 years, increased rates of diarrhoea and anaemia in the fedratinib 400 and 500 mg groups were also observed in the placebo group. A total of 66 patients >75 yrs were included in Safety Pool #2, of which 59 received doses ≥300 mg. Caution must be taken in this comparison due to the small number of subjects in the > 75 years of age.

Treatment-emergent adverse events reported with the recommended posology of 400 mg daily are presented in Table below according to age subgroups. In patients aged 75 to <85 years, there was an apparent trend towards increased Treatment-Emergent SAE requiring or prolonging hospitalisation and towards an increase in other medically important events (~26% vs <10% in younger patients), a pattern which may reflect additional precautionary care in elderly patients. In patients aged ≥75 years the rate of TEAE leading to permanent study drug discontinuation was not higher than in younger patients and there were no cases of treatment-emergent SAE leading to death. Due to the small number of subjects aged ≥75 years of age (n=28) caution must also be taken in this evaluation.

Table 61 Summary of treatment-emergent adverse events by criteria or Me-dDRA terms and age subgroups during the entire treatment duration of fedratinib 400 mg treatment in safety pool (Safety Population)

Criteria or MedDRA Terms Subjects with ≥ 1	Age Subgroups (years) for Fedratinib 400 mg			
	< 65 (N = 98) n (%)	65 to < 75 (N = 77) n (%)	75 to < 85 (N = 27) n (%)	≥ 85 (N = 1) n (%)
TEAE	98 (100.0)	77 (100.0)	27 (100.0)	1 (100.0)
Treatment-emergent SAE:[a]	29 (29.6)	30 (39.0)	14 (51.9)	1 (100.0)
Resulting in death	4 (4.1)	8 (10.4)	0	0
Requiring/prolonging hospitalization	26 (26.5)	28 (36.4)	11 (40.7)	1 (100.0)
Congenital anomaly/birth defect	0	0	0	0
Life-threatening	2 (2.0)	2 (2.6)	1 (3.7)	0
Persistent/significant disability/incapacity	0	0	0	0
Other medically important event	6 (6.1)	3 (3.9)	7 (25.9)	0
TEAE leading to permanent treatment discontinuation	21 (21.4)	19 (24.7)	9 (33.3)	0
Psychiatric disorders (SOC)	13 (13.3)	10 (13.0)	3 (11.1)	0
Nervous system disorders (SOC)	44 (44.9)	23 (29.9)	8 (29.6)	0
Injury, poisoning, and procedural complications (SOC)	19 (19.4)	20 (26.0)	9 (33.3)	1 (100.0)
Cardiac disorders (SOC)	11 (11.2)	16 (20.8)	7 (25.9)	0
Vascular disorders (SOC)	9 (9.2)	9 (11.7)	3 (11.1)	0
Infection and infestations (SOC)	43 (43.9)	50 (64.9)	11 (40.7)	1 (100.0)
Cerebrovascular disorders (SMQ)[b]	0	1 (1.3)	0	0
Anticholinergic syndrome (PT)	0	0	0	0
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures[c]	23 (23.5)	16 (20.8)	5 (18.5)	0
Anaemia	51 (52.0)	36 (46.8)	18 (66.7)	0
Asthenia	11 (11.2)	10 (13.0)	6 (22.2)	0

HLGT = High Level Group Term; HLT = High Level Term; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SMQ = Standardized MedDRA Query; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] Subjects may have met more than one SAE criteria.

[b] Narrow scope of Sub-SMQ Conditions associated with central nervous system haemorrhages and cerebrovascular accidents, Narrow scope of Sub-SMQ Haemorrhagic central nervous system vascular conditions, and Narrow scope of Sub-SMQ Ischaemic central nervous system vascular conditions.

[c] Search includes PTs of orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, dizziness exertional, dizziness postural, persistent postural-perceptual dizziness, and procedural dizziness; HLT Gait disturbances and HLT Coordination and balance disturbances; and HLGT Fractures.

Note: A TEAE is defined as an adverse event that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of study drug. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936. For the subjects in Study EFC12153, only subjects initially randomized to 400 mg are included.

Source: Table.OSEB.LoQ.149.2, Table.OSEB.LoQ.149.4, Table.OSEB.LoQ.149.6, Table.OSEB.LoQ.149.8, and Table.OSEB.LoQ.149.10.

- **Gender**

A total of 137 (43%) of patients were female in Safety Pool #1. There was generally no consistent pattern of differences in the occurrence of TEAEs between male and female subjects. Female subjects experienced somewhat higher frequencies of Gastrointestinal Disorders, especially for nausea and vomiting.

- **Race**

Most patients were white race (286, 89.1%), 28 (8.7%) were Asian in Safety Pool #1. The safety profiles of the white and Asian subgroups were consistent with the overall fedratinib safety profile. Interpretation of the race subgroups of black and other were too small to provide meaningful evaluation.

- **Baseline platelet count**

Fedratinib has not been studied in patients with a baseline platelet count <50 x 10^9/L. Patients with low baseline platelet count (<100 x 10^9/L) were 48/203. In general, the frequency and distribution of TEAEs were similar across baseline platelet count subgroups and were similar to the frequency and distribution of all TEAEs in Safety Pool #1. In the 400 mg group, common TEAEs reported in ≥15% of fedratinib subjects with baseline platelet count <100 $\times$ 10^9/L that were observed at higher frequencies (≥5% difference between subgroups) than the baseline platelet count ≥100 $\times$ 10^9/L group included the haematological events of anaemia and thrombocytopenia.

- **Baseline Hb level**

In general, the frequency and distribution of TEAEs was similar in subjects with baseline haemoglobin level ≤ 10 g/dL and > 10 g/dL and similar relationships were observed when comparing the placebo and fedratinib treated groups. However, anaemia and ≥Grade 3 anaemia was reported more frequently in the subgroup with Hb ≤10 g/dL (65.5% any grade and 60.9% ≥Grade 3 vs 25.0% any grade and 12.9% ≥Grade 3 in patients with Hb > 10 g/dl). Thrombocytopenia was also reported at numerical higher frequencies.

- **Pregnancy and lactation**

There are no studies with the use of fedratinib in pregnant women. Studies in animals have shown reproductive toxicity.

There are no data on the presence of fedratinib or its metabolites in human milk.

No human data on the effect of fedratinib on fertility are available. Studies in animals have not shown adverse effects on fertility apart from an increase in post-implantation loss with a reduction in viable foetuses.

- **Liver impairment**

Within safety Pool #1, patients with mild/moderate baseline hepatic function were 76/203 in the 400 mg group and 109/321 (34%) overall. In general, the frequency and distribution of TEAEs was similar in subjects with normal or impaired hepatic function at baseline and similar relationships were observed when comparing the placebo and fedratinib treated groups. There are no data in patients with severe hepatic impairment.

- **Renal impairment**

In safety Pool #1, patients with mild/moderate baseline renal function were 135/203 in the 400 mg group and 218/321 (68%) overall. In general, the frequency and distribution of TEAEs was similar in subjects with normal or impaired renal function at baseline and similar relationships were observed when comparing the placebo and fedratinib treatment groups.

2.6.5. Immunological events

None.

2.6.6. Safety related to drug-drug interactions and other interactions

Agents that strongly induce CYP3A4 may decrease fedratinib exposure (Fedratinib-DMPK-2852) and should be avoided in patients receiving fedratinib. Concomitant administration of fedratinib with strong and moderate CYP3A4 inhibitors can increase fedratinib exposure (Study INT12893; Fedratinib-DMPK-2852), requiring fedratinib initial dose to be reduced to 200 mg and 300 mg with strong or moderate CYP3A4 inhibitor, respectively.

Fedratinib can increase plasma levels of drugs that are metabolised by CYP3A4, CYP2C19, or CYP2D6 (Study INT12497).

2.6.7. Overdose

Overdose was reported for 6 subjects in the fedratinib clinical development programme. All events were ≤Grade 2 and non-serious events.

2.6.8. Discontinuation due to adverse events

The percentage of subjects with TEAEs leading to permanent treatment discontinuation during the entire treatment duration was 24.1% in the 400 mg pooled group and 33.3% in the 500 mg pooled group (24.1% versus 33.3%). The most frequent TEAEs leading to permanent treatment discontinuation in Safety Pool #1 were primarily GI and haematological TEAEs (Table 62). Thrombocytopenia and vomiting led to permanent treatment discontinuation more frequently in the 500 mg group compared with the 400 mg group. Up to 6 cycles, frequency of TEAEs leading to discontinuation was numerically higher in the pre-treated patients (study ARD12181) compared to the naïve population (study EFC12153) for the 400 mg group (19.6% vs 13.5%).

Table 62: Treatment-emergent adverse events leading to permanent treatment discontinuation reported in ⩾ 2% of subjects in any 400 mg or 500 mg fedratinib treatment group during entire treatment duration in Study EFC12153, Study ARD12181, and Safety Pool #1 (Safety Population).

MedDRA System Organ Class Preferred Term	Study EFC12153			Study ARD12181	Safety Pool #1		
		Fedratinib		Fedratinib	Fedratinib Pool		
	Placebo[a] (N = 95) n (%)	400 mg (N = 96) n (%)	500 mg (N = 97) n (%)	400 mg (N = 97) n (%)	300 mg (N = 10) n (%)	400 mg (N = 203) n (%)	500 mg (N = 108) n (%)
Subjects with ≥ 1 TEAE leading to treatment discontinuation	8 (8.4)	26 (27.1)	35 (36.1)	19 (19.6)	2 (20.0)	49 (24.1)	36 (33.3)
Blood and lymphatic system disorders	**2 (2.1)**	**9 (9.4)**	**9 (9.3)**	**3 (3.1)**	**1 (10.0)**	**13 (6.4)**	**10 (9.3)**
Thrombocytopenia	0	4 (4.2)	6 (6.2)	2 (2.1)	0	6 (3.0)	7 (6.5)
Anaemia	0	2 (2.1)	1 (1.0)	1 (1.0)	1 (10.0)	3 (1.5)	2 (1.9)
Neutropenia	0	0	2 (2.1)	0	0	0	2 (1.9)
Gastrointestinal disorders	**0**	**6 (6.3)**	**10 (10.3)**	**4 (4.1)**	**0**	**11 (5.4)**	**10 (9.3)**
Diarrhoea	0	2 (2.1)	2 (2.1)	2 (2.1)	0	4 (2.0)	2 (1.9)
Nausea	0	2 (2.1)	2 (2.1)	1 (1.0)	0	4 (2.0)	2 (1.9)
Vomiting	0	0	4 (4.1)	1 (1.0)	0	1 (0.5)	4 (3.7)
Cardiac disorders	**2 (2.1)**	**8 (8.3)**	**2 (2.1)**	**2 (2.1)**	**0**	**10 (4.9)**	**2 (1.9)**
Cardiac failure	2 (2.1)	3 (3.1)	1 (1.0)	0	0	3 (1.5)	1 (0.9)
Myocardial ischaemia	0	2 (2.1)	0	0	0	2 (1.0)	0
Investigations	**0**	**5 (5.2)**	**5 (5.2)**	**4 (4.1)**	**0**	**10 (4.9)**	**5 (4.6)**
Blood creatinine increased	0	2 (2.1)	2 (2.1)	1 (1.0)	0	3 (1.5)	2 (1.9)
Lipase increased	0	1 (1.0)	3 (3.1)	0	0	2 (1.0)	3 (2.8)
General disorders and administration site conditions	**0**	**1 (1.0)**	**2 (2.1)**	**1 (1.0)**	**0**	**2 (1.0)**	**2 (1.9)**
Fatigue	0	0	2 (2.1)	1 (1.0)	0	1 (0.5)	2 (1.9)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] Adverse events for placebo subjects who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

Note: Adverse events are coded using MedDRA Version 20.1. A TEAE is defined as an adverse event that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of study drug. Table is sorted by the 400-mg column of Safety Pool #1 by descending AE frequency for SOC and within each SOC, sorting is done by descending AE frequency of PT. Safety Pool #1 includes Studies EFC12153, ARD12181, and ARD11936.

Source: CSR EFC12153 Table 14.3.2.12.2, CSR ARD12181 Table 14.3.1.8, and ISS Table 3.9.4.1

TEAEs leading to dose reduction

TEAEs leading to dose reduction were reported in 33.0% and 50.0% in the 400 mg and 500 mg group in Safety Pool #1, respectively. In the pooled 400 mg group, TEAEs most commonly leading to dose reduction were anaemia (6.4%), thrombocytopenia (3.4%) and gastrointestinal events; nausea (4.9%), diarrhoea (4.4%), and vomiting (2.5%). Dose reduction due to TEAEs occurred more frequently in the 500 mg group compared to the 400 mg group, the most notable difference is seen for anaemia (14.4% for 500 mg vs 7.3% for 400 mg in study EFC12153). TEAEs leading to dose reduction were more commonly reported in the pre-treated patients (study ARD12181) when comparing the 400 mg dose up to 6 cycles (ARD12181: 36.1% vs ECF12153: 18.8% for the 400 mg group). The pattern of AEs was comparable between studies.

TEAEs leading to dose interruption

TEAEs leading to dose interruption were reported in 32.0% and 48.1% in the 400 mg and 500 mg group in Safety Pool #1, respectively. In the pooled 400 mg group, TEAEs most commonly leading to dose interruption were nausea (6.4%), diarrhoea (5.9%), vomiting (5.4%), anaemia (3.0%) and thrombocytopenia (2.5%). TEAEs leading to dose interruption were more commonly reported in the pre-treated patients (study ARD12181) when comparing the 400 mg dose up to 6 cycles (ARD12181: 26.8% vs ECF12153: 20.8% for the 400 mg group). The pattern of AEs was comparable between studies.

2.6.9. Post marketing experience

Fedratinib was approved by the FDA on 16 Aug 2019 and therefore, at the time of this submission, no notable post-marketing safety data have been received.

2.6.10. Discussion on clinical safety

Safety data for fedratinib has been provided from 608 patients receiving continuous doses, of which 539 received treatment for myeloproliferative disorders (dose range 30-800 mg/day) and 69 for solid tumours (500 mg dose) (Safety Pool #2). The safety evaluation is focussed primarily on the pivotal studies EFC12153 (naïve population, placebo-controlled, 400 mg and 500 mg dose) and ARD12181 (ruxolitinib-pretreated population, single arm, 400 mg dose) which are combined in Safety Pool #1 together with data from the phase 2 study ARD11936 (naïve population, n=31, 300 mg. 400 mg, 500 mg dose). A total of 203 patients received the proposed recommended dose of 400 mg, 108 patients received the 500 mg dose. The median number of cycles was 6 for study ARD12181 and 14-16 for study EFC12153. For the pooled 400 mg group, median number of cycles was 9. Overall, 128 patients received 400 mg and 77 patients received 500 mg dose for ≥6 months. A total of 77 patients received 400 mg and 61 received 500 mg dose for ≥12 months. Therefore, the safety database is sufficient to assess the safety profile of fedratinib and the requirements as laid down in ICH E1 (CPMP/ICH/375/95) (about 300-600 patients for 6 months and 100 patients for 12 months) are met. Uncertainties remain on long term safety due to early study termination, while treatment exposure is likely to be substantial longer in clinical practice with a median survival of 3.5 to 5.5 years, depending on prognostic score. Long-term data for ruxolitinib in the COMFORT-I study showed that about one quarter of patients with intermediate-2 or high-risk MF were still on treatment after 5 years (Verstovsek et al, 2017[15]). This study was part of the MAA of ruxolitinib and included patients with palpable splenomegaly (at least 5 cm below costal margin) that were refractory to or not candidates for available therapy. It is partly reassuring that there were no new or unexpected safety signals identified in this long-term study, given the overlap in mechanism of action between ruxolitinib and fedratinib.

AEs were reported for almost all patients who received fedratinib. Dose delays or reductions due to TEAEs were frequently seen (>25% each within the pivotal studies). A substantial part of the patients discontinued treatment due to TEAEs (12% before end of cycle 6 and almost 25% overall for the pooled 400 mg dose), indicating a non-negligible safety profile limiting patient's benefit from fedratinib treatment. Most TEAEs were reported in 1 or 2 subjects. Treatment-related grade 3 or 4 TEAEs were more common with the 500 mg dose and more patients discontinued treatment due to TEAEs compared to the 400 mg dose. The lower tolerability in combination with a marginal added benefit with the 500 mg dose, supports the choice of 400 mg as the recommended dose.

Gastrointestinal events (diarrhoea, nausea and vomiting) were very common with fedratinib treatment and occurred soon after start of treatment. Most were grade 1 and grade 2 events and only few patients discontinued treatment due to these events. Events were treated with dose modifications and symptomatic treatment. Appropriate statements including dose modifications for ≥Grade 3 events and warnings are included in the SmPC (section 4.2 and 4.4). Prophylactic use of anti-emetics and administration with high fat meal are proposed to reduce the risk of these events. The impact of these measurements to reduce GI events is further investigated in the planned study PASS FEDR-MF-002 included in the RMP. Higher frequencies of constipation were also observed, especially with the 500 mg dose (16.5% vs 7.4% placebo) and part of these events were considered treatment-related (7.4% patients in the 400 mg group and 8.3% patients in the 500 mg group). Therefore, constipation is

[15] Verstovsek S, Mesa R, Gotlib J, Gupta V, DiPersio J, Catalano J, et al. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomised, double-blind, placebo-controlled, phase 3 COMFORT-I trial. J Hematol Oncol. 2017; 10(1): 55

included as an ADR in section 4.8 of the SmPC. Nevertheless, it can not be excluded that part of the events is related to the complications of the disease (increased spleen) or use of antidiarrhoeals.

Other AEs commonly reported with fedratinib treatment were anaemia and thrombocytopenia. These events are directly related to the mechanism of action of JAK inhibition. Anaemia and thrombocytopenia were commonly reported as ≥Grade 3 events and primarily treated with blood/platelet transfusions and dose modifications. Adequate warnings and dose modifications are included in section 4.2 and 4.4 of the SmPC. The higher rates of anaemia and especially thrombocytopenia in the pre-treated population may be explained by the more advanced disease status of these patients, with lower baseline Hb levels and platelet count compared to the naïve population.

Thrombocytopenia results in an increased risk of bleeding events and thrombocytopenia/bleeding are followed-up by questionnaires in the RMP. A warning on thrombocytopenia and increased risk of bleeding is included in section 4.4 SmPC. Among patients enrolled into JAKARTA2, 33% were reported as being intolerant to ruxolitinib, with haematologic toxicity (particularly thrombocytopenia and anaemia) quoted as being the most common type of intolerance (reported for 25.8% of patients). Although there is overlap in haematological toxicology between ruxolitinib and fedratinib, a substantial portion of patients intolerant to ruxolitinib due to haematologic toxicity were able to remain on fedratinib treatment without re-emergence of unmanageable haematologic intolerance. Though based on a limited dataset (n=25), these data indicate that fedratinib is a possible treatment option for these patients.

Fedratinib was not studied in patients with platelet count $<50 \times 10^9$/L and treatment is not recommended. In addition, fedratinib was not studied in patients with baseline ANC count $<1 \times 10^9$/L. Appropriate warnings are included in section 4.4 with reference to section 4.2 and 4.8 of the SmPC. Given the risk of cytopenias, a complete blood count should be obtained prior to start of fedratinib treatment. This is adequately stated in section 4.2 and 4.4 of the SmPC.

GI and haematological events were also the most frequently reported treatment-related events with higher incidence in the fedratinib group compared to placebo. Exposure-safety analyses indicated that increasing fedratinib exposure increases probability of nausea/vomiting of any grade. The effect exposure on the probability of anemia or thrombocytopenia was less clear, but likely masked by the effect of baseline Hb level and platelet count which were important covariates.

ALT and AST increased have been reported more frequently with fedratinib compared to placebo, indicative of hepatotoxicity. This is in line with what is known of ruxolitinib and JAK inhibitors in general. There was only one case meeting Hy's law criteria in Safety Pool #2. In addition, lipase and amylase levels were commonly increased with fedratinib with one case of pancreatitis in Safety Pool #2. Warnings are included in section 4.4, including recommendations for monitoring of enzymes and dose modifications in section 4.2 in case of ≥Grade 3 events. These warnings are considered adequate. In addition, a study is being conducted to characterise the effects of moderate and severe HI on the PK of fedratinib to provide guidance on the use of fedratinib in patients with HI, the results have been requested as part of the pharmacovigilance plan (please see RMP section below).

Other AEs reported more frequently with fedratinib compared to placebo and included in section 4.8 are muscle spasms, bone pain, pain in extremity, blood creatinine increased, headache, dizziness, dysuria, and urinary tract infection. Dyspepsia and dysuria were added given the imbalance between fedratinib (4.4% each) versus placebo (0%) and hypertension and fatigue/asthenia based on the number of ≥Grade 3 events. Hypertension is also a known adverse drug reaction (ADR) for ruxolitinib, although the mechanism of action is unknown. There was no increase in severe infections and virus zoster infections compared to placebo. Infections including viral reactivation are a potential risk with JAK inhibitors given that the JAK/STAT pathway is a signaling pathway for inflammatory/many

cytokines. Fedratinib does not inhibit JAK1, in contrast to ruxilotinib, which is involved in antiviral responses through Type I interferon signaling. Nevertheless, severe infection is included as a potential risk in the RMP based on the class effect which is agreed upon. This is of importance as infections are a major complication and cause of death in MF patients. Also non-clinical data indicate an immunosuppressive effect of fedratinib.

On-treatment deaths and TEAEs leading to death were comparable between fedratinib and placebo groups. Most events occurred in single subjects and were not considered treatment-related. There was no signal for an increased risk of cardiac failure. This was initially of concern in combination with the reports on Wernicke's encephalopathy because of the potential association with thiamine deficiency. Fedratinib did not show QTc prolongation.

Overall, rate of serious adverse events was comparable between fedratinib and placebo and most events occurred in 1 or 2 subjects. Pneumonia was reported more frequently, especially in the pre-treated population. There was no relationship with neutropenia and it is agreed that pneumonia is not included as an ADR. Patients with MPN-associated MF have an increased risk of transformation to AML which is a major cause of death. Leukemic transformation was the most frequently reported secondary malignancy, besides basal cell carcinoma and squamous cell carcinoma of the skin. There is currently no signal of an increased risk for secondary malignancies based on the data, however long-term follow-up to identify secondary malignancies is limited and malignancies are a known potential risk for JAK inhibitors. Therefore, secondary malignancies is explicitly stated as missing information in the safety specification of the RMP (please see RMP section below).

There were 8 potential cases of encephalopathy, including Wernicke's, which led to the clinical hold of the fedratinib studies. WE is not known for ruxolitinib or other JAK inhibitors. Fedratinib does cross the Blood Brain Barrier (BBB) to a certain extent, and although preclinical data do not suggest WE-like symptoms or central nervous system pathology upon administration of fedratinib, these models are not very predictive for humans due to low exposure levels. Wernicke's encephalopathy is an acute neurological disorder as a result of thiamine deficiency. There is no direct interaction of fedratinib with the thiamine receptor impacting thiamine absorption based on non-clinical data. One explanation could be that the cases are the results of poor control of the fedratinib associated GI AEs (nausea, vomiting, and diarrhoea) in undernourished subjects in combination with other risk factors. All potential cases of WE occurred in the 500 mg group, in which in general more ≥Grade 3 GI events were reported. However, the exact cause of potential WE in patients treated with fedratinib remains unknown.

Though thiamine levels were not measured in most cases, almost all patients received thiamine supplementation as part of their treatment. Risk mitigation strategies incorporated in the SmPC for fedratinib include measurement of thiamine levels before start of treatment and periodically during treatment. Thiamine should be replenished in case of deficiency. Further, dose modifications are included in section 4.2 and a warning in section 4.4. This is agreed upon. Risk of WE is also included as an identified risk in the RMP. Additional information on risk mitigation strategies and thiamine levels in the target population will become available from the ongoing study FEDR-MF-002.

Apart from the known pharmacokinetic interaction with potent CYP3A4 inhibitors, there is also a potential pharmacodynamic interaction with haematopoietic growth factor drugs, such as G-CSF and erythropoietin, which could be a potential important safety problem if it means that cytopenic patients will be unresponsive to treatment with the needed growth factor in question. In the absence of data, no recommendations can be included in the SmPC, a warning is included in section 4.4 and 4.5 of the SmPC. Further follow-up is needed through routine pharmacovigilance activities and cases of potential reduced efficacy due to PD interactions will be described.

There was no clinical evidence of any ill effects associated with cessation of therapy. This in contrast to ruxolitinib where in some cases MF symptoms returned more severely after stopping treatment. The

difference may be explained by the differences in mechanism of action, with ruxolitinib stabilising the kinase active formation and fedratinib the kinase inactive formation.

The safety profile in important subgroups is in general comparable to that of the total population. Data in patients >75 years is limited, with 38 patients exposed in Safety Pool #1 and 66 patients in Safety Pool #2. A statement on limited data in patients >75 years is included in section 4.4 of the SmPC. Patients with low baseline Hb and platelet count have an increased risk of anaemia and thrombocytopenia and a warning is included in section 4.4 of the SmPC.

There are no direct comparative safety data with ruxolitinib, which is the current standard of care in patients with intermediate-2 or high-risk MF. The safety profile partly overlaps due to JAK2 inhibition, however fedratinib does not act on JAK1 which may result in a different safety profile. Based on indirect comparison, the discontinuation rate appears lower for ruxolitinib (about 10%). Also, infections and bleedings appear less frequent with fedratinib whereas amylase/lipase increased is more frequent. Further, the type of GI events differ. Overall, based on differences in safety profile, fedratinib could be an alternative to ruxolitinib in JAK-inhibitor naïve patients and an addition to the therapeutic arsenal for treating physicians.

Available post-marking data from the USA does not indicate new safety signals. Preliminary safety data from the currently ongoing studies with fedratinib in ruxolitinib-experienced patients does not raise new concerns.

Uncertainties remain with regards to the long-term safety due to the early study discontinuations, including the risk of secondary malignancies, therefore the study results of the ongoing FEDR-MF-002 study have been requested as part of the RMP.

In addition, a study is being conducted to characterise the effects of moderate and severe HI on the PK of fedratinib to provide guidance on the use of fedratinib in patients with HI, the results have been requested as part of the pharmacovigilance plan (please see RMP section below).

2.6.11. Conclusions on the clinical safety

The safety data support the recommended proposed dose of 400 mg. Still the profile of fedratinib is non-negligible with about a quarter of patients discontinuing treatment. The safety profile of fedratinib is characterised mainly by the haematological events anaemia and thrombocytopenia and GI events (nausea, vomiting, and diarrhoea). Anaemia and thrombocytopenia are directly related to the mechanism of action of JAK2 inhibition, often severe but manageable by transfusions or dose modifications. GI events were mostly of mild severity.

Several AEs like AST/ALT increased and creatinine increased are in line with what is known for other JAK inhibitors. A study is being conducted to characterise the effects of moderate and severe HI on the PK of fedratinib to provide guidance on the use of fedratinib in patients with HI, the results have been requested as part of the pharmacovigilance plan (please see RMP section below). The risk of severe infections including viral reactivation appears low but is included in the safety specifications as potential risk based on the class effect. Uncertainties remain regarding long term safety due to the early study discontinuations, including the risk of secondary malignancies, therefore the study results of the ongoing FEDR-MF-002 study have been requested as part of the RMP (please see RMP section below).

Encephalopathy, including Wernicke's, is a serious AE of concern which might be related to fedratinib's GI toxicity contributing to thiamine deficiency in a vulnerable population. However, the exact cause remains unknown. This risk is considered manageable with monitoring of thiamine levels and thiamine supplementation.

Overall, the safety profile can be considered acceptable in the target population with limited treatment options and no major objections are identified precluding marketing authorisation.

2.7. Risk Management Plan

Safety concerns

Table 63: 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:	• Use in patients with severe hepatic impairment • Long-term safety, including secondary malignancies

Pharmacovigilance plan

Table 64: Ongoing and planned additional pharmacovigilance activities in the pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
-	-	-	-	-
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				
-	-	-	-	-
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.	Anaemia Thrombocytopenia/bleeding Encephalopathy, including Wernicke's Gastrointestinal toxicities (diarrhoea, nausea, vomiting) Pancreatitis Severe hepatotoxicity Severe infections including viral reactivation	Original Protocol Protocol Amendment No. 1 Protocol Amendment No. 2 FSFD LSLV DBL	26 Sep 2018 01 Feb 2019 08 Oct 2019 09 Sep 2019 24 May 2022[a] 23 Aug 2025[a]

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	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.	Long-term safety, including secondary malignancies	CSR with FUP	22 Nov 2025[a]
FEDR-CP-001/ Ongoing	Study being conducted to characterise the effects of moderate and severe HI on the PK of fedratinib to provide guidance on the use of fedratinib in patients with HI.	Use in patients with severe HI	Original Protocol Protocol Amendment No. 1 Protocol Amendment No. 2 FSFD LSLV CSR	22 Apr 2019 31 Jul 2019 08 Oct 2019 04 Oct 2019 Q4 2021[a] Q2 2022[a]

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

Risk minimisation measures

Table 65: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures
Important Identified Risks	
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 proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
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. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.

Safety Concern	Risk Minimisation Measures
Encephalopathy, including Wernicke's	**Routine risk minimisation measures:** SmPC Section 4.2 – includes guidance on thiamine replenishment if levels are low and dose recommendations. SmPC Section 4.4 – advice on 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 proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
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 proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Important Potential Risks	
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), details of side effects of increased lipase and amylase. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.

Safety Concern	Risk Minimisation Measures
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 proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Severe infections including viral reactivation	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Missing Information	
Use in patients with severe hepatic impairment	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2 – include statement that fedratinib PK have not been studied in patients with severe HI and warning to avoid use of fedratinib in patients with severe HI (Child-Pugh class C, or TBL > 3 times ULN and any AST increase). **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Long-term safety, including secondary malignancies	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 16.08.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of fedratinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers fedratinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing to patients access to the most recent approved package leaflet in their selected language has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: Package Leaflet

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Inrebic (fedratinib) is included in the additional monitoring list as this is a new active substance additional information should be collected as early as possible to further elucidate the risk profile of the product when used in clinical practice.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Myelofibrosis (MF) belongs to the category of myeloproliferative neoplasms (MPNs) and may present as a primary disorder (primary myelofibrosis [PMF]) or evolve from polycythaemia vera (PV) or essential thrombocythaemia (ET) to post-PV or post-ET MF. It is characterised by the clonal proliferation of a pluripotent haematopoietic stem cell, in which the abnormal stem cell population releases several cytokines and growth factors into the bone marrow microenvironment, thus leading to an increase in bone marrow fibrosis, stromal changes, involvement of extramedullary organs such as the spleen and liver, and consequent clinical manifestations. The symptoms mainly include those associated with splenomegaly (abdominal distension and pain, early satiety, splenic infarction, dyspnoea, and diarrhoea) and constitutional symptoms such as fatigue, cachexia, pruritus, bone pain, weight loss, and fever, impacting QoL. The diagnosis is based on WHO criteria (2008, updated in 2016) and the prognostic score is based on IWG-MRT criteria. Median survival ranges from approximately 3.5 to 5.5 years and depends on the prognostic score. Most frequent cause of death in patients with MF is transformation to acute myeloid leukaemia (20%). Most patients die because of other disease-related events, such as progression without transformation, infections, and thrombo-haemorrhagic complications. Mutations in JAK2, CALR, and MPL activating the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, may play a role in the pathogenesis of MF. However, the exact cause remains unknown.

The proposed indication for Inrebic is:

Fedratinib is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, who are JAK inhibitor naïve or have been treated with ruxolitinib."

3.1.2. Available therapies and unmet medical need

Currently the only curative option for MF is haemaetopoietic stem cell transplantation (allo-HSCT), however most patients are ineligible for HSCT. Considering the clinical manifestations of the disease the aim of treatment is to gain symptom control. Ruxolitinib (Jakavi, JAK1/1 inhibitor) is the only available targeted treatment which has been shown to reduce spleen size, symptom burden and improve survival. Other therapeutic options for MF include erythropoiesis-stimulating agents (ESAs), danazol, and immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide) for improvement of anaemias and hydroxyurea and interferon for the treatment of splenomegaly and/or constitutional symptoms. The selection of appropriate treatment is based on the risk score and presence of symptoms. There is no standard of care for patients progressing on ruxolitinib. Hence, there is a clear unmet medical need for patients with MF.

3.1.3. Main clinical studies

The main evidence for the JAK-naïve population is from a phase 3, randomised, double-blind, placebo-controlled, 3-arm study in adult patients with intermediate-2 or high-risk primary MF, post-PV MF, or post-ET MF with splenomegaly (study EFC12153 - JAKARTA). Patients were randomised (1:1:1) to 400 mg (n=97) or 500 mg (n=97) fedratinib or placebo (n=96) once daily. Fedratinib treatment was

continued as long as patients benefitted from therapy, patients on placebo could cross-over to fedratinib at the end of cycle 6.

The main evidence for the ruxolitinib-pretreated population is from a phase II, open-label, single arm study in adult patients previously treated with ruxolitinib and with a current diagnosis of intermediate or high-risk MF post-PV MF, or post-ET MF with splenomegaly (study ARD12181 – JAKARTA2). Patients (n=97) received fedratinib once daily for at least 6 cycles and treatment could be continued as long as patients benefitted from therapy. Due to the clinical hold of the fedratinib development programme, 17.5% of patients discontinued treatment before the end of cycle 6. At inclusion, patients were required to be resistant or intolerant to ruxolitinib as per investigators' assessment and retrospectively, 79 patients were identified as R/R or intolerant to ruxolitinib (cohort 1) using expert-based criteria.

In both studies, the primary endpoint was spleen response rate defined as the proportion of subjects with ≥35% SVR from baseline to End of Cycle 6 measured by MRI/CT scan (with confirmation 4 weeks later in study EFC12153).
Key secondary endpoint in these studies was symptom response rate defined as the proportion of subjects with ≥50% reduction in the total symptom score (TSS, average of the sum of the daily scores of all 6 items of the modified MFSAF - night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain) from baseline to end of cycle 6.

In study EFC12153 (JAKARTA) Bonferroni adjustment was used to test the primary hypothesis to compare the RR of each treatment arm to the placebo at a 2-sided 2.5% alpha level. A fixed sequence procedure was planned for the multiplicity considerations for each of the fedratinib arms (400 and 500 mg) versus placebo at a 2-sided 2.5% alpha level, being Spleen response rate (Spleen RR), Symptom response rate (Symptom RR), Spleen RR of ≥25% SVR (RR25), Overall survival (OS), Progression-free survival (PFS). Thus, the overall alpha level for the primary endpoint (spleen RR) and the key secondary endpoints (symptom RR, RR25, OS, PFS) was maintained at a 5% level.

In study ECF12153 (JAKARTA) HRQOL was assessed using EuroQol-5D (EQ-5D™) questionnaire (a standardised health-related QOL designed to provide a simple, generic measure of health for clinical and economic appraisal). In study ARD12181 (JAKARTA2) the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) (a self-administered questionnaire chosen as a cancer-specific instrument) was used.

3.2. Favourable effects

The dose-finding studies provided support for the proposed posology of 400 mg/day.

In the randomised placebo-controlled study ECF12153 (JAKARTA) in treatment naïve patients, the primary endpoint of spleen response rate was 36.5% in the fedratinib 400 mg arm, 40.2% in the fedratinib 500 mg arm compared to 1.0% in the placebo arm.

In the single arm study ARD12181 (JAKARTA2) in ruxolitinib-treated patients (predominantly relapsed/refractory/intolerant), the primary endpoint of spleen response rate, was 30.9%. This rate is in the ITT population without using LOCF but considering all missing data as non-response, thus a more conservative estimate of the rate. When patients who received doses > 400 mg (up-titration) were excluded from the analysis a more conservative estimate for the spleen RR of 22.7% was obtained.

In study ECF12153 (JAKARTA), the median (95% CI) percentage change in spleen volume at the End of Cycle 6 in the ITT Population with available baseline and EOC6 assessments, was -40.0% (-39.9, -31.3) in the 400 mg arm, and -46.0% (-47.3, -37.3) in the 500 mg arm compared to +8.0% (+5.1, +15.5) in the placebo arm.

In study ARD12181 (JAKARTA2), the median (95% CI) percent change in spleen volume at End of Cycle 6 (ITT population without using the LOCF method) was -38% (−41.9, −26.9).

In study ECF12153 (JAKARTA), taking into account the wide, overlapping confidence intervals for the difference in spleen RR between the 400 mg and 500 mg fedratinib arms and placebo, there was a consistent picture of similar difference across subgroups. The Spleen RR was also fairly consistent in the various subgroups, including in important baseline subgroups of interest in relation to disease characteristics such as myelofibrosis risk category and myelofibrosis subtype.

In study ARD12181 (JAKARTA2) a similar situation was observed.

Similar Spleen RRs were observed between subjects in the 65 to 74 years age group and the smaller subgroup of subjects 75 to 84 years who received fedratinib 400 mg in Studies ECF12153 (JAKARTA) and ARD12181 (JAKARTA2) and these rates were consistent with those in the overall population.

For the patients included in the primary analysis (i.e. treatment for 6 cycles, so 6 months), the time to spleen response was 3.0 - 3.5 months in the pivotal studies.

In study EFC12153 (JAKARTA) the median treatment duration of treatment was approximately 60 weeks and during the study, 11.1% (6/54) and 14.0% (8/57) of responders in the 400 and 500 mg arms, respectively, the response ended due to PD or death. This indicates that there was not a high rate of loss of response during this period.

In Study ARD12181 (JAKARTA2), in subgroup analyses of Spleen RR by the subgroups ruxolitinib relapsed/refractory (n=65) and intolerant (n=14) (Cohort 1) the Spleen RR was approximately 30% in both subgroups.

In study ECF12153 (JAKARTA), the Symptom RR was 39.6% in the fedratinib 400 mg arm, 34.1% in the fedratinib 500 mg arm compared to 8.2% in the placebo arm.

In study ARD12181 (JAKARTA2), the Symptom RR was 25.8%. When patients who received doses > 400 mg (up-titration) were excluded from the analysis a more conservative estimate for the Symptom RR of 21.5% was obtained.

For individual symptoms in the MFSAF, in both pivotal studies (in both arms of ECF12153 (JAKARTA), the largest reductions in scores were recorded for pain under ribs on left side, night sweats and early satiety with median percent of changes (reduction) of approximately 50% to 80% with night sweats close to 80% in both studies. For abdominal discomfort and itching the median percent of changes were approximately in the range 44% to 50% and lowest for bone or muscle pain at approximately 22% to 30%.

In both studies there was an improvement from baseline in Health Related Quality of Life in both studies. In study ECF12153 (JAKARTA), improvements relative to baseline were reported for both fedratinib arms compared to disimprovement in the placebo arm.

In study ARD12181 (JAKARTA2) a moderate improvement was seen with no disimprovement from baseline.

3.3. Uncertainties and limitations about favourable effects

An important limitation to the efficacy data is the fact that both pivotal studies were terminated early due to reports of cases of Wernicke's encephalopathy which necessitated a clinical hold of the fedratinib studies. This impacted ARD12181 (JAKARTA2) more than Study EFC12153 (JAKARTA) as not all patients reached the end of cycle 6, the treatment duration for evaluation of the primary endpoint.

There are insufficient long-term data to establish the median duration of response.

A lack of direct comparison with ruxolitinib in Study EFC12153 (JAKARTA) in JAK inhibitor naïve patients and the fact that Study ARD12181 (JAKARTA2) in patients who had previously been treated with ruxolitinib was a single arm trial, are factors which hamper evaluation of the efficacy relative to other treatments.

Small sizes of some subgroups limit interpretation of spleen RR in these subgroups.

In Study EFC12153, in the fedratinib 400 mg arm, for male subjects the Spleen RR at 27.8% was lower than for females in whom it was 47.6%. This was not seen in the fedratinib 500 mg arm, in which the Spleen RR was 42.6% in male subjects and 36.1% in females. In study ARD 12181 (JAKARTA2) the spleen RR was also lower in males at 24.5% than in females in whom it was 38.6% but with more overlap in the 95% confidence intervals. However further analysis could not establish that males will have a lower response to fedratinib in terms of spleen volume reduction than females.

With respect to the clinical pharmacology, the warning on the combination of fedratinib with dual CYP2C19 and CYP3A4 inhibitors like fluconazole and fluvoxamine, as well as on the effect of fedratinib on drug transporter activity should be confirmed by results of ongoing DDI studies on these situations which are acknowledged as recommendations.

3.4. Unfavourable effects

Gastrointestinal events (diarrhoea, nausea, and vomiting) were the most frequent AEs for fedratinib in the pivotal studies, with incidences of 44.8% to 67.5% based on the pooled data during the entire treatment duration. These occurred early upon treatment (within first week), were mostly grade 1 and 2 and resolved with symptomatic treatment or dose modifications within 1-2 months. The following recommendation has been included in section 4.2 of the SmPC that the "Administration with a high fat meal may reduce the incidence of nausea and vomiting and thus fedratinib is recommended to be taken with food".

The cytopenias anaemia and thrombocytopenia were the most frequent haematological AEs occurring in about 50% and 20% of patients, respectively. These AEs are expected based on the mechanism of action. Most events were grade 3 or higher (incidence >40% for anaemia and about 17-18% for thrombocytopenia), occurred within 3-4 months and were treated with transfusions or dose modifications. Frequencies of ≥grade 3 AEs anaemia were increased compared to placebo (400 mg dose: 30.2% vs 7.4% naïve population up to 6 cycles) but not for thrombocytopenia. Blood transfusions were common (about 60%) but appear comparable to placebo when adjusted for follow-up time. The frequency of platelet transfusions was about 9% for patients on fedratinib compared to 3% in the placebo group (up to 6 cycles). About 10% of patients had bleeding events associated with thrombocytopenia that required clinical intervention. There does not appear to be an increased risk in severe or SAEs compared to placebo. The incidence of ≥grade 3 AEs thrombocytopenia was numerically higher in pre-treated patients compared to naïve patients (400 mg: 21.6% vs 5.2% up to 6 cycles across studies). Pre-treated patients also more frequently had low baseline platelet count ($<100x10^9$/L) compared to the naïve population. A recommendation has been added in section 4.4 of the SmPC that a "Complete blood counts should be obtained at baseline, periodically during treatment and as clinically indicated (see sections 4.2 and 4.8). Inrebic has not been studied in patients with a baseline platelet count < 50 x 109/L and ANC < 1.0 x 109/L."

Increase in transaminases (AST and ALT), mostly grade 1 or 2, were common. These are known events for JAK inhibitors. In addition, amylase and especially lipase increase was commonly observed with fedratinib treatment. The following warning has been included in section 4.4 of the SmPC:

"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."

Treatment-related grade 3 or 4 TEAEs were more common with the 500 mg dose compared to the 400 mg dose (66.0% vs 47.9%) and more patients discontinued treatment due to TEAEs (36.1% vs 27.1%) within the naïve population. GI events appear dose-related based on exposure-safety relationship.

The safety profile in the pre-treated population appears comparable to that of the naïve population, whereas quantitative differences (higher frequencies of some AEs) can be explained by the more advanced disease status.

There was 1 case of hepatic encephalopathy (400 mg dose) and 7 potential cases of encephalopathy, including Wernicke's, throughout the entire safety database (all receiving 500 mg fedratinib). One case was confirmed as WE. A warning has been included in section 4.4 of the SmPC.

A contraindication in pregnancy is included in section 4.3 of the SmpC.

The safety profile was largely comparable among the subgroups studied.

3.5. Uncertainties and limitations about unfavourable effects

The median duration of exposure in the pooled safety population was 36 weeks in the pooled 400 mg group and 60 weeks in the 500 mg group. For about one half of the patients in the key studies treatment was stopped due to early study termination, and treatment exposure is likely to be substantial longer in clinical practice with estimated median survival of 3.5 to 5.5 years. The limited long-term safety data is especially of relevance for AEs that might occur after long-term exposure, like secondary malignancies. This is reflected in the RMP as important missing information, and additional safety data up to 3 years will be available from the ongoing study FEDR-MF-002 in the pretreated population (please see RMP).

The risk of encephalopathy, including Wernicke's, is a serious AE of concern which was unexpected and resulted in the clinical hold of the fedratinib studies. Wernicke's encephalopathy is an acute neurological disorder resulting from thiamine deficiency. The exact reason is unknown but does not appear to be the result of a direct interaction of fedratinib with the thiamine receptor based on preclinical data. Preclinical data do not suggest WE-like symptoms or central nervous system pathology upon administration of fedratinib, however, the preclinical models are not very predictive for humans because of low exposure levels. It is reassuring that there were no other safety signals in the studies indicative of neurological toxicities. Possibly, GI toxicities of fedratinib can attributed to thiamine deficiency in an otherwise vulnerable population. This can be manageable by thiamine monitoring and supplementation in case of early signs of insufficiency. Adequate measures are included in the SmPC. Further data will become available from the ongoing study FEDR-MF-002 which incorporated the proposed risk minimisation measures currently included in the SmPC.

There was only one case meeting Hy's law criteria, it is unclear whether there is an increased risk of hepatotoxic events in clinical practice as patients with transaminases ≥2.5 x ULN were excluded from the studies. In addition, there was one case of pancreatitis but patients with serum amylase and lipase >1.5 x ULN were excluded. These are included in the RMP and further followed through routine risk measurements which is acceptable. Dose recommendations and warnings have been included in the SmPC.

Fedratinib was not associated with an increased risk of severe infections, including viral reactivation, which is a potential risk with JAK inhibitors given the mechanism of action. The frequency in long-term use is uncertain and severe infections is included as an important potential risk in the RMP.

Data on secondary malignancies is limited due to lack of long-term data. This is included in the RMP.

No information is available on functional CYP3A4 polymorphisms, e.g. CYP3A4*22, and whether a dose reduction would be needed as e.g. recommended for the combination with strong CYP3A4 inhibitors. The applicant commits to submit a pharmacogenetic sub-report on the effect of CYP3A4*22 as investigated in the ongoing study FEDR-MF-002.

No data is available in patients with severe hepatic impairment. An ongoing study in patients with severe hepatic impairment is included in the RMP which will provide data on this subject. In addition, an interaction study is planned to investigate the potential effect of fedratinib as perpetrator on a number of drug transporter proteins (P-gp and others), in order to evaluate potential relevance of such interactions.

No teratogenic effects were observed in non-clinical studies, however the exposure to fedratinib in these studies was well below the clinical exposure and the relevance of these studies for human safety is therefore limited. In line with other JAK inhibitors a contraindication for pregnancy is included in the SmPC.

A satisfactory risk evaluation concerning the presence of nitrosamine impurities in the drug product has been provided. No potential risk for the presence of nitrosamine impurities in the product has been identified.

3.6. Effects Table

Table 66 Effects table for Inrebic in primary and secondary myelofibrosis

Effect	Short Description	Unit	Treatment	Control		Uncertainties/ Strength of evidence	References
Favourable Effects Study EFC12153 (JAKARTA) - (ruxolitinib naïve) ITT population							
			400 mg	**500 mg**	**Placebo**	**(ruxolitinib naïve)**	
			N=97	N=97	N=96		
Spleen RR	Subjects with ≥35% SVR at EOC6, confirmed 4 weeks later	% *95% CI*	36.5 *26.8, 46.1*	40.2 *30.4, 50.0*	1.0 *0, 3.1*	Up to cycle 6, the discontinuation rate in the fedratinib 500 mg arm was 21.9%, 32.0 % in the fedratinib 400 mg arm and 25.3% in the placebo arm.	
Symptom RR	Subjects with≥50% reduction in TSS from baseline to EOC6	% 95% CI	39.6	34.1	8.2		
Favourable Effects Study ARD12181 (JAKARTA2) - (prior ruxolitinib)							
			Total	**Cohort 1**		39 of the 97 patients discontinued before end of cycle 6, n=17 due to early study termination and n=14 due to adverse events.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
			N=97	N=79		
Spleen RR	Subjects with ≥35% SVR at EOC6. Not confirmed	% *95% CI*	30.9 *21.9, 41.1* Only dose 400 mg: % *95% CI*	30.4 *20.5, 41.8*	<u>Primary Endpoint:</u> ITT (n=97) with non-responder imputation at EOC6 Post-hoc analysis by Celgene to address potential bias due to administrative early closure of the study, most conservative approach. Cohorts 1 and 1a were defined retrospectively. See footnote. Dose up-titration to 500 mg or 600 mg was allowed if predefined efficacy and safety criteria were met.	
			N=93	N=74		
Symptom RR	Subjects with≥50% reduction in TSS from baseline to EOC6	% *95% CI* % *95% CI*	25.8 *16.9, 34.7* Only dose 400 mg: 21.5 *13.7, 31.2*	27.0 *17.4, 38.6*		

Unfavourable Effects[1]

			N=203 400 mg	N=108 500 mg	N=95 placebo		
Diarrhoea	Incidence of diarrhoea	%	67.5	62.0	15.8	Grade 3 or 4 TEAE were infrequent	
Nausea	Incidence of nausea	%	61.6	56.5	15.8	Grade 3 or 4 TEAE infrequent, numerically higher for 500 mg	
Vomiting	Incidence of vomiting	%	44.8	57.4	5.3	Grade 3 or 4 TEAE were infrequent, numerically higher for 500 mg	
Anaemia	Incidence of anaemia	%	51.7	49.1	13.7	Mostly Grade 3 or 4 TEAE Related to MoA	
Thrombo-cytopenia	Incidence of thrombocyte-penia	%	21.7	22.2	8.4	Mostly Grade 3 or 4 TEAE were frequent. Related to MoA	
ALT increased	Incidence of ALT increased	%	8.9	11.1	1.1	Grade 3 or 4 TEAEs were uncommon. Known class-effect JAK inhibitors	
AST increased	Incidence of AST increased	%	5.9	11.1	0	Grade 3 or 4 TEAEs were uncommon. Known class-effect JAK inhibitors	
≥Grade 3 Hyperamylasaemia or -lipasaemia	Incidence of ≥Grade 3 Hyperamylasaemia or -lipasaemia	%	8.9	12.0	1.1	One case of pancreatitis	
Encephalopathy, including Wernicke's	Incidence of encephalopathy, including WE	%	1.3[2]		0	1 WE confirmed, 6 potential WE, all with 500 mg. 1 case not WE (hepatic encephalopathy)	

Abbreviations:
Notes: (1) Safety Pool #1 including pooled fedratinib TEAEs from pivotal study EFC12153 (median 14-16 cycles, n=96 400 mg and n=97 500 mg), study ARD12181 (up to 6 cycles, n=97 400 mg), and phase 2 dose range study ARD11936 (median 22-25 cycles, n=10 400 mg and n=10 500 mg), placebo data from study EFC12153 up to 6 cycles. (2) Based on entire safety data base including 608 patients.
EOC6 = End of Cycle 6. SVR = spleen volume reduction. TSS = total symptom score defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified MFSAF.
Study RAD12181 (JAKARTA2): Additional cohorts were identified retrospectively based on expert meeting defining relapse, refractory, intolerant.
Cohort 1: R/R and intolerance to ruxolitinib

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The reduction in spleen volume and associated symptoms of abdominal discomfort and pain, early satiety achieved with treatment with fedratinib are of major clinical relevance in treating patients with myelofibrosis. Similarly, alleviation of debilitating symptoms such as night sweats and pruritus also have a major impact on the disease burden of MF.

Despite the uncertainties due to the early termination of the studies, the available data are considered sufficient to show that clinically relevant effects on the phenomena caused by myelofibrosis have been obtained and the reduction in disease burden achieved can be viewed as being of considerable benefit to the patient.

There is a clear and large absolute effect of fedratinib in reducing splenomegaly and MF symptoms as seen in the placebo-controlled RCT. Apart from ruxolitinib, there is no currently approved treatment for myelofibrosis which results in the same reduction in spleen size/volume, with a spleen RR of 36.5% as seen in JAK inhibitor naïve patients in study EFC12153 (JAKARTA). This response rate is in the same order of magnitude as that of ~42% reported for a very similar primary endpoint in JAK inhibitor naïve patients in the ruxolitinib pivotal study (COMFORT-I).

Absence of a control arm in study ARD12181 (JAKARTA2) hampers evaluation of the efficacy relative to other available treatments in patients relapsed after or refractory to treatment with ruxolitinib but the spleen and symptom response rates seen in this study are clinically relevant although lower (the spleen RR was 22.7% and the Symptom RR was 21.5% when 8 and 4 patients respectively who received doses > 400 mg with up-titration were excluded from these analyses) than in JAK inhibitor naive patients treated with 400 mg/day in study EFC12153 (JAKARTA) (spleen RR 36%, symptom RR 40%).

In Study EFC12153 (JAKARTA), in the fedratinib 400 mg arm, for male subjects the Spleen RR (rate of ≥ 35% spleen volume reduction at EOC6) at 27.8% (95% CI:15.8, 39.7) was lower than for females in whom it was 47.6% (95% CI: 32.5, 62.7) and in Study ARD2181 (JAKARTA2) it was 24.5% (95% CI 12.9, 36.1) in males and 38.6% (95% CI 24.2, 53.0) in females but with more overlap in the 95% confidence intervals. The mean changes of spleen volume from baseline to EOC6 for males and females respectively showed reductions in study EFC12153 (JAKARTA) of 42% vs 46% with fedratinib 500 mg, 26% vs 42% with fedratinib 400 mg and in ARD12181 this was 33% and 33% for both males and females (apparently without exclusion of patients who had had dose up-titration). Overall, from currently available information and analyses it is not considered established that males will have a lower response to fedratinib in terms of spleen volume reduction than females.

While there is uncertainty concerning the duration of the spleen response, it can be taken into consideration that in study EFC12153 (JAKARTA) the median treatment duration was approximately 60

weeks and during the study, 11.1% (6/54) and 14.0% (8/57) of responders in the 400 and 500 mg arms, respectively, the response ended due to PD or death. During the study there was not a high rate of loss of response.

The situation is comparable to that of the ruxolitinib MAA for which the median duration of exposure in all three pooled safety populations was around 10 months (Jakavi EPAR). In the combined pivotal studies, 75% of the patients in the ruxolitinib arms were still receiving the randomised treatment at data cut-off. Progression-free survival, overall survival and leukaemia-free survival data for ruxolitinib became available post-approval. For the new study (FEDR-MF-002), OS data will be collected and made available to CHMP. This study is listed as a Category 3 study in the RMP.

These efficacy results need to be weighed against the safety profile, which is characterised by GI events (diarrhoea, nausea, vomiting) and the cytopenias anaemia and thrombocytopenia. Events are manageable and individual AEs infrequently led to treatment discontinuations. However, overall treatment discontinuation is high indicating a non-negligible safety profile of fedratinib. The safety data support the recommended 400 mg dose based on better tolerability. Anaemia is among the cardinal features of MF, associated with inferior quality of life and poor prognosis of MF and many patients become RBC-transfusion dependent. Due to the increased risk of anaemia by fedratinib, the burden of anaemia remains for the MF patient.

A key serious safety concern of fedratinib appears to be Wernicke's encephalopathy (WE) (1.3% of the patients; 1 WE confirmed, 6 potential WE, all with 500 mg), which results from thiamine deficiency. When recognised early, low thiamine levels are manageable with parenteral thiamine and discontinuation of fedratinib. The frequent GI events appear to have contributed to thiamine deficiency in a vulnerable population. The incidence of potential WE's might be lower for the recommended 400 mg dose. Further, risk minimisation measures like prophylactic anti-emetics and intake with high food may reduce the risk of nausea and vomiting and thus the contribution to low thiamine levels.

Given the known class effects of other marketed JAK inhibitors, concern for exposure to fedratinib during pregnancy has been established. Fedratinib should be contraindicated during pregnancy, in line with other JAK inhibitors.

Long-term safety data is limited with fedratinib. However, long-term exposure is available for JAK inhibitors in general. Class effects for JAK inhibitors and relevant for the target population include risk of severe infections and secondary malignancies. These are of relevance as transformation to acute myeloid leukaemia as well as infections are among the important disease-related events in MF that may lead to death.

Additional long-term safety data will become available from study FEDR-MF-002 in the ruxolitinib pretreated population. This study will also provide some data on the impact of risk minimisation measures in the SmPC on frequent GI events.

The safety profile of fedratinib partly overlaps with that of ruxolitinib due to JAK2-mediated effects, but also shows differences due to the lack of JAK1 inhibition. Type of GI events differ and appear more common with fedratinib, whereas haematological events might occur at a lower rate based on indirect comparisons.

In conclusion, fedratinib offers a treatment alternative to ruxolitinib for the JAK-inhibitor naïve population. In addition, fedratinib offers the option of a targeted therapy for patients previously treated with ruxolitinib.

3.7.2. Balance of benefits and risks

The improvement in spleen volume and disease-related symptoms are clinically relevant in the target populations of naive and ruxolitinib-pretreated patients with MF in the context of an acceptable safety profile.

3.8. Conclusions

The overall B/R of Inrebic (fedratinib) for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Inrebic is favourable in the following indication:

"Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib".

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that fedratinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union has not been authorised previously in the European Union.