CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212327Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Cross-Discipline Team Leader Review

Date	August 15, 2019
From	Kathy M. Robie-Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 212327
Applicant	Impact Biomedicines, Inc. (subsidiary of Celgene Corporation)
Date of Submission	Letter date, January 4, 2019 (received January 3, 2019)
PDUFA Goal Date	September 3, 2019
Proprietary Name / Established (USAN) names	Inrebic (fedratinib)
Dosage forms / Strength	100 mg capsules
Indication(s)	Proposed indication being sought: "Inrebic (fedratinib) is indicated for the treatment of intermediate – or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) (b) (4)
Recommended:	Approval for indication: "Inrebic (fedratinib) is indicated for the treatment of intermediate – or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)"

1. Introduction

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 not approved anywhere in the world for any indication. In this application the applicant (sponsor) is seeking approval of fedratinib for the indication "for the treatment of intermediate – or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) (b) (4)".

To support this application the sponsor has provided the final reports for one concurrently - controlled clinical trial (Study EFC12153 (JAKARTA)) and one open-label, single arm trial (Study ARD12181 (JAKARTA2)).

Fedratinib has been granted orphan designation for the "treatment of secondary and primary myelofibrosis" (5/18/2009) and for the "treatment of polycythemia vera" (3/21/2013). The sponsor requested priority review of the application asserting that most patients are not eligible for allogeneic stem cell transplant (SCT), which is the only curative treatment for patients with MF, and that despite availability of ruxolitinib for the treatment of patients with intermediate or high-risk MF, more than half of patients on ruxolitinib require dose reductions due to myelosuppression which limits continuation of treatment. Priority review was granted for this application.

See the Multi-Disciplinary Review and Evaluation (signed 8/15/2019) for detailed review and discussion of the application.

2. Background

Myelofibrosis (MF) is a serious and life-threatening, stem-cell derived clonal myeloproliferative neoplasm. It can present either de novo as primary myelofibrosis (PMF) or following previously diagnosed polycythemia vera (PV) and essential thrombocythemia (ET) (post-PV MF and post-ET MF, respectively [i.e., secondary MF]). Clinical manifestations include splenomegaly, anemia, thrombocytopenia, fatigue, constitutional symptoms (night sweats, fever, cachexia), bone marrow reticulin and collagen fibrosis, increased risk of leukemic transformation as well as symptoms associated with bone pain, pruritus, thrombosis and related bleeding in the setting of thrombocytopenia and platelet dysfunction. Symptomatic enlargement of the spleen and liver, the need for red blood cell (RBC) transfusions, cachexia, and the other MF associated symptoms result in greatly compromised quality of life (QoL) in patients with MF. Onset is usually age 50 or older and patients have shortened survival. Primary MF, PV and ET are Philadelphia chromosome (Ph1)-negative myeloproliferative disorders. Almost all primary MF and about half of PV and ET myeloproliferative neoplasms

have a Janus kinase (JAK2) mutation. Abnormal activation of JAK2 is associated with myeloproliferative neoplasms (MPNs), including myelofibrosis and polycythemia vera.

Ruxolitinib (JAKAFI), a small molecule inhibitor of JAK1 and JAK2, was approved on 11/16/2011 for the treatment of intermediate or high-risk myelofibrosis, including primary MF, post-polycythemia vera MF (post-PV MF) and post-essential thrombocythemia MF (post-ET MF), based on results of two randomized Phase 3 studies in patients with MF, which demonstrated an increase in proportion of patients showing a ≥35% reduction in spleen volume (measured by MRI or CT) at Week 24 and also showed improvement in patient symptom score. 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). In cell models expressing mutationally active JAK2 or FLT3, fedratinib reduced phosphorylation of STATs, inhibited cell proliferation, and induced apoptotic cell death.

Fedratinib product development has been conducted by three manufacturers:

- The IND for fedratinib was opened in October 2007 by TargeGen with a first-in-human (FIH) Phase 1 dose-escalation study in patients with MF followed by an extension study.
- TargeGen was acquired by Sanofi in September 2010 and the clinical development program was expanded; however, Sanofi terminated the clinical development program in November 2013 because of safety concerns of Wernicke's encephalopathy (WE) and heart failure. At the time of the clinical hold/program termination, the FIH dose-escalation study in myelofibrosis subjects had been completed as well as 10 clinical pharmacology studies. Ongoing studies at the time of the clinical hold/program termination were: One clinical pharmacology study (a QT interval [QT] study); the randomized, double-blind, placebo-controlled Phase 3 study (Study EFC12153, JAKARTA); the long-term extension study to the Phase 1 study; the Phase 2 study in MF subjects previously exposed to Ruxolitinib (Study ARD12181, JAKARTA2); a Phase 2 dose-ranging study; a Phase 2 study in Japan in MF subjects; and a Phase 2 study in subjects with PV or ET who were resistant or intolerant to hydroxyurea.
- Impact Biomedicines, Inc. acquired fedratinib in November 2016.
- Celgene acquired Impact and the fedratinib compound and the IND was transferred to Celgene in February 2018. The sponsor indicates that Impact is a wholly owned subsidiary of Celgene.

For this application the sponsor has provided the final report for one controlled clinical trial, Study EFC12153 (JAKARTA) and a supporting single-arm trial, Study ARD12181 (JAKARTA2) as shown in the sponsor's table below:

Table 3: Overview of Clinical Studies Supporting the Proposed Indication

KEY STUDIES IN MYELOFIBROSIS			
Study	**Study Title**	**Doses**	**Number of Subjects[a]**
Subjects Naïve to Treatment with a JAK Inhibitor			
EFC12153 (JAKARTA) Phase 3	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	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-randomized to receive active treatment[b]
Subjects Previously Exposed to Ruxolitinib			
ARD12181 (JAKARTA 2) Phase 2	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	400 mg fedratinib daily[c]	97 total 400 mg/day, N = 97 Cohort 1 = 79[d] Cohort 1a = 66[d]

EOC6 = End of Cycle 6; SCE = Summary of Clinical Efficacy.
[a] Total randomized/assigned to treatment.
[b] Placebo subjects were re-randomized to receive 400 mg or 500 mg at EOC6 or at the time of progressive disease prior to EOC6.
[c] Up titration permitted to 500 mg and 600 mg if pre-defined 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."
Source: SCE, in-text Table 1

Sponsor's table from section 2.5 Clinical Overview of the application

JAKARTA was a randomized, placebo-controlled, multicenter, Phase 3 study in subjects with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly. JAKARTA2 was an open-label, single-arm Phase 2 study in subjects with intermediate-1 with symptoms, intermediate-2, or high-risk PMF, post-PV MF, or post-ET MF who had been previously exposed to ruxolitinib. JAKARTA enrolled patients who were naïve to a JAK inhibitor, while JAKARTA2 enrolled patients who were previously exposed to ruxolitinib.

The JAKARTA Study was a randomized (1:1:1), double-blind, parallel-group, multicenter, multinational clinical trial of two fedratinib (SAR302503) dosing regimens in patients with intermediate-2 or high-risk primary MF, post-PV MF or post-ET MF with splenomegaly. Patients were to receive either 400 mg or 500 mg fedratinib or placebo daily for at least 6 consecutive 28-day cycles. Dose could be interrupted and/or decreased for toxicity, notably for Grade 4 thrombocytopenia, Grade ≥3 hepatic transaminase or total bilirubin elevation, Grade ≥3 nausea, vomiting diarrhea, constipation, or fatigue unresponsive to therapeutic/supportive measures within 48 hrs, and any Grade ≥3 nonhematologic/nongastrointestinal toxicity or Grade ≥2 peripheral neuropathy. Efficacy assessments included spleen volume, spleen size, myelofibrosis-associated symptoms using the modified MFSAF, investigator assessment of response using the modified IWG-MRT criteria, HRQOL and utility using the EQ-5D questionnaire, MPN-associated symptoms using the MPN-SAF, and hospitalizations. The primary objective was to evaluate the efficacy of

daily oral doses of 400 mg or 500 mg of fedratinib compared to placebo in the reduction of spleen volume as determined by magnetic resonance imaging (MRI) (or computed tomography (CT) scan in patients with contraindications for MRI). The primary efficacy assessment was spleen response rate (RR) which was defined as the proportion of subjects with ≥ 35% spleen volume reduction (SVR) at the End of Cycle 6 (EOC6). A confirmatory MRI/CT was required 4 weeks later. Assessments were by Independent Review Committee (IRC) review of the MRI/CT images done in a blinded manner.

3. CMC

The primary Quality Assessment Review of the application with regard to drug substance was conducted by Sharon Kelly, CDER Office of Biotechnology Products (final signature in Panorama 5/16/2019) and with regard to the drug product primary review was conducted by Xing Wang (final signature in Panorama 5/7/2019). The primary Biopharmaceutics Review was conducted by Mei Ou, final signature in Panorama, 5/23/2019).

The Drug Substance Quality Review found the application to be acceptable from a drug substance perspective. The review commented,

> "The fedratinib dihydrochloride monohydrate drug substance process development began at (b) (4) and the proposed commercial manufacturer is (b) (4) . The fedratinib free base, 100 mg, is the basis equivalent to 117.30 mg of fedratinib hydrochloride drug substance for manufacture of the drug product. (b) (4) uses the same manufacturing process as described by (b) (4) The manufacturing process evaluation is provided in detail, with critical process parameters identified and clearly justified. Several parameters are established for each step and ensure a well controlled process. The (b) (4) data adequately supports the data obtained by (b) (4) The Specification adequately controls the impurities, as demonstrated by spiking/purging studies (acceptance criteria Total impurities (b) (4)%). Sufficient batch data is provided to bridge the data from all three manufacturing sites (including information on the commercial drug substance used to produce the commercial/stability drug product batches).
>
> Based on the results of the long term primary stability studies performed by (b) (4) months) and ongoing stability studies at (b) (4) (b) (4) months), a retest period of (b) (4) months is proposed when stored at (b) (4) C/ (b) (4) %RH. This is acceptable."

There were no outstanding drug substance issues.

The Drug Product Quality Assessment Review recommended that the application was adequate from product quality perspective. There were no outstanding issues and no recommendations for post-approval commitments. The review summarized the pertinent product quality aspects as follows:

***Review Recommendation:* Adequate**

Review Summary:
Fedratinib is a kinase inhibitor indicated for the treatment of primary or secondary myelofibrosis. Fedratinib capsules are for oral use with the appearance as: reddish brown, opaque size 0 capsule, printed with "FEDR 100 mg" in white ink. Each Fedratinib 100 mg capsule contains 117.30 mg Fedratinib dihydrochloride monohydrate drug substance that is equivalent to 100 mg Fedratinib free base. The inactive ingredients are silicified microcrystalline cellulose and sodium stearyl fumarate. The capsule shell contains gelatin, red iron oxide, titanium dioxide and white ink. The primary commercial packaging is a round white opaque HDPE bottle (250 mL) with an (b) (4) (b) (4) The HDPE bottle contains 120 capsules to accommodate a 30-day treatment for the patient.

The drug product specifications consist of appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, (b) (4) and microbial limits. Refer to the reviews of Biopharm and OPF for the evaluations of dissolution and microbial limits respectively. The drug product specification is deemed adequate per ICH guidelines to assure identity, strength, purity, and quality of Fedratinib capsules.

Based on the primary and supportive stability data, a shelf life of 48 months may be granted. Fedratinib capsules should be stored below 86°F (30°C).

The Biopharmaceutics Review focused on the evaluation of: i) the in vitro dissolution method and acceptance criterion of the proposed drug product, ii) the need of in vitro bridging between the clinical and commercial formulations. The Review concluded, "From the Bopharmaceutics perspective, NDA 212327 for the proposed Inrebic (Fedratinib Hydrochloride) Capsules, 100 mg, is recommended for APPROVAL."

The CMC Quality Assessment Executive Summary (Sherita McLamore, Office of Product Quality (OPQ), 6/5/2019) concluded for the application:

> OPQ recommends APPROVAL of NDA 212327 for INREBIC (fedratinib) Capsules, 100 mg. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance when stored between (b) (4) C and a 48-month expiration period for the drug product when stored at or below 30°C (86°F). There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

4. Nonclinical Pharmacology/Toxicology

The primary review for Nonclinical Pharmacology-Toxicology was conducted by Pedro Delvalle as part of the Multi-Disciplinary Review and Evaluation (signed 08/15/2019)

The Review describes that studies of fedratinib in cell models expressing mutationally active JAK2 or FLT3, demonstrated that fedratinib reduces phosphorylation of signal transducer and activator of transcription (STAT3/5) proteins, inhibits cell proliferation, and induces apoptotic cell death. Half-maximal inhibitory concentration (IC_{50}) of fedratinib against JAK2 and

$JAK2^{V617F}$ were 2.3 and 2.4 nM, respectively. Fedratinib showed higher potency for JAK2 over other family members JAK1, JAK3 and TYK2. In vivo studies in mouse models of $JAK2^{V617F}$-driven myeloproliferative disease showed that twice daily oral doses of fedratinib at 60 or 120 mg/kg blocked phosphorylation of STAT3/5, increased survival to 100% at the highest dose after 42 days of treatment, and improved disease-associated symptoms, including reduction of white blood cells, hematocrit, splenomegaly, and fibrosis. The established pharmacological class for fedratinib is kinase inhibitor based on its mechanism of action.

The Review states that safety pharmacology studies showed: "Fedratinib inhibited six human cardiac sodium, potassium, and calcium ion channels with IC_{50}s in the low micromolar range: 2.1-17.8 μM for hERG, 10.8 μM for hNav1.5, 20.6 μM for hKvLQT1/mink, 31.2 μM for hKv4.3, 8.2 μM for hCav3.2, and 2.8 μM for hKir6.2/SUR2A. In vivo, fedratinib was not associated with toxicologically significant effects on cardiovascular or respiratory parameters in dogs. There were no clear drug-related CNS effects in rats; eye miosis and lack of pupillary responses were observed but were non-dose-dependent. Gait abnormalities were also observed in high-dose animals."

Based on studies in mice, rats and dogs, with regard to absorption, distribution, metabolism and excretion the review indicates:

- Time to maximal plasma concentration (tmax) of fedratinib following oral administration is approximately 0.5 to 4 hours, and oral bioavailability ranges from 19 to 37%.
- Fedratinib is approximately 85% bound to plasma proteins in animals and approximately 92% in humans.
- Radiolabeled [^{14}C]-fedratinib was distributed throughout the whole body of the rat.
- After a single oral administration of radiolabeled fedratinib to mice, rats, dogs and human, the parent drug was the main circulating compound in human (80% of radioactivity AUC) and in all animal species (66 to 88% of radioactivity AUC).
- Fedratinib undergoes hepatic metabolism through four identified metabolic pathways. The main circulating metabolite in human was SAR317981 (metabolite 2) which was also detected in rodents at higher exposure than in human.
- After a single oral administration of radiolabeled fedratinib radioactivity was mainly excreted in feces as parent drug across species, 21% to 56% of the administered dose, suggesting a moderate to extensive metabolism (depending on oral absorption).
- Three metabolites identified in humans and animals, SAR317753, SAR317981, and SAR317793, are pharmacologically active against JAK2, with IC_{50}s of 3.8, 3.5, and 46 nM, respectively.
- The elimination half-life of fedratinib is 6 to 12 hours in rats and dogs, with the fecal route as the major pathway (>78%) and the urinary route as a minor pathway (< 5%). Elimination from the eyes was slower (approximately 40 days).

Repeat dose toxicology studies were done in dogs and rats. Target organs of toxicity in the rat were the liver (hypertrophy of bile ducts) and bone marrow (hypoplasia). In the dog target organs of toxicity included adrenals, GI track, liver, kidney, pancreas, lymphatic organs (bone marrow, spleen, thymus, lymph nodes), reproductive organs (epididymides, prostate, testes, ovaries, uterus), heart, lungs, thymus and thyroids. Decreases in red cell mass corresponded

with bone marrow effects, decreases in leukocytes and neutrophils alone with increases in reticulocytes were indicative of anemia and neutropenia; increases in liver enzymes (AST, ALT, ALP) and decreases in total bilirubin corresponded with findings in the liver.

Fedratinib was not mutagenic or clastogenic in *in vitro* tests (Ames test and chromosomal aberration test in Chinese hamster ovary cells). Fedratinib was not carcinogenic in a mouse model.

Developmental and reproductive toxicology studies in rats and rabbits showed the following:

- There were no remarkable fedratinib-related effects on fertility and early embryonic development.
- In the rat embryo fetal development study fedratinib was maternally toxic at the middle and high dose levels with lower gestational body weight gain and decreased gravid uterine weights. There was an apparent dose-related increase in pre-implantation loss in rats; however, the concurrent control value was much less than the historical control values, suggesting the study finding is of questionable toxicological significance. Numerically decreased mean live fetuses were noted in the middle and high dose levels compared to controls.
- Structural abnormalities were seen in fetal rats including: additional ossification centers of neuronal arches, irregular superior borders of scapula, and misaligned sternebrae. [The Review noted the JAK/STAT pathway has been implicated in bone formation and metabolism and its inhibition may cause bone abnormalities, e.g. in developing bone]. No fedratinib-related effects on maternal or developmental parameters occurred in the rabbit embryo fetal development study.
- In the pre- and post-natal development study, fedratinib-related effects were limited decreased body weight parameters.

The review concluded there are no outstanding issues from a nonclinical perspective that would prevent approval of fedratinib for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology (OCP) review was completed as part of the Multi-Disciplinary Review and Evaluation (signed 8/15/2019). The OCP primary review overall was conducted by Siram Subramaniam, the OCP primary review for Pharmacometrics was conducted by Liang Li, the OCP primary review for PM-PBPK was conducted by Manuela Grimstein, and the OCP primary review for Genomics was completed by Oluseyi Adeniyi.

The Review described that the clinical pharmacology section of the NDA application is supported by the evaluations and analyses of single and repeat dose pharmacokinetics (PK) of fedratinib, effect of food on fedratinib PK, population PK, exposure-response relationships for

efficacy and safety, potential for QT/QTc prolongation, drug-drug interactions (DDI) between fedratinib and strong cytochrome P450 (CYP) 3A4 inhibitors and acid reducing agents, and physiologically based PK (PBPK) modeling and simulations of CYP3A4 modulators and dual CYP2C19 and CYP3A4 inhibitors. Summary general findings of the review include:

- Mechanism: Fedratinib inhibits (IC_{50}) Janus Kinase 2 (JAK2) (3 nM for WT & mutant), inhibits (IC_{50}) JAK1 (46 nM), JAK3 (96 nM), and TYK2 (171 nM), and inhibits FLT3 (15 nM).

- Major metabolite, SAR317981, was 9% of total AUC and ~2-fold less active than parent in vitro.

- Fedratinib inhibited hERG current with an IC_{50} of 18 µM in vitro. Thorough QT study showed no large mean increase in the QTc interval (> 20 ms) with daily dosing of fedratinib 500 mg (1.25 times the recommended dose) for 14 days.

- Mean T½ after single dose was 42-78 hrs in healthy subjects between 30 to 680 mg. Mean T½ of 114 hrs at steady state in patients with MF. Apparent oral clearance (CL/F) of 13 (51%) L/hr and volume of distribution (%CV) 1770 L at steady state in patients with MF. CL/F of 21-64 L/hr and Vd of 1030-2630 L after single dose of 30 to 680 mg in healthy subjects.

- AUC and C_{max} were found to be greater than dose proportional over the range of 30 mg to 800 mg in patients with MF after single and multiple doses. Over the range of 300 mg to 500 mg in patients with MF after single and multiple doses, AUC and C_{max} were found to be dose proportional.

- PK parameters and drug exposure at steady state following the therapeutic dosing regimen (once daily) are summarized in the following table from the Review:

PK Parameter	Once Daily dosing*		
	300 mg (n=10)	400 mg (n=10)	500 mg (n=11)
AUC0-tau, ng·h/mL	22371 (56)	26870 (43)	38712 (61)
Cmax, ng/mL	1534 (66)	1804 (49)	2539 (52)
Racc	3.2	2.9	3.9
* at C2D1 in Trials ARD11936			

- The median observed accumulation ratio (Rac) for fedratinib ranged from 3-4 in patients with MF at 300 to 500 mg QD. Rac for fedratinib ranged from 2.1 to 5.4 in patients with MF at 30 to 800 mg QD

- Median T_{max} was 3 hours (range: 2 to 4 hours) at 400 mg QD

- A low-fat, low-calorie (total 162 calories: 6% from fat, 78% from carbohydrate and 16% from protein) or a high-fat, high-calorie (total 815 calories: 52% from fat, 33% from carbohydrate and 15% from protein) meal increased AUC_{inf} up to 22% or 24% and C_{max} up to 12% or 14% of a single 500 mg dose of fedratinib. High fat meal decreased the incidence of nausea and vomiting.

- Plasma protein binding was 92-98%

- Fedratinib is a substrate of P-glycoprotein (P-gp), but not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3),

organic cation transporter (OCT2), and multidrug and toxin extrusion proteins (MATE1, MATE2K).

- Fedratinib disposition is biphasic, with an effective half-life of 41 hours, a mean elimination half-life ($t_{1/2}$) of fedratinib of 114 hours, and a mean (%CV) apparent oral clearance (CL/F) of fedratinib 13 L/h (51%) in patients with MF.

- Unchanged fedratinib (80%) was the major circulating component. Primary metabolic pathways for fedratinib are oxidations of the ethyl pyrrolidine moiety of fedratinib. The molecule is metabolized by CYP3A4 (0 to 70%), CYP2C19 (0-20%), and FMO3 (0-33%) in vitro.
- Excretion is 77% in (23% as unchanged drug) and 5% in urine (3% as unchanged drug) of total dose with recover of 82%.

- With regard to inhibition/induction of metabolism: (1)Modeling and simulation with multiple doses of fedratinib show that fedratinib exposure at steady state increased by 2-fold with strong CYP3A4 inhibitor, and 1.2-fold with a moderate CYP3A4 inhibitor. (2)Clinical study showed that multiple doses of fedratinib increased exposure of CYP3A substrate by 4-fold, CYP2C19 substrate by 3-fold and CYP2D6 substrate by 2-fold. (3) Proton pump inhibitor, pantoprazole, with a single dose of fedratnib showed that fedratinib exposure increased 1.2 fold. (4)Induction of CYP3A4 mRNA in vitro, but net result is inhibition of CYP3A4 enzyme activity. (For the labeling dose reduction to 200 mg once daily is recommended with strong CYP3A4 inhibitors).

- In vitro data suggests that fedratinib inhibits P-gp, BCRP, MATE1 and MATE2K, OCT2, and OATP1B1 and OATP1B3, but does not inhibit OAT1 and OAT3.

The submission included a dedicated Renal Impairment (RI) study, which showed a 1.5 and 2-fold increase in fedratinib $AUC_{0\text{-}Inf}$ in moderate (n=8) and severe (n=7) RI, respectively, compared to their matched control subjects with normal renal function (n=9). The clinical trials allowed enrollment of patients with mild to moderate RI with no dose adjustments. The safety assessment based on pooled data from patients with MF across the clinical trials indicated no clear trends in the incidence of AEs, serious AEs, and dose reductions or interruptions due to AEs in patients with moderate RI treated with 400 mg compared to those treated with placebo, or in patients with mild RI or normal renal function treated at 400 mg. The review stated that increase in Grade 3 or 4 adverse events in patients with moderate renal impairment can be managed with dose modification strategy for toxicity.

The review examined relationship between liver function and PK in a population PK analysis. Fedratinib PK were found to be similar between patients with mild (n=115) and moderate (n=17) hepatic impairment and those with normal hepatic function (n=320). However, the effect of severe hepatic impairment (HI) (total bilirubin >3x ULN and any AST) is unknown, as no patients with severe HI were included during clinical development. The review commented that safety assessment of clinical data in patients indicated similar relative dose intensity and similar incidence of serious AEs and manageable Grade 3/4 AEs at 400 mg in patients with moderate HI versus mild HI or normal hepatic function groups at 400 mg.

The Review explored the impact of germline variation in genes encoding drug metabolizing enzymes and transporters (DMET) on fedratinib PK in both healthy volunteers (HV) (Study PMH1043) and fedratinib-treated patients (Study PMH0144). The review determined that no genotype-guided dosage adjustment appears to be indicated based on the results.

Age (20-95 years), sex, (399 White (88%) and 44 (10%) Asian) races, body weight (39.5 to 135.1 kg), had no clinically meaningful effect on the PK of fedratinib.

Importantly, the clinical pharmacology review assessed the association between fedratinib exposure and Wernicke's encephalopathy (WE). (There were 7 cases of WE in the database [See Clinical Safety Review section 7 below). Examining 132 cases with at least one adverse event related to WE, the review did not find a clear association between fedratinib exposure and WE or encephalopathy. However, the review notes the available data are limited.

Clinical Pharmacology comments and recommendations from the Multi-Disciplinary Review and Evaluation are summarized in the following table from the review:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness[†]	Trial EFC12153 (phase 3, patients with MF) demonstrated an improvement in SVR at the EOC6 and confirmed 4 weeks later compared to placebo.
General dosing instructions	400 mg orally once daily, with or without food. Administration with high-fat meal may reduce incidence of nausea and vomiting.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Avoid coadministration of strong and moderate CYP3A4 inducers, and dual CYP2C19 and CYP3A4 inhibitors. • Reduction of dose to 200 mg is recommended with strong CYP3A4 inhibitors • Reduction of dose to 200 mg is recommended in patients with severe renal impairment. • No dose adjustments are recommended in patients with mild to moderate hepatic impairment, mild to moderate renal impairment, and co-administration with moderate CYP3A4 inhibitors or gastric acid reducing agents.
Labeling	• Consider alternative therapies that are not strong CYP3A4 inhibitors. If unavoidable, reduce dose to 200 mg with strong CYP3A4 inhibitors. • No dose adjustment is necessary with concomitant use of a moderate CYP3A4 inhibitor or gastric acid reducing agents. • Avoid coadministration of dual CYP2C19 and CYP3A4 inhibitors, and strong and moderate CYP3A4 inducers. • Reduce dose to 200 mg in patients with severe renal impairment. • No dose adjustment is necessary in patients with mild to moderate hepatic impairment or renal impairment. The PK and safety of INREBIC in patients with severe hepatic impairment has not been studied. • Monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates as necessary when co-administered with INREBIC.
Bridge between the to-be-marketed and clinical trial formulations	No. However, the pharmacokinetic exposures of initial, 1A1, and 1B1 capsule formulations used during clinical development of fedratinib were found to be comparable, and population PK analysis indicated that formulation was not a clinically significant covariate.

The Review concluded the proposed fedratinib dosing regimen of 400 mg orally once daily in patients with myelofibrosis with the dose reduction schema in the event of adverse reactions is acceptable. From a Clinical Pharmacology standpoint the NDA was found to be is approvable pending agreed upon labeling.

The Review also recommended Post-marketing Commitments (PMC) and Post-marketing Requirements (PMR) described below. (See approval letter for exact wording of PMRs and PMC).

- PMR: Study of single dose of fedratnib in otherwise healthy subjects with severe hepatic impairment compared to healthy subjects, in order to determine an appropriate fedratinib dose for patients with severe hepatic impairment.
- PMR: Study of single dose of fedratinib with and without coadministration of repeat doses of a moderate dual CYP2C19 and CYP3A4 inhibitor in cancer patients, in order to determine an appropriate fedratinib dose for patients with co-administration of a dual CYP2C19 and CYP3A4 inhibitor.
- PMR: Study of single dose of drugs that are P-gp, BCRP, MATE-1 /2K, and OCT2 transporter substrates with and without multiple dose of fedratinib in cancer patients, to determine PK and safety of drugs that are P-gp, BCRP, MATE-1 /2K, or OCT2 transporter substrates for patients with multiple doses of fedratinib.
- PMC: Study of single dose of fedratinib with and without coadministration of repeat doses of a moderate and a strong CYP3A4 inducer in cancer patients, to determine an appropriate fedratinib dose for patients with co-administration of a moderate and a strong CYP3A4 inducer.

There were no other outstanding issues for the application from the Clinical Pharmacology perspective.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

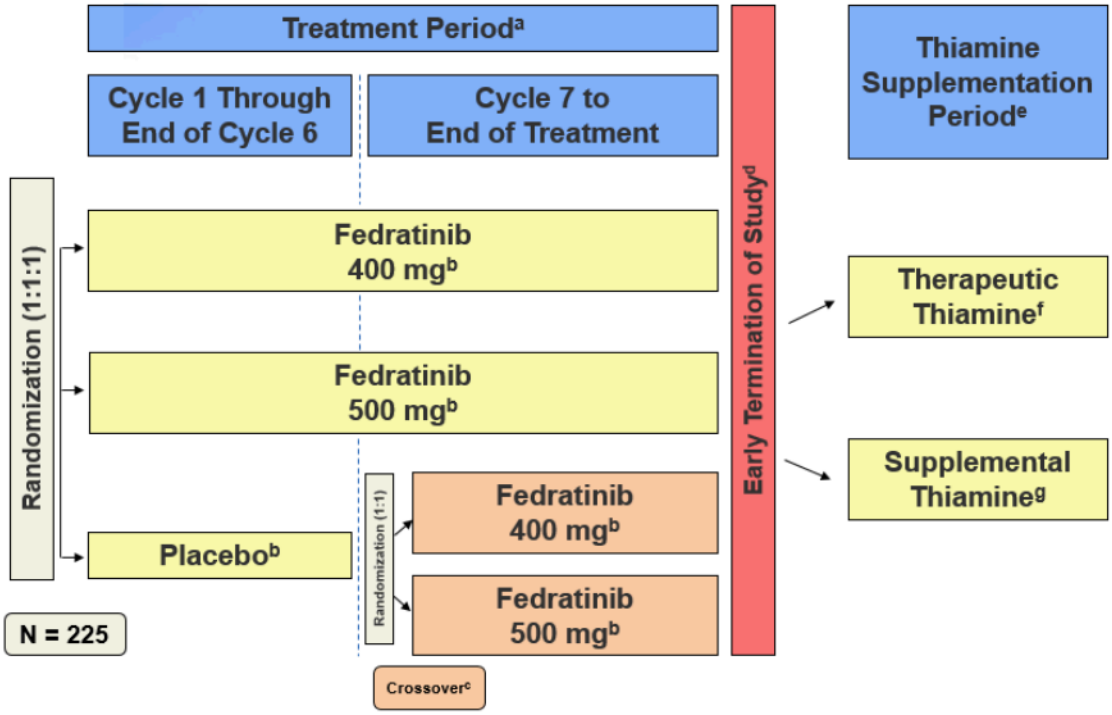
The primary Clinical Review for efficacy of this application was conducted by Saleh Ayache, M.D. and the primary Statistical Review was conducted by Laura Fernandes, Ph.D. as part of the Multi-Disciplinary Review and Evaluation (signed 8/15/2019).

The sponsor is seeking approval of fedratinib for the indication "for the treatment of intermediate – or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) (b) (4)".
To support efficacy the sponsor has provided the final reports for two clinical studies, Study EFC12153 (JAKARTA) and Study ARD12181 (JAKARTA2). The JAKARTA Study was a multicenter, randomized, placebo-controlled, Phase 3 study in subjects with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly. The JAKARTA2 Study was an open-label, single-arm Phase 2 study in subjects with intermediate-1 with symptoms,

intermediate-2, or high-risk PMF, post-PV MF, or post-ET MF who had been previously exposed to ruxolitinib.

The JAKARTA Study was a randomized (1:1:1), double-blind, parallel-group, multicenter, multinational clinical trial of two fedratinib dosing regimens versus placebo in patients with intermediate-2 or high-risk primary MF, post-PV MF or post-ET MF with splenomegaly. Patients were to receive either 400 mg or 500 mg fedratinib or placebo daily for at least 6 consecutive 28-day cycles. Dose could be interrupted and/or decreased for toxicity, notably for Grade 4 thrombocytopenia, Grade ≥3 hepatic transaminase or total bilirubin elevation, Grade ≥3 nausea, vomiting diarrhea, constipation, or fatigue unresponsive to therapeutic/supportive measures within 48 hrs, and any Grade ≥3 nonhematologic/nongastrointestinal toxicity or Grade ≥2 peripheral neuropathy. Efficacy assessments included spleen volume, spleen size, myelofibrosis-associated symptoms using the modified MFSAF, investigator assessment of response using the modified IWG-MRT criteria, HRQOL and utility using the EQ-5D questionnaire, MPN-associated symptoms using the MPN-SAF, and hospitalizations. The primary objective was to evaluate the efficacy of daily oral doses of 400 mg or 500 mg of fedratinib compared to placebo in the reduction of spleen volume as determined by magnetic resonance imaging (MRI) (or computed tomography (CT) scan in patients with contraindications for MRI). The primary efficacy assessment was spleen response rate (RR) which was defined as the proportion of subjects with ≥ 35% spleen volume reduction (SVR) at the End of Cycle 6 (EOC6). A confirmatory MRI/CT was required 4 weeks later. Assessments were by IRC review of the MRI/CT images done in a blinded manner.

The study design for JAKARTA as displayed in the Multidisciplinary Review is shown below:



a The Treatment Period refers to the date of the first dose of any study drug up to 30 days after the last dose of any study drug. Treatment continued as long as subjects were benefitting and had not experienced progressive disease or relapse or unacceptable toxicity requiring discontinuation of study drug.
b Fedratinib and placebo were administered on a daily basis, in consecutive 28-day cycles.
c Eligible subjects initially randomized to placebo were allowed to cross over to receive fedratinib 400 or 500 mg after a second 1:1 randomization in either of the 2 following scenarios:

1) When a subject had completed 6 cycles of treatment, had completed the End-of-Cycle 6 imaging assessments, and had met the protocol-specified entry eligibility criteria.
2) When a subject had experienced progressive disease prior to completing the first 6 cycles of treatment based on protocol-defined criteria and had met the protocol-specified entry eligibility criteria.

d Sanofi terminated the development of fedratinib on 18 Nov 2013.
e Per Protocol Amendment 4, which was implemented after the clinical hold, all subjects permanently discontinued fedratinib treatment. All subjects, including those previously discontinued from treatment, were given the option to receive thiamine supplementation for at least 90 days and were followed for safety for 90 ± 3 days after initiation of thiamine supplementation.
f All subjects with neuropsychiatric or cardiac symptoms consistent with thiamine deficiency were to begin immediate treatment with thiamine at therapeutic dosages in accordance with institutional practice.
g Subjects without symptoms or signs of thiamine deficiency started thiamine daily supplementation.

JAKARTA was conducted from 12/22/2011 to 6/25/2014 and enrolled patients at 94 centers in 24 countries. The last patient was randomized on 9/24/2012. At the time fedratinib development was halted on 11/18/2013 all patients were permanently discontinued from fedratinib treatment and were offered thiamine supplementation. At the time of study termination, 144 subjects were still receiving fedratinib: 51 of the 96 subjects randomized to 400 mg, 45 of the 97 subjects randomized 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 12/2/2013, and the last subject's last visit was on 6/25/2014, which includes all available information on the 90-day Thiamine Supplementation Period.

In the JAKARTA study a total of 289 patients were randomized (ITT population). [One patient assigned to placebo was not treated]. From the Applicant's study report mean age of patients was 64.2 years, 53.3% of patients were 65 years or older, 58.8% were male, 88.9% were White, 43.6% of patients were from Western Europe, 11.1% were from North America and these demographic characteristics were similar across the treatment arms. Most patients (63.3%) had primary MF, 26.3% had post-PV MF and 10.4% had post-ET MF. At study entry mean time since diagnosis was 53.84 months (median 27.79 months, range 0.2 to 412.5 months). Most patients (73.7%) had constitutional symptoms (weight loss > 10% over a year before screening, fever persisting for > 1 month, or sweats persisting for > 1 month), spleen size was >10 cm in 70.6% (mean spleen size 15.6 cm; mean spleen volume), about 63% of patients had received hydroxyurea. Per the study criteria, no patients had received prior treatment with a JAK2 inhibitor. However, most patients 73.4% had received at least 1 prior MF therapy (56.1% had received only one prior and an additional 17.3% had received 2 or more prior). Almost all the patients were compliant and completed treatment for Cycles 1 to 6 per protocol for the primary efficacy analysis. Treatment compliance in the JAKARTA study is summarized in the table below from the Multi-Disciplinary Review.

Table 27: Treatment Compliance –Subjects treatment (All Treated Population)

	Fedratinib 400 mg N = 96 n/N1 (%)	Fedratinib 500 mg N = 97 n/N1 (%)	Placebo N = 95 n/N1 (%)
Cycles 1 to 6	96/96 (100)	87/97 (90)	94/95 (99)
After Cycle 6	74/75 (99)	63/66 (96)	3/3 (100)
Entire Treatment Duration	96/96 (100)	93/97 (96)	94/95 (99)

N1= the number of subjects assessed.

Source: Table 14.3.1.1.7

The primary efficacy analysis (with each fedratinib group being compared to placebo) is shown in the table below from the Multi-Disciplinary Review.

Table 28: Confirmed Spleen Response Rate (≥ 35% SVR) at the EOC6 (ITT Population)

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

Source: ADSL.XPT, ADEFF.XPT, ADTTE.XPT datasets.

Regarding the primary efficacy analysis the Reviewers commented: *"As per the SAP the 95% CI reported used the Normal Approximation. The corresponding 95% CI using the exact method are 36% (95% CI:27, 47), 40% (95% CI:30, 51) and 1% (95% CI:0, 6) in the 400mg, 500 mg and placebo groups, respectively."*

Secondary efficacy endpoints for the study were symptom response rate (SRR) [defined as the proportion of patients with ≥50% reduction from baseline to the end of Cycle 6 in total symptom score (TSS)], overall survival (OS), progression free survival (PFS), proportion of patients with at least 25% reduction in volume of spleen size at the end of Cycle 6 (RR25), duration of spleen response and safety.

The Multidisciplinary Review describes the analysis of the symptom response rate (SRR). The SRR was defined as the proportion of subjects with ≥ 50% reduction in the TSS from baseline to the End of Cycle 6 using the modified MFSAF was to capture the symptom burden. [Note: See comments from the Clinical Outcome Assessment (COA) Consult Review for the application under section 11 below]. The MFSAF had six 6 items (night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain) and responses ranged from 0 (absent) to 10 (worst imaginable). Lower scores suggested lower symptom burden as compared to higher scores and reductions in TSS from baseline suggest an

improvement in symptom burden. Patients with a TSS score of zero at baseline were excluded from the analysis. For the analysis patients with at least 5 assessments available within the week before the next cycle were considered evaluable at that visit. At baseline, 89.5% (85/96) of patients in the placebo arm, 94.8% (91/96) of patients in the 400 mg arm, and 93.8% (91/97) of patients in the 500 mg arm had evaluable data. Four patients on placebo, and two patients each on 400 mg and 500 mg arms, had a TSS score of zero at baseline and hence were excluded from the Symptom Analysis Population. At the End of Cycle 6, the evaluable patients on placebo, 400 mg and 500mg arms were 91.8% (56/61), 94.9% (75/79), and 89.9% (62/69), respectively. Results of the analysis for the Symptom Analysis Population and for the ITT population are shown in the tables below from the Multi-Disciplinary Review.

Table 29: Symptom Response Rate (≥ 50% Reduction in Total Symptom Score) at the EOC6 – Patients in the Symptom Analysis Population

	Fedratinib		Placebo (N= 81) n (%)
	400 mg (N= 89) n (%)	500 mg (N= 89) n (%)	
n (%)	36 (40.4)	31 (34.8)	7 (8.6)
95 % CI	(30.3, 50.6)	(24.9, 44.7)	(2.5, 14.8)
Difference	31.81	26.19	
P-value	< 0.0001	< 0.0001	
97.5% CI of difference	(18.2, 45.4)	(12.9, 39.5)	

Source:ADSL.XPT, ADEFF.XPT, ADTTE.XPT datasets.

Table 30: Symptom Response Rate (≥ 50% Reduction in Total Symptom Score) at the EOC6 – Patients in the ITT Population with Non-missing Baseline Total Symptom Score

	Fedratinib		Placebo (N= 85) n (%)
	400 mg (N= 91) n (%)	500 mg (N= 91) n (%)	
n (%)	36 (39.6)	31 (34.1)	7 (8.2)
95 % CI	(29.5, 49.6)	(24.3, 43.8)	(2.4, 14.1)
Difference	31.33	25.83	
97.5% CI of difference	(18.0, 44.6)	(12.8, 38.8)	

Source: ADSL.XPT, ADEFF.XPT, ADTTE.XPT datasets.

Regarding the efficacy results for fedratinib in the application the Multi-Disciplinary Review concludes: "The results from the pivotal trial (JAKARTA) demonstrated that treatment with oral fedratinib 400 mg once daily and 500 mg once daily both resulted in a significant meaningful clinical benefit but did not establish a significant benefit of the 500 mg dose over the 400 mg dose. Results from the supporting trial (JAKARTA-2) were consistent with efficacy results from JAKARTA." Both trials showed significant improvement in the primary

endpoint of spleen volume reduction and key secondary endpoint of total symptoms score reduction with fedratinib 400 mg treatment.

8. Safety

The primary review of safety data for this application was conducted by Saleh Ayache, M.D. (See Multi-Disciplinary Review and Evaluation (signed 8/15/2019)). Consult reviews for safety signal of Wernicke's encephalopathy (WE) in the clinical development program were completed by Dr. Steven Dinsmore, Division of Neurology Products (final signature in DARRTS 5/3/2019) and Dr. Joohee Sul, Oncology Center of Excellence, final signature in DARRTS 7/18/2019 .

As summarized in the safety review (section 8) of the Multi-Disciplinary Review, in the clinical development of fedratinib a total of 807 subjects received 1 or more doses of fedratinib. The main data supporting safety of fedratinib for the indication come from 9 clinical trials 608 patients with primary or secondary myelofibrosis (MF), polycythemia vera (PV), essential thrombocythemia (ET), or solid tumors, who received >1 dose (ranging from 30 mg to 800 mg) of fedratinib as a single agent. The comparative safety of fedratinib for the indication was derived from phase 3 pivotal randomized study EFC12153 (JAKARTA). The safety population for the JAKARTA study included all patients who received any dose of study drug (placebo, 95; fedratinib 400 mg, 96; fedratinib 500 mg, 97)

As stated in the Multi-Disciplinary Review the median time of exposure was similar between the 400 mg and the 500 mg groups. Approximately, 82% of patients in the 400 mg fedratinib group received at least 6 cycles and 62% received at least 12 cycles. Adverse events during th randomized treatment period are summarized in the following table from the Multi-disciplinary Review. [Note: In the table "Entire Treatment Duration" refers to the entire time patients were being followed on that treatment arm. For patients in the fedratinib 400 mg arm the mean treatment duration was 52.0 weeks (median, 62.1; range 1.0-91.9). For patients in the fedratinib 500 mg arm mean treatment duration was 46.4 weeks (median, 59.7; range, 0.9-89.0). For patients in the Placebo arm mean treatment duration was 19.8 weeks (median, 24.0; range 1.7-43.7). Only one placebo patient had placebo treatment beyond Cycle 6. For patients in the Placebo arm this period ended after 6 cycles due to eligibility to cross-over to active fedratinib treatment. The crossed-over placebo patients are not included in the table]. Thus, this table summarizes the safety data from JAKARTA for the maximum fedratinib exposure available.

Table 41: Overall Summary of TEAEs in the Arms for the Entire Treatment Duration (All Treated Population- JAKARTA Study)

	Fedratinib 400 mg N=96 n (%)	Fedratinib 500 mg N=97 n (%)	Placebo* N=95 n (%)
At least one TEAE	96 (100)	95 (98)	89 (94)
At least one Grade 3 or 4 TEAE	68 (71)	76 (78)	29 (31)
TEAE Leading to Death	5 (5)	8 (8.2)	6 (6)
Treatment-emergent Serious AE (SAE)	37 (39)	43 (44)	22 (23)
TEAE Leading to Permanent Treatment Discontinuation	26 (27)	35 (36)	8 (8)
TEAE Leading to Dose Reduction or Dose Interruption	43 (45)	65 (67)	14 (15)

*Placebo treated patients received treatment for maximum of 6 cycles.

Rates of adverse events during the controlled portion of the treatment duration are shown in the second table below from the JAKARTA study report to permit better comparison of rates in fedratinib arms compared to placebo. Notably 4 of the 5 deaths due to treatment emergent adverse events (TEAE) in the fedratinib 400mg treatment arm occurred after Cycle 6.

Table 14.3.1.2.1
Adverse Events Data
Overview of Safety Profile Up to 6 Cycles
All Treated Population

Category	Placebo (N=95) n(%)	Fedratinib 400 mg (N=96) n(%)	Fedratinib 500 mg (N=97) n(%)
Subjects with any TEAE	89 (93.7)	95 (99.0)	94 (96.9)
Subjects with worst grade = grade 3-4 TEAE	29 (30.5)	50 (52.1)	63 (64.9)
Subjects with any treatment-emergent SAE	22 (23.2)	20 (20.8)	26 (26.8)
Subjects with any TEAE leading to permanent treatment discontinuation	8 (8.4)	13 (13.5)	24 (24.7)
Subjects with any TEAE leading to death	6 (6.3)	1 (1.0)	5 (5.2)

Patients who completed Placebo were allowed to cross-over to randomly assigned fedratinib 400mg or fedratinib 500 mg. For patients who crossed-over, the mean treatment duration in the fedratinib 400 group was 42.4 weeks (median, 43.9; range 2.7-68.0) and mean treatment duration in the fedratinib 500 mg group was 38.4 weeks (median, 44.2; range, 2.0-82.6). A summary of adverse events for the cross-over patients is shown in the following table from the JAKARTA study report.

Table 14.3.1.2.3
Adverse Events Data
Overview of Safety Profile of Crossover Placebo Subjects
Crossover Safety Population

Category	Placebo Crossed Over to	
	400 mg (after crossover) (N=35) n(%)	500 mg (after crossover) (N=36) n(%)
Subjects with any TEAE	34 (97.1)	36 (100.0)
Subjects with worst grade = grade 3-4 TEAE	23 (65.7)	27 (75.0)
Subjects with any treatment-emergent SAE	13 (37.1)	13 (36.1)
Subjects with any TEAE leading to permanent treatment discontinuation	6 (17.1)	12 (33.3)
Subjects with any TEAE leading to death	1 (2.9)	1 (2.8)

Rates of serious adverse events and discontinuations due to adverse events tended to be a bit higher in the cross-over patients than in the initially randomized population for both fedratinib doses; however, possibly this is due to patients being sicker or more advanced that at study enrollment.

Deaths that occurred in JAKARTA including the randomized on-treatment period (up to 6 cycles) and the time after cross-over are summarized in the following table from the Multi-Disciplinary Review.

Table 43: Deaths occurring in JARKARTA Study (all treated population)

	Fedratinib		Placebo
	400 mg (N=96)	500 mg (N=97)	(N=95) n (%)
	n (%)	n (%)	
Death On study up to 6 cycles	**7 (7)**	**14 (14)**	**12 (13)**
Due to adverse reaction	1 (1)	4 (4)	4 (4)
Progressive disease	4 (4)	7 (7)	6 (6)
Other	2 (2)	3 (3)	2 (2)
Death that occurred during the entire treatment duration	**15 (16)**	**24 (25)**	**-**
Progressive disease	9 (9)	11 (11)	-
Due to adverse reaction	2 (2)	7 (7)	-
Other[a]	4 (4)	5 (5)	-
Death[b]	0	1 (1)	-

[a] Other primary causes of death = heart failure (2 subjects), and pneumonia and unknown cause (1 subject each) in the 400 mg arm and colon neoplasm (adenocarcinoma), complication post-transplant, multiorgan failure after infectious complications and bone marrow transplantation, sepsis/pneumonia/myelofibrosis, and unknown cause in the 500 mg arm (1 subject each).
[b] One additional death was reported by the investigator with the cause of death is "not collect" on the Death e-CRF.

Reviewer comments in the review stated: *"The overall death rate during the entire study duration was lower in the 400 mg (16%) compared to the 500 mg group (25%) or the placebo group (13%). Death due to adverse reactions during the entire treatment duration was lower among the 400 mg group (2%) than that of the 500 mg group (7%)."*

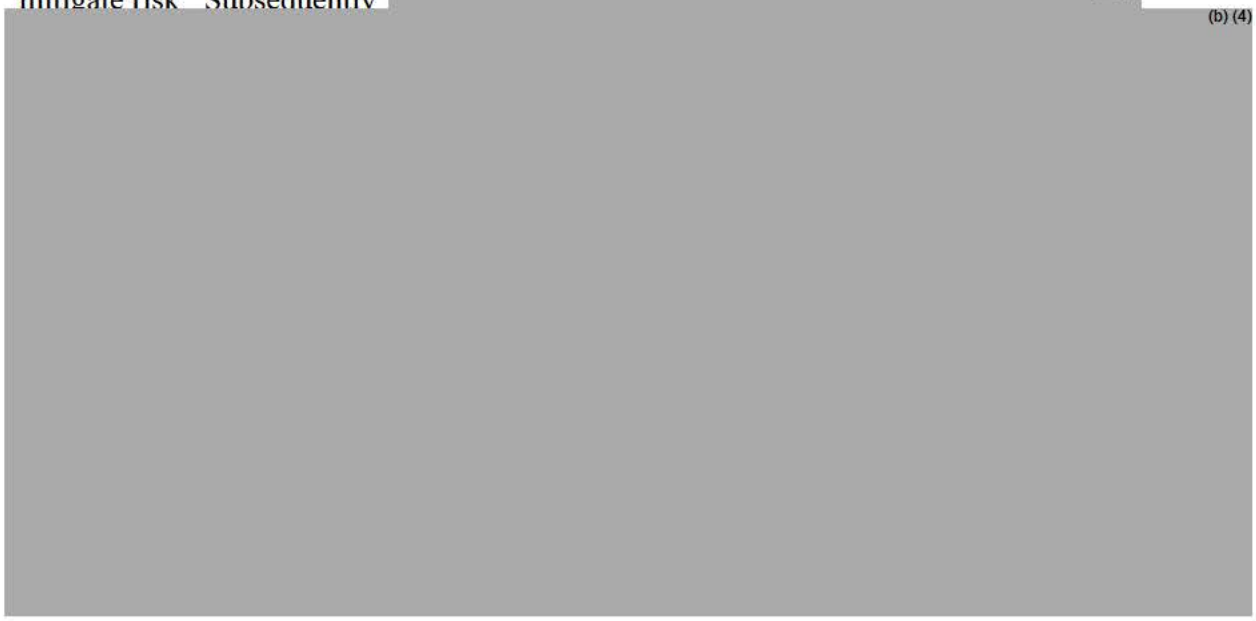
The review found that during the entire treatment duration, *"The rate of Grade 3 or 4 TEAEs was slightly higher in the 500 mg arm (78%) compared to the 400 mg arm (71%) and significantly higher than in the placebo arm. The frequency of anemia was slightly higher in the 400 mg arm (45%) compared to the 500 mg arm (41%). The frequencies of thrombocytopenia and neutropenia were lower in the 400 mg arm compared to the 500 mg arm (12%, 4% vs 19%, 10%, respectively). The most common Grade 3 or 4 adverse events that occurred in the 400 mg arm were anemia, thrombocytopenia, fatigue and GI toxicity."*

With regard to the most common adverse events in the study the review states, "*The TEAEs reported in ≥ 10% of patients during the entire treatment duration with at least 5% difference between the fedratinib and the placebo arms were GI toxicity (nausea, vomiting, diarrhea), anemia, thrombocytopenia, urinary tract infection, fatigue and asthenia, peripheral edema, liver enzymes increased (AST and ALT), muscle spasm, bone pain, pain in the extremity, cough, dyspnea, dizziness and headache. Most common hematological AEs in the 400 mg arm were anemia and thrombocytopenia. Most common nonhematological AEs reported in the 400 mg arm were diarrhea, nausea, vomiting, fatigue and asthenia."*

Rates of treatment discontinuation due to adverse events during the JAKARTA study were 27% (26/96) in the fedratinib 400mg arm, 36% (35/97) in the fedratinib 500mg arm and 8% (8/95) in the placebo arm, with the most common cause of fedratinib discontinuation being thrombocytopenia (4 in fedratinib 400mg, 6 in fedratinib 500mg) and gastrointestinal disorders (diarrhea/nausea/vomiting)(6 in fedratinib 400mg, 10 in fedratinib 500mg). Similarly there were more patients with dose reductions or dose interruptions in the fedratinib 500mg arm than in the fedratinib 400mg arm (67% compared to 45%). Notable clinical laboratory findings in the study included decrease in mean hemoglobin, decline in mean platelet counts, increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), increase in serum creatinine, lipase increase and serum amylase increase in both fedratinib groups compared to placebo during treatment.

With regard to the single-arm fedratinib treatment JAKARTA2 trial the Multi-Disciplinary Review describes that, "Treatment was discontinued due to early study termination in 63 (65%) subjects. The median time of exposure was 24 weeks (6 Cycles). However, since the study was not designed to evaluate a dosing regimen, 33 patients had their dose titrated up to 500 mg (17 patients) and up to 600 mg (15 patients). One patient received a maximum dose of 800 mg." The reviewer commented further, "*Only half of patients in the JAKARTA-2 study were exposed to 6 cycles of fedratinib treatment. Approximately 40% of patients required at least one dose reduction. One third of patients received a fedratinib dose higher than the 400 mg."* The review indicates there were 7 deaths during treatment, 4 due to disease progression and 3 due to adverse events (pneumonia; shock; cardio-respiratory arrest).

A safety signal for encephalopathy including Wernicke's encephalopathy was identified during clinical trials of fedratinib which resulted in the IND (IND 78286) being placed on Complete Clinical Hold on 11/15/2013. Ensuing protocol modifications, additional information submitted by the sponsor, and discussions with the Agency allowed the clinical hold to be lifted on 8/18/2017. However, the letter indicated that questions remain regarding the clinical adverse event findings documented in the trials and what further steps need to be taken to mitigate risk. Subsequently (b) (4)



For the NDA submission the Division of Neurology Products (DNP) was consulted regarding the signal of Wernicke's encephalopathy identified during clinical drug development and possibility of other neurotoxicity risk. The DNP Review was completed by Steven Dinsmore, final signature in DARRTS 5/3/2019. Based on examination of the entire fedratinib clinical trial database, the review identified 7 cases of valid WE diagnosis. One additional potential WE case was identified as best explained by hepatic encephalopathy. For the remaining 7 cases the review found: "In 5 of the 7 cases there is evidence of a substantial nutritional challenge, either based on adverse events associated with gastrointestinal intolerance, negative trends in body weight, and / or nutritional status metrics. In two cases the evidence of nutritional challenge as a cause of critical thiamine depletion is weak and opens the possibility that there is a contribution by fedratinib to the dysfunction of thiamine economy leading to a WE event." For this assessment, nutritional challenge was defined as events in the database with "preferred terms identified in the ADAE datasets that can reduce the ability to maintain adequate thiamine intake or indicate that conditions have existed that reduce nutritional intake. These will include nausea, vomiting, decreased appetite, weight decreased, and abnormal loss of weight."

Review of the cases of possible Wernicke's Encephalopathy was also conducted by Joohee Sul, Oncology Center for Excellence (OCE), final signature in DARRTS 7/18/2019). The Review concluded:

CONCLUSION:
Although the Applicant contends that the incidence of WE in fedratinib program is comparable to the incidence in the general population, there were no such cases identified in patients enrolled to receive placebo (to this reviewer's knowledge). In addition, although it is also likely that WE is underdiagnosed in patients with cancer, WE does not appear to be a commonly identified adverse drug reaction (ADR) reported across all oncology clinical trials. Finally, inhibition of thiamine function by chemotherapeutic agents has been proposed as a mechanism for chemotherapy related WE and a similar mechanism may be implicated in these cases, despite the Applicant's contention that the data are not supportive.

Regardless of whether these cases meet the clinical criteria for WE, they do qualify as cases of serious encephalopathy occurring disproportionately in patients receiving fedratinib compared with patients receiving placebo.

Dr. Sul's Review agreed with the proposal for a Boxed Warning in the label for fedratinib. The Review (b) (4)

(b) (4)

Review of the applicant's studies for QT evaluation was conducted by the Interdisciplinary Review Team for QT Studies (final signature 4/25/2019). The Review concluded that no large QTc prolongation effect (e.g., 20 ms) of fedratinib was detected in the assessment. The review proposed wording in the labeling under 12.2 Pharmacodynamics, Cardiac Electrophysiology stating, "The potential for QTc prolongation with fedratinib was evaluated in (b) (4) patients with solid tumors. No large mean increase in the QTc interval (> 20 ms) was detected with daily dosing of fedratinib 500 mg for 14 days."

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

10. Pediatrics

Pediatric patients were not enrolled in the studies supporting this application.

Fedratinib has been granted Orphan Drug Designation for the treatment of secondary and primary myelofibrosis (5/18/2009). Therefore, this application for the treatment of intermediate – or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) is exempt from the requirements of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

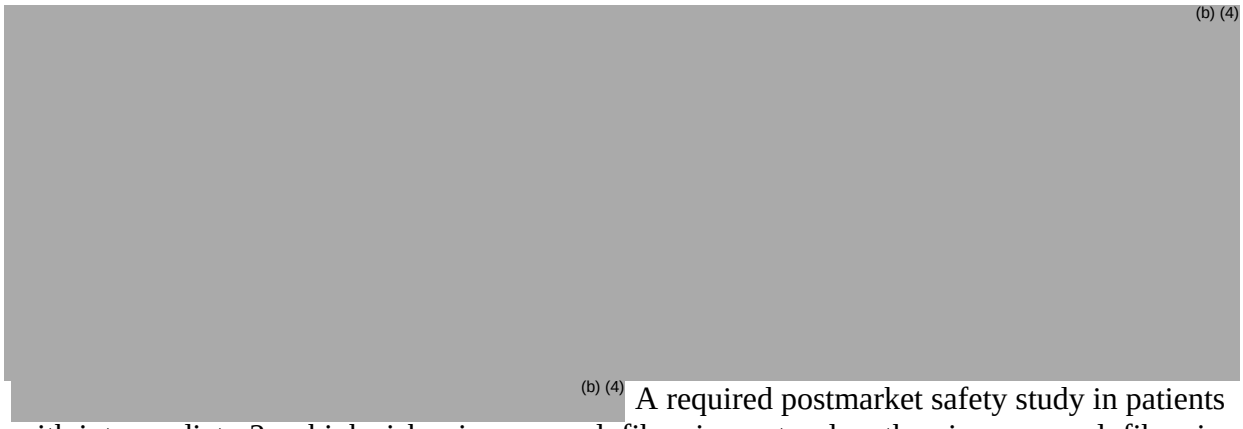
Primary review for the Clinical Inspection Summary of the clinical sites inspections was completed by Anthony Orencia, Division of Clinical Compliance Evaluation, Office of Scientific Investigations (OSI), final signature in DARRTS 6/14/2019). OSI inspection of three clinical sites was conducted for this application. The overall assessment of findings and recommendations for the evaluation stated:

> Three clinical sites (Drs. Animesh Pardanani, Emanuil Gheorghita, and Kazimierz Kuliczkowski) were selected for inspection in support of NDA 212327. The study appears to have been conducted adequately, and the data from these clinical sites, as reported by the sponsor to the NDA, are considered to be reliable in support of the requested indication.
>
> The preliminary regulatory compliance classification of Drs. Gheorghita's and Kuliczkowski's sites is No Action Indicated. The regulatory compliance classification of Dr. Pardanani's site is Voluntary Action Indicated.

Because the two clinical trials (JAKARTA and JAKARTA2) used patient-reported outcome (PRO) instruments in assessing secondary endpoints, the study results were reviewed by the Clinical Outcome Assessment staff (primary review by Christopher St. Clair, final signature in DARRTS 7/18/2019). The Clinical Outcome Assessment (COA) Consult Review described that the Modified Myelofibrosis Symptom Assessment Form v2.0 (MFSAF v2.0; PRO was used for assessment of the secondary endpoint of MF-related symptoms. The Review concluded:

- The modified MFSAF v2.0 includes concepts that are content relevant to MF patients based on literature and discussion with Clinical. This review concludes that the modified MFSAF v2.0 is adequate to support labeling of efficacy data from JAKARTA provided that the symptoms assessed by the instrument are clearly described in the label.
- (b) (4)

The Division of Risk Management (DRISK), Office of medication Error and Prevention and Risk Management (OMEPRM) review of the application was conducted by Brad Moriyama (signed in DARRTS 8/7/2019). The review evaluated whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Inrebic (fedratinib) is necessary to ensure the benefits outweigh its risks. The review noted that the sponsor had proposed a (b) (4)



A required postmarket safety study in patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib will include assessment and management of nausea, diarrhea, vomiting, thiamine deficiency, and encephalopathy. Labeling with a boxed warning and a Medication Guide will be used to communicate the serious risk of encephalopathy including Wernicke's." The review concluded that, "DRISK and Division of Hematology Products (DHP) agree that a REMS is not necessary to ensure the benefits of fedratinib outweigh its risks."

Proprietary Name Review (Stephanie DeGraw, Division of Medication Error Prevention and Analysis (DMEPA) of the Office of Surveillance and Epidemiology (OSE), 3/12/2019) did not identify any names that represent a potential source of drug name confusion and concluded the proposed proprietary name, Inrebic, is acceptable.

12. Labeling

The applicant included proposed labeling (package insert and Patient Information leaflet) in the submission. Recommendations for labeling were provided by the respective review disciplines and revised labeling was developed in discussions with the entire review team.

The Division of Medication Error Prevention and Analysis (DMEPA) of the Office of Surveillance and Epidemiology (OSE) reviewed the prescribing information and container labeling (Labeling Reviews, Stephanie DeGraw, final signature 6/4/2019 and 7/15/2019 and Hina S. Mehta, 5/10/2019). Based on the risk assessment review of the proposed package insert and container labeling, recommendations were made to improve the labeling readability and format. The DMEPA review of revised container label received July 12, 2019 found it acceptable from a medication error perspective.

The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) conducted a combined review of the patient labeling (Patient Labeling Review by Shawna Hutchins and Robert Nguyen, final signature 5/6/2019; Pre-decisional Agency Information memo, Robert Nguyen, 7/18/2019). (See also Memorandum by Rober Nguyen, OPDP, signed 7/25/2019). The review recommended changes to the sponsor's proposed patient labeling (PPI) to reduce redundancy, to make the information more consistent

and concise, and to ensure consistency with the Prescribing Information (PI). The recommendations for the PPI were included in the labeling negotiations with the sponsor.

The Division of Hematology Products (DHP) Labeling Review by Virginia Kwitkowski, signed 5/2/2019, includes draft labeling incorporating most of the review team's recommendations and including additional recommendations to improve the labeling working and format for consistency with current guidelines.

Final wording of the labeling has been developed in discussion with all involved review disciplines and negotiations with the Applicant.

13. Recommendations/Risk Benefit Assessment

Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm that can present either de novo as primary myelofibrosis (PMF) or following previously diagnosed polycythemia vera (PV) and essential thrombocythemia (ET) (post-PV MF and post-ET MF, respectively [ie, secondary MF]). Ruxolitinib (JAKAFI), a small molecule inhibitor of Janus Associated Kinase 1 (JAK1) and JAK2, is approved for treatment of MF. The Applicant is seeking approval of fedratinib, an oral kinase inhibitor with activity against wild type and mutationally activated JAK2 and FMS-like tyrosine kinase 3 (FLT3) "for the treatment of intermediate – or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) (b) (4)". Based on review of the application it is determined that a favorable benefit/risk has been demonstrated for and that approval be granted for the indication:

> "for the treatment of intermediate – or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)"

Support for approval is provided by efficacy data from the JAKARTA Study, a randomized (1:1:1), placebo-controlled clinical trial of two dose regimens of fedratinib in patients without previous exposure to a JAK inhibitor. In the JAKARTA Study for the primary efficacy endpoint of spleen response rate (defined as a ≥35% reduction in volume of spleen at the end of Cycle 6), only one patient (1%) on the placebo arm achieved response while 36.5% and 40.2% of patients on the fedratinib 400 mg and 500 mg treatment arms, respectively, achieved a response, with both fedratinib doses showing significant benefit over placebo. Also, for the important secondary efficacy endpoint of symptom response rate (≥50% reduction in total symptom score at the end of Cycle 6) using a validated tool (modified MFSAF) the study showed significantly greater response in the fedratinib arms compared to placebo. It is recommended that the applicant's proposed wording " (b) (4) " be deleted from the Indications statement, (b) (4) "for the treatment of intermediate – or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)". (b) (4)

The recommended dose of fedratinib is 400mg daily based on the efficacy data which did not establish a significant benefit of the 500 mg dose over the 400 mg dose and the safety data which showed an important safety concern for Wernicke's encephalopathy and with possible but unclear relation to dose.

Labeling recommendations have been provided by each of the review disciplines and consulting offices and all review disciplines have been engaged in negotiation of the final wording of the labeling with the Applicant. Importantly, a Boxed Warning for risk of Wernicke's encephalopathy and encephalopathy is recommended for inclusion in the product label.

This NDA is exempt from the requirements of PREA due to Orphan Drug status for the indication.

Post-marketing requirements (PMR) are being recommended for:

From Clinical Pharmacology

- PMR: Study of single dose of fedratnib in otherwise healthy subjects with severe hepatic impairment compared to healthy subjects, in order to determine an appropriate fedratinib dose for patients with severe hepatic impairment. (See letter for exact wording).
- PMR: Study of single dose of fedratinib with and without coadministration of repeat doses of a moderate dual CYP2C19 and CYP3A4 inhibitor in cancer patients, in order to determine an appropriate fedratinib dose for patients with co-administration of a dual CYP2C19 and CYP3A4 inhibitor.
- PMR: Study of single dose of drugs that are P-gp, BCRP, MATE-1 /2K, and OCT2 transporter substrates with and without multiple dose of fedratinib in cancer patients, to determine PK and safety of drugs that are P-gp, BCRP, MATE-1 /2K, or OCT2 transporter substrates for patients with multiple doses of fedratinib.
- PMC: Study of single dose of fedratinib with and without coadministration of repeat doses of a moderate and a strong CYP3A4 inducer in cancer patients, to determine an appropriate fedratinib dose for patients with co-administration of a moderate and a strong CYP3A4 inducer.

From Clinical

- PMR: Conduct a randomized, concurrently controlled clinical trial comparing fedratinib 400 mg once daily to best available therapy in patients with DIPSS-intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. The trial will enroll a sufficient number of patients to ensure that at least 150 subjects are treated with at least 6 cycles of fedratinib and are followed for at least 3 years to provide long term safety outcome data. The protocol should include measures to assess and manage adverse events of nausea, diarrhea, vomiting, thiamine deficiency, and encephalopathy at baseline and during the trial. The final protocol must be agreed upon with the Agency.

Exact wording for the PMR/PMCs is being developed in discussions with the review team.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHY M ROBIE SUH
08/15/2019 11:51:55 AM

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212327
Priority or Standard	Priority
Submit Date(s)	January 3, 2019
Received Date(s)	January 3, 2019
PDUFA Goal Date	September 3, 2019
Division/Office	DHP/OHOP
Review Completion Date	06/03/2019
Established/Proper Name	Fedratinib
(Proposed) Trade Name	INREBIC®
Pharmacologic Class	Kinase inhibitor
Code name	SAR302503
Applicant	Impact Biomedicines, Inc., a wholly owned subsidiary of Celgene Corporation
Dosage form	100-mg hard gelatin capsules
Applicant proposed Dosing Regimen	400 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	INREBIC® is a kinase inhibitor indicated for the treatment of intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	52967002 | Myelofibrosis (disorder)
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	400 mg daily

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
PLT=Patient Labeling Team
COA=Clinical Outcomes Assessment
DNP=Division of Neurology Products
IRT/QT=Interdisciplinary Review Team for QT Studies

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
ET	Essential thrombocythemia
FLT3	Fibromyalgia syndrome-like tyrosine kinase 3
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
JAK2	Janus kinase 2 or Janus Associated Kinase 2, depending on context
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PV	Polycythemia vera
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SVR	Spleen volume reduction
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

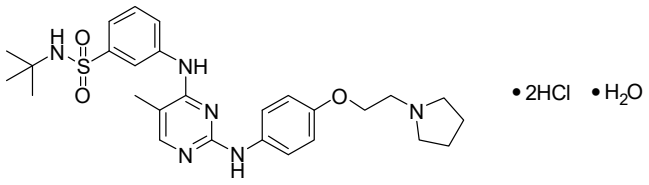
Fedratinib (INREBIC®) is an oral kinase inhibitor with activity against wild type and mutationally activated Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3).

Fedratinib chemical name: N-tert-butyl-3-[(5-methyl-2-{[4-(2-pyrrolidin-1-lethoxy)phenyl]amino}pyrimidin-4-yl)amino]benzenesulfonamide dihydrochloride monohydrate.

Fedratinib empirical formula is C27H36N6O3S·2HCl·H2O and it has a molecular weight of 615.62.

Fedratinib chemical structure is shown in Figure 1:

Figure 1: Fedratinib's Structural Formula



Source: NDA submission, Module 2

Fedratinib capsules contain 100 mg of fedratinib drug substance in a reddish brown opaque size 0 hard gelatin capsule printed with "FEDR 100 mg" in white ink. The active ingredient is fedratinib dihydrochloride monohydrate.

The Applicant's proposed indication at the time of NDA submission was:
INREBIC® is a kinase inhibitor indicated for the treatment of intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (b) (4) .

The recommended indication for approval is:
INREBIC® is a kinase inhibitor indicated for the treatment of intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.

The regular approval is based on demonstration of meaningful clinical benefit and statistically significant reduction in spleen volume and myelofibrosis related symptoms.

The recommended dose for fedratinib is 400 mg orally daily with or without food. Treatment should be continued until disease progression or unacceptable toxicity.

The major safety concern is for encephalopathy including Wernicke's for which a Boxed Warning is recommended for the labeling.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The evidence of effectiveness of fedratinib 400 mg once daily for the proposed indication for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis is derived from one randomized control trial (Study EFC12153, JAKARTA) and supported by a single arm trial (Study ARD12181, JAKARTA-2). The JAKARTA Study was a Phase 3 randomized, double-blinded, placebo-controlled trial in which 289 adult patients with intermediate-2 or high-risk primary or secondary myelofibrosis were randomly assigned in 1:1:1 ratio to receive once daily fedratinib, at a dose of 400 mg or 500 mg, or placebo. The supporting trial (JAKARTA-2) was a Phase 2, single arm, open label trial in 97 patients with primary or secondary myelofibrosis who were previously exposed to ruxolitinib and received fedratinib 400 mg once daily.

The primary endpoint in the JAKARTA and JAKARTA-2 trials was the spleen response rate (RR) defined as the proportion of subjects with ≥ 35% of spleen volume reduction (SVR) at the end of Cycle 6 (EOC6) assessed by MRI/CT scan and confirmed 4 weeks later. For the supportive study (JAKARTA-2) assessment at the EOC6 by MRI/CT was compared to the baseline.

The analysis of the primary efficacy endpoint in the JAKARTA trial showed that 36.5% of patients in the 400 mg fedratinib arm compared to 1% of patients in the placebo arm achieved ≥ 35% of spleen volume reduction (SVR) at the EOC6 confirmed 4 weeks later ($p < 0.0001$). The median duration of spleen response in the fedratinib 400 mg arm was 18.2 months.

In the JAKARTA-2 trial, 30.9% of patients achieved SVR. The median duration of spleen response was not fully evaluable due to early termination of the study.

The results for these primary endpoints for fedratinib 400 mg in the two trials are shown below In Table 1.

Table 1: Spleen Response Rate by MRI/CT at the EOC6 – Study EFC12153 and Study ARD12181 (ITT Population)

	Study EFC12153		**Study ARD12181**
EOC6	Placebo N=96	Fedratinib 400 mg N=96	Fedratinib 400 mg N=97
n (%)	1 (1)	35 (36.5)	30 (30.9)
95 % CI	0.0, 3.1	27, 46	21.9, 41.1

The key secondary endpoint in the JAKARTA trial, the percentage of patients with a ≥50% reduction in the total symptom score (TSS) from baseline to the End of Cycle 6 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, also showed a statistically significant benefit favoring fedratinib. The modified MFSAF v2.0 is a patient diary capturing the 6 core symptoms of MF: night sweats, itching, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. The modified MFSAF diary was completed daily during the week prior to Day 1 of each treatment cycle, and at the End of Cycle 6. Symptom scores ranged from 0 ("absent") to 10 ("worst imaginable"). These scores were added to create the Total Symptom Score, which has a maximum score of 60.

Table 2: Symptom Response Rate at the EOC6 – Patients in the Symptom Analysis Population, JAKARTA

	Fedratinib		**Placebo** (N= 81) n (%)
	400 mg (N= 89) n (%)	500 mg (N= 89) n (%)	
n (%)	36 (40.4)	31 (34.8)	7 (8.6)
95 % CI	(30.3, 50.6)	(24.9, 44.7)	(2.5, 14.8)
Difference	31.81	26.19	
P-value	< 0.0001	< 0.0001	
97.5% CI of difference	(18.2, 45.4)	(12.9, 39.5)	

The results from the pivotal trial (JAKARTA) demonstrated that treatment with oral fedratinib 400 mg once daily and 500 mg once daily both resulted in a significant meaningful clinical benefit but did not establish a significant benefit of the 500 mg dose over the 400 mg dose. Results from the supporting trial (JAKARTA-2) were consistent with efficacy results from JAKARTA.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm characterized by stem cell-derived clonal myeloproliferation, typically Janus Associated Kinase 2 (JAK2) mutation, abnormal cytokine expression, bone marrow fibrosis, anemia, splenomegaly, extramedullary hematopoiesis, constitutional symptoms, cachexia, leukemic progression, and shortened survival. The overall survival of patients with intermediate-2 or high-risk MF is estimated to be 3 years or less. Currently the only curative treatment for patients with MF is hematopoietic stem cell transplant (HSCT). However, most patients with MF are not eligible for HSCT due to age (median age at diagnosis is 65), comorbidities and high risk of mortality associated with transplant. The other existing treatment options are geared toward reduction of disease burden (i.e., splenomegaly, anemia, constitutional symptoms). Ruxolitinib (JAK inhibitor) is the only approved treatment for patients with MF. However, discontinuation rates are high with 1- 2- 3- year discontinuation rates reported to be 49%, 71%, and 86%, respectively, for patients treated with ruxolitinib (Abdelrahman, 2015). The major reasons for treatment discontinuation were loss of therapeutic effect, lack of response and drug induced cytopenia.

Fedratinib is an oral JAK2 and FMS-like tyrosine kinase 3 (FLT3) inhibitor. Fedratinib has been developed for the treatment of patients with primary myelofibrosis (PMF), post polycythemia vera (post-PV) MF, and post essential thrombocythemia (post-ET) MF. The benefit of fedratinib in the treatment of MF was demonstrated in Study EFC12153 (JAKARTA Study), "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". In that study 289 adult patients were randomized in 1:1:1 ratio and received 400 mg/day (N=96) or 500 mg/day (N=97) fedratinib orally or placebo (N=96) for at least 6 consecutive 4-week Cycles (24 weeks). The primary endpoint was spleen response rate (≥35% reduction in spleen volume from baseline as determined by magnetic resonance imaging (MRI) or computed tomography (CT)) at week 24 and confirmed 4 weeks later. The main secondary endpoint was symptom response rate (≥50% reduction in total symptom score (TSS) from baseline to the EOC6 as reported by the subject using the modified MFSAF e-diary, assessed using the modified Myelofibrosis Symptom Assessment Form). Results from the JAKARTA Study demonstrated that the primary endpoint was met in 35/96 (36.5% [95%CI, 27%-46%]) patients in the fedratinib 400-mg in 39/97 (40.2% [95% CI, 30.4, 30.4%, 50.0%] in the fedratinib 500 mg vs 1/96 (1% [95%CI, 0%-3.1%]) in the placebo group (P <0.001). The key secondary endpoint of symptom response rate at week 24 was also met in 36/89 (40.4%) of patients in the fedratinib 400-mg group, in 31/89 (34.8%) in the fedratinib 500 mg group and in 7/81 (8.6%) of patients in the placebo group (P < 0.0001).

Available for the analysis of safety were over 608 patients who received multiple doses of fedratinib as a single agent (ranging from 30 mg to

800 mg) in 9 clinical studies (JAKARTA, ARD11936, JAKARTA2, ARD12042, ARD12888, TED12037/ TED12015, INT12497, and TES13519) in patients with myelofibrosis polycythemia vera (PV) and essential thrombocythemia (ET), or solid tumors, including 459 patients with myelofibrosis. A total of 358 of the 608 (59%) patients were exposed for 6 months or longer and 237 (39%) were exposed for 12 months or longer. The most common adverse reactions including laboratory abnormalities were diarrhea, nausea, anemia, vomiting, fatigue, thrombocytopenia, and constipation.

The primary safety endpoint in the JAKARTA study was evaluated in 96 patients who received 400 mg fedratinib daily and was compared to 95 patients who received placebo. Patients who received 400 mg fedratinib had a median duration of exposure of 15.5 months (treated period and extension period) compared to 6 months in the placebo group, where patients were treated up to 6 months or until disease progression after which patients were allowed to crossover to active (fedratinib) treatment. Eighty-two percent (82%) of patients received 400 mg fedratinib for at least 6 months and 65% for at least one year.

Table below summarizes Adverse Reactions:

	During Randomization period		**During entire treatment duration**
	Fedratinib 400 mg N= 96	Placebo N=95	Fedratinib 400 mg N= 96
Grade 3-4 adverse reactions, n (%)	50 (52)	29 (31)	68 (71)
Death due to Adverse reactions, n (%)	1 (1)	6 (6)	5 (5)
Serious adverse events, n (%)	20 (21)	22 (23)	37 (39)
Adverse reactions leading to discontinuation, n (%)	13 (14)	8 (8)	26 (27)
Adverse reactions leading to dose interruption or dose reduction, n (%)	29 (30)	14 (15)	43 (45)

During randomization period (up to 6 cycles):
Serious adverse reactions occurred in 21% of fedratinib treated patients. Most common adverse reactions were cardiac failure (5%) and anemia (2%).

During Entire Study Period:
Serious adverse reactions reported in 3 or more patients were cardiac failure (6%), pneumonia (4%), and cardiac arrhythmia (3%). Common reasons for permanent discontinuation were thrombocytopenia (4%) and cardiac failure (3%). The most common reasons for dose interruption or dose reduction were anemia, vomiting, diarrhea, and nausea. Common adverse reactions with 400 mg fedratinib treatment were anemia, gastrointestinal (GI) symptoms (diarrhea, nausea, and vomiting), fatigue, thrombocytopenia, increased liver enzymes, serum creatinine, dizziness, headache and increased pancreatic enzymes (lipase and amylase). An increased risk of encephalopathy, including Wernicke encephalopathy, was identified in patients who received fedratinib.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm that is characterized by stem cell-derived clonal myeloproliferation, abnormal cytokine expression, bone marrow fibrosis, anemia, splenomegaly, extramedullary hematopoiesis, constitutional symptoms, cachexia, leukemic progression, and shortened survival. • Four risk categories based on the Dynamic International Prognostic Scoring System (DIPSS) Plus risk factors have been identified: low, intermediate-1, intermediate-2, and high risk. The median survival of patients with MF based on DIPSS Plus risk factors are 15, 6.5, 2.9, and 1.3 years, respectively.	• Myelofibrosis is a serious and life-threatening disease. • Patients with intermediate-2 or high-risk MF have a shortened median survival. • Common causes of death in patients with MF are transformation to AML, bleeding, portal hypertension and liver failure.
Current Treatment Options	• Allogeneic Stem Cell Transplant (ASCT): The only available curative therapy for the disease. ASCT in patients with MF associated with at high rate of transplant-related deaths or severe morbidity. Most patients with MF are excluded form allograft because of age (average age at diagnosis with MF is 65 years).	• ASCT is the only curative therapy. Unfortunately, most patients with MF are not eligible due to age and comorbidities, and high mortality associated with transplants.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Ruxolitinib (JAK 1/2 inhibitor) approved in November 2011 for the treatment of patients with intermediate or high-risk MF. The approval was based on results of randomized controlled studies that demonstrated clinical benefit, with a higher proportion of patients in the ruxolitinib arms exhibiting a ≥ 35% reduction in spleen volume as measured by magnetic resonance imaging (MRI) at 24 weeks in COMFORT-I Study (42% ruxolitinib versus 0.7% placebo) and at 48 weeks in COMFORT-II Study (28.5% ruxolitinib versus 0% best available therapy (BAT)). • Other available therapies include chemotherapy (e.g., hydroxyurea), busulfan, anagrelide, corticosteroids, hematopoietic growth factor, immunomodulating agents, androgens, interferon rarely splenectomy for the treatment of splenomegaly and/or constitutional symptoms.	• Treatment with ruxolitinib is associated with high rates of discontinuation (rates at 1-, 2-, and 3-years of 49%, 71%, and 86%, respectively). Patients with platelet count < 100 x 10^9/L required dose modifications which may affect ruxolitinib efficacy.
Benefit	• Results from one randomized controlled trial (JAKARTA) in patients treated with 400 mg fedratinib daily, provides clinically meaningful and statistically significant improvement in spleen volume reduction (SVR) and total symptoms reduction compared to placebo. ○ Analysis of the primary efficacy endpoint of SVR of 35% or more at end of cycle 6 (EOC6) showed endpoint met in 36.5% of patients treated with 400 mg fedratinib compared to 1% in placebo arm. ○ Analysis of key secondary endpoint of symptoms reduction rate of 50% or more at EOC6 showed endpoint met in 40.4%	The results from the pivotal trial showed that treatment with 400 mg of fedratinib resulted in meaningful clinical benefit (demonstrated by SVR and symptoms reduction) in patients with intermediate-2 to high risk primary or secondary MF. Although, the supporting trial had limitations (single arm trial and upward dose escalation was allowed), the results from the trial showed clinically meaningful improvement in SVR and symptoms reduction compared to baseline, in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of patients treated with 400 mg fedratinib compared to 8.6% in placebo arm. ○ The estimated median duration of spleen response in the fedratinib 400 mg arm was 18.2 months. ○ No demonstrated benefit of 500 mg over 400 mg dose. • The supporting trial (JAKARTA-2) results showed that treatment with 400 mg fedratinib resulted in clinically significant SVR reduction and symptom reduction at EOC6 compared to the baseline.	patients with primary or secondary MF treated with 400 mg fedratinib.
Risk and Risk Management	• In JAKARTA, death due to adverse reactions was reported in 2% of patients who received fedratinib, which was lower than in placebo arm (4%). • In JAKARTA, in the fedratinib 400mg treatment group, TEAEs leading to permanent discontinuation during the entire treatment duration (median, 52 weeks) occurred in 27% of patients, with thrombocytopenia (4%) and cardiac failure (3%) being most common listed causes. • In JAKARTA, the most common Grade 3 or 4 adverse reactions in 400 mg fedratinib treated patients were anemia (45%), thrombocytopenia (12%), fatigue (7%), cardiac failure (6%) and diarrhea (5%). • In JAKARTA, serious adverse reactions were reported in 21% of patients, which was similar to that reported in placebo. Most common serious adverse reaction were cardiac failure, pneumonia and cardiac arrhythmia.	The safety profile of fedratinib 400 mg is mostly manageable by dose adjustments. Thrombocytopenia, neutropenia, GI toxicity does not respond to supportive care required dose reduction. Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with fedratinib. Wernicke's encephalopathy is a neurologic emergency required immediate thiamine replacement. The risk of WE will be mitigated by monitoring patient's thiamine levels, early recognition of signs and symptoms of WE, and supplementing thiamine as needed as well as monitoring GI toxicity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In JAKARTA, most common adverse reactions were anemia, thrombocytopenia, fatigue/asthenia, and gastrointestinal toxicity (nausea, vomiting and diarrhea). • Safety signal of encephalopathy, including Wernicke's encephalopathy (WE) adverse reactions had been identified in patients treated with fedratinib. The estimated WE incidence is approximately, 7/608 (1.2%). All 7 cases of WE occurred in patients who received 500 mg of fedratinib and in some cases patients had predisposing factors (including baseline malnutrition and treatment-emergent GI AEs) that may led to thiamine deficiency. However, the relationship between fedratinib and thiamine deficiency is not clearly established. The applicant reported that in some patients with WE, a positive response occurred when patients received thiamine replacement administered within 7 days of clinical onset.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**		Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
	☒	Clinical outcome assessment (COA) data, such as	Section 8.1.2, section 8.2.6
		☒ Patient reported outcome (PRO)	
		☐ Observer reported outcome (ObsRO)	
		☐ Clinician reported outcome (ClinRO)	
		☐ Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify):	
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
☐	**Patient experience data was not submitted as part of this application.**		

Kathy Robie Suh, MD, PhD
Cross Discipline Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Myelofibrosis (MF), a myeloproliferative neoplasm, is a serious and life-threatening disease characterized by clonal myeloproliferation, ineffective erythropoiesis, bone marrow fibrosis, hepatosplenic extramedullary hematopoiesis, abnormal cytokine expression and shortened survival.[1] MF can present as de novo or primary myelofibrosis (PMF) or it may evolve from previous polycythemia vera (post-PV MF) or essential thrombocythemia (post-ET MF). Primary myelofibrosis is a Philadelphia chromosome (Ph1)-negative myeloproliferative neoplasm (MPNs), which also includes PV and ET.[2] Majority of patients with PV and about one half of patients with ET and PMF have a Janus kinase 2 (JAK2) mutation.[3]

Myeloproliferative neoplasms are uncommon before the age of 50 years. The median age at diagnosis for patients with myelofibrosis is 65 years. The estimated prevalence of primary myelofibrosis is approximately 13,000 cases in the United States (U.S.) in 2012.[2] Also, the prevalence of post-PV MF in the U.S. was reported as 0.3 to 0.7 per 100,000 and as 0.5 to 1.1 per 100,000 for post-ET MF.[4]

Myelofibrosis clinical manifestations include anemia, thrombocytopenia, splenomegaly, debilitating symptoms (i.e., fatigue, night sweats, fever, cachexia, itching, left upper quadrant abdominal pain, early satiety, and bone pain). Symptomatic enlargement of the spleen and liver, the need for red blood cell (RBC) transfusions, cachexia, and the other MF associated symptoms result in greatly compromised quality of life (QoL) and survival in patients with MF.

The International Prognostic Scoring System (IPSS) was developed in 2009 for patients with primary myelofibrosis (PMF) as an independent predictor of inferior survival. IPSS includes age >65 years, hemoglobin <10 g/dL, leukocyte count >25 × 10^9/L, circulating blasts ≥1% and presence of constitutional symptoms. Based on presence of 0, 1, 2, or 3 of the adverse factors, patients with myelofibrosis are classified as having low, intermediate 1, intermediate-2 and high-risk disease. The median survival was found to be 11.3, 7.7, 4, and 2.3 years, respectively.[5] The majority of patients with MF are in the intermediate or high risk category.

2.2. Analysis of Current Treatment Options

Allogeneic stem-cell transplantation (SCT) is currently the only treatment that is potentially curative and can induce long term remission in patients with MF. However, the majority of patients with myelofibrosis are not eligible for the SCT due to age and comorbidities. Also, allogeneic stem-cell transplantation (ASCT) associated with substantial morbidity and mortality.

The current other available therapy for myelofibrosis are primarily geared toward symptoms amelioration by helping to mitigate the clinical presentation of splenomegaly, anemia, constitutional symptoms.

Ruxolitinib (Jakafi®), a JAK 1 /2 inhibitor, received marketing approval in the US in November 2011 for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

Other therapeutic options for MF include prednisolone, bisphosphonates, and radiotherapy and are used with or without ruxolitinib for management of symptoms associated with myelofibrosis. In addition, drugs commonly used to manage anemia, thrombocytopenia, or leukocytosis include androgens, erythroid-stimulating agents, thalidomide, or, rarely, other IMiDs, hydroxycarbamide/hydroxyurea, and, as discussed previously, IFN-a (Harrison CN, McLornan DP., Hematology Am Soc Hematol Educ Program, 2017).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The current application is the first submission of an NDA for fedratinib. The product is not marketed anywhere in the world.

3.2. Summary of Presubmission/Submission Regulatory Activity

The initial IND 078286 for fedratinib was submitted by TargeGen on October 24, 2007, for the treatment of patients with myelofibrosis.

Fedratinib received orphan designation for the "treatment of secondary and primary myelofibrosis" on May 18, 2009.

End of Phase 1 meeting was held on May 25, 2010, with TargeGen, Inc. to discuss the results from the phase 1 and open-label, extension studies, MF-TG101348-001 and MF-TG101348-002.

The IND was transferred to Sanofi-Aventis U.S. Inc. on September 21, 2010. Sanofi subsequently embarked on a full clinical development program for fedratinib.

A Special Protocol Assessment (SPA) for Study EFC12153 (JAKARTA), entitled "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," was submitted on May 23, 2011. SPA agreement was reached with the FDA on September 09, 2011.

Fedratinib received orphan designation for the "treatment of polycythemia vera" on March 21, 2013.

On June 25, 2013 a Pre-NDA meeting was held with Sanofi to discuss the content of the NDA submission.

On November 15, 2013, all studies of fedratinib were placed on Full Clinical Hold due to safety concerns of Wernicke's encephalopathy (WE) and congestive heart failure. Also, the SPA was rescinded on December 17, 2013 due to the safety concerns that led to full clinical hold. However, on November 18, 2013, Sanofi in their Clinical Hold Complete Response stated that "Given the lack of sufficient information available to minimize the risk of significant toxicity, Sanofi agreed that a full clinical hold should remain on all studies conducted under the IND" and decided to terminate the fedratinib clinical development program.

At the time of the clinical hold/program termination the following studies were ongoing:

- Study TES13519: Clinical Pharmacology study (a QT interval [QT]study)
- Phase 3 study (EFC12153): A randomized, double-blind, placebo-controlled study (JAKARTA)
- Long-term extension study (TED12015):
- Phase 2 study (ARD12181): Open label single arm study in patients previously exposed to ruxolitinib (JAKARTA-2)
- Study ARD11936: A Phase 2 dose-range finding study
- Study ARD12888: A Phase 2 study in Japan in patients with myelofibrosis
- Study ARD12042: A Phase 2 study in patients with polycythemia vera or essential thrombocythemia who were resistant or intolerant to hydroxyurea

Impact Biomedicines, Inc. acquired fedratinib from Sanofi on November 17, 2016.

On May 16, 2017, Type A Meeting was held to discuss the removal of the full clinical hold and plans for a future NDA submission. FDA recommended that Impact perform and submit a detailed review of all data regarding possible WE and cardiomyopathy cases and evaluate thiamine levels in subjects on fedratinib therapy.

On July 20, 2017, a complete response to clinical hold was submitted and the full clinical hold on IND 078286 was lifted on August 18, 2017. The Agency stated that questions remain regarding the clinical adverse event findings documented and what further steps need to be taken to mitigate risk. A follow-up type A meeting was held on November 1, 2017, to discuss risk mitigation strategies to address the concern for WE and the clinical data available to support a proposed NDA for fedratinib.

On February 13, 2018, Impact Biomedicines, Inc was acquired by Celgene Corporation.

On May 15, 2018 A Type B (PreNDA) meeting was held with Celgene to discuss the NDA submission.

On January 3, 2019, Impact Biomedicines, Inc., a Wholly-owned Subsidiary of Celgene Corporation, submitted NDA 212327 to support registration of fedratinib for the treatment of intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (b) (4).

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Hematology Products (DHP) consulted the Office of Scientific Investigation (OSI) to perform an audit of three clinical trial sites (site # 840008 Dr. Animesh Pardanani, Rochester, Mayo Clinic of Rochester, MN, US; site # 642003, Dr. Emanuil Gheorgita, Spitalul Clinic Judetean de Urgenta Brasov, Hematologie, Brasov, Romania; site # 616003 Dr. Kazimierz Kuliczkowski, Samodzielny Publiczny Szpital Kliniczny, Dolnoslaskie, Poland), the applicant site to identify any issues could affect the quality and interpretation of the data submitted with this application regarding clinical study EFC12153. The Division, in consultation with OSI, selected clinical sites for inspection based on enrollment characteristics and patterns of efficacy and safety reporting.

The preliminary regulatory compliance of the three clinical sites inspected (Drs. Animesh Pardanani, Emanuil Gheorghita, and Kazimierz Kuliczkowski) indicated that classification of Drs. Gheorghita's and Kuliczkowski's sites is No Action Indicated, and Voluntary Action Indicated for Dr. Pardanani's site. The overall assessment concluded that the study appears to have been conducted adequately, and the data from these clinical sites, as reported by the applicant to the NDA, are considered to be reliable in support of the requested indication.

4.2. Product Quality

[Insert text here.]

4.3. Clinical Microbiology

[Insert text here.]

4.4. Devices and Companion Diagnostic Issues

N/A

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Fedratinib (also known as SAR302503) is an orally administered drug with activity against wild type and mutationally activated Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). Abnormal activation of JAK2 is associated with myeloproliferative neoplasms (MPNs), including myelofibrosis and polycythemia vera. The established pharmacological class for fedratinib is kinase inhibitor based on its mechanism of action.

Pharmacological activity of fedratinib was evaluated using studies in cell models expressing mutationally active JAK2 ^{V617F} or FLT3^{ITD}, providing evidence that fedratinib reduces phosphorylation of signal transducer and activator of transcription (STAT3/5) proteins, inhibits cell proliferation, and induces apoptotic cell death. Biochemical assays were utilized and characterized the half-maximal inhibitory concentration (IC_{50}) of fedratinib against JAK2 and JAK2^{V617F} as 2.3 and 2.4 nM, respectively. Fedratinib has higher inhibitory activity for JAK2 over other family members JAK1, JAK3 and TYK2. In vivo studies in mouse models of JAK2^{V617F}-driven myeloproliferative disease showed that twice daily oral doses of fedratinib at 60 or 120 mg/kg blocked phosphorylation of STAT3/5. After 42 days of treatment at the highest dose, fedratinib improved survival, white blood cell counts, hematocrit, splenomegaly, and fibrosis.

In secondary pharmacology screens fedratinib had nanomolar activity against M1 and M5 muscarinic receptors and the dopamine transporter, and micromolar activity against other muscarinic receptors, serotonin 5-HT1B, the sigma (nonselective) receptor, the Na+ channel, and the norepinephrine and serotonin 5-HT transporters. The safety pharmacology evaluation of fedratinib included a panel of in vitro and in vivo studies. Fedratinib inhibited six human cardiac sodium, potassium, and calcium ion channels with IC_{50}s in the low micromolar range: 2.1-17.8 µM for hERG, 10.8 µM for hNav1.5, 20.6 µM for hKvLQT1/mink, 31.2 µM for hKv4.3, 8.2 µM for hCav3.2, and 2.8 µM for hKir6.2/SUR2A. In vivo, fedratinib was not associated with toxicologically significant effects on cardiovascular or respiratory parameters in dogs. There were no clear drug-related CNS effects in rats; eye miosis and lack of pupillary responses were observed but were non-dose-dependent. Gait abnormalities were also observed in high-dose animals.

The pharmacokinetics of fedratinib was characterized in multiple species, including mice, rats, and dogs. The time to maximal plasma concentration (tmax) of fedratinib following oral administration is approximately 0.5 to 4 hours, and oral bioavailability ranges from 19 to 37%. Fedratinib is approximately 85% bound to plasma proteins in animals and approximately 92% in humans. Radiolabeled [^{14}C]-fedratinib was distributed throughout the whole body of the rat, including to the skin and eyes (i.e. melanin-containing tissues). Elimination from the eyes was approximately 40 days. Fedratinib undergoes hepatic metabolism through four identified metabolic pathways. After a single oral administration of $^{[14C]}$-SAR302503 to mice, rats, dogs and

human, the parent drug was the main circulating compound in human (80% of radioactivity AUC) and in all animal species (66 to 88% of radioactivity AUC). The main circulating metabolite in human was SAR317981 (metabolite 2 or M2) which was detected in rodents at higher exposure than in human. Radioactivity was mainly excreted in feces as parent drug across species, 21% to 56% of the administered dose, suggesting a moderate to extensive metabolism. Besides, 26 metabolites were detected in excreta across species. In all species, the main metabolites were SAR318031 (M14) and M17. Metabolites SAR317753 (M8) and SAR317793 (M13) were detected using hepatocytes and microsomes, respectively, from human, dog and rat. Three metabolites identified in humans and animals, SAR317753, SAR317981, and SAR317793, were pharmacologically active against JAK2, with IC_{50}s of 3.8, 3.5, and 46 nM, respectively. The elimination half-life of fedratinib was 6 to 12 hours in dogs, with the fecal route as the major pathway (>78%) and the urinary route as a minor pathway (< 5%).

Repeat-dose toxicology studies of up to 6-month in rats and 9-month in dogs were conducted. In the rat study, fedratinib was administered at 0, 3, 10, or 30 mg/kg/day. Toxicological findings at the high dose included decreases in red cell mass, leukocytes and lymphocytes that corresponded with bone marrow hypoplasia, increases in platelets potentially secondary to hemorrhage, and increases in alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), indicating liver toxicity. Additional liver findings included bile duct hypertrophy. Increases in organ weight may be secondary to inflammation and was seen in several organs (e.g. heart, lungs, reproductive organs). Minimal to mild inflammation (kidney, liver, trachea and prostate) and hemorrhage (pituitary gland, stomach, lymph node, thymus and lungs) occurred at different dose levels at low incidence. In the 9-month dog study, fedratinib was administered at 0, 2, 6, or 20 mg/kg/day. The high dose was not tolerated resulting in mortality, and it was reduced to 15 mg/kg/day on Day 25. Toxicological findings at the high dose included decreases in red cell mass corresponding with multi-organ hemorrhage (e.g. GI tract, heart) noted on histopathology and was accompanied by increases in reticulocytes. These findings together with decreases in leukocytes and neutrophils corresponded with bone marrow effects (hematopoietic hypoplasia). Increases in liver enzymes (AST, ALT, ALP) and decreases in total bilirubin corresponded with findings in the liver of centrilobular degeneration, congestion, and hematopoiesis; these changes occurred at 10 and 30 mg/kg/day with statistical significance at the high dose. Inflammatory responses were observed in animals and included swelling of limbs and the muzzle in moribund animals, increased organ weights (e.g. liver, heart, lungs), and multi-organ inflammation on histopathology (e.g. GI tract, heart, liver, lungs). Decreases in the weights of epididymides, prostate and testes, and aspermia occurred at the high dose.

Fedratinib was not mutagenic in a bacterial reverse mutation (Ames) assay, or clastogenic in an in vitro chromosomal aberration assay in Chinese hamster ovary cells or in vivo in a micronucleus test in rats. Fedratinib was not carcinogenic in the 6-month Tg.rasH2 transgenic mouse model.

Developmental and reproductive toxicology studies conducted with fedratinib include: fertility and early embryonic development (FEED) in rats, embryo fetal development (EFD) in rats and

rabbits, and pre- and postnatal development (PPND) in rats. There were no remarkable fedratinib-related effects in the FEED study. In the EFD study in rats, fedratinib was maternally toxic at the middle and high dose levels with lower gestational body weight gain and decreased gravid uterine weights. There was an apparent dose-related increase in pre-implantation loss in rats; however, the concurrent control value was much less than the historical control values, suggesting the study finding is of questionable toxicological significance. Numerically decreased mean live fetuses were noted in the middle and high dose levels compared to controls. There were also numerous instances of numerically increased structural abnormalities noted in fetal rats from the middle dose group, but not in the high dose group, suggesting the findings are of questionable toxicological significance. Toxicologically significant skeletal variations in rats included additional ossification centers of neuronal arches, irregular superior borders of scapula, and misaligned sternebrae. The jak/stat pathway has been implicated in bone formation and metabolism and its inhibition may cause bone abnormalities, e.g. in developing bone. No fedratinib-related effects on maternal or developmental parameters occurred in the rabbit EFD study. In the PPND study, fedratinib-related effects were limited to decreased body weight parameters.

The Applicant conducted a 1-month repeat-dose toxicology study in rats with 4-weeks recovery to qualify the impurity (b) (4) to a level of (b) (4) %. The study mimicked the 28-Day GLP study conducted with a lower level of (b) (4). The non-glandular stomach and skeletal muscle were identified as additional targets organs. After the recovery period of 4 weeks, microscopic findings were limited to minimal submucosal edema in the non-glandular stomach in males at 30 mg/kg. In a chromosome aberration assay of (b) (4) in human lymphocytes, there was no evidence of clastogenic potential.

Encephalopathy, including Wernicke's encephalopathy (a life-threatening illness caused by thiamine deficiency), occurred in 7/608 (1.2%) of patients who received 500 mg of fedratinib in clinical trials. The ability of fedratinib to inhibit human thiamine transporters ThTr-1 and ThTr-2 was evaluated using biochemical assays, and to change thiamine levels was assessed in a GLP-compliant 28-day repeat-dose pharmacodynamic study in rats. Fedratinib in vitro inhibition of ThTr1 and ThTr2 was 24.5% and 44.2%, respectively, at 300 µM (about 100-fold the C_{max} in patients at the recommended daily dose of 400 mg). Fedratinib did not alter thiamine concentrations or those of its phosphate forms in the plasma or brain of rats at doses tested but, systemic exposure in animals at the highest dose tested was only 0.3-fold those reported in patients at the recommended daily dose of 400 mg.

There are no outstanding issues from a nonclinical perspective that would prevent approval of fedratinib for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

The applicant characterized the inhibitory activity of fedratinib for the Janus kinase (JAK) family of enzymes. JAKs share significant homology across all 4 family members: JAK1, JAK2, JAK3, and Tyk2. In a series of studies, fedratinib was shown to inhibit JAK2 with an IC_{50} of 1.26 nM and was more than 36-fold more selective for JAK2 than other JAKs. In a second test using CALIPER, similar inhibitory activity of wild type and $JAK2^{V617F}$ was observed (Study: PH-07-101348-041). Fedratinib was also evaluated in a screen of 223 kinases using 0.5 µM fedratinib concentration (Study: PH-06-101348-019). A unique subset of 37 kinases were inhibited with an IC_{50} of < 25 nM; IC_{50}s for three variants of JAK2 were 3 to 12 nM and the IC_{50} for FLT3 was 15 nM.

Fedratinib (SAR302503) and its metabolites SAR317753, SAR317981, and SAR317793 were evaluated for inhibitory activity against JAK family kinases and screened against a panel of 192 kinases using 0.1 and 1 µM of parent drug or metabolites (Study: ONVT0048). SAR317753 and SAR317981 were active against JAK2 with IC_{50}s of 3.8 and 3.5 nM, respectively, while the third metabolite, SAR317793, was less active with an IC_{50} of 46 nM. Potencies of fedratinib and its metabolites were similar against the wild type JAK2 and its V617F mutant, 2 to 41-fold lower against JAK1, and approximately 2 orders of magnitude lower against JAK3 and TYK2 compared to their potencies against JAK2. Fedratinib inhibited ≥90% of the activity of 6 kinases (JAK2, ZIRK, $FGFR1^{V561M}$, NUAK1, $FLT3^{D835Y}$, and DAPK1) and ≥50% of the activity of 38 kinases (including those whose activity was inhibited ≥90%) at concentrations tested. In comparison with the parental compound, SAR317753 and SAR317981 metabolites were similarly active against JAK2 and $FGFR1^{V651M}$ and less active against the other kinases.

Fedratinib selectivity was assessed in [redacted] (b) (4) Ba/F3 cells engineered to express JAK1, JAK2, JAK3, or TYK2, by measuring proliferation and STAT3 phosphorylation (Study: ONVT0063). Fedratinib inhibited proliferation of JAK2 expressing cells (IC_{50} = 0.36 µM) and downstream p-STAT3 formation (IC_{50} = 0.65 µM). Fedratinib did not produce ≥50% inhibition for cells expressing JAK1, JAK3, or TYK2, at the concentrations tested.

The $JAK2^{V617F}$ mutation is found in approximately 99% of patients with polycythemia vera (PV), 70% of patients with post-essential thrombocythemia (ET), and 50% of primary patients with myelofibrosis (MF). A patient-derived, HEL cell line that endogenously expresses $JAK2^{V617F}$ and a transgenic mouse pro-B cell line that expresses human $JAK2^{V617F}$ (Ba/F3:$JAK2^{V617F}$) were used to evaluate the activity of fedratinib. Fedratinib inhibited proliferation with an EC_{50} of approximately 0.3 µM for both cell lines (Study: PH-07-101348-027). A dose-dependent reduction of STAT5 phosphorylation was observed in HEL and Ba/F3:$JAK2^{V617F}$ cells achieving approximately 50% reduction at 0.3 µM.

DNA laddering assays were conducted to evaluate whether inhibition of $JAK2^{V617F}$ by fedratinib in HEL and Ba/F3:$JAK2^{V617F}$ cells led to apoptosis (Study: PH-07-101348-027). DNA

fragmentation was detected in both HEL and Ba/F3:JAK2^{V617F} cells treated with fedratinib at 1 and 3 µM. No DNA fragmentation was detected in normal human dermal fibroblasts, which lack the JAK2^{V617F} mutation. Fedratinib also inhibited the phosphorylation of STAT5, Erk, protein kinase B (Akt), and FLT3 receptor in a dose-dependent manner and produced DNA fragmentation leading to apoptosis in the human AML cell line, MV411, which harbors the FLT3^{ITD} mutation (Study: PH-07101348-077).

A distinctive pathology of patients with PV is the excessive production of erythroid cells arising at the stem cell level due to the presence of JAK2^{V617F}. Hematopoietic stem cells (HSCs), progenitor cells, or common myeloid progenitor cells from JAK^{V617F}-positive patients with PV were clone-sorted and treated with fedratinib in human cytokine-supplemented methyl cellulose (Study: PH-07-101348-076). Fedratinib inhibited erythroid colony formation with IC_{50} values ≤ 300 nM for all the tested cell fractions. Subsequent genotyping studies of colonies after treatment revealed that JAK2^{V617F} allele could not be detected in some surviving colonies treated with 300 nM fedratinib, suggesting that fedratinib preferentially targeted JAK2^{V617F} colony progenitors.

A. <u>In Vivo Studies</u>

Fedratinib activity was tested in a mouse model of PV, using syngeneic JAK2^{V617F} positive HSCs. The mice produced aggressive myeloproliferative neoplasms (MPN)-like phenotypes, and developed erythrocytosis and other features of human PV. Animals received placebo, or oral gavage doses of fedratinib at 60 or 120 mg/kg BID for 42 days (based on half-life of murine erythrocytes) (Study: PH-07-101348-068). Median survival in placebo treated mice was slightly higher than 60% by the end of the study, and 100% for the fedratinib groups. Fedratinib also reduced WBC counts and hematocrit, reduced splenomegaly, and reduced markers of extramedullary hematopoiesis in spleens and livers. These results corresponded with a statistically significant reduction of CD71^{+} early erythroid precursors in the bone marrow, Ter119^{+} late erythroid precursors in the spleen, as well as Gr1^{+}Mac1^{+} myeloid cells in both bone marrow and spleen.

Data was generated from two xenograft models in RAG2-/-γc-/- mice. In one, human progenitors from patients with JAK2^{V617F} mutant PV transduced with green fluorescent protein-luciferase (GFP-Luc) were transplanted intrahepatically, and the other was transplanted with normal umbilical cord cells transduced with JAK2^{V617F} and GFP-Luc (Study: PH-07-101348-081). Noninvasive in vivo imaging was used to visualize the engraftment before (4 weeks after transplant), during (Day 5), and after (Day 12) treatment. Fedratinib treatment for 12 days inhibited erythroid engraftment in the mice. Fedratinib targeted myeloid progeny from JAK2^{V617F} mutant progenitors while sparing CD3 T cells.

<u>Secondary pharmacology</u>

In a receptor binding study (Study: PH-07-101348-029), 1 µM fedratinib inhibited ligand binding by > 50% for the following 13 receptors and/or transporters: Adenosine A1 and A2A receptors; muscarinic M1, M2, M3, M4, and M5 receptors; serotonin 5-HT1B receptor; sigma

(nonselective) receptor; Na+ channel (site 2); norepinephrine NE transporter; dopamine DA transporter; serotonin 5-HT transporter. IC_{50} values of 33 nM for muscarinic M1, 21 to 71 nM for M5, and 36 nM for dopamine transporter were determined in a subsequent screen (Study: PH-07-101348-030).

Thiamine receptor 1, ThTr1 (SLC19A2), and receptor 2, ThTr2 (SLC19A3), evolved from the same family of solute carriers, SLC19.[1] The central difference among members of this enzyme family is the localization and function. ThTr1 (SLC19A2) and ThTr2 (SLC19A3) transport thiamine ion (T^+) across cell membranes; however, they do not bind folates. SLC19A1, the reduced folate carrier, is a transporter of the thiamine monophosphate (TMP), thiamine pyrophosphate (TPP), and thiamine triphosphate (TTP) forms of thiamine, but not T^+.[2] SLC19A1 is expressed in all human and murine cells, and it is the major route of folate transport into systemic tissues. This transporter is also expressed in a variety of epithelia: the apical brush border membranes of the entire intestine, the choroid plexus and retinal pigment epithelium; the basolateral membrane of the proximal renal tubule and at the vascular blood brain barrier.[2] In contrast, ThTr1 is localized in skeletal muscles and systemic tissues with a thiamine influx constant Kt of 2.5 µM, whereas ThTr2 is expressed in the intestines mediating intestinal thiamine absorption with an influx constant Kt of 25 nM.[2] Wernicke's encephalopathy is a condition associated with thiamine deficiency and more likely involve deficiencies and/or inhibition of the ThTr2 responsible for intestinal thiamine absorption.

Because of claims that cases of Wernicke's encephalopathy occurred in fedratinib clinical trials, the Applicant evaluated fedratinib for the ability to inhibit human thiamine transporter ThTr1 and ThTr2 (Study: OPT-2017-097). Fedratinib was tested from 1 to 300 µM using polarized monolayer of Madin Darby Canine Kidney (MDCK)-11 cells expressing ThTr1 or ThTr2. Fedratinib inhibition of ThTr1 and ThTr2 was 24.5% and 44.2%, respectively, at 300 µM (about 100-fold the C_{max} in patients at the recommended daily dose of 400 mg). The C_{max} in rats after 28-day of dosing at 80 mg/kg/day was approximately 383 ng/mL or 0.73 µM.

The in vivo effects of fedratinib on thiamine transport to plasma and brain were assessed in a GLP-compliant 28-day repeat-dose study in Sprague Dawley rats (Study: 01046002). Fedratinib (lot number C17051538-BF17603M) was administered by oral gavage, to male and female rats at dose levels of 0 (0.5% methylcellulose), 40, or 80 mg/kg, once daily for 28 days. A dosage level of 80 mg/kg was selected as the highest feasible dose based on the findings of a previous 28-day toxicity study in Sprague Dawley rats, in which moderate to severe toxicity was observed (Study: TX-07-101348-074F). The 80 mg/kg in rats translates to a HED of 774 mg for a 60 kg patient (representing almost 2X the recommended human dose), but the AUC in animals at the high dose of 80 mg/kg was 0.3-fold the human AUC at the recommended dose of 400

[1] Zhao, R. and Goldman, D. 2013. Folate and Thiamine Transporters mediated by Facilitative Carriers (SLC19A1-3 and SLC46A1) and Folate Receptors. *Mol Aspects Med*. 34(0): doi:10.1016/j.mam.2012.07.006.
[2] Manzetti, S., Zhang, J., van der Spoel, D. 2014. Thiamin Function, Metabolism, Uptake, and Transport. *Biochemistry* 53: 821−835. dx.doi.org/10.1021/bi401618y

mg/day. Blood was collected from rats at different times on Day 1, 7, 14, and 29 for toxicokinetic and thiamine analysis. The brain was collected from rats at study termination, rinsed with phosphate-buffered saline, weighed, snap frozen in liquid nitrogen and shipped for analysis and determination of fedratinib, thiamine, TMP, TPP, and TTP using a validated bioanalytical method. When compared to control values, the thiamine concentration in brain and plasma appeared similar with few exceptions of decrease/increased values. Results indicate that daily treatment with fedratinib did not alter the concentration of thiamine or its phosphate forms in the plasma or brain of rats.

Safety pharmacology

The Applicant evaluated the ability of fedratinib to inhibit the hERG potassium channel using whole cell patch clamp in stably-transfected HEK293 cells (Study: PAT0257). The IC_{50} identified in this assay was 2.1 µM. An additional in vitro study was conducted to evaluate the ability of fedratinib to inhibit 11 cardiac ion channels (including hERG) responsible for the major components of the cardiac action potential (Study: SPH-08-101348-021). The IC_{50} values were determined for the following 6 human sodium, potassium, and calcium channels: hERG - 17.8 µM; hNav1.5 - 10.8 µM; hKvLQT1/minK - 20.6 µM; Kv4.3 - 31.2 µM; hCav3.2 - 8.2 µM; and Kir6.2/SUR2A - 2.8 µM. The IC_{50} values could not be determined for the following 5 human potassium and calcium channels (hKv1.5, hCav1.2, hKir2.1, hHCN4, and hKir3.1/3.4) at concentrations up to 30 µM.

A cardiovascular and respiratory study was conducted in conscious telemetered beagle dogs (Study: SPH-09-1 01348-045). Surgically-telemetered male dogs (iliac-based vascular access port) were administered a single oral dose fedratinib of 0 (0.5% methylcellulose vehicle control), 2, 6, and 20 mg/kg (40, 120, and 400 mg/m^2) at a volume of 2 mL/kg on days 1, 8, 15, and 22 using a Latin square cross-over study design. Doses were separated by a 1-week washout. Doses were selected based on the results of a 28-day toxicity study in dogs (Study: TX-07-101348-075F). There was no evidence of fedratinib-related changes in blood pressure (diastolic, systolic, and mean arterial pressure), heart rate, or ECG intervals (PR, QRS, QT, and QTc) or respiratory rate and arterial blood gases (pH, pCO_2, pO_2, SO_2, or HCO_3^-), at doses tested.

The effects of fedratinib on the CNS was assessed following oral gavage single doses of 0, 3, 10, or 30 mg/kg in Sprague-Dawley rats (Study: SPH-09-1 01348-049). There was increased eye miosis and/or lack of pupillary responses compared to controls, but no dose relationship was noted. Fedratinib-related gait abnormalities (walking on tip toes or paws pointed out) were present in the high-dose (HD).

5.4. ADME/PK

Absorption

Table 3: Fedratinib Plasma Pharmacokinetic Parameters in Rats and Dogs

Species (Study #)	Sex	Route	Food	Dose (mg/kg)	t_{max} (h)	C_{max} (ng/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (h)	F (%)
Rat (PDM-07-101348-025	M	IV bolus	Fed	5	NA	NA	1990	6.68	NA
		Oral	Fasted	25	3	436	3640	NE	37
			Fed	25	3	196	1810	NE	19
Dog (PDM-07-101348-056	M	IV bolus	Fasted	2	NA	NA	894	9.2	NA
		Oral	Fasted	10	3.7	105	1180	NE	26

NA: Not applicable
NE: Not evaluated

Distribution

- Fedratinib showed a large steady-state volume of distribution (Vss) after IV administration compared to the volume of total body water of 0.6 to 0.7 L/kg in all species studied, with values of 32, 13.5-17.4, 22, and 10.7 L/kg in mice, rats, dogs, and monkeys.
- The parent drug or the metabolites were well distributed in tissues of rats. Distribution was also seen in the skin and eyes of pigmented Long-Evans rats, with slow elimination from the eyes (approximately 40 days).

Table 4: Fedratinib Distribution in Various Species

Parameter/ Analysis Method	Concentrations Tested	Mouse	Rat	Dog	Human
% Plasma Protein Binding/Dialysis-LCMS/MS	5 µg (2630 ng/mL)	83.3	85.7	87.2	92.1
Blood:Plasma Partitioning/Radiolabel Liquid Scintillation Counting	25 mg/kg rats 5 mg/kg dogs	NE	1.1 to 2.0	1.1 to 1.2	NE
Brain:plasma ratios 24 h post-dose/Radiolabel Liquid Scintillation Counting	25 mg/kg [^{14}C]-fedratinib	NE	Males: 7.6 Females: 3.7	NE	NE

NE: not evaluated

Data was summarized from the following study reports:
Plasma protein binding: PDM-07-101348-047 and LPR1082
Blood to plasma portioning: PDM-08-101348-022 and AEB0480
Tissue distribution: PDM-08-101348-022 and AEB0484
Brain concentrations: PDM-07-101348-054 and AEB0484
Distribution in the eye (uveal tract): DIS0568 and PDM-08-101348-022

Metabolism

Table 5: Interspecies Comparison of the In Vivo Metabolic Profiles of [14C]-Fedratinib in Plasma and Excreta

Study No.	MIS0123			
Test Article	[14C]-SAR302503A			
Species (Strain)	Mouse (C57Bl/6)	Rat (Sprague Dawley, OFA)	Dog (beagle)	Human
Gender	male	male and female	male	healthy male subjects
Metabolism report	MET0910	MET0895	MET0893	MEH0082
Vehicle/ formulation	0.5% methyl cellulose	0.5% Methyl cellulose	0.5% Methyl cellulose	water
Feeding conditions	fasted	fasted	fasted	fasted
Method of Administration	Single oral administration	Single oral administration	Single oral administration	Single oral administration
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 masse spectrometry			

Compound	Male mouse (0-24h)	Male rat (0-24h)	Female rat (0-24h)	Male dog (0-24h)	Human[a] (0-6h to -12h)
	PLASMA - % of radioactivity				
SAR302503	66.2	78.7	87.7	72.3	79.8
M2=SAR317981 (pyrrolidone of UD)	5.2	21.3	12.3	blq	9.4
M7 (hydroxylation on ethyl pyrrolidone of UD)	5.4	blq	blq	blq	blq
M14=SAR318031 (N-butyric acid of UD)	3.6	blq	blq	blq	blq[b]
	TOTAL EXCRETION (% of administered dose)				
SAR302503	30.3	55.7	39.9	21.4	26.2
M7 (hydroxylation on ethyl pyrrolidone of UD)	3.6	1.8	3.7	3.6	2.2
M13=SAR317793 (hydroxylation on methyl pyrimidine of UD)	1.9	1.8	1.5	3.1	1.0
M14=SAR318031 (N-butyric acid of UD)	8.1	10.2	10.8	39.7	10.1
M17 (aminophenol-ethanoic acid of UD)	4.3	8.7	8.3	6.0	5.6

SAR302503= parent drug; blq= below the limit of quantification; M= metabolite
(a)=mean data n=6; (b)=detected in only one subject

Excretion

Biliary route was the major excretory pathway. In animal studies, fecal elimination was ≥78% of the administered oral dose and urinary excretion was <5%. Recovered parent drug was 2%. Studies AEB0497 (mouse), PDM-08-101348-022 (rat), AEB0484 (rat), and AEB0480 (dog). Humans: Fecal route ≈77%; urinary excretion ~ 5%. Recovered parent drug was 26%.

TK data from general toxicology studies

A 6-Month Toxicity Study of TG101348 Administered by Oral Gavage to Rats / Study Report TX-09-101348-044

Table 6: Summary of TK Parameters of Fedratinib in Rats in the 6-month Repeat-Dose Study

Day	Dose (mg/kg/day)	Male			Female		
		3	10	30	3	10	30
1	Cmax (ng/mL)	7.03	62.1	150	9.65	86.5	302
	Tmax (h)	4	4	4	4	4	4
	AUC (0-24) (ng·hr/mL)	42.5	363	1,430	66.3	680	3,210

180	Cmax (ng/mL)	6.25	87.8	200	10.6	67.8	357
	Tmax (h)	0.5	4	4	4	0.5	1
	AUC (0-24) (ng·hr/mL)	76.9	716	3,080	76.6	725	4,440

A 9-Month Toxicity Study of TG101348 Administered by Oral Gavage to Dogs / Study Report TX-09-101348-046A

Table 7: Summary of TK Parameters of Fedratinib in Dogs in the 9-month Repeat-Dose Study

Day	Dose (mg/kg/day)	Male				Female			
		2	6	15	20	2	6	15	20
1	Cmax (ng/mL)	8.36	58.9	NE	428	9.82	64.4	NE	427
	t_{max} (hours)	1	1	NE	4	1	1	NE	4
	AUC (0-24) (ng·hr/mL)	75.6	495	NE	4,560	83.4	430	NE	4,450
	$t_{1/2}$ (hours)	10.3	8.25	NE	6.42	9.60	8.35	NE	5.93
271	Cmax (ng/mL)	16.0	117	246	NE	23.3	76.4	345	NE
	t_{max} (hours)	2.5	1	4	NE	1	1	1	NE
	AUC (0-24) (ng·hr/mL)	184	1,200	2,880	NE	192	836	3,840	NE
	$t_{1/2}$ (hours)	10.9	9.15	ND	NE	11.8	8.42	6.67	NE

NE: not evaluated
ND: not determined; there were not enough values in the post-distribution phase

TK data from reproductive toxicology studies

Study for Effects on Embryo-Fetal Development in Rats / Study Report TX-09-101348-057

Table 8: Summary of TK Parameters of Fedratinib in Pregnant Rats on GD 6 and GD 17

TG101348 (mg/kg/day)	Cmax, ng/mL	T_{max}, h	$T_{1/2}$, h	$AUC_{(0-24)}$, ng·h/mL	$Cmax_{GD\ 17}/Cmax_{GD\ 6}$ Ratio	$AUC_{GD\ 17}/AUC_{GD\ 6}$ Ratio
GD 6 (Day 1 of dosing)						
3	8.23	4.00	ND	60.5	-	-
10	42.3	4.00	4.54	349	-	-
30	265	6.00	ND	3310	-	-
GD 17 (Day 12 of dosing)						
3	2.76	6.00	ND	26.1	0.335	0.431
10	46.8	4.00	5.27	419	1.11	1.20
30	294	6.00	ND	3250	1.11	0.982

ND – Not Determined, insufficient values in the post-distribution phase

(Excerpted from Submission)

Exposure in rats at 10 mg/kg or 30 mg/kg is approximately 0.01X or 0.1X the clinical exposure based on AUC at the recommended human daily dose of 400 mg.

Study for Effects on Embryo-Fetal Development in Rabbits / Study Report TX-09-101348-058A

Table 9: Summary of TK Parameters of Fedratinib in Pregnant Rabbits on GD 6 and GD 18

TG101348 Dose (mg/kg/day)	Gestation Day 6[a]			Gestation Day 18[b]		
	3	10	30	3	10	30
Cmax, ng/mL	3.09	20.2	157	7.02	40.2	501
Tmax, h[c]	1.00	1.00	1.00	1.00	1.00	2.00
T1/2, h[d]	ND	3.03	4.38	2.77	3.01	3.91
AUC(0-24), ng·h/mL	5.53	76.4	722	21.6	148	2,320
Cmax GD 18/Cmax GD 6 Ratio	ND	ND	ND	2.27	1.99	3.19
AUC GD18/AUC GD 6 Ratio	ND	ND	ND	3.91	1.94	3.21

[a] Day 1 of dosing
[b] Day 13 of dosing
[c] Expressed as a median
[d] Expressed as a harmonic mean
ND - Not Determined; insufficient values in the post-distribution phase

(Excerpted from Submission)

Reviewer comments: Exposure in rabbits at 10 mg/kg or 30 mg/kg is approximately 0.005X or 0.08X the clinical exposure based on AUC at the recommended human daily dose of 400 mg.

5.5. Toxicology

5.5.1. General Toxicology

A 6-Month Toxicity Study of fedratinib Administered by Oral Gavage to Rats/ Study Report TX-09-101348-044

- HD rats presented decreases in red cell mass that corresponded with bone marrow effects; increases in platelets, monocytes, neutrophils, and decreases in leukocytes and lymphocytes that corresponded with findings of inflammation and hemorrhage; and increases in alkaline phosphatase and γ-glutamyl-transferase that corresponded with liver findings.
- Changes in organ weight included significant decreases in pituitary (F) and spleen, and significant increases in adrenals (F), brain, heart, lungs, ovaries, seminal vesicles, and testis. The low-dose (LD) and mid-dose (MD) groups presented decreases in thymus weight.
- Additional findings included hypertrophy of bile ducts and bone marrow hypoplasia that corresponded with decreased red cell mass findings. Minimal to mild inflammation (kidney, liver, trachea and prostate) and hemorrhage (pituitary gland, stomach, lymph node, thymus and lungs) occurred at different dose levels at low incidence.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 3, 10, or 30 mg/kg/day Based on the results of a 28-day study with a 14-day recovery period in rats
Route of administration:	Oral gavage
Formulation/Vehicle:	Aqueous solution of 0.5% methylcellulose
Species/Strain:	Sprague Dawley Crl:CD(SD) rats
Number/Sex/Group:	30/sex/group for toxicity study; 12/sex/group for toxicokinetics
Age:	Approximately 8 weeks of age (at randomization)
Satellite groups/ unique design:	Low, mid and high dose for toxicokinetics; no control rats assigned for toxicokinetic assessment / Interim necropsy at 3 month 10/sex/group Terminal necropsy at 6 months 20/sex/group
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	At 10 mg/kg: One male on Day 106 due to gavage error. At 30 mg/kg: One male on Day 66, undetermined cause but thymic hemorrhage noted; two females on Days 40 and 137 due to gavage error.
Clinical Signs	No fedratinib-related clinical signs occurred
Body Weight Gain	Day 90: HD males ↓17%. Day 183: HD males ↓11.4%; HD females ↓9% Corresponded with decreased food consumption ↓4.6 to 11.9% in HD males
Ophthalmoscopy	No fedratinib-related findings
Hematology	Day 183 ↓ red cell mass (↓4.4% erythrocytes, ↓4.5% hemoglobin, and↓3.9% hematocrit) at HD; ↓4.7% Leukocytes and ↓17% lymphocytes at HD; ↑20.3% Platelets at HD; ↑20.4-34% Monocytes at MD males and females and at HD males; ↑28.2-74% Neutrophils at MD and at HD.
Clinical Chemistry	

Table 10: Fedratinib-related Changes in relative Serum Chemistry Parameters in the 6-month Toxicology Study in Rats

	Day 183	
	Male	Female
ALP	HD: ↑13	HD: ↑115
ALT		LD: ↓32; MD: ↓33; HD: ↓27
AST		LD: ↓25; MD: ↓29; HD: ↓11
GGT	LD: ↓54; MD: ↓13	LD: ↓52; MD: ↓27; HD: ↑15
Total Bilirubin	-	LD: ↓12; MD: ↓18; HD: ↓29
Cholesterol	-	HD: ↓49
Triglyceride	-	HD: ↓37%
Glucose	LD: ↑16; MD: ↑13	MD: ↑11;
Urea Nitrogen	MD: ↓15	HD: ↓13
Phosphorus	LD: ↑12	HD: ↑22%
Potassium		HD: ↑14%

↑↓= % decrease/increase compared to control group
-: not remarkable

Urinalysis

Day 91 and 183: ↑100% urine volume in HD females

Gross Pathology

Macroscopic findings were limited to early decedents, see Mortality.
No fedratinib-related macroscopic findings occurred

Organ Weights

Table 11: Fedratinib-related Changes in relative Organ Weight in the 6-month Toxicology Study in Rats

	Day 183	
	Male	Female
Body weight	HD: ↓11.4	HD: ↓9
Adrenals	-	HD: ↑25*
Pituitary	-	HD: ↓24*
Brain	HD: ↑12*	HD: ↑8
Heart	HD: ↑11*	HD: ↑18*
Lungs	HD: ↑10*	HD: ↑11*
Spleen	HD: ↓16*	HD: ↓25*
Ovaries	-	HD: ↑28*
Seminal vesicles	HD: ↑16	-
Testis	HD: ↑15*	-

↑↓= % decrease/increase compared to control group; * = P<0.05
-: not remarkable

Histopathology Adequate battery: Yes	Day 183 HD group: Hypertrophy of bile duct epithelial cells in the liver (8/20 males; 20/20 females); bone marrow hypoplasia (7/20 females). Both microscopic findings increased in incidence but not severity compared to the 3-month findings. Inflammation: mild (1/20) and marked (1/20) in the kidney at HD, minimal periductal (1/20) in the liver at LD females, mild neutrophilic (1/20) in the trachea at MD males, and an increased incidence (4/20) in the prostate gland at HD males. At the 3-month euthanasia, inflammation also occurred in the same organs with similar incidence. Hemorrhage: mild (1/20) in the pituitary gland at MD females, minimal (1/20) in the stomach at the HD females, minimal (1/20) in the thymus at LD and MD females, and an increased incidence (6/20) in the lungs at HD females. At the 3-month euthanasia, mild (1/10 males; 2/10 females) in the lung at HD, mild (2/10) in the mandibular lymph node at HD males, and mild (1/10) in the thymus at HD.
Dose Formulation Analysis	Concentration: within acceptable limits of ±15% error. Homogeneity: within the acceptable range of ≤5% for the 1 mg/g to 10 mg/g formulations. Stability: confirmed for 18 days for formulations concentrations from 1-125 mg/g and storage conditions at room temperature.

A 9-Month Toxicity Study of fedratinib Administered by Oral Gavage to Dogs / Study Report TX-09-101348-046A

- Mortality at 20/15 mg/kg/day was associated with clinical signs of decreased activity, ataxia, impaired mobility of forelimbs, facial edema, labored breathing, gastrointestinal irritation, significant body weight loss, decreased food consumption and increased body temperature.
- Decreases in red cell mass corresponded with multi-organ hemorrhage (e.g. GI tract, heart) and was accompanied by increases in reticulocytes. These findings together with decreases in leukocytes and neutrophils corresponded with bone marrow effects (hematopoietic hypoplasia); increases in liver enzymes (AST, ALT, ALP) and decreases in total bilirubin corresponded with findings in the liver of centrilobular degeneration, congestion, and hematopoiesis; these changes occurred at MD and HD with statistical significance at the HD.
- Inflammatory responses included swelling of limbs and the muzzle in moribund dogs, increased organ weights (e.g. liver, heart, lungs), and multi-organ inflammation on histopathology (e.g. GI tract, heart, liver, lungs). Decreases in the weights of epididymides, prostate and testes, and aspermia occurred at the high dose.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 2, 6, or 20/15 mg/kg/day Based on the results of a 28-day study with a 14-day recovery period in dogs. HD was reduced to 15 mg/kg/day on Day 26 because of mortality.
Route of administration:	Oral gavage
Formulation/Vehicle:	Aqueous solution of 0.5% methylcellulose
Species/Strain:	Beagle dogs
Number/Sex/Group:	10/sex/group/Study Phase
Age:	Approximately 5-6 months of age (at randomization)
Unique design:	Interim necropsy at 3 and 6 month, 3/sex/group Terminal necropsy at 9 months 3/sex/group ECG measurements pre-dose, 3, 6 and 9 months.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	At 20 mg/kg: Three females and 1 male moribund euthanized on Days 18-26. At 15 mg/kg: Four males moribund euthanized on Days 61-232. One male found dead on Day 188. Deaths were associated with effects on bone marrow, inflammation, and GI toxicity.
Clinical Signs	Adverse clinical signs in moribund dogs included ↑body temperature, ↓activity, impaired mobility and swelling of limbs, edema labored breathing and swelling of the muzzle. Clinical signs in surviving fedratinib-treated dogs included higher incidence and frequency of ocular discharge, salivation and gastrointestinal irritation such as vomiting, soft/mucoid stools, mucoid material, and diarrhea compared to controls.
Body Weights	Significant effects on body weights noted in males given 20/15 mg/kg/day, with decreases of 9.5%, 11.2%, and 18.5% compared to controls on Day 90, 181, and 271, respectively.
Food Consumption	Decreases in food consumption in HD individual dogs prompted supplemental can food feeding.
Ophthalmoscopy	No fedratinib-related findings occurred during the study
ECG	Terminal: no statistical differences were detected between groups for the heart rate, PR interval, QRS duration, QT interval, or QTc.

Hematology

Symptoms of anemia and red cell regenerative responses with moderate neutropenia were noted throughout the study.

Day 272	Males		Females	
Dose (mg/kg)	6	20/15	6	20/15
Erythrocytes	↓11#*	↓19#*	↓10*	↓13*
Hemoglobin	↓7#	↓19#*	↓9*	↓13*
Hematocrit	↓8#	↓18#*	↓8	↓11*
Reticulocytes	↑90*	↑139*	↓51	-
Platelets	-	-	-	↑19
Leukocytes	↓13	↓24	↓14	↓25
Monocytes	↓11	↑86	↓15	↓5
Neutrophils	↓16	↓39	↓25	↓47*
Basophils	↓10	↓60	↓61	↓42

*: differences were statistically significant (P<0.05)
↑↓= % decrease/increase compared to control group
#: Because of mortality, values are from Day 182 with n=6-7; no differences with control on Day 272 n=2;
-: not remarkable

Clinical Chemistry

At the 20/15 mg/kg dose level, ALT levels were increased relative to controls on Days 24 to 182; from 403%-520% in males and 111%-222% in females

Day 272	Males		Females	
Dose (mg/kg)	6	20/15	6	20/15
AST	↑65*	↑123*	-	↑72*
ALT	↑171	↑246#	↑51	↑117
ALP	↑73	↑154*	↓11	-
GGT	↓14	↓9	↑14	-
Total bilirubin	↓6	↓12#	↓14	↓10
Cholesterol	↑18	↓32*	↓15	↓46*
Albumin	-	↓16*	-	-
Globulin	↑21*	↑37	-	-
A/G Ratio	↓20*	↓37*	-	-
Urea nitrogen	↓20*	-	-	-
Creatinine	-	↓16#	-	-
Phosphorus	-	↓24*	-	-

*: differences were statistically significant (P<0.05)
↑↓= % decrease/increase compared to control group
values on Day 182 reached statistically significance
-: not remarkable

Urinalysis

No fedratinib-related findings occurred during the study

Gross Pathology

HD early decedents: body fat depletion; discoloration of carcass (possible jaundice), GI track, lymph nodes and thymus; reduced thymus size, enlarged lymph nodes, stomach foci, and mucoid black stools consistent with GI bleeding. One male exhibited red solid material in the right ventricle of the heart and thickening of the heart.

Organ Weights

Day 272	Males			Females		
Dose (mg/kg)	2	6	20/15	2	6	20/15
Adrenals	-	-	↑34	↑22	-	-
Thyroids	↑15	-	↑22	↑11	↓17	↓19
Liver	↑9	-	↑28	↓11	-	-
Brain	-	↓10	↑14	-	-	-
Heart	-	-	↑28	-	-	↑11
Kidneys	-	-	↑19	-	-	-
Lungs	-	↓13	↑12	-	-	-
Salivary glands	-	↓15	-	-	↓13	-
Spleen	↓24	↓49	↓48	↑21	-	↓20
Thymus	-	↑22	↑50	-	↑44	-
Epididymides	↓11	↓14	↓23	-	-	-
Prostate	↓16	↓25	↓41	-	-	-
Testes	-	↓10	↓18	-	-	-
Ovaries	-	-	-	↑21	-	-
Uterus	-	-	-	↓46	-	↓21

All differences were statistically significant (P<0.05)
↑↓= % decrease/increase compared to control group
-: not remarkable

Histopathology

Adequate battery: Yes

Findings in females were unremarkable except for one event in the liver so only male data is presented for euthanasia on Day 182 and 272.

	Fedratinib (mg/kg/day)		
	Day 182		Day 272
	Males		
n	3	4	3
Organ	20/15	6	20/15
Adrenal gland marked congestion			1
Aorta mild hemorrhage			1
Bone marrow, sternum			
Minimal megakaryocyte hyperplasia	2		
Stem cell hyperplasia			
Mild	1		1
Moderate			1
Marked	1		1
Hematopoietic hypoplasia			
Mild			1
Moderate			1
Marked	2		1
Epididymis			
Aspermia	1		
Mild Debris in lumen			1
GI track			
Minimal to mild congestion	2		
Heart			
Mild hemorrhage			1
Mild epicardium, mesothelium left hyperplasia	1	1	
Mild epicardium chronic inflammation	1	1	
Rectum			
Minimal hemorrhage			1
Mild chronic inflammation			1
Liver			
Mild congestion			1
Mild centrilobular degeneration			1
Minimal to moderate hematopoiesis	1 female		2
Minimal stem cell infiltration	1		1
Lung			
Moderate congestion			1
Mandibular Lymph node			
Hemorrhage			
Mild			1
Moderate	1		
Moderate Erythrophagocytosis	1		
Mild hyperplasia	1		
Pancreas			
Mild zymogen depletion	1		1
Minimal islet atrophy	1		1
Moderate islet hyperplasia	1		1
Mild chronic active inflammation	1		1
Prostate gland atrophy			
Mild	1		
Moderate			1
Spleen			
Mild congestion	1		
Moderate hematopoiesis	1		
Mild hemosiderin pigmentation	1		
Minimal stem cell infiltration	1		
Moderate lymphoid depletion			1
Mild stem cell infiltration			1

	Testis Aspermia Moderate seminiferous epithelium degeneration	 1	 	 1 1	
	Thymus Lymphoid depletion Mild Moderate marked	 1	 2 1 	 2 1	
	Thyroid gland mild congestion	1			
Dose Formulation Analysis	Concentration: within acceptable limits of ±15% error. Homogeneity: within the acceptable range of ≤5% for the 1 mg/g to 10 mg/g formulations. Stability: confirmed for 18 days for formulations concentrations from 1-125 mg/g and storage conditions at room temperature.				

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial Reverse Mutation (Ames) Assay with fedratinib / TX-07-101348-084

Key Study Findings:

- There was no increase the number of revertant colonies in the range-finding or the confirmatory assay.
- Fedratinib was negative in the Ames assay.

GLP compliance: Yes

Test system: S. typhimurium tester strains TA98, TA100, TA1535, and TA1537 and E. coli strain WP2uvrA were incubated with and without metabolic activation.

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: In vitro Mammalian Chromosome Aberration Test with fedratinib in Chinese Hamster Ovary (CHO) Cells / TX-09-101348-050

Key Study Findings:

- No statistically significant increase in structural or numerical chromosome aberrations was observed at fedratinib concentrations tested (0.625 - 45 µg/mL). These concentrations resulted in at least 50% toxicity in the presence or absence of S9 as compared to controls.
- Fedratinib was considered negative for the induction of chromosome aberrations in this assay.

GLP compliance: Yes

Test system: CHO cells in both the absence and presence of an Aroclor induced S9 activation system

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Rat Bone Marrow Erythrocyte Micronucleus Test Following Oral Administration of fedratinib / TX-09-1 01348-051

Key Study Findings:

- No statistically significant increase was noted in the incidence of micronucleated polychromatic erythrocytes in fedratinib groups as compared to vehicle control groups.
- Fedratinib was considered negative in the rat mammalian micronucleus assay at doses up to and including 80 mg/kg.

GLP compliance: Yes

Test system: TG101348 single oral gavage dose of 0, 5, 30, and 80 mg/kg was administered to male and female Sprague-Dawley rats (n=5/sex/group). No mortality occurred in the study.

Study is valid: Yes

5.5.3. Carcinogenicity

Daily oral gavage administration of fedratinib to 001178-T (hemizygous) CByB6F1-Tg(HRAS)2Jic mice for at least 26 weeks at doses of 3, 10, and 30 mg/kg/day (9, 30, and 90 mg/m^2/day) resulted in no effect on survival and no fedratinib-related neoplastic or hyperplastic effects.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: Oral male and female fertility study of fedratinib in rats / FER0500

Key Study Findings

- Parental toxicity was limited to reduced body weight and/or body weight gains at 30 mg/kg.
- Minimal decreased pregnancy rates (1, 3, and 1 females at 3, 10, and 30 mg/kg/day) were observed relative to controls; however, the fertility rate remained within the biological variation and the historical control range.
- The exposure (AUC) at the dose of 30 mg/kg/day is approximately 0.10 to 0.13 times the clinical exposure at the recommended daily dose.

Conducting laboratory and location:	Sanofi-aventis 3 digue d'Alfortville 94140 Alfortville France
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 3, 10, or 30 mg/kg/day M: daily for at least 91 days (including 10 weeks before cohabitation) F: daily for at least 22 days (up to 27 days): 15 days prior to cohabitation, 1 to 6 days of cohabitation and then 7 first days of gestation.

	Based upon the results of a previous embryo-fetal developmental toxicity study and of a combined 3- and 6-month toxicity study in rats.
Route of administration:	Oral gavage / 5 mL/kg
Formulation/Vehicle:	Aqueous solution of 0.5% methylcellulose
Species/Strain:	Sprague-Dawley Crl:CD(SD) rats
Number/Sex/Group:	M: 24/group; F:25 control, 24/other groups
Satellite groups:	None
Study design:	Standard ICH S5(R2)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	None
Body Weights	

Table 12 Fedratinib-related Effects on Body Weight Gain in the Fertility Study in Rats

Dose (mg/kg/day)	Males				Females		
	Pre-Cohabitation			Post-Cohabitation	Pre-Cohabitation		Gestation
	Interval 1 – 4		Interval 1 - 71	Interval 74 - 92	Interval 1 - 15		Interval 1 - 14
	N	Mean ± SD	Mean ± SD	Mean ± SD	N	Mean ± SD	Mean ± SD
Control	24	14.1	173.3	43.5	25	8.1	70.9
3	24	13.9	178.9	33.6	24	15.4	72.4
10	24	14.7	166.1	24.0	24	22.1	68.7
30	24	7.3	128.2	25.7	24	11.7	59.9

Necropsy findings

Table 13 Fedratinib-related Effects on Fertility and Mating Performance

Observation	Fedratinib Dose (mg/kg/day)			
	0	3	10	30
Fertility and Mating Performance				
Cohabited pairs	25	24	24	24
Mated females	25	24	24	24
Pregnant females	25	23	21	23
Fertility rate	25/25 (100%)	23/24 (95.8%)	21/24 (87.5%)	23/24 (95.8)
Laparohysterectomy Evaluations				
Unscheduled deaths	0	0	0	0
Surviving females				
with live fetuses	25	23	21	23
With Postimplantation loss	0	0	0	0
Nonpregnant	0	0	0	0
Weight Gravid uterus	13.28	14.32	14.40	13.22
Corrected mean maternal weight	316.6	323.3	318.1	299.2*
Corpora lutea	16.0	16.6	16.7	16.1
Implantation sites	15.4	15.9	15.9	15.4

Live fetuses Absolute	14.7	15.2	15.2	14.5
Live fetuses % Implantations	95.2	95.5	96.2	94.0

* = Significant trend ($p \leq 0.05$)

Organ Weight Changes for HD males compared to control:
Statistically significant lower terminal body weight (↓10%) on Day 96
Statistically significant lower testes and relative weight (↓9%)
Statistically significant lower prostate weight (↓12%) but not relative weight (↓3%).
No fedratinib-related sperm anomalies (motility, counts or morphology) were noted.

Embryo-Fetal Development

Study title/ number: Study for Effects on Embryo-Fetal Development in Rats / TX-09-101348-057

Key Study Findings

- Maternal toxicity at ≥MD including lower gestational body weight gain and decreased gravid uterine weight.
- Lower fetal weight at all dose levels.
- A single malformation of herniation in the abdominal cavity.
- Variations included additional ossification center in the cervical neural arch(es) at HD, an irregular superior border in the scapula at ≥MD, and an increased incidence of misaligned sternebra(e) at all dose levels.
- Malformations in the forelimbs, hind limbs, and pectoral and pelvic girdle in the MD but not HD.
- The NOAEL for maternal toxicity and developmental toxicity in rats was 3 mg/kg/day. Exposure ratios compared to the recommended human dose in patients with MF are 0.0008X, 0.014X, and 0.112X for the LD, MD, and HD, respectively.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 3, 10, or 30 mg/kg/day
GD 6 through GD 17
Based upon the results of a non-GLP range-finding EFD study in rats

Route of administration: Oral gavage / 10 mL/kg

Formulation/Vehicle: Aqueous solution of 0.5% methylcellulose

Species/Strain: Time-mated female CD® [Crl:CD®(SD)] rats

Number/Sex/Group: 25/group

Satellite groups: Toxicokinetics: 3 non-pregnant females in control and 6 non-pregnant females in other groups

Study design:	Standard ICH S5(R2)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	None
Body Weights	Fedratinib-related decreased mean body weight gain occurred during different study intervals at MD and HD. Overall mean body weight gain from GD 6 to GD 18 and from GD 6 to GD 20 were significantly different from controls in the 10 mg/kg/day (9.4% and 8.5%, respectively) and 30 mg/kg/day (15.7% and 12.9%, respectively).

Necropsy findings
Cesarean Section Data

Post-implantation loss of 30.4% increase at the HD compared to controls.
A 9.1% decrease in live fetuses at the MD and HD.
Significantly lower fetal weight in males at all doses and in females at the HD.
Significantly lower gravid uterine weight at the MD and HD that corresponded with significantly lower mean body weight gain from GD 6 to GD 18 and from GD 6 to GD 20.

Table 14 Fedratinib-related Effects on Laparohysterectomy Evaluations in the Rat EFD Study

Dose (mg/kg/day)	0	3	10	30
Number of females tested	25	25	25	25
Number of females pregnant	24	25	25	25
Number of surviving pregnant females	24	25	25	25
Dams with any resorptions N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean corpora lutea	12.8	13.2	12.8	13.2
Mean no. of implantations	12.6	12.2	11.5	11.7
Mean pre-implantation loss	1.42	7.34**	9.72**	10.33**
Mean percent post-implantation loss	4.24	3.58	4.34	5.53 (↑30.4%)
Mean early resorptions	0.5	0.4	0.5	0.6
Mean live fetuses	12.1	11.7	11.0 (↓9.1%)	11.0 (↓9.1%)
Mean fetal sex ratio	52.7	42.6	49.1	44.9
Fetal weight (Mean g ± SD) Combined Males + Females	4.18 (0.177)	3.99 (0.260)*	4.01 (0.228)*	3.77 (0.202)**
Summary of Gravid Uterine Weight and Adjusted Body Weight/Body Weight Change Values				
Mean gravid uterine weight (g)	76.1	71.4	67.4*	64.9**
Mean final body weight (g)	375.4	376.2	364.0	356.4
Mean adjusted final body weight (g)	299.3	304.9	296.6	291.5
Mean adjusted weight change from Day 0	97.0	99.5	93.6 (↓4.0%)	89.2 (↓8.0%)

Percent Pre-implantation loss = [(# corpora lutea - # implantations) / # corpora lutea] x 100
Percent Post-implantation loss = [(# implantations - # live fetuses) / # implantations] x 100
* Significantly different from control ($p<0.05$)
** Significantly different from control ($p<0.01$)

Necropsy findings
Offspring

External Examinations
No fedratinib-related fetal external malformations or variations were observed.
Visceral Examinations
A single malformation of herniation in the abdominal cavity was present in one HD fetus. This finding was present in 1 liter (4%) and 1 fetus (0.7%). The historical control data included in the study report did not include this finding.
Skeletal Examinations
Fedratinib-related findings included an increased litter incidence of additional ossification centers on the cervical vertebral neural arches in the HD that reached statistical significance, an irregular superior border of the scapula with similar litter and fetal incidence in the MD and HD, and an increased incidence of misaligned sternebra(e) at all doses compared to controls. All other variations and malformations in rat skeleton listed below were slightly above the historical control range. These skeletal variations and malformations in rats are considered fedratinib-related based on demonstrated effects of the JAK/STAT pathway intervention on the differentiation of osteoclasts and bone homeostasis observed in knockout mice studies.

Table 15 Fedratinib-related Effects on Fetal Skeletal in the Rats EFD Study

Dose (mg/kg)		0	3	10	30
Total number of litters examined		24	25	25	25
Total number of fetuses examined		142	145	136	138
V- Cervical Neural arch(es): additional ossification center	Litter incidence (%)	-	-	-	7 (28.0)**
	Fetal incidence (%)	-	-	-	11 (8.0)
V- Scapula: superior border irregular	Litter incidence (%)	-	-	1 (4.0)	1 (4.0)
	Fetal incidence (%)	-	-	1 (0.7)	1 (0.7)
V- Pubis: not ossified	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-
V- Ribs, costal cartilage: misaligned	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	1 (0.7)	-
V- Sternebra(e): misaligned	Litter incidence (%)	1 (4.2)	3 (12.0)	5 (20.0)	3 (12.0)
	Fetal incidence (%)	1 (0.7)	3 (2.1)	6 (4.4)	3 (2.2)
M- Neural arch(es): Arches fused	Litter incidence (%)	-	1 (4.0)	-	-
	Fetal incidence (%)	-	1 (0.7)	-	-
Forelimbs					
M- Humerus: short	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-
M- Radius: short	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-
M- Ulna: short	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-
M- Radius: short	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-
Hind limbs					

M- Femur: short	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-
M- Fibula: short	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-
M- Tibia: short	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-
Pectoral girdle					
M- Scapula: misshapen	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-
Pelvic girdle					
M- Ilium: short	Litter incidence (%)	-	-	1 (4.0)	-
	Fetal incidence (%)	-	-	2 (1.5)	-

** Significantly different from control (p<0.01)

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: Study for Effects on Embryo-Fetal Development in Rabbits / TX-09-101348-058A

Key Study Findings

- No fedratinib-related effects on maternal or embryo-fetal parameters were observed.
- The NOEL for maternal and developmental toxicity in rabbits was 30 mg/kg/day.
- Exposure ratios compared to the recommended human dose in patients with MF are 0.005X and 0.075X for the MD and HD, respectively.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 3, 10, or 30 mg/kg/day
GD 6 through GD 18
Based upon the results of a non-GLP DRF EFD study in rabbits

Route of administration: Oral gavage / 4 mL/kg

Formulation/Vehicle: Aqueous solution of 0.5% methylcellulose

Species/Strain: Time-mated female New Zealand White Hra:(NZW)SPF rabbits

Number/Sex/Group: 23/group

Satellite groups: Toxicokinetics: 3 non-pregnant females in all groups

Study design: Standard ICH S5(R2)

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	One MD female died on GD 16 due to gavage error. One HD female was euthanized on GD 21 because of impaired right forelimb function (abscess noted in the right axillary region).
Clinical Signs	None
Body Weights	No effects
Necropsy findings Cesarean Section Data	
No maternal macroscopic findings were observed. The pregnancy index was 100%, 95.7%, 100%, and 100% in the control, LD, MD and HD, respectively. No effects on any cesarean section or fetal parameters. No effects on uterine weights or adjusted GD 29 body weights or adjusted body weight change GD 0-29.	
Necropsy findings Offspring	
No effects on fetal body weight <u>External Examinations</u> HD: exencephaly, open eye, microphthalmia, small pinnae, forelimb flexures, and malrotated hind limbs were seen in a single fetus, but in the absence of other external malformations among fetuses in this group, this was considered a spontaneous occurrence and unrelated to the test article. The incidence of these findings was also within the historical control range for the laboratory. <u>Visceral and Skeletal Examinations</u> The overall incidence of litters containing fetal visceral or skeletal malformations was comparable to control and within historical control data. <u>Total Malformations</u> The incidence of litters containing one or more fetuses with a malformation identified from the external, visceral and/or skeletal evaluations was 40.9% (9/22 litters), 36.4% (8/22 litters), 27.3% (6/22 litters), and 27.3% (6/22 litters) in the control LD, MD and HD, respectively.	

LD: low dose; MD: mid dose; HD: high dose

<u>Prenatal and Postnatal Development</u>

Study title/ number: Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function with fedratinib in Rats / DPN0371

Key Study Findings

- Decreased body weight gain during gestation in HD F0 dams.
- Decreased body weight (precull to weaning) and decreased body weight and food consumption in F1 males during maturation.
- The NOAEL for F0 maternal toxicity is 30 mg/kg/day (180 mg/m^2/day) and the NOEL for F1 pup development is 10 mg/kg/day (60 mg/m^2/day).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 3, 10, or 30 mg/kg/day GD 6 through parturition and through Lactation Day (LD) 20 Based upon the results of a previous embryo-fetal developmental toxicity study in rats (Study: TX-09-1 01348-057)
Route of administration:	Oral gavage / 10 mL/kg
Formulation/Vehicle:	Aqueous solution of 0.5% methylcellulose
Species/Strain:	Time-mated female CD® [Crl:CD®(SD)] rats
Number/Sex/Group:	24/group
Satellite groups:	None
Study design:	Standard ICH S5(R2)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	
Body weight gain GD 6-8: LD: ↓21%; MD: ↓14%; HD: ↓ 48% Body weight gain GD 10-12: HD: ↓22% Body weight gain GD 16-18: HD: ↓17%. One time-mated HD female was not pregnant. NOAEL for F0 maternal toxicity is 30 mg/kg/day (180 mg/m^2/day).	
F1 Generation	
Fedratinib-related decreases in HD preweaning pup body weights (pre- and postcull) were noted when compared to control.	

Table 16 Fedratinib-related Effects in Preweaning Pup Body Weight

Day	Males	Females
0	↓10.7*	↓12.4*
4 precull	↓10.7*	↓11.7*
7 postcull	↓9.1*	↓9.5*
21	↓4.6	↓5.6

↑↓= % decrease/increase compared to control group

Fedratinib-related decreases in HD males body weight during postweaning through maturation were noted when compared to control. HD male post-pairing (day 14) body weight was ↓10.7% compared to control. Decreases in body weight and body weight gain may be related to ↓6% in food consumption throughout maturation and post-pairing. NOEL for F1 pup development is 10 mg/kg/day (60 mg/m^2/day).

Table 17 Fedratinib-related Macroscopic Findings in F1 Males

Fedratinib Dose (mg/kg)	Sex	Macroscopic Finding
3	M	kidney and urinary bladder calculus, and testis adhesion
	M	large kidney
	M	small epididymis and small testis

		M	small epididymis, discolored and large testis
	10	M	small epididymis
		M	stomach adhesion
		M	large testis
	30	M	large kidney
F2 Generation			
No fedratinib effects.			

5.5.5. Other Toxicology Studies

Impurities

1-month oral toxicity study in rats with a 4-week recovery period / Study Report TSA1485

This GLP-compliant repeat-dose was conducted to qualify the starting material impurity (b) (4) at a level of approximately (b) (4)%. Male and female Crl:CD(SD) rats (6-7 weeks of age 10 animals/sex/group) were administered fedratinib at 0 (0.5% methylcellulose [vehicle control group]), 5, 30, or 80 mg/kg (0, 30, 180 or 480 mg/m^2) by oral gavage, once daily for 28 days. Additional 5 rats/sex/group were assigned in all groups for a 4-week recovery period. The main target organs were the bone marrow, liver (bile ducts), lymphoid tissues (thymus, spleen, and mesenteric lymph nodes), lungs, heart, non-glandular stomach and skeletal muscle. The non-glandular stomach and skeletal muscle were identified as targets in this study but not in the 28 day fedratinib study. Hepatocellular hypertrophy was also observed in this study. After the recovery period of 4 weeks, microscopic findings were limited to minimal submucosal edema in the non-glandular stomach in males at 30 mg/kg.

In vitro chromosome aberration test in cultured human peripheral blood lymphocytes / Study Report MAF0133

A GLP-compliant chromosome aberration assay was conducted in human lymphocytes to evaluate the clastogenic potential of the impurity (b) (4). No statistically significant or biologically relevant increases in the number of cells with structural aberrations were found with or without metabolic activation, when tested up to 10 mM (2950 µg/mL) or at concentrations exhibiting cytotoxicity.

In vitro phototoxicity using 3T3 cells / Study Report PHV0056

This non-GLP compliant study assessed the phototoxic potential of fedratinib using the in vitro phototoxicity test with 3T3 cells. Fedratinib did not show any in vitro phototoxicity potential in 3T3 cells.

Pedro L. Del Valle, PhD, ATS
Primary Reviewer

Christopher Sheth, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant seeks approval of INREBIC (fedratinib) for the treatment of intermediate-2 or high-risk primary or secondary [post-polycythemia vera (PV) or post-essential thrombocythemia (ET)] myelofibrosis (MF). The proposed INREBIC dosing regimen is 400 mg orally once daily (QD), with or without food.

The Clinical Pharmacology section of the NDA is supported by the evaluations and analyses of single and repeat dose pharmacokinetics (PK) of fedratinib, effect of food on fedratinib PK, population PK, exposure-response relationships for efficacy and safety, potential for QT/QTc prolongation, drug-drug interactions (DDI) between fedratinib and strong cytochrome P450 (CYP) 3A4 inhibitors and acid reducing agents, and physiologically based PK (PBPK) modeling and simulations of CYP3A4 modulators and dual CYP2C19 and CYP3A4 inhibitors.

Based on the efficacy and safety results in the registration trial for patients with MF, the proposed INREBIC dosing regimen of 400 mg orally QD with the dose reduction schema in the event of adverse reactions is acceptable. The proportion of patients who had 35% or higher spleen volume reduction at the end of cycles 6 (EOC6) and confirmed 4 weeks later, was not appreciably different at 500 mg QD (40%) compared to 400 mg QD (37%). However, higher incidence rates of adverse events (AE) were observed in the 500 mg group, including Grade ≥3 AE, Grade ≥3 anemia, Grade ≥3 thrombocytopenia, serious AEs, any grade diarrhea/nausea, AEs, and AEs leading to treatment discontinuation & dose reduction. The exposure-response (E-R) relationships for efficacy and safety were consistent with the observed dose-response results.

The key review questions focused on dose recommendations for patients taking concomitant strong and moderate cytochrome P450 (CYP)3A inhibitors or inducers, or dual CYP2C19 and CYP3A inhibitor, and for patients with hepatic and renal impairment. Dose reduction to 200 mg once daily is recommended in patients with severe renal impairment or co-administration of strong CYP3A inhibitors. No dose adjustment recommended for patients with mild or moderate renal impairment. The population PK analyses did not identify clinically important covariates influencing fedratinib PK, including mild to moderate hepatic impairment and mild renal impairment; no dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Recommendations

The proposed INREBIC dosing regimen of 400 mg orally once daily in patients with MF with the dose reduction schema in the event of adverse reactions is acceptable. From a Clinical Pharmacology standpoint, the NDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness[†]	Trial EFC12153 (phase 3, patients with MF) demonstrated an improvement in SVR at the EOC6 and confirmed 4 weeks later compared to placebo.
General dosing instructions	400 mg orally once daily, with or without food. Administration with high-fat meal may reduce incidence of nausea and vomiting.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Avoid coadministration of strong and moderate CYP3A4 inducers, and dual CYP2C19 and CYP3A4 inhibitors. • Reduction of dose to 200 mg is recommended with strong CYP3A4 inhibitors • Reduction of dose to 200 mg is recommended in patients with severe renal impairment. • No dose adjustments are recommended in patients with mild to moderate hepatic impairment, mild to moderate renal impairment, and co-administration with moderate CYP3A4 inhibitors or gastric acid reducing agents.
Labeling	• Consider alternative therapies that are not strong CYP3A4 inhibitors. If unavoidable, reduce dose to 200 mg with strong CYP3A4 inhibitors. • No dose adjustment is necessary with concomitant use of a moderate CYP3A4 inhibitor or gastric acid reducing agents. • Avoid coadministration of dual CYP2C19 and CYP3A4 inhibitors, and strong and moderate CYP3A4 inducers. • Reduce dose to 200 mg in patients with severe renal impairment. • No dose adjustment is necessary in patients with mild to moderate hepatic impairment or renal impairment. The PK and safety of INREBIC in patients with severe hepatic impairment has not been studied. • Monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates as necessary when co-administered with INREBIC.
Bridge between the to-be-marketed and clinical trial formulations	No. However, the pharmacokinetic exposures of initial, 1A1, and 1B1 capsule formulations used during clinical development of fedratinib were found to be comparable, and population PK analysis indicated that formulation was not a clinically significant covariate.

Postmarketing Requirements and Commitments

The Applicant is requested to conduct the following clinical and clinical pharmacology studies as a postmarketing requirement (PMR) or postmarketing commitment (PMC). The PMR/PMC studies will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☒ PMR	Determination of an appropriate fedratinib dose for patients with severe hepatic impairment.	77% of the administered dose (23% as unchanged fedratinib) was recovered in the feces, indicating that hepatic elimination is the major elimination pathway.	Single dose of fedratinib in otherwise healthy subjects with severe hepatic impairment compared to healthy subjects.
☐ PMC ☒ PMR	Determination of an appropriate fedratinib dose for patients with co-administration of a dual CYP2C19 and CYP3A4 inhibitor.	Fedratinib is metabolized by CYP3A4 and CYP2C19. There is potential for increased exposure with dual CYP2C19 and CYP3A4 inhibitor that may increase the risk of toxicity.	Single dose of fedratinib with and without coadministration of repeat doses of a moderate dual CYP2C19 and CYP3A4 inhibitor in cancer patients.
☒ PMC ☐ PMR	Determination of an appropriate fedratinib dose for patients with co-administration of a moderate and a strong CYP3A4 inducer.	Fedratinib is metabolized by CYP3A4, and there is potential for reduced exposure with CYP3A4 inducers that may affect fedratinib efficacy.	Single dose of fedratinib with and without coadministration of repeat doses of a moderate and a strong CYP3A4 inducer in cancer patients.
☐ PMC ☒ PMR	Determination of PK and safety of drugs that are P-gp, BCRP, MATE-1 /2K, or OCT2 transporter substrates for patients with multiple doses of fedratinib.	Fedratinib is an inhibitor of P-gp, BCRP, MATE-1 /2K and OCT2 transporters in vitro.	Single dose of drugs that are P-gp, BCRP, MATE-1 /2K, and OCT2 transporter substrates with and without multiple dose of fedratinib in cancer patients.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Fedratinib (molecular weight of 525 g/mol as free base) is a selective Janus Kinase 2 (JAK2) inhibitor.

The following is a summary of the clinical pharmacokinetics (PK) and pharmacodynamics (PD) of fedratinib:

Pharmacodynamics

Fedratinib inhibited cytokine-induced STAT3 phosphorylation in patients with MF. The inhibition of STAT3 phosphorylation was maximal ~2 hours after the first dose, returning to near baseline at 24 hours post-dose. The level of mean inhibition (40% to 52%) of STAT3 phosphorylation at steady state PK after once daily administration was comparable to the maximal inhibition (~46% to 50%) after the first dose at 300, 400, or 500 mg of fedratinib.

Pharmacokinetics

At dose of 300 mg to 500 mg once daily, systemic exposure was close to dose proportional in patients with MF. Steady-state was achieved by 15 days, with a median accumulation ratio of 3- to 4-fold following fedratinib once daily dosing in patients with MF.

At the dose of 400 mg once daily, the geometric mean (coefficient of variation, %CV) fedratinib steady state C_{max} is 1804 ng/mL (49%), C_{avg} of 1214 ng/mL, and AUC_{tau} is 26870 ng.hr/mL (43%) in patients with MF.

Absorption
The median T_{max} at steady-state was 3 hours (range 2 to 4 hours) following 400 mg once daily oral dosing of fedratinib in patients with MF.

Effect of Food: A low-fat, low-calorie (total 162 calories: 6% from fat, 78% from carbohydrate and 16% from protein) meal or a high-fat, high-calorie (total 815 calories: 52% from fat, 33% from carbohydrate and 15% from protein) meal increased area under the curve over time to infinity ($AUC_{0\text{-}inf}$) up to 22%-24% and C_{max} up to 12%-14% of a single 500 mg dose of fedratinib.

Distribution
Fedratinib was bound by 92% or greater to human plasma proteins *in vitro*. The human blood-to-plasma concentration ratio was 0.62 to 0.75. The geometric mean apparent volume of distribution (V_d/F) (%CV) of fedratinib at steady-state was 1770 L.

Elimination
Fedratinib exhibited a biphasic disposition, with a rapid decline following by a prolonged elimination phase. The effective half-life was 41 hours, mean terminal elimination half-life (%CV) of fedratinib was 114 hours and the geometric mean (% CV) apparent clearance (CL/F) was 13 L/hr (51%) in patients with MF.

Metabolism: Fedratinib is metabolized by CYP3A4 (up to 77%), CYP2C19 (up to 20%) and flavin monooxygenase 3 (up to 33%) *in vitro*. The major metabolic pathway includes oxidations of the ethyl pyrrolidine moiety of fedratinib. Unchanged fedratinib (80%) was the major circulating component. The main circulating metabolite was 9% of the total AUC and was ~2-fold less active than the parent drug. No metabolite contributed to >10% of total drug exposure.

Excretion: Following a single 200 mg oral dose of ^{14}C-fedratinib in a human mass balance study (% CV), 77% (9%) of the dose was recovered in feces (23% of dose as unchanged drug) and 5% (19%) of the dose was recovered in urine (3% of dose as unchanged drug).

Specific Populations

Age (20-95 years), body weight (40-135 kg), sex, White (399 (88%)) and Asian (44 (10%)) races, mild (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1 to 1.5 x ULN and any AST) to moderate (total bilirubin >1.5 to 3 x ULN, and any AST) hepatic impairment or mild renal impairment (creatinine clearance [CLcr] 60 to <90 mL/min) did not have clinically meaningful effects on the PK of fedratinib. The effect of severe hepatic impairment (total bilirubin > 3 x ULN and any AST) on fedratinib pharmacokinetics is unknown.

Effect of Renal Impairment

Following a single 300 mg dose of INREBIC, the $AUC_{0\text{-}inf}$ of fedratinib increased by 1.5-fold in subjects with moderate renal impairment (CLcr 30 mL/min to 59 mL/min) and 1.9-fold in subjects with severe renal impairment (CLcr 15 mL/min to 29 mL/min) , compared to that in subjects with normal renal function (CLcr ≥90 mL/min). However, safety assessment indicate that the higher incidence of Grade 3 or 4 adverse events in patients with moderate renal impairment were manageable by dose modifications.

Drug Interactions Studies

Effect of Strong and Moderate CYP3A4 Inhibitors on Fedratinib:

Co-administration of ketoconazole (a strong inhibitor of CYP3A4: 200 mg twice-daily for 14 days) with a single dose of INREBIC (300 mg) increased the fedratinib $AUC_{0\text{-}inf}$ by 3.1-fold (90% CI: 2.5, 3.8) and C_{max} by 1.9-fold (90% CI: 1.6, 2.1).

Based on PBPK modeling and simulation, coadministration of ketoconazole (400 mg once daily), with INREBIC 400 mg once daily is predicted to increase fedratinib AUC at steady state by 2-fold. Fedratinib has the potential to inhibit its own metabolism, as multiple doses of fedratinib increased the exposure of CYP3A substrate, midazolam, by 4-fold in patients with cancer.

Based on PBPK modeling and simulation, coadministration of moderate CYP3A4 inhibitors, erythromycin (500 mg three times daily) or diltiazem (120 mg twice daily), with INREBIC 400 mg had once daily is predicted to increase fedratinib AUC at steady state only by 20% and 10%, respectively.

Effect of Dual CYP2C19 and CYP3A4 Inhibitors on Fedratinib:

The effect of concomitant administration with a dual CYP2C19 and CYP3A4 inhibitor on fedratinib pharmacokinetics is not known. No clinical drug interaction studies with dual CYP2C19 and CYP3A4 inhibitor were conducted. Fedratinib has the potential to inhibit its own

metabolism, as multiple doses of fedratinib increased the exposure of CYP2C19 substrate, omeprazole, by 3-fold in patients with cancer.

Effect of Strong and Moderate CYP3A4 Inducers on Fedratinib:
The effect of concomitant administration with a strong or moderate CYP3A4 inducer on fedratinib pharmacokinetics is not known. No clinical drug interaction studies with CYP3A4 inducers were conducted and PBPK model was not sufficient to predict effect of CYP3A4 inducers.

Effect of Fedratinib on CYP3A, CYP2C19, and CYP2D6 Substrates:
Coadministration of a single dose of midazolam (CYP3A substrate: 2 mg), omeprazole (CYP2C19 substrate: 20 mg), and metoprolol (CYP2D6 substrate: 100 mg) increased midazolam, omeprazole, or metoprolol $AUC_{0\text{-}inf}$ by 4-, 3-, and 2-fold, respectively, with multiple doses of fedratinib.

Victim	**AUC_{Inf} Ratio (90% CI)**	**C_{max} Ratio (90% CI)**
20 mg Omeprazole	2.8 (2.3, 3.5)	1.1 (0.8, 1.5)
100 mg Metoprolol	1.8 (1.3, 2.5)	1.6 (1.3, 2.1)
2 mg Midazolam	3.8 (2.6, 5.6)	1.8 (1.5, 2.2)

Effect of Gastric Acid Reducing Agents on Fedratinib:
Co-administration of pantoprazole (a proton pump inhibitor: 40 mg daily for 7 days) with a single dose of INREBIC (500 mg on Day 7) did not alter fedratinib $AUC_{0\text{-}inf}$ (1.2; 90% CI: 1.0, 1.3) and C_{max} (1.1; 90% CI: 1, 1.3).

In Vitro Studies

The Effects of Cytochrome P450 (CYP) and Flavin Monooxygenase enzymes (FMO) on Fedratinib
In vitro studies indicate that fedratinib is mainly metabolized by CYP3A (up to77%), CYP2C19 (up to 20%), and FMO (up to 33%), with minor contributions from CYP2D6, 2C8, 2C9, 2E1 and FMO1 & 5 in vitro. CYP3A4 and FMO3 were the predominant isoforms of CYP3A and FMO for metabolism of fedratinib.

Effect of Fedratinib on CYP Substrates
Fedratinib inhibits CYP2C19, CYP2D6, and CYP3A *in vitro*. Fedratinib does not inhibit CYP1A2, CYP2B6, CYP2C8, and CYP2C9 in vitro.

Effect of Transporters on Fedratinib
Fedratinib is a substrate of P-glycoprotein (P-gp).

Effect of Fedratinib on Transporters
Fedratinib inhibits P-glycoprotein (P-gp), breast cancer resistant protein (BCRP), multidrug and toxin extrusion (MATE) protein 1, MATE-2K, and organic cation transporter (OCT)2, and weakly

inhibits organic anion transporting polypeptide (OATP)1B1, OATP1B3, but does not inhibit organic anion transporter (OAT)1 and OAT3 in vitro.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposes INREBIC dosing regimen of 400 mg orally once daily, with or without food. The proposed INREBIC dosing regimen was evaluated in patients with MF (n=289) in the Phase 3 of Trial EFC12153 (JAKARTA). Following administration of the proposed INREBIC dosing regimen in Trial EFC12153, there was a significant improvement in proportion of patients with ≥35% SVR at end of cycle 6 and confirmed 4 weeks later compared to placebo (37% vs. 1%, p<0.0001). The proposed dosing regimen is also supported by dose- or exposure-response relationships for efficacy and safety (refer to Section 6.3.2).

Food did not affect fedratinib exposure; therefore, INREBIC is recommended to be administered without regards to food.

Therapeutic Individualization

CYP3A4 modulators and acid reducing agents:

- Alternative therapies that are not strong CYP3A4 inhibitors during treatment with INREBIC are recommended. If unavoidable, dose reduction to 200 mg once daily is recommended with concomitant use of strong CYP3A4 inhibitors as modeling and simulations predict a 2-fold increase in fedratinib exposure at steady state with strong CYP3A4 inhibitors. No dose reduction is recommended with moderate CYP3A4 inhibitors, as modeling and simulation predict no significant change in fedratinib exposure at steady state when coadministered with moderate CYP3A4 inhibitors.
- Avoidance of co-administration of strong and moderate CYP3A4 inducers is recommended as the effect of concomitant administration of strong and moderate CYP3A4 inducers on fedratinib exposure are unknown.
- Avoidance of co-administration of dual CYP2C19 and CYP3A4 inhibitors is recommended as the effect of concomitant administration of dual CYP2C19 and CYP3A4 inhibitor on fedratinib exposure is unknown.
- No dose adjustments are recommended with gastric acid reducing agents as fedratinib exposure was not affected by pantoprazole, a proton pump inhibitor.

Renal impairment: Dose reduction to 200 mg once daily is recommended in patients with severe (CLcr 15 to <30 mL/min) renal impairment based on 2-fold increase in exposure in this patient population. No dose adjustment is recommended in patients with mild (CLcr 60 to 89 mL/min) or moderate (CLcr 30 to 59 mL/min) renal impairment based on the assessment of pharmacokinetics and safety. Due to potential for increased exposure, frequent monitoring for

adverse events in patients with moderate renal impairment is recommended and if necessary, dose modifications based on toxicity.

Hepatic impairment: No dose adjustments are recommended for patients with mild (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1 to 1.5 x ULN and any AST) and moderate (total bilirubin >1.5 to 3x ULN and any AST) hepatic impairment as there was no clinically meaningful changes in fedratinib PK and safety assessment in these patient populations compared to patients with normal hepatic function. The PK and safety of fedratinib in patients with severe hepatic impairment (total bilirubin >3 x ULN and any AST) has not been studied.

Outstanding Issues

No outstanding issues other than the requested PMR/PMC studies identified from a clinical pharmacology perspective (refer to Section 6.1).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The ADME and PK parameters listed in Table 18 are from the clinical pharmacology studies in healthy subjects and patients.

Table 18: Summary of General Pharmacology and Pharmacokinetic Characteristics of Fedratinib

Pharmacology	
Mechanism of Action	Fedratinib (molecular weight of 525 as free base): • Inhibits (IC_{50}) Janus Kinase 2 (JAK2) (3 nM for WT & mutant). • Inhibits (IC_{50}) JAK1 (46 nM), JAK3 (96 nM), and TYK2 (171 nM) • Inhibits FLT3 (15 nM).
Active Moieties	Major metabolite, SAR317981, was 9% of total AUC and ~2-fold less active than parent in vitro.
QT Prolongation	Fedratinib inhibited hERG current with an IC_{50} of 18 µM in vitro. Thorough QT study showed no large mean increase in the QTc interval (> 20 ms) with daily dosing of fedratinib 500 mg (1.25 times the recommended dose) for 14 days.
General Information	
Bioanalysis	Fedratinib was measured using validated LC-MS/MS assay methods.
Healthy vs. Patients	Mean T½ after single dose was 42-78 hrs in healthy subjects between 30 to 680 mg. Mean T½ of 114 hrs at steady state in patients with MF. Apparent oral clearance (CL/F) of 13 (51%) L/hr and volume of distribution (%CV) 1770 L at steady state in patients with MF. CL/F of 21-64 L/hr and Vd of 1030-2630 L after single dose of 30 to 680 mg in healthy subjects.

<table>
<tr><td>Drug Exposure at Steady State Following the Therapeutic Dosing Regimen</td><td>The following table provides a summary of PK of fedratinib following once daily dosing in patients with MF:
<table>
<tr><th rowspan="2">PK Parameter</th><th colspan="3">Once Daily dosing*</th></tr>
<tr><th>300 mg (n=10)</th><th>400 mg (n=10)</th><th>500 mg (n=11)</th></tr>
<tr><td>AUC0-tau, ng·h/mL</td><td>22371 (56)</td><td>26870 (43)</td><td>38712 (61)</td></tr>
<tr><td>Cmax, ng/mL</td><td>1534 (66)</td><td>1804 (49)</td><td>2539 (52)</td></tr>
<tr><td>Racc</td><td>3.2</td><td>2.9</td><td>3.9</td></tr>
<tr><td colspan="4">* at C2D1 in Trials ARD11936</td></tr>
</table></td></tr>
<tr><td>Dose Proportionality</td><td>AUC, & Cmax was greater than dose proportional over the range of 30 mg to 800 mg in patients with MF after single and multiple doses.
AUC, & Cmax was dose proportional over the range of 300 mg to 500 mg in patients with MF after single and multiple doses.
<table>
<tr><th rowspan="2">PK Parameter</th><th colspan="3">Once daily dosing</th></tr>
<tr><th>300 mg (n=10)</th><th>400 mg (n=10)</th><th>500 mg (n=11)</th></tr>
<tr><td>AUC0-24hr, ng·h/mL</td><td>7016 (101)</td><td>9133 (33)</td><td>9982 (55)</td></tr>
<tr><td>Cmax, ng/mL</td><td>1065 (91)</td><td>1294 (47)</td><td>1267 (55)</td></tr>
<tr><td>AUC0-tau, ng·h/mL*</td><td>22371 (56)</td><td>26870 (43)</td><td>38712 (61)</td></tr>
<tr><td>Cmax, ng/mL*</td><td>1534 (66)</td><td>1804 (49)</td><td>2539 (52)</td></tr>
<tr><td colspan="4">* at C2D1 in Trials ARD11936</td></tr>
</table></td></tr>
<tr><td>Accumulation</td><td>• The median observed accumulation ratio (Rac) for fedratinib ranged from 3-4 in patients with MF at 300 to 500 mg QD.
• Rac for fedratinib ranged from 2.1 to 5.4 in patients with MF at 30 to 800 mg QD</td></tr>
<tr><td>Variability</td><td>• Following a 400 mg once daily, the between-subject variability (%CV) for fedratinib C_{max} was 49% and AUC_{tau} was 43%.</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Median T_{max}</td><td>3 hours (range: 2 to 4 hours) at 400 mg QD</td></tr>
<tr><td>Food effect [a] (Fed/fasted)</td><td>A low-fat, low-calorie (total 162 calories: 6% from fat, 78% from carbohydrate and 16% from protein) or a high-fat, high-calorie (total 815 calories: 52% from fat, 33% from carbohydrate and 15% from protein) meal increased AUC_{inf} up to 22% or 24% and C_{max} up to 12% or 14% of a single 500 mg dose of fedratinib. High fat meal decreased the incidence of nausea and vomiting.</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Volume of Distribution</td><td>1770 L</td></tr>
<tr><td>Plasma Protein Binding</td><td>92-98%</td></tr>
<tr><td>Blood to Plasma Ratio</td><td>0.6 to 0.75.</td></tr>
<tr><td>As Substrate of Transporters</td><td>• Substrate of P-glycoprotein (P-gp).
• Not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT2), and multidrug and toxin extrusion proteins (MATE1, MATE2K).</td></tr>
<tr><td colspan="2">Elimination</td></tr>
</table>

Terminal Elimination Half-Life	Fedratinib has a biphasic disposition, with an effective half-life of 41 hours, a mean elimination half-life ($t_{1/2}$) of fedratinib of 114 hours, and a mean (%CV) apparent oral clearance (CL/F) of fedratinib 13 L/h (51%) in patients with MF.
Metabolism	
Fraction Metabolized (% dose)	Unchanged fedratinib (80%) was the major circulating component. Major circulating metabolite was 9% of the total AUC and was ~2-fold less active than the parent compound. No metabolite contributed to >10% of total drug exposure.
Primary Metabolic Pathway(s)	Primary metabolic pathways for fedratinib comprised of oxidations of the ethyl pyrrolidine moiety of fedratinib. Metabolized by CYP3A4 (0 to 70%), CYP2C19 (0-20%), and FMO3 (0-33%) in vitro.
Excretion	
Primary Excretion Pathways (% dose) ±SD	6 healthy subjects, 200 mg (~100 uCi) of ^{14}C-fedratinib. Urine & plasma samples collected up to 840 h or earlier. • Feces: 77% ± 7% (23% as unchanged drug) of total dose. • Urine: 5% ± 1% (3% as unchanged drug) of total dose. Recovery 82%
Interaction liability (Drug as Perpetrator)	
Inhibition/Induction of Metabolism	• Modeling and simulation with multiple doses of fedratinib show that fedratinib exposure at steady state increased by 2-fold with strong CYP3A4 inhibitor, and 1.2-fold with a moderate CYP3A4 inhibitor. • Clinical study showed that multiple doses of fedratinib increased exposure of CYP3A substrate by 4-fold, CYP2C19 substrate by 3-fold and CYP2D6 substrate by 2-fold. • Proton pump inhibitor, pantoprazole, with a single dose of fedratinib show that fedratinib exposure increased 1.2 fold. • Induction of CYP3A4 mRNA in vitro, but net result is inhibition of CYP3A4 enzyme activity.
Inhibition/Induction of Transporter Systems	• In vitro data suggests that fedratinib inhibits P-gp, BCRP, MATE1 and MATE2K, OCT2, and OATP1B1 and OATP1B3, but does not inhibit OAT1 and OAT3.

*PK parameters are presented as geometric mean (%CV) or median (minimum, maximum) unless otherwise noted

6.3.2. Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of 400 mg QD for patients with MF is generally supported by the safety and efficacy results from the registration trial EFC12153 (Section 8.4), as well as the dose/exposure-response relationships for efficacy and safety.

Applicant's Dose Selection Rationale
The Applicant's dose selection for the registration trial was based on findings from the dose escalation study (TED12037):

- Clinical activity was observed at a minimum dose of 240 mg once daily in the dose escalation study.

- The fedratinib trough concentrations at steady state (accounting for PK variability) at greater 360 mg once daily were expected to be in the range for 90% inhibition of kinase activity (in vitro IC_{50} of 1 µM).
- Doses up to 680 mg once daily (maximum tolerated dose) were well tolerated in the dose escalation phase in patients with MF.
- At doses of 520 mg once daily or greater, there was increased toxicity, including increase in anemia and transfusion requirements.

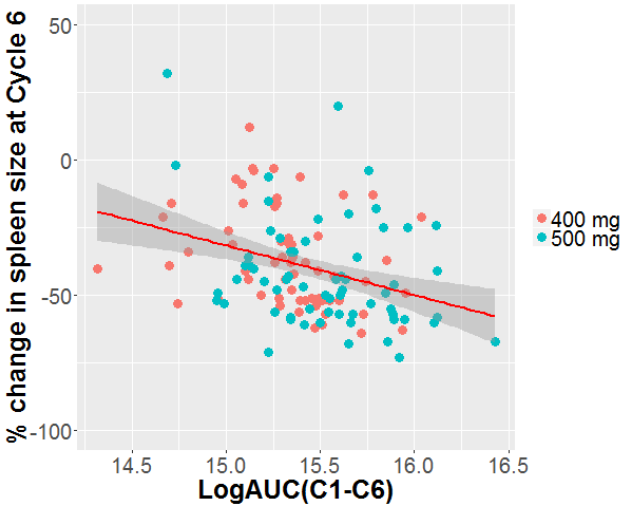
Further, an exploratory phase 2 trial (ARD11936) indicated incidence of ≥35% SVR at end of cycles 3 and 6 to be higher in 400 mg and 500 mg dose groups compared to 300 mg group, and the mean trough concentrations at steady state at 300 mg and above were in range of EC_{50} (915 ng/mL, 29% CV) for inhibition of STAT3 phosphorylation.

Based on the reasons above, the Applicant selected two dose levels, 400 mg and 500 mg QD to be studied in the randomized, placebo-controlled Trial EFC12153.

Dose/Exposure-Response Relationships for Efficacy and Safety

In the randomized, placebo-controlled Trial EFC12153, the proportion of patients who met the primary efficacy endpoint were not appreciably different at 500 mg QD (40%) compared to 400 mg QD (37%). Exposure-response (E-R) analysis for change in spleen volume from baseline at the end of cycle 6 (EOC6) indicates greater spleen volume reduction (SVR) associated with higher fedratinib exposure (cumulative AUC from Cycles 1 to 6) in patients with MF in Trial EFC12153 (Figure 2). However, no substantial benefit in ≥35% SVR is expected at 500 mg versus 400 mg, given the highly overlapping exposure between the two dose groups, caused by higher incidence of dose modifications (51%) due to AEs at the 500 mg dose in Trial EFC12153. The exposure-efficacy response is consistent with dose-response findings.

Figure 2: Linear Regression of Percent Change in Spleen Volume from Baseline at End of Cycle 6 vs $LogAUC_{C1-C6}$ from Trial EFC12153



The red line is the fitting curve from linear regression model, and the grey shaded area represents the 95% confidence band from linear regression.

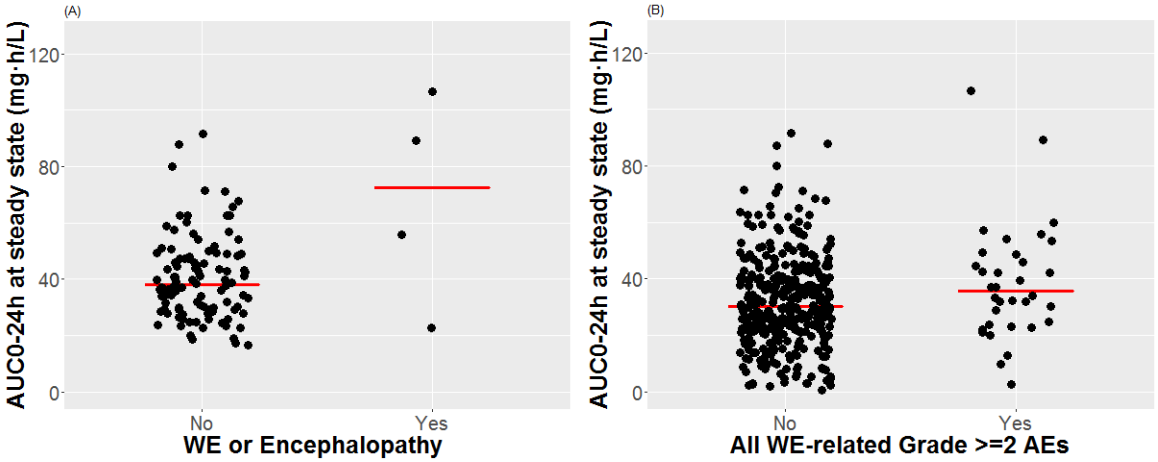
For safety, the incidence of Grade ≥3 anemia and thrombocytopenia, fedratinib dose reductions and discontinuations were lower at 400 mg QD compared to 500 mg QD, and the adverse reactions were mostly managed by dose modifications.

In addition, dose/exposure-safety analysis based on pooled data in patients with MF from 5 clinical trials indicates increase in toxicity with higher doses and increasing exposure (dose ranges from 100 to 600 mg). Significant E-R relationship was identified for safety endpoints, including Grade ≥3 AEs, Grade ≥3 anemia, Grade ≥3 thrombocytopenia, serious AEs, any grade diarrhea/vomiting, and AEs leading to dose discontinuation and reduction. Refer to Appendix 19.5.7.2 and Appendix 19.5.7.4 for details on the E-R analyses on efficacy and safety.

Association between Exposure and Wernicke's encephalopathy

Wernicke's encephalopathy (WE) is a major safety concern for fedratinib. There were 7 confirmed cases of WE. The time to onset of WE ranged from 44 to 529 days post-dose (DNP Consult, DARRTS 4428769) across clinical studies, and all the patients with confirmed WE were dosed with 500 mg. There were 132 patients with at least one AE related to WE, of which 34 were Grade ≥2. There was no clear association between fedratinib exposure ($AUC_{24h,ss}$) and WE or encephalopathy, or Grade ≥2 AEs related to WE (Figure 3). This conclusion should be interpreted with caution as available data is limited and the comparisons are potentially confounded by imbalance in baseline disease factors. In addition, no apparent relationship between fedratinib dose and incidence of all grade WE-related AEs was observed. Refer to Appendix 19.5.7.4 for details of the analyses.

Figure 3: Comparison of Fedratinib Exposure between (A) Patients with and without WE or Encephalopathy on Fedratinib 500 mg QD, and (B) Patients with and without Grade ≥2 AEs Related to WE on Fedratinib Any Dose



Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. A dose reduction to 200 mg once daily is recommended in patients with severe (CLcr 15 to <30 mL/min) renal impairment (RI) based on the results of the dedicated RI study and population PK (popPK) analysis. No dose reduction is recommended in patients with mild RI (CLcr 60 to <90 mL/min) and moderate (creatinine clearance (CLcr) 30 to <60 mL/min) RI based on the results of the dedicated RI study, population PK analysis, and the summary of safety results from patient data in clinical trials.

No dose modification is recommended in patients with mild (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1 to 1.5 x ULN and any AST) and moderate (total bilirubin >1.5 to 3x ULN, and any AST) hepatic impairment (HI) based on the results of the population PK analysis and subgroup safety assessments.

Table 19: Effect of renal (RI) and hepatic (HI) impairment on fedratinib exposure

Organ Function	Dedicated Study		Population PK Analysis	
Ratio (90% CI)	**N**	**$AUC_{0\text{-}inf}$: RI / Normal***	**N**	**CL/F: RI/Normal****
Renal Impairment				
Mild RI	--	--	194	0.9 (0.8, 0.98)
Moderate RI	8	1.5 (0.9, 2.6)	109	0.73 (0.66, 0.80)
Severe RI	7	1.9 (1.2, 2.9)	3	0.63 (0.43, 0.92)
Ratio (90% CI)		**$AUC_{0\text{-}inf}$: HI / Normal***		**CL/F: HI/Normal****
Hepatic Impairment				
Mild HI	8	1.07 (0.74, 1.54)	115	1.01
Moderate HI	-	--	17	1.02

* Matched controls: n=6 for moderate RI, 5 for severe RI, and 8 for mild HI.
**Population PK analysis: n=146 for normal renal function and 320 for hepatic function.

Effect of Renal Impairment

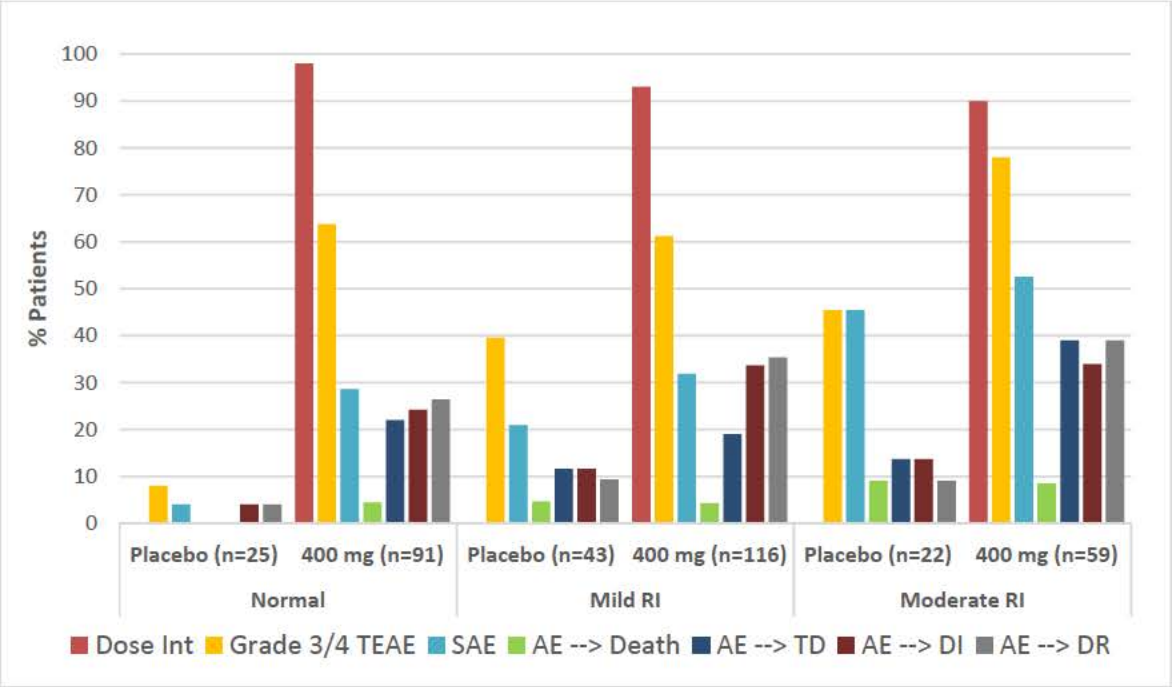
The dedicated RI study showed a 1.5-fold and 2-fold increase in fedratinib $AUC_{0\text{-}Inf}$ in moderate (n=8) and severe (n=7) RI, respectively, compared to their matched control subjects with normal renal function (n=9) (Table 19, and Appendix 19.5.4).

The population PK analysis included mild (n=194), moderate (n=109) and severe (n=3) renal impairment patients. The results indicated that CLcr was a significant covariate. While the trend towards a decrease in total clearance (CL/F) with severity of RI (Table 19, and Appendix 19.5.7.1) were in line with the results of the dedicated RI study, the estimates of the increase in exposure with moderate and severe RI were 14 to 27% lower than observed in the dedicated RI study. Only 3 patients with severe RI were included in the population PK analysis.

The clinical trials allowed enrollment of patients with mild to moderate RI with no dose adjustments. The safety assessment based on pooled data from patients with MF across the clinical trials indicated no clear trends in the incidence of AEs, serious AEs, and dose reductions or interruptions due to AEs in patients with moderate RI treated with 400 mg compared to those treated with placebo, or in patients with mild RI or normal renal function treated at 400

mg (Figure 4, and Appendix 19.5.4). The increase in Grade 3 or 4 AEs in patients with moderate RI at 400 mg can be managed with dose modification strategy for toxicity. Also, the mean relative dose intensities in the mild and moderate renal impairment groups and normal renal function groups at 400 mg once daily were similar (Figure 4).

Figure 4: Safety summary of renal impairment (RI) in the fedratinib and placebo groups from patients with MF in Trials EFC12153, ARD12181, ARD11936, ARD12181, and ARD12888 (All treated population)



Dose Int.= mean relative dose intensity (%), AE= adverse event, SAE=serious AE, AE→TD =treatment discontinuation due to AEs, AE→DI = dose interruption due to AEs, AE→DR = dose reduction due to AEs
Source: Tables IR052019.1.1 and 2.2, Response to IR, 5/20/19

Therefore, while there was a 1.5-fold increase in exposure, no dose adjustment is proposed for moderate RI based on safety assessments. The labeling will recommend frequent monitoring for adverse events in patients with moderate renal impairment and if necessary, dose modifications based on toxicity.

Effect of Hepatic Impairment

Baseline albumin, ALT, AST, liver function classification (normal, mild or moderate) were not statistically significant covariates affecting fedratinib PK based on the results of the population PK analysis (Table 19, and Appendix 19.5.7.1). Fedratinib PK were similar between patients with mild (n=115) and moderate (n=17) hepatic impairment and normal hepatic function (n=320). However, the effect of severe hepatic impairment (total bilirubin >3x ULN and any AST) is unknown, as no patients with severe hepatic impairment were included during clinical development. The safety assessment of clinical data in patients indicated similar relative dose intensity and similar incidence of serious AEs and manageable Grade 3/4 AEs at 400 mg in

patients with moderate HI versus mild HI or normal hepatic function groups at 400 mg (Figure 16, Appendix 19.5.4).

Other Specific Populations

Age (20-95 years), sex, (399 White (88%) and 44 (10%) Asian) races, body weight (39.5 to 135.1 kg), had no clinically meaningful effect on the PK of fedratinib (Appendix 19.5.7.1).

Genetics

The applicant explored the impact of germline variation in genes encoding drug metabolizing enzymes and transporters (DMET) on fedratinib PK in both healthy volunteers (HV) (Study PMH1043) and fedratinib-treated patients (Study PMH0144). Germline DNA samples were genotyped using the Affymetrix DMET Plus Assay. In both studies, 7 genes (CYP3A4, CYP3A5, CYP2D6, CYP2C9, CYP2C19, FMO1 and FMO3) were considered more likely to be involved in the metabolism of fedratinib metabolism and constituted the high priority set.

In Study PMH0143, data from 58 White subjects who had pharmacogenetic (PGx) and PK samples and received at least 100 mg of fedratinib in 8 Phase 1 HV studies were pooled for analysis (ALI13451, BEX12257, FED12258, INT12893, INT12894, POP13449, POP13450, and TDU12620). Of 241 variants examined across 42 DMET genes, 105 variants remained after QC. According to the applicant's analyses, no association ($p>0.05$) between fedratinib AUC or Cmax and any variants or genotype-inferred phenotypes examined was observed.

In Study PMH0144, 86 White patients with myelofibrosis enrolled in the EFC12153 who had PGx and PK samples, and who received fedratinib 400 or 500 mg, were evaluated. Of 238 variants examined across 42 DMET genes, 109 variants remained after QC. Two CYP3A4 variants, (CYP3A4*1B [rs2740574; −392A>G] and CYP3A4*3 [rs4986910; c. 1334T>C; p.M445T]) were associated with PK parameters. Fedratinib AUC was 1.9-fold lower for patients heterozygous for CYP3A4*1B (A/G, n= 5) compared to those homozygous for the wild-type allele (A/A, n= 81); adjusted p-value= 0.019 for log-transformed AUC (logAUC). Conversely, fedratinib AUC was 1.8-fold higher for patients heterozygous for CYP3A4*3 (T/C, n= 2) compared to those homozygous for the wild-type allele (T/T, n= 84 adjusted p-value = 0.046 for logAUC). These results were generally consistent with the pharmacometrics reviewer's exposure-response analyses of EFC12153. See Appendix 19.5.7.3 for details.

*Reviewer's comment: No genotype-guided dosage adjustment appears to be indicated based on these results. Of note, CYP3A4*1B allele frequency varies amongst different racial/ethnic groups (2- 9.6% of Whites, 35–67% of African- Americans, ≥ 0.4 % of East-Asians and >64 % of*

*African populations). CYP3A4*3 is rare (global 0.5%)[3, 4, 5]. The functional impact of these variants on CYP3A4 enzymatic activity and metabolism of fedratinib, along with the relative contribution of CYP3A5, which is more commonly functional in populations descended from Africa, remains inconclusive.*

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. Dose reduction of INREBIC to 200 mg once daily is recommended with strong CYP3A4 inhibitors. No dose reduction of INREBIC is recommended for moderate CYP3A4 inhibitors. The effects of dual CYP2C19 and CYP3A4 inhibitors, and strong and moderate CYP3A4 inducers are not known. Therefore, a description for avoidance of coadministration of dual CYP2C19 and CYP3A4 inhibitors, and strong and moderate CYP3A4 inducers with INREBIC will be included in the labeling.

No dose adjustment is recommended with gastric acid reducing agents.

Monitoring for adverse reactions and adjusting the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates as necessary are recommended when coadministered with INREBIC, as fedratinib increased the exposure of these CYP substrates.

Drug-Drug Interactions

Effects of Other Drugs on Fedratinib

Strong and Moderate CYP3A4 Inhibitors

Drug interaction clinical study indicated that single dose fedratinib $AUC_{0\text{-inf}}$ increases up to 3-fold and C_{max} by 2-fold with a strong CYP3A inhibitor, ketoconazole (Table 20).

Table 20: Effect of strong and moderate CYP3A4 inhibitors on fedratinib exposure

CYPA4 Inhibitors		Fedratinib	Single-Dose	Steady State
			Observed AUC Ratio (90% CI)	
Strong CYP3A4 Inhibitor	200 mg BID Ketoconazole*	300 mg SD	3.06 (2.46, 3.80)*	--
			PBPK Predicted AUC Ratio (90% CI)	
	200 mg BID Ketoconazole	300 mg SD	3.17 (2.91, 3.45)	--

[3] Lamba, J. K., Lin, Y. S., Schuetz, E. G., & Thummel, K. E. (2012). Genetic contribution to variable human CYP3A-mediated metabolism. *Advanced drug delivery reviews*, *64*, 256-269.
[4] Garsa, A. A., McLeod, H. L., & Marsh, S. (2005). CYP3A4 and CYP3A5 genotyping by Pyrosequencing. *BMC medical genetics*, *6*(1), 19.
[5] Database of Single Nucleotide Polymorphisms (dbSNP). Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine. dbSNP accession:{rs4986910}, (dbSNP Build ID: {152}). Available from: http://www.ncbi.nlm.nih.gov/SNP/

	400 mg QD Ketoconazole	400 mg QD	2.88 (2.65, 3.12)	**1.95** (1.82, 2.08)
Moderate CYP3A4 Inhibitors	500 mg TID Erythromycin	400 mg QD	1.85 (1.73, 1.97)	**1.18** (1.15, 1.20)
	120 mg BID Diltiazem	400 mg QD	1.62 (1.55, 1.69)	**1.13** (1.11, 1.14)

*From the dedicated DDI study with single dose (300 mg) of fedratinib
SD=single dose, QD=once daily, BID = twice daily, TID=thrice daily
Source: Table 67 & Table 83

In a pharmacokinetic clinical trial, multiple doses of fedratinib were shown to inhibit CYP3A metabolism (i.e., increased midazolam exposure by 4-fold: Appendix 19.5.3, Table 71,). Since fedratinib has the potential to inhibit its own metabolism, PBPK modeling and simulations were conducted to predict the effects of CYP3A4 inhibitors on fedratinib exposure at steady state. The PBPK model verified the results of the single dose drug interaction study with a strong CYP3A inhibitor, ketoconazole (Table 20). The modeling and simulations predicted a 2-fold increase in fedratinib AUC at steady state when ketoconazole is coadministered with INREBIC 400 mg once daily (Table 20, and Table 83, Appendix 19.5.6,). However, coadministration of moderate CYP3A4 inhibitors with INREBIC 400 mg once daily predicted only a 1.2-fold increase fedratinib AUC at steady state (Table 20, and Table 83, Appendix 19.5.6).

Effect of Strong and Moderate CYP3A4 Inducers

No clinical drug-drug interaction (DDI) study was conducted to ascertain the effects of strong and moderate CYP3A4 inducers. The PBPK model was not reliable to predict the net clinical CYP3A4 (and CYP2C19) activity resulting from the interplay of different time-dependent and counteracting mechanisms by the perpetrators and fedratinib (i.e., induction of CYP3A4 and CYP2C19 by rifampin, and induction of CYP3A4 and inhibition of CYP2C19 and CYP3A4 by fedratinib) (Appendix 19.5.6).

Effect of Dual CYP2C19 and CYP3A4 Inhibitors

No clinical drug-drug interaction (DDI) study was conducted to ascertain the effect of dual CYP2C19 and CYP3A4 inhibitors. The PBPK model was inadequate to assess the effects of such dual inhibitors as the contribution of CYP2C19 to fedratinib metabolism had not been established and there is a potential for auto-inhibition of CYP2C19 by fedratinib (Appendix 19.5.6, and Table 71, Appendix 19.5.3).

Effect of CYP Enzymes In Vitro

In vitro studies indicate the contribution to fedratinib metabolism is primarily from CYP3A (up to 77%), CYP2C19 (up to 20%) and FMO (up to 33%), while CY1A2, 2C8, 2C9, 2D6 has a low contribution (<5%). In vitro, among recombinant CYP3A and FMO isoforms, CYP3A4 and FMO3 were the major contributors for fedratinib metabolism (Appendix 19.5.3).

Effect of Fedratinib

On CYP3A, CYP2C19, and CYP2D6 Substrates:

Drug interaction clinical study indicated that multiple doses of fedratinib with coadministration of a single dose of midazolam (CYP3A substrate: 2 mg), omeprazole (CYP2C19 substrate: 20

mg), and metoprolol (CYP2D6 substrate: 100 mg) increased midazolam, omeprazole, or metoprolol $AUC_{0\text{-}inf}$ by 4-, 3-, and 2-fold, respectively (Table 73, Appendix 19.5.3).

On Transporters: In vitro, fedratinib has the potential to inhibit P-gp (IC_{50} 10 µM) and BCRP (IC_{50} 30 µM), OCT2 (IC_{50} 0.8 µM), MATE-1 (IC_{50} 0.4 µM), and MATE-2K (IC_{50} 0.2 µM). This may translate into clinically relevant inhibition at the dose of 400 mg for P-gp and BCRP (I_{gut}/IC_{50} >11), MATE-1 and MATE-2K ($I_{max,u}/IC_{50}$ >0.02), and OCT2 ($I_{max,u}/IC_{50}$ >0.1), according to the FDA guidance for drug interaction studies (2017) (Table 74, Appendix 19.5.3 for details).

Food-Drug Interactions

No dose adjustment of INREBIC is recommended with food. However, a description that high-fat meal may decrease the incidence of nausea and vomiting will be included in the labeling.

A low-fat, low-calorie (total 162 calories: 6% from fat, 78% from carbohydrate and 16% from protein) meal increased AUC_{inf} up to 22%, and a high-fat, high-calorie (total 815 calories: 52% from fat, 33% from carbohydrate and 15% from protein) meal increased AUC_{inf} up to 24% of a single 500 mg dose of fedratinib (Table 65, Appendix 19.5.2). The increase in fedratinib C_{max} was less than 15% with a high-fat or low-fat meal. However, the incidence of nausea and vomiting was prominently reduced only with a high-fat meal (see Appendix 19.5.2 for details). In the registration trial, INREBIC was administered under fasting conditions (i.e., 1 hour before or 2 hours after a meal).

Does this drug prolong the QT or QTc interval?

No large mean increase in the QTc interval (> 20 ms) was detected with daily dosing of fedratinib 500 mg (1.25 times the recommended dose) for 14 days (DARRTS ID 4423200).

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 21: Overview of Clinical Studies

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
EFC12153 (JAKARTA)	NCT01437787	Phase 3, randomized double blind, placebo controlled, 3 arms study in patients with intermediate-2 or high-risk primary or post-polycythemia vera (post-PCV), post-essential thrombocythemia (post-ET) myelofibrosis (MF)	Arm1 = 500 mg/daily/oral Arm2 = 400 mg/daily/oral Arm3 = Placebo/daily/oral	Primary endpoint was spleen response rate A key secondary endpoint was symptom response rate (RR)	6 months	Total= 289 Arm1 =97 Arm2 = 96 Arm3 = 96	Naïve treatment patients with MF	94 sites in 24 countries
ARD12181 (JAKARTA2)	NCT01523171	Phase 2, open-label, single-arm in patients with intermediate or high-risk primary or post-PCV, post-ET myelofibrosis who are previously treated with ruxolitinib	400 mg/daily/oral with maximum of 600 mg/daily	Primary endpoint was spleen RR (compare to baseline) Key secondary endpoint was symptom RR (compare to baseline)	6 months	Total = 97	Previously exposed to ruxolitinib	42 sites in 10 countries
		Studies to Support Safety						
TED12037	NCT00631462	phase 1 open label, dose escalation study.	30 to 800 mg/day Fedratinib PO	Determine safety and tolerability, DLTs, MTD, and recommended phase 2 doses	Up to 6 consecutive 28-day cycles (168 days) plus follow-up 30 days after last dose	Total = 59	Patients with primary or secondary MF	6 sites in 1 country
TED12015	NCT00724334	Phase 1/2 randomized, open label extension study to TED12037.	Starting doses of 30, 60, 120, 240, 360, 520, 680, and 800 mg/day fedratinib PO	Determine long term effects of continued treatment with fedratinib	Until disease progression	Total = 43	patients with primary or secondary MF who have stable disease, CI, PR, or CR and	6 sites in 1 country

							tolerated 6 cycles of fedratinib.	
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
ARD11936	NCT01420770	Phase 2, randomized, open-label, dose-ranging study of the efficacy and safety of fedratinib in patients with intermediate-2 or high-risk primary or post-PCV, post-ET myelofibrosis with splenomegaly	300, 400, or 500 mg fedratinib orally daily	PK, PD for doses of 300 mg, 400 mg, and 500 mg QD	At least one 28-day cycle; treatment could continue until DP or unacceptable toxicity	Total= 31 300mg=10 400mg=10 500mg=11	Patients with primary or secondary MF	4 sites in 1 country
TED12037	NCT00631462	Phase 1, open-label, dose-escalation study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered tg101348 in patients with primary, post-PCV, or post-ET myelofibrosis	30 to 800 mg fedratinib daily	To determine the MTD 680 mg/day (n=31) was determined to be the MTD	Up to 6 consecutive 28-day cycles	59 total Doses 30 to 800 mg	Previously exposed to ruxolitinib	6 sites in 1 country
TED12042	NCT01420783	Phase 2 randomized, open-label, multicenter study with 2 phases: a dose ranging phase and dose expansion phase.	100, 200, 400 (600 mg, ET patients only) fedratinib daily	Evaluate efficacy and safety of fedratinib in patients with PV and ET who were resistant to or could not tolerate hydroxyurea.	up to 8 consecutive 28-day cycles (32 weeks)	81 total	Patients with PV or ET who were resistant or intolerant to hydroxyurea	35 sites in 9 countries
ARD12888	NCT01692366	Phase 2a randomized, open-label, dose ranging study of the efficacy and safety of orally administered fedratinib in Japanese patients with intermediate-2 or high-risk PMF, post-PV MF or post-ET MF with	300, 400, or 500 mg fedratinib daily	Evaluate the safety, tolerability, and PK of fedratinib. Evaluate the effect of fedratinib on MF symptoms.	At least one 28-day cycle.	8 total 300 mg, N=3 400 mg, N=2 500 mg, N=3	Japanese patients with intermediate-2 or high-risk PMF, post-PV MF or post-ET MF with splenomegaly	7 sites in 1 country

		splenomegaly.						
INT12497	NCT01585623	Phase 1 nonrandomized, open-label, multicenter drug interaction study with 2 segments with segment 1 a single sequence and segment 2 of open label treatment with fedratinib.	500 mg/day fedratinib PO	Assess the effect of 15-day repeated doses of 500 mg fedratinib on CYP activity and safety.	Until disease progression, unacceptable toxicity, or withdrawal of consent.	Total 16	Patients with confirmed advanced solid tumor malignancy	3 sites in 1 country
TES13519	NCT01836705	Phase 1 nonrandomized, prospective, single blind, placebo-controlled, multicenter study.	500 mg fedratinib PO Placebo capsule PO	Assess the effect of fedratinib (500 mg) administered as 14-day repeated doses on the QTcF interval compared to 1-day placebo	7-10 weeks (including screening)	Total 60	Patients with advanced solid tumors	10 sites in 2 countries

7.2. **Review Strategy**

In support of the proposed indication, the Applicant submitted one phase 3 pivotal trial Study EFC12153 (JAKARTA), comparing two doses (400 mg, 500 mg) of fedratinib to placebo and one supporting trial Study ARD12181 (JAKARTA-2), which was a phase 2 open label single arm study in patients with myelofibrosis who were previously exposed to ruxolitinib.

To establish the efficacy of fedratinib in patients with primary or secondary myelofibrosis, the JAKARTA and JAKARTA-2 studies will be evaluated. The efficacy results from JAKARTA trial will be focused on the comparison of 400 mg dose and placebo since the proposed dose will not exceed 400 mg daily. The primary endpoint in both trials was the percent of patients who experienced ≥35% reduction of spleen volume by MRI/CT at 24 weeks confirmed four weeks later in JAKARTA trial and at 24 weeks in JAKARTA-2, compared to baseline. The key secondary endpoint in both trials was the percentage of patients with ≥ 50% reduction of total symptoms score based on the modified MFSAF.

The overall safety evaluation will include all patients exposed to fedratinib from 18 clinical trials (A Phase 3 placebo-controlled study, 4 Phase 2 studies, 1 Phase 1/2 extension study, and 12 Phase 1 studies), with focus given to the treatment of subjects

with primary or secondary myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) (i.e., primary myelofibrosis [PMF], PV MF, or post-ET MF; collectively referred to as "MPN-associated MF").

In total, 807 subjects received at least 1 dose of fedratinib in studies that included multiple-dose (614 subjects) or single-dose (193 subjects) regimens. Nine studies in the fedratinib clinical development program used a multiple-dose design (continuous daily dosing) that enrolled subjects with PMF, post-PV MF, post-ET MF, PV, ET, or solid tumors. Nine clinical pharmacology studies that included healthy subjects used a single-dose study design. Seven of the studies did not run to completion due to termination of the clinical development of fedratinib by Sanofi.

The main assessment of fedratinib safety data will be derived from JAKARTA and JAKARTA-2 studies. There were total of 361 patients who received fedratinib either 400 or 500 mg in the JAKARTA and JAKARTA-2 studies. The safety analysis focused on patients entered onto the JAKARTA trial because the randomized nature of this trial provides the opportunity to test whether adverse events observed on the fedratinib arms of this trial can be attributed to fedratinib or not by comparison to the control. The JAKARTA trial included 96 patients who received 400 mg and 97 patients who received 500 mg. Also, included in the safety analysis were 71 patients originally randomized to placebo who were crossed over and rerandomized to receive at least 1 partial dose of fedratinib 400 mg (35 patients) or 500 mg (36 patients).

Supportive safety evaluation will be derived from the JAKARTA-2 trial which includes 97 patients who received fedratinib.

The safety signal of Wernicke's encephalopathy will be evaluated on all patients who received at least one dose of fedratinib throughout the clinical development program. The review will also incorporate the findings from the Division of Neurology Products in response to DHP consult request.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. STUDY EFC12153 (JAKARTA)- Study Description

Study EFC12153 (JAKARTA): 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

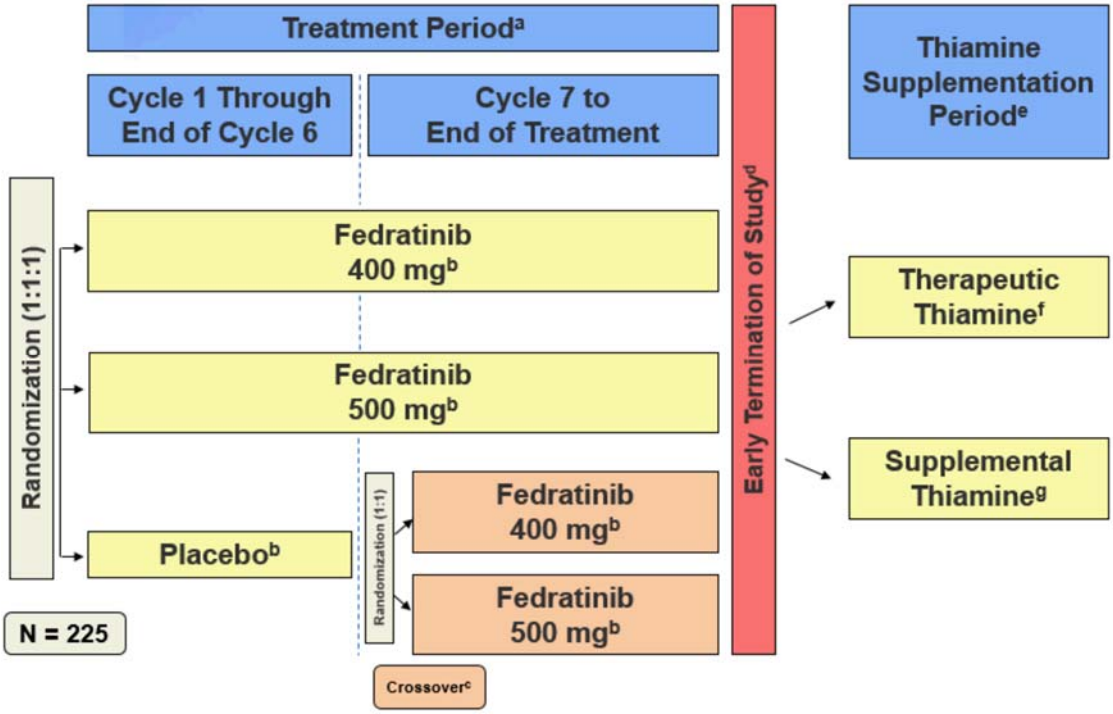
Trial Design

The JAKARTA study was a Phase 3, multicenter, placebo controlled, randomized, 3-arm study of fedratinib in patients with intermediate-2 or high-risk primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), or post-essential thrombocythemia myelofibrosis (post-ET MF) with splenomegaly.

Eligible patients were randomized (1:1:1) in a blinded manner via an Interactive Voice Response System (IVRS) to receive either 400 or 500 mg fedratinib or matching placebo, once daily for at least 6 consecutive 28-day cycles. A total of 289 patients were randomized to the three treatment arms, with 96 patients to 400 mg (Arm 1), 97 patients to 500 mg fedratinib (Arm 2) and 96 patients to the placebo (Arm 3). Patients in the placebo arm were allowed to crossover to receive treatment with either 400 or 500 mg fedratinib. Patients in the 400 and 500 mg treatment arms were continued on the same treatment assigned at the initial randomization. Rerandomization in the placebo arm occurred either when a patient:

- had completed 6 cycles of treatment and had completed the End-of-Cycle 6 imaging assessments, or
- when a patient experienced progressive disease (PD) prior to completing the first 6 cycles of treatment based on ≥ 1 of the protocol-defined criteria for PD.

Figure 5: Study EFC12153 Design (JAKARTA)



a The Treatment Period refers to the date of the first dose of any study drug up to 30 days after the last dose of any study drug. Treatment continued as long as subjects were benefitting and had not experienced progressive disease or relapse or unacceptable toxicity requiring discontinuation of study drug.
b Fedratinib and placebo were administered on a daily basis, in consecutive 28-day cycles.
c Eligible subjects initially randomized to placebo were allowed to cross over to receive fedratinib 400 or 500 mg after a second 1:1 randomization in either of the 2 following scenarios:
1) When a subject had completed 6 cycles of treatment, had completed the End-of-Cycle 6 imaging assessments, and had met the protocol-specified entry eligibility criteria.
2) When a subject had experienced progressive disease prior to completing the first 6 cycles of treatment based on protocol-defined criteria and had met the protocol-specified entry eligibility criteria.
d Sanofi terminated the development of fedratinib on 18 Nov 2013.
e Per Protocol Amendment 4, which was implemented after the clinical hold, all subjects permanently discontinued fedratinib treatment. All subjects, including those previously discontinued from treatment, were given the option to receive thiamine supplementation for at least 90 days and were followed for safety for 90 ± 3 days after initiation of thiamine supplementation.
f All subjects with neuropsychiatric or cardiac symptoms consistent with thiamine deficiency were to begin immediate treatment with thiamine at therapeutic dosages in accordance with institutional practice.
g Subjects without symptoms or signs of thiamine deficiency started thiamine daily supplementation.
Source: NDA submission Module 5.3.5, Study 121351 CSR, P35.

The fedratinib clinical development program, including JAKARTA, was placed on full clinical hold on November 15, 2013 due to reports of several cases consistent with events of Wernicke's encephalopathy (WE) and heart failure. Consequently, Sanofi terminated the development of fedratinib on November 18, 2013. All patients worldwide were permanently discontinued from fedratinib treatment, and all patients were given the option to receive thiamine supplementation for at least 90 days and were followed for safety for 90 ± 3 days after initiation of thiamine supplementation. This period was referred to as the "Thiamine Supplementation Period."

Main eligibility Criteria:

1. Adult patients 18 years of age or older who have a diagnosis of PMF or post-PV MF or post-ET MF, according to the 2008 World Health Organization (WHO) and International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria (Cervantes, 2009)
2. Myelofibrosis classified as high-risk or intermediate-risk level 2, as defined by modified IWG-MRT criteria (according to Cervantes, 2009 at screening)
3. Enlarged spleen, palpable at least 5 cm below costal margin
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0, 1, or 2 at study entry
5. Subjects have the following laboratory values within 14 days prior to initiation the study:
    a. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
    b. Platelet count ≥ 50 x 10^9/L
    c. Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
    d. Serum amylase and lipase ≤ 1.5 x ULN
6. Subjects should not have active (acute or chronic) hepatitis A, B, or C, or hepatitis B and C carriers
7. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) < 2.5 X ULN
8. Total bilirubin (TBL) should be < 3.0 x ULN.
9. Subjects should not have splenectomy.
10. Subjects should not have uncontrolled congestive heart failure (New York Heart Association Classification) 3 or 4.

Study Endpoints

Primary Efficacy Endpoint:
The primary efficacy endpoint was spleen response rate defined as the proportion of subjects with ≥ 35% spleen volume reduction (SVR) from baseline at the End of Cycle 6 (EOC6) with confirmatory MRI/CT 4 weeks later. The Independent Review Committee (IRC) reviewed the MRI/CT images in a blinded manner.

The secondary efficacy endpoints:

- Symptom response rate (SRR), defined as the proportion of subjects with ≥ 50% reduction in the total symptoms score (TSS) from baseline to the End of Cycle 6. Baseline TSS was the TSS value the week before randomization 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 MFSAF
- Overall survival (OS): Defined as the time interval from the date of randomization 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 randomization to the date of the first investigator-assessed disease progression or the date of death due to any cause, whichever occurred first. In the absence of PD or death, PFS was censored at the date of the last valid assessment performed.
- Spleen response rate (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.
- 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.

Dose Modification for Toxicity:
Based on Protocol amendment 2, if subjects experienced drug toxicity as specified below, the dosing was interrupted, or the dose may have been reduced by 100 mg/day during the study, depending upon investigator judgement. Dosing was interrupted for the following events:

- For Grade 4 thrombocytopenia (platelet count < 25×10^9/L) or neutropenia (ANC < 0.5×10^9/L), dosing may have been held for up to 28 days and reinitiated if values returned to ≤ Grade 2, according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03, as follows:
  - Platelet count: ≥ 50×10^9/L
  - ANC: ≥ 1.0×10^9/L
- Grade ≥ 3 ALT, AST, or TBL elevation.
- Grade 3 or higher nausea, vomiting, diarrhea, constipation, or fatigue that did not respond to therapeutic or supportive measures within 48 hours. In such cases, dosing may have been held for up to 14 days and reinitiated if the toxicity resolved to Grade 1.
- Any Grade ≥ 3 nonhematologic/gastrointestinal toxicity or Grade ≥ 2 peripheral neuropathy. In such cases, dosing may have been held for up to 14 days and reinitiated if the toxicity resolved to Grade 1.

If a subject had an LFT abnormality, the following dose and monitoring modifications were performed:

- Study treatment was interrupted, and subjects had at least weekly monitoring of liver function tests until the AE returned to Grade ≤ 1. Subjects could resume treatment after elevated LFTs returned to Grade ≤ 1. If treatment was resumed, all subjects with the above-mentioned elevations had their dose reduced by 1 dose level. The monitoring of AST, ALT, and bilirubin (total and direct) was performed every 2 weeks for at least the 3 subsequent treatment cycles.
- If study drug was interrupted for > 14 days (i.e., the AE had not returned to

Grade ≤ 1), the subject was withdrawn from study treatment.
- No dose re-escalation was permitted after dose reduction due to Grade ≥ 3 ALT, AST, or TBL elevation.
- If the Grade ≥ 3 elevations described above occurred again (second episode) despite dose reduction, the subject was withdrawn from study treatment.
- Any subject who had Grade 4 ALT, AST, or TBL elevations in the absence of other demonstrable cause (nontreatment related) was withdrawn from study treatment.

Statistical Analysis Plan

In order to maintain 5% alpha level of the primary analyses, 2.5% alpha was allocated to the comparison of each of the fedratinib 400 mg and the fedratinib 500 mg dose groups with the placebo control.

The sample size calculations for JAKARTA for the different endpoints are as follows:

Response Rate (Primary endpoint)
Assuming the RR is 30% in either fedratinib group and 5% in the placebo group, 63 patients per group would provide 90% power at a 2-sided 2.5% alpha level. Assuming 15% drop out rate, the RR will be 26% in either IMP group and 4.3% in the placebo group in the intent-to-treat (ITT) population. Thus 75 patients per study arm (total 225 patients) were planned to be randomized.

Overall survival (Secondary endpoint)
Assuming an exponential OS and a median in the placebo group of 30 months, 84 pair-wise deaths (i.e., 84 deaths between the placebo arm and the 400 mg and 84 deaths between the placebo and 500 mg IMP arms) will provide 80% power to detect a hazard ratio (HR) of 0.5. The primary OS analysis was timed to occur after a total of approximately 126 deaths.

Progression Free Survival (Secondary endpoint)
Assuming an exponential PFS and a median of 25 months in the placebo group, then the number of events observed with the same study duration will provide >95% power for PFS to detect a HR of 0.4.

Study duration (final overall survival and progression free survival analyses)
The planned study duration is a total of 55 months (4.6 years) based on the power for OS. Assuming the accrual will require 9 months (25 patients per month), a 55-month study duration provides an average follow up of 50.5 months (assuming 9.0 months accrual can provide 4.5 months follow up in average).

Multiplicity Considerations
Bonferroni adjustment is used to test the primary hypothesis to compare the RR of each dose group to placebo at a 2-sided 2.5% alpha level. The following fixed sequence

procedure is planned for the other secondary endpoints following testing of RR.

1. Spleen response rate (RR)
2. Symptom response rate (RR)
3. Overall Survival (OS)
4. Progression Free Survival (PFS)
5. Spleen Response Rate of ≥ 25% SVR (RR25) RR25

Each of the secondary endpoints will be tested in the two dose groups of fedratinib 400 mg and 500 mg groups at a 2-sided 2.5% alpha level. The timing of the PFS analysis will be the same as that of the primary OS.

Efficacy Assessment: Efficacy assessments included spleen volume, spleen size, myelofibrosis-associated symptoms using the modified MFSAF, investigator assessment of response using the modified IWG-MRT criteria, HRQOL and utility using the EQ-5D questionnaire, MPN-associated symptoms using the MPN-SAF, and hospitalizations.

Spleen volume: Spleen volume was measured by MRI/CT at the screening visit, on Cycle 4 Day 1, at the End of Cycle 6, at the beginning of every 6 cycles thereafter (e.g., Cycle 12, 18, etc.) for up to 2 years, and at the End of Treatment.

Spleen size: Palpation was used to assess spleen size (variable for post-hoc analysis) at baseline (i.e., screening), on Day 1 of each cycle, at the End of Cycle 6, at the End-of-treatment visit, and at the 30-day Follow-up visit.

Myelofibrosis-associated Symptoms (Modified MFSAF): The modified MFSAF included 6 key MF-associated symptoms: night sweats, itching (pruritus), abdominal discomfort, filling up quickly when you eat (early satiety), pain under ribs on left side, and bone or muscle pain. The modified MFSAF was assessed via an e-diary. The symptoms were recorded daily for 1 week prior to Day 1 of each treatment cycle up to Cycle 6 and during the week prior to the End of Cycle 6. The TSS for any visit was the average of the daily total symptom scores for 7 days prior to dosing at baseline and during the last week of each cycle. The daily TSS was calculated as the sum of the score of each of the 6 MF-associated symptoms measured. 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).

Investigator Assessment of Response: The investigator assessment of response included determination of CR, PR, clinical improvement, SD, PD, and relapse based on the modified IWG-MRT response criteria.

The death proportion was calculated based on the number of patients who died during the study period (on study, within 30 days of last dose, occurring >30 days after last

dose).

Safety Analysis:
Safety population consisted of all randomized patients who received at least one dose (even if partial) of the study drug.

Safety Assessment:
The observation periods for the evaluation of safety were as follows:

- The pretreatment period was defined as the time between the date of informed consent and the start of any study drug.
- The on-treatment period was the period from the date of the first dose of any study drug up to 30 days after the last dose of any study drug. For subjects in the placebo arm who crossed over, the on-treatment period was the period from the date of first dose until the crossover date (i.e., date of first fedratinib administration) - 1.
- The post crossover on-treatment period was the period from the date of first dose of study drug after crossover up to 30 days after the last dose of any study drug.
- The posttreatment period was defined as the period starting from 31 days after the last dose of any study drug (after the on-treatment period or the post crossover on-treatment period) until the end of the follow-up period.
- The on-study period was defined as the time from first intake of study drug until the end of the study (defined as the last protocol-planned visit or the resolution/stabilization of all SAEs and AEs with prespecified monitoring).

Protocol Amendments

Amendment 1 (Dated July 26, 2011): The secondary endpoint of symptoms reduction rate was changed from 40% to 50% from baseline to the End of Cycle 6 in the TSS. Alert was added regarding the use of strong inhibitors of CYP2C1917 with fedratinib. Also, additional ECG assessment was added to the schedule.

Amendment 2 (dated February 17, 2012): The subject inclusion criteria for patients who may have been at risk for liver function test (LFT) abnormalities was updated. More frequent monitoring of LFTs during the first 3 cycles of treatment and in case of severe liver enzyme elevations was added.

Amendment 3 (dated November 20, 2012): Added central pathology review of bone marrow biopsy samples and the definition of the Bone Marrow Fibrosis Population. Added guidance regarding dose reduction in case of Grade 3 or 4 AEs and transfusion dependency.

Amendment 4 (dated November 27, 2013): After reviews of 7 cases consistent with events of WE in subjects treated with fedratinib, Sanofi terminated the development of fedratinib (including trials in myelofibrosis, PV, ET, and solid tumors). All subjects were permanently discontinued from fedratinib treatment, and the following changes were made to the study design:

- Initiation of thiamine supplementation (therapeutic thiamine in subjects with signs or symptoms of thiamine deficiency and supplemental thiamine in subjects without signs or symptoms of thiamine deficiency)
- Initiation of appropriate alternative therapy after a wash-out period of at least 2 weeks following the last dose of fedratinib
- Addition of Follow-up visits for subjects who had previously discontinued fedratinib
- Subject participation in the study was considered complete after the last thiamine supplementation Follow-up visit (90 ± 3 days initiation of thiamine supplementation) and the resolution or stabilization of all serious adverse events and adverse events of special interest.
- Added a DSMB to review data across the program

Reviewer's Comments: *Due to the termination of the trial, there was insufficient follow-up data on the patients for the estimation of OS. The trial failed to show a statistically significant difference in OS thereby precluding the testing of all other secondary endpoints beyond OS in the hierarchical testing.*

8.1.2. JAKARTA STUDY RESULTS

Compliance with Good Clinical Practices

The applicant stated investigator meetings and training sessions for clinical research associates (CRAs) as well as individual site initiation meetings to develop a common understanding of the clinical study protocol, case report form, and study procedures, in compliance with GCP were conducted.

During Study EFC12153, significant GCP noncompliance was observed and addressed at 2 study sites (348003 in Hungary and 826001 in the United Kingdom [UK]). The deviations did not lead to exclusion of subjects from the Intent-to-treat (ITT) Population, as it was considered that none would affect the interpretation of the results.

Site 826001 (4 subjects randomized)/UK: Subject (b) (6) was screened and registered in the Interactive Voice Response System (IVRS), but informed consent was not obtained due to a miscommunication between site staff. Since the subject was a screen failure, no specific study procedures were conducted, and only very limited baseline demographic data were included in the database.

Site 348003 (3 subjects randomized)/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. Noncompliance included protocol deviations, the quality of source documents, late serious adverse event reporting, inappropriate study drug storage, issues with ICF completion, and lack of investigator involvement. The subjects were transferred to another site, and the case was notified to the local ethics committee, the local health authority, and the United States (US) Food and Drug Administration (FDA). A directed site inspection conducted by the local health authority confirmed the notified significant GCP noncompliance.

Otherwise, there were no notable departures regarding compliance with applicable international GCP standards.

Financial Disclosure

A FDA Financial Disclosure Form 3454 dated December 14, 2018 and signed by Jennifer Dudinak of Impact Biomedicine Inc., was submitted on behalf of all the investigators and subinvestigator of the clinical trial sites.

The applicant stated that despite due diligent effort to obtain financial disclosure from all Principal Investigator (PIs) and Sub-investigators (SIs) there were 1 PI and 40 SIs are missing financial disclosure. The key studies supporting the efficacy claim had the following missing financial disclosure forms:

- JAKARTA (EFC12153): missing FDFs for 1 PI and 8 SIs (1.6%); (9 FDFs missing out of 550 total)
- JAKARTA2 (ARD12181): missing FDFs for 0 PIs and 7 SIs (2.5%); (7 FDFs missing out of 278 total)

According to the applicant, an efficacy analysis comparing the efficacy where no financial disclosure forms available versus on those where financial forms available showed no influence on the outcome.

Data Quality and Integrity

The submitted data are of sufficient quality and integrity.

Patient Disposition (JAKARTA Study)

The first patient was screened on December 22, 2011. Patient randomization occurred from January 10, 2012 to September 24, 2012. The last patient last visit date (primary clinical cut-off) for this trial occurred on June 25, 2014.

From the total of 351 patients screened, 289 patients were randomized (62 patients were screen failure). There were 96 patients randomized to 400 mg, 97 patients to 500 mg and 96 patients randomized to placebo. All randomized patients except one patient in the placebo group received the study drug. A total of 71 patients (11 patients prior to complete 6 cycles) randomized to the placebo were rerandomized to 400 mg (N= 35) or 500 mg (N= 36) groups.

Study Populations
The ITT population included 289 randomized patients. The All Treated Population included 288 randomized patients who received at least one dose of the study drug. One patient on the placebo arm was randomized but died before receiving treatment.

The Symptom Analysis Population included a total of 259 patients, 81 patients on the placebo arm, 89 patients on the 400 mg arm, and 89 patients on the 500 mg arm. A total of 30 (10.4%) patients were excluded from the Symptom Analysis Population, 15 (placebo), 7 (400mg), and 8 (500mg). The reasons for exclusion were a missing baseline TSS (11.5%, 5.2%, and 6.2%) and a baseline TSS of 0 (4.2%, 2.1%, and 2.1%).

Table 22: Different Analysis Populations in JAKARTA Study

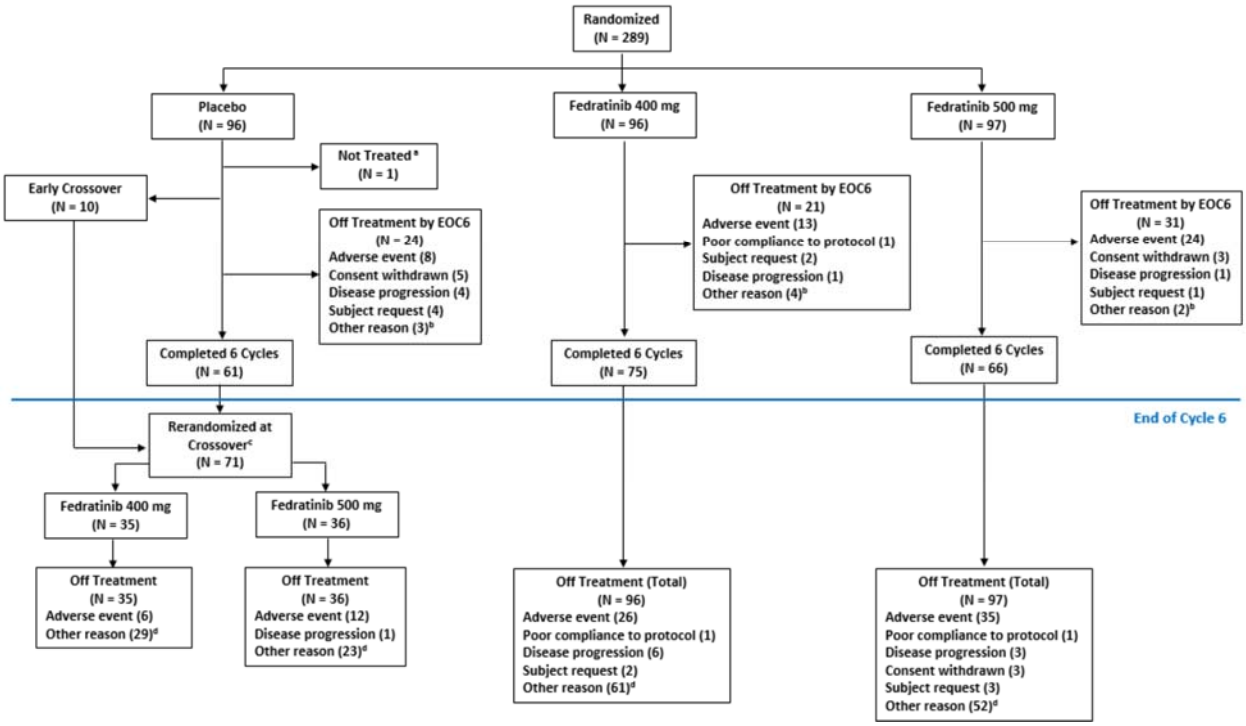
Population	Fedratinib 400 mg N	Fedratinib 500 mg N	Placebo N	Total N
All randomized (ITT)	96	97	96	289
Safety Population: All Treated Patients	96	97	95	288
Symptom Analysis Population	89	89	81	259
Follow-up Population	71	70	63	204

Source: ASDL.XPT dataset

Reviewer's Comments:
The primary efficacy analysis is based on the ITT patient population. The symptom analysis population is used for the evaluation of the TSS endpoint.

On November 18, 2013 at the time of study termination, 144 patients were still receiving fedratinib (51/96 patients randomized to 400 mg, 45/97 patients randomized to 500 mg, 26 patients who crossed over from placebo to 400 mg, and 22 patients who crossed over from placebo to 500 mg). The last fedratinib administration for this study was on December 02, 2013, and the last subject's last visit was on June 25, 2014, which includes all available information on the 90-day Thiamine Supplementation Period. All treated patients in the trial had a median treatment duration of 425.5 days.

Figure 6: Overall Patients Disposition During the Entire Treatment Duration (ITT Population)



[a] One subject randomized to placebo died before receiving treatment.

[b] The most common reason for "other reasons" were consent withdrawal followed by patient's refusal to receive treatment

[c] Includes subjects with early crossover and subjects rerandomized after completion of Cycle 6. Three subjects received placebo past Cycle 6 due to rerandomization deviations at the site level.

[d] The most common "other reason" for permanent discontinuation after the EOC6 was study termination by Sanofi

Source: Table 14.1.2.2.

Table 23: Reasons for Permanent Treatment Discontinuation (All Treated Population)

	Fedratinib 400 mg N=96 n (%)	**Fedratinib 500 mg N=97 n (%)**	**Placebo N=96 n (%)**
Permanently Discontinued Treatment up to 6 Cycles	**21 (22)**	**31 (31)**	**24 (25)**
Adverse events	13 (14)	24 (25)	8 (8)
Disease Progression	1 (1)	1 (1)	4 (4)
Consent withdrawn	0 (0)	3 (3)	5 (5)
Poor compliance	1 (1)	0 (0)	0 (0)
Patient request	2 (2)	1 (1)	4 (4)
Others	4 (4)	2 (2)	3 (3)

Permanently Discontinued Treatment up to 3 Cycles	**10 (10)**	**22 (22)**	**20 (21)**

Source: Table 14.1.2.5

Reviewer comments: The rate of patients who permanently discontinued treatment prior to cycle 6 in the 400 mg group (22%) was lower than in the 500 mg group (31%) or the placebo group (25%). Permanent discontinuation due to adverse events was reported in 14%, 25%, and 8% of patients in the 400, 500 mg and placebo groups, respectively. Approximately, half of patients in the 400 mg group discontinued treatment in the first 3 cycles. The majority of permanent discontinuations among the 500 mg and placebo groups occurred in the first 3 cycles.

The frequency of fedratinib-treated subjects who permanently discontinued during the entire treatment duration due to AEs was lower in the 400 mg arm (27%) than in the 500 mg arm (36%).

Protocol Violations/Deviations

Protocol deviations were defined as any individual fact or finding that constituted a lack of compliance to the clinical trial protocol, applicable standard operating procedures, GCP, or applicable regulatory requirements. However, important deviations were defined as those that constituted conditions, practices, or processes that might harm/violate the rights, safety or wellbeing of subjects, or the quality and integrity of data.

A summary of important protocol deviations in Table 24 below.

Table 24: Important Protocol Deviations (ITT Population)

	Fedratinib 400 mg N=96 n (%)	Fedratinib 500 mg N=97 n (%)	Placebo N=96 n (%)
Any Important Protocol Deviations	11 (12)	18 (19)	13 (14)
Rerandomization issue – subject not rerandomized due to error at site level	6 (6)	5 (5)	3 (3)
Treatment number dispensed not equal to treatment number allocated	0 (00	6 (6)	2 (2)
Prior history of chronic liver disease	1 (1)	2 (2)	1 (1)
Further anticancer therapy before and during treatment period	0 (0)	1 (1)	1 (1)
Serum amylase or lipase > 1.5 x ULN	3 (3.1)	1 (1)	4 (4)
ANC < 1.0 x 10^9/L	1 (1)	0 (0)	2 (2)

Serum creatinine > 1.5 x ULN	1 (1)	0 (0)	1 (1)
AST or ALT ≥ 2.5 x ULN	0 (0)	2 (2)	0 (0)
Direct bilirubin > 2.0 x ULN	1 (1)	0 (0)	0 (0)
Subject diagnosis was not MF	0 (0)	1 (1)	0 (0)

A subject could have had more than 1 important protocol deviation

Sources: Table 14.1.3.1 and Table 14.1.3.2

Reviewer comments: Important deviations occurred in approximately 15 % of the overall population with similar frequency in the 400 mg and placebo arms. More than half of the violations that occurred in the 400 mg group were related to rerandomization issues which occurred after Cycle 6, therefore, we do not think that the deviations have significant impact on the interpretation of the study results.

Table of Demographic Characteristics (JAKARTA Study)

Table 25 summarizes the demographics of the ITT population.

Table 25: Baseline Demographics, JAKARTA Study (ITT population)

Demographic Parameters	Fedratinib		Placebo (N= 96) n (%)
	400 mg (N= 96) n (%)	500 mg (N= 97) n (%)	
Sex			
Male	54 (56)	61 (63)	55 (57)
Female	42 (44)	36 (37)	41 (43)
Age			
Mean years (SD)	62.9 (9.6)	64.7 (9.2)	64.9 (9.5)
Median (years)	63	65	66
Min, max (years)	39, 86	39, 80	27, 85
Age Group			
≤ 65 years	61 (63.5)	49 (50.5)	44 (45.8)
> 65 years	35 (36.5)	48 (49.5)	52 (54.2)
≤ 75 years	86 (89.6)	87 (89.7)	90 (93.8)
> 75 years	10 (10.4)	10 (10.3)	6 (6.3)
Race			
White	86 (89.6)	81 (83.5)	90 (93.8)
Black or African American	1 (1)	2 (2.1)	1(1)
Asian	8 (8.3)	14 (14.4)	5 (5.2)
Other	1 (1)	0 (0)	0 (0)
Region			
United States	9 (9)	8 (9)	6 (6)
Rest of the World	87 (81)	88 (81)	90 (94)
Canada	5 (5)	0 (0)	3 (3)
Europe	62 (65)	67 (69)	72 (75)
Asia	8 (8)	13 (14)	3 (3)
South America	0 (0)	1 (1)	3 (3)
Australia	12 (13)	7 (7)	9 (10)

Source: Table 14.1.4.1

Reviewer comments: More male than female patients enrolled in the trial. The groups in the trial were balanced for age, sex and race. However, there was a higher percentage of patients in age group of 65 years or less in the 400 mg group (64%) compared to that in the 500 mg group (51%) or placebo group (46%). There was not enough representation of Black/African American race probably due to the lower proportion of patient enrollment in the US.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline disease characteristics based on key prognostic factors for primary or secondary myelofibrosis (e.g., ECOG PS, risk status, constitutional symptoms, spleen volume, and spleen size) are summarized in Table 26.

Table 26: Baseline Disease Characteristics- JAKARTA Study (ITT Population)

Demographic Parameters	Fedratinib		Placebo (N= 96) n (%)
	400 mg (N= 96) n (%)	500 mg (N= 97) n (%)	
Type of Myelofibrosis			
Primary MF	62 (65)	63 (65)	58 (60)
Post-PV MF	24 (25)	25 (26)	27 (28)
Post-ET MF	10 (10)	9 (9)	11 (12)
Time Since Diagnosis of MF (months)			
Mean (SD)	68.5 (73.5)	38.7 (46.4)	54.2 (69.0)
Median	43	22	28
Min, max	0.8, 310	0.5, 232	0.2, 412
Risk Status			
Intermediate-2	57 (59)	47 (49)	46 (48)
High Risk	50 (41)	50 (51)	50 (52)
JAK2 Mutational Profile			
Wild Type	30 (31)	20 (21)	32 (33)
Mutant	62 (65)	72 (74)	59 (62)
Missing	4 (4)	5 (5)	5 (5)
Fibrosis Grade			
0	1 (1)	3 (3)	3 (3)
1	7 (7)	11 (11)	2 (2)
2	36 (38)	34 (35)	40 (42)
3	49 (51)	45 (46)	47 (49)
Missing	3 (3)	4 (4)	4 (4)
Constitutional Symptoms[A]			
Yes	73 (76)	70 (72)	70 (73)
No	23 (24)	27 (28)	26 (27)
ECOG PS Score			
0	41 (43)	31 (32)	31 (32)
1	47 (49)	55 (57)	56 (58)
2	8 (8)	11 (11)	8 (8)
Missing	0 (0)	0 (0)	1 (1)

RBC Transfusion Dependence Status[B]			
Yes	8 (8)	5 (5)	6 (6)
No	88 (92)	92 (95)	90 (94)
Total Symptom Score[c], n	91	91	85
Mean (SD)	17.5 (13.5)	16.9 (12.5)	14.7 (11.9)
Median	15.2	16.0	12.4
Min, max	0, 57	0, 47.6	0, 52.7
Baseline Spleen Volume (mL), n	94	92	91
Mean (SD)	2755 (1353)	2524 (1342)	2927 (1483)
Median	2652	2366	2660
Min, max	316, 6430	388, 8244	662, 7911
Spleen Size > 10 cm			
Yes	68 (71)	65 (67)	71 (74)
No	28 (29)	32 (33)	25 (26)
Prior Hydroxyurea			
Yes	69 (72)	59 (61)	54 (56)
No	27 (28)	38 (39)	42 (44)

[A] 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.
[B] Transfusion dependence was defined as receiving ≥ 2 units/month of RBC transfusions over 3 months per
[C] 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

Source: Table 14.1.4.2, Table 14.1.4.8, Table 14.1.4.9, and Table 14.1.4.10

Note: Grading of bone marrow fibrosis was based on the European Consensus. The scale of grading is 0 to 3 as follows:

- 0: Scattered linear reticulin with no intersections corresponding to normal bone marrow
- 1: Loose network of reticulin with many intersections, especially in perivascular areas
- 2: Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
- 3: Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

Reviewer comments: Overall, baseline disease characteristics appear to be balanced among the treatment groups except for time since diagnosis and prior treatment with hydroxyurea. The median time since diagnosis was longer in patients randomized to 400 mg (43 months) compared to 500 mg (22 months) or placebo (28 months). A lower percentage of patients in the 400 mg arm had high-risk status (41%) compared with the placebo and 500 mg arms (52%). The median baseline TSS was slightly lower in the placebo arm (12) compared with the 400 and 500 mg arms (15 and 16, respectively). The

percentage of patients with prior treatment with hydroxyurea was higher in patients who received 400 mg (72%) compared to those who received 500 mg (61%) or placebo (56%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was assessed at the beginning of each treatment cycle by counting all returned study drug bottles and study drug capsules from the previous cycle. Subjects were considered compliant with the protocol-defined dosing regimen if they took ≥ 80% of the intended dose as instructed by the investigator while receiving treatment.

Treatment compliance is summarized in Table 27 below.

Table 27: Treatment Compliance –Subjects treatment (All Treated Population)

	Fedratinib 400 mg N = 96 n/N1 (%)	Fedratinib 500 mg N = 97 n/N1 (%)	Placebo N = 95 n/N1 (%)
Cycles 1 to 6	96/96 (100)	87/97 (90)	94/95 (99)
After Cycle 6	74/75 (99)	63/66 (96)	3/3 (100)
Entire Treatment Duration	96/96 (100)	93/97 (96)	94/95 (99)

N1= the number of subjects assessed.
Source: Table 14.3.1.1.7

Reviewer comments: Treatment compliance was similar among the arms with almost all patients compliant. Also, compliance to treatment during the entire treatment duration was similar between the fedratinib treatment arms.

Efficacy Results – Primary Endpoint

The proportion of patients who have a ≥35% reduction in volume of spleen at the end of Cycle 6 confirmed with a scan 4 weeks after the end of Cycle 6 is presented in Table 28. Only one patient on the placebo arm achieved response while 36.5% and 40.2% of the patients on the fedratinib 400mg and 500mg treatment arms achieved a response. The chi-square test comparing the difference in proportions between the two treatment arms and placebo yielded statistically significant results ($p<0.0001$).

Table 28: Confirmed Spleen Response Rate (≥ 35% SVR) at the EOC6 (ITT Population)

	Fedratinib		**Placebo**
	400 mg	500 mg	(N= 96)

	(N= 96) n (%)	(N= 97) n (%)	n (%)
n (%)	35 (36.5)	39 (40.2)	1 (1)
95 % CI	(26.8, 46.1)	(30.4, 50.0)	(0, 3.1)
Difference	35.42	39.16	
P-value	< 0.0001	< 0.0001	
97.5% CI of difference	(24.2, 46.7)	(27.8, 50.6)	

Source: ADSL.XPT, ADEFF.XPT, ADTTE.XPT datasets.

Reviewers Comments: *As per the SAP the 95% CI reported used the Normal Approximation. The corresponding 95% CI using the exact method are 36% (95% CI:27, 47), 40% (95% CI:30, 51) and 1% (95% CI:0, 6) in the 400mg, 500 mg and placebo groups, respectively.*

Efficacy Results – Secondary and other relevant endpoints

Symptom RR (SRR) was defined as the proportion of subjects with ≥ 50% reduction in the TSS from baseline to the End of Cycle 6. The modified MFSAF was used to capture the symptom burden and had six 6 items of the MFSAF: night sweats, pruritus (itching), abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. Responses ranged from 0 (absent) to 10 (worst imaginable), lower scores suggesting lower symptom burden as compared to higher scores. Reductions in TSS from baseline suggest an improvement in symptom burden. Patients with a TSS score of zero at baseline were excluded from the analysis.

Patients with at least 5 assessments available within the week before the next cycle were considered evaluable at that visit. At baseline, 89.5% (85/96) of patients in the placebo arm, 94.8% (91/96) of patients in the 400 mg arm, and 93.8% (91/97) of patients in the 500 mg arm had evaluable data. Four patients on placebo, and two patients each on 400 mg and 500 mg arm had a TSS score of zero at baseline and hence excluded from the Symptom Analysis Population. At the End of Cycle 6, the evaluable patients on placebo, 400 mg and 500mg arms were 91.8% (56/61), 94.9% (75/79), and 89.9% (62/69), respectively.

At the End of Cycle 6, the symptom RR (≥ 50% reduction in TSS) for the Symptom Analysis Population was 8.6% in the placebo arm, 40.4% in the 400 mg arm, and 34.8% in the 500 mg arm (Table 29). Both active treatment arms showed a statistically significant difference compared with placebo ($p < 0.0001$ for each comparison). This statistical comparison controlled for multiplicity using the step-down testing procedure. At baseline, the mean Total Symptom Score was 15.45 in the placebo group, 17.95 in the 400mg group and 17.36 in the 500 mg group.

The proportion of patients 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% in the placebo arm, 39.6% in the 400 mg arm, and 34.1% in the 500 mg arm. At baseline, the mean TSS was 14.72 in the placebo group, 17.56 in the 400mg group and 16.98 in the 500 mg group. The results of SSR in the ITT population are consistent with the results from the Symptom Analysis Population and are presented in Table 30.

Table 29: Symptom Response Rate (≥ 50% Reduction in Total Symptom Score) at the EOC6 – Patients in the Symptom Analysis Population

	Fedratinib		**Placebo** (N= 81) n (%)
	400 mg (N= 89) n (%)	500 mg (N= 89) n (%)	
n (%)	36 (40.4)	31 (34.8)	7 (8.6)
95 % CI	(30.3, 50.6)	(24.9, 44.7)	(2.5, 14.8)
Difference	31.81	26.19	
P-value	< 0.0001	< 0.0001	
97.5% CI of difference	(18.2, 45.4)	(12.9, 39.5)	

Source:ADSL.XPT, ADEFF.XPT, ADTTE.XPT datasets.

Table 30: Symptom Response Rate (≥ 50% Reduction in Total Symptom Score) at the EOC6 – Patients in the ITT Population with Non-missing Baseline Total Symptom Score

	Fedratinib		**Placebo** (N= 85) n (%)
	400 mg (N= 91) n (%)	500 mg (N= 91) n (%)	
n (%)	36 (39.6)	31 (34.1)	7 (8.2)
95 % CI	(29.5, 49.6)	(24.3, 43.8)	(2.4, 14.1)
Difference	31.33	25.83	
97.5% CI of difference	(18.0, 44.6)	(12.8, 38.8)	

Source: ADSL.XPT, ADEFF.XPT, ADTTE.XPT datasets.

The change in TSS scores from baseline at Week 24 are summarized in the Table 32 below.

As described in Section 3.2, all studies of fedratinib were placed on Full Clinical Hold

due to safety concerns of Wernicke's encephalopathy (WE) and congestive heart failure on November 15, 2013. There was insufficient follow-up time for conducting the OS and PFS analysis.

Reviewers comment: *There were 19 (20%) patients who had both a SVR and a TSS response on the 400 mg treatment arm. The proportion of patients having responses on both endpoints was 20% (19/97) on the 500mg arm.*

Dose/Dose Response

In the JAKARTA study, patients received either 400 mg or 500 mg fedratinib or placebo. The results showed a slight increase in spleen response rate at the end of Cycle 6, as assessed by spleen volume reduction of ≥35%, in patients who received 500 mg (40%) over those who received 400 mg (37%). However, given the increased toxicity in general which was associated with 500 mg over 400 mg and the incidence of WE in patients who received 500 mg the applicant only pursued the 400 mg dosing.

The applicant conducted exposure response modeling to better assess the relationship between dose, exposure, and treatment effect of fedratinib at the selected doses from 300 mg to 500 mg used in clinical studies. The exposure response analyses evaluated the relationships between PK exposure and efficacy. The exposure response analyses indicated greater spleen volume reduction associated with higher fedratinib exposure (cumulative AUC from Cycles 1 to 6) in patients with MF in JAKARTA study (Section 6.3.2). However, no substantial benefit in ≥35% spleen volume reduction is expected at 500 mg versus 400 mg, given the highly overlapping exposure between the two dose groups, caused by higher incidence of dose modifications (decreases) due to adverse events at the 500 mg dose in the JAKARTA study. The exposure-efficacy findings are consistent with dose-response findings.

Durability of Response

The duration of spleen response was calculated for patients who had an IRC-assessed spleen response (i.e., having ≥ 35% SVR) confirmed with a scan four weeks later. The duration of spleen response was calculated 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. Kaplan-Meier analysis was used to estimate duration of spleen response. Patients without subsequent IRC-assessed PD or death were censored at the last assessment date. The duration of response among the patients with a SVR response is summarized in Table 31 below.

Table 31: Duration of SVR Response in JAKARTA (All Responders)

	Fedratinib		Placebo
	400 mg (N= 35)	500 mg (N= 39)	(N= 1)
Death, n (%)	4 (11%)	5 (13%)	0
Ongoing, n (%)	30 (89%)	34 (87%)	1 (100%)
Median (95% CI) Months	18.20 (NE)	19.68 (NE)	NE
Responders with <6 months of response	3 (9%)	2 (5%)	0
Responders with ≥6 months of response	32 (91%)	37 (95%)	1 (100%)
Responders with ≥12 months of response	17 (49%)	21 (54%_	1 (100%)
Responders with ≥18 months of response	1 (3%)	1 (3%)	0

Source: ADSL.XPT, ADTTE.XPT datasets. NE=Not Estimable

Persistence of Effect

Assessment of long term effects of fedratinib was limited due to early termination of both studies JAKARTA (median duration of exposure was 62 weeks (range, 1 to 91.9 weeks) for the 400 mg arm) and JAKARTA-2 (median duration of exposure was 24 weeks (range, 0.7 to 79.4 weeks)). The median duration of spleen response in JAKARTA study based on Kaplan-Meier estimates was 18.2 months in the 400 mg arm with 11% of responders in the 400 mg arm died or progressed.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The symptom response rate, a PRO endpoint, was analyzed as part of the hierarchical testing procedure. This section provides additional details of the other PRO endpoints.

Total Symptom Score (TSS)

Change From Baseline TSS

Symptom scores, including the TSS, were measured with the modified MFSAF. The percentage change in total symptom scores from baseline up to 6 cycles are summarized for the Symptom Analysis Population in Table 32. The scores at baseline and at the end of cycle 6 for the individual items are summarized in Table 33 and Table 34. The scores at baseline and at the end of cycle 6 for the individual items are summarized in Table 33 and Table 34. Only patients with a non-zero baseline score are considered in the change from baseline analysis. The proportion of patients having a greater than 50% reduction in the symptom scores is plotted in Figure 7. The change from baseline for the six individual symptoms constituting the TSS are summarized in Table 34.

Table 32: TSS Scores in Symptom Analysis Population

TSS	Fedratinib		Placebo
	400 mg n mean (SD)	500 mg n mean (SD)	n mean (SD)
Baseline	89 17.95 (13.41)	89 17.36 (11.82)	81 15.45 (11.77)
End of Cycle 6	71 10.71 (9.38)	57 8.42 (7.60)	49 13.74 (10.28)
Change from Baseline at End of Cycle 6	71 19.17 (385.61)	57 -38.17 (64.77)	49 15.59 (75.09)

Source: Tables 14.2.12.5.1 and 14.2.12.4 from the CSR.

Table 33: Individual Symptom Scores in Symptom Analysis Population

	Fedratinib		
	400 mg	500 mg	Placebo
Night Sweats			
Zero at Baseline (n)	17	17	22
Baseline Non-Zero Scores n/mean (SD)/Median	72 3.8 (2.85) 2.9	72 3.9 (2.8) 3.3	59 3.5 (2.83) 2.6
Cycle 6 Scores n/mean (SD)/Median	59 1.5 (1.95) 0.4	46 0.6 (1.21) 0	34 2.8 (2.84) 1.8
Cycle 6, >50% reduction from baseline n (%)*	42 (58.3)	41 (56.9)	13 (22)
Itching			
Zero at Baseline (n)	22	28	27
Baseline Non-Zero Scores n/mean (SD)/Median	67 3.1 (2.73) 2.3	61 2.9 (2.45) 2.1	54 3 (2.31) 2.4
Cycle 6 Scores n/mean (SD)/Median	53 2 (1.96) 1.4	36 1.4 (1.5) 1.1	30 2.1 (2.3) 1.4
Cycle 6, >50% reduction from baseline n (%)*	26 (38.8)	19 (31.1)	11 (20.4)
Abdominal Discomfort			
Zero at Baseline (n)	8	9	10
Baseline Non-Zero Scores n/mean (SD)/Median	81 3.5 (2.49) 2.9	80 3.5 (2.51) 3	71 3.2 (2.35) 2.9
Cycle 6 Scores n/mean (SD)/Median	65 2.1 (1.89) 1.6	49 1.9 (1.62) 2	43 3.1 (2.37) 2.9

Cycle 6, >50% reduction from baseline n (%)*	33 (40.7)	27 (33.8)	11 (15.5)
Filling up quickly when you eat			
Zero at Baseline (n)	14	14	14
Baseline Non-Zero Scores n/mean (SD)/Median	75 4.2 (2.24) 4	75 4 (2.49) 4	67 4 (2.29) 3.9
Cycle 6 Scores n/mean (SD)/Median	60 1.8 (1.78) 1.3	47 1.7 (1.68) 2	41 3.2 (2.16) 3.1
Cycle 6, >50% reduction from baseline n (%)*	38 (50.7)	29 (38.7)	12 (17.9)
Pain under ribs on the left side			
Zero at Baseline (n)	20	17	26
Baseline Non-Zero Scores n/mean (SD)/Median	69 3.4 (2.66) 2.8	72 3.1 (2.35) 2.5	55 3.1 (2.4) 2.4
Cycle 6 Scores n/mean (SD)/Median	54 1.7 (1.77) 1.4	47 1.4 (1.48) 1	30 2.7 (2.42) 2.5
Cycle 6, >50% reduction from baseline n (%)*	29 (42)	26 (36.1)	13 (23.6)
Bone or muscle pain			
Zero at Baseline (n)	16	16	15
Baseline Non-Zero Scores n/mean (SD)/Median	73 4 (2.69) 3.4	73 3.8 (2.75) 3.3	66 3.3 (2.42) 3.1
Cycle 6 Scores n/mean (SD)/Median	59 3.2 (2.46) 2.7	45 2.7 (2.35) 2.3	40 3.3 (2.71) 2.6
Cycle 6, >50% reduction from baseline n (%)*	24 (32.9)	17 (23.3)	9 (13.6)

*Source: ADQS.XPT, ADSL.XPT datasets, Reviewer Generated. *percentage based on patients with non-zero baseline scores.*

Table 34: Percent Change from Baseline in Individual Symptom Scores in Symptom Analysis Population

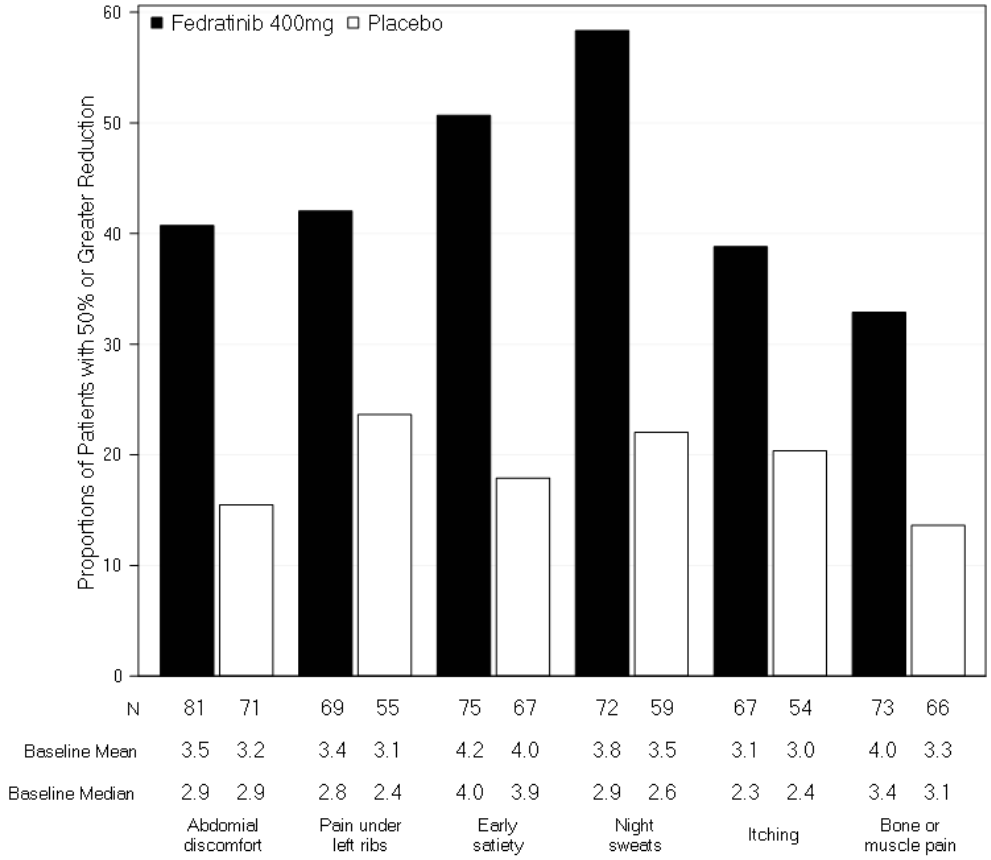
	Fedratinib		**Placebo**
	400 mg **n** **mean (SD)**	**500 mg** **n** **mean (SD)**	**n** **mean (SD)**
Night Sweats			
End of Cycle 6	59 -20.53 (249.442)	46 -81.12 (32.449)	34 50.34 (253.764)
Itching			
End of Cycle 6	53 36.31 (298.097)	36 -17.10 (124.414)	30 -18.96 (85.048)
Abdominal Discomfort			

End of Cycle 6	65 -14.37 (154.407)	49 -35.07 (79.903)	43 102.80 (338.829)
Filling up quickly when you eat			
End of Cycle 6	60 -47.08 (73.397)	47 -35.86 (159.610)	41 27.09 (147.255)
Pain under ribs on the left side			
End of Cycle 6	54 -27.42 (121.671)	47 -43.06 (70.099)	30 38.05 (278.005)
Bone or muscle pain			
End of Cycle 6	59 90.92 (537.145)	45 -6.89 (138.330)	40 67.68 (224.354)

Source: Table 14.2.12.4 from the CSR.

Reviewers comment: *Except for itching and bone/muscle pain there was a reduction in scores for the other individual questions for patients on the 400mg dose group. Patients on 500mg dose group had a reduction scores for all of the individual questions while patients on the placebo group did not have any score reductions on any of the individual questions at the end of Cycle 6.*

Figure 7: Proportion of Patients Achieving 50% or Greater Reduction in Individual Symptom Scores at the End of Cycle 6 with Non-Zero Baseline Scores



Source: USPI

Additional Analyses Conducted on the JAKARTA Trial

Subgroup analysis of the SVR by age, race, gender and baseline platelet counts is presented in Table 35. These are exploratory analyses with no adjustment for multiplicity. Limited inference can be drawn for patients on the placebo group given that there was only a single patient with a response.

Table 35: Subgroup Analyses of SVR by Age, Race, Gender and Baseline Platelet Count

Subgroup	Fedratinib 400 MG n/N % (95%CI)[a]	Fedratinib 500 MG n/N % (95%CI)[a]	PLACEBO n/N % (95%CI)[a]

All Randomized	35/96 36 (27, 47)	39/97 40 (30, 51)	1/96 1 (0, 6)
Age Category			
Age<=65	24/61 39 (27, 53)	17/49 35 (22, 50)	0/44 0 (0, 8)
Age>65	11/35 31 (17, 49)	22/48 46 (31, 61)	1/52 2 (0, 10)
Race[b]			
White	31/86 36 (26, 47)	32/81 40 (29, 51)	1/90 1 (0, 6)
Asian	3/8 38 (9, 76)	7/14 50 (23, 77)	0/5 0 (0, 52)
Gender			
Female	20/42 48 (32, 64)	13/36 36 (21, 54)	0/41 0 (0, 9)
Male	15/54 28 (16, 42)	26/61 43 (30, 56)	1/55 2 (0, 10)
Baseline Platelet Count			
<50 10^9/L	0/1 0 (0, 98)	0/1 0 (0, 98)	NA
50 10^9/L - 100 10^9/L	3/13 23 (5, 54)	5/14 36 (13, 65)	0/18 0 (0, 19)
≥100 10^9/L	32/82 39 (28, 50)	34/82 41 (31, 53)	1/77 1 (0, 7)

Source: ADSL.XPT and ADTTE. XPT datasets. [a]Exact 95% confidence intervals are reported; Black and Other race category not presented because it included only four and one patient respectively.

8.1.3 Study ARD12181 (JAKARTA-2)

Study Title: A Phase II, Multicenter, Open-Label, Single-Arm Study of SAR302503 In

Subjects Previously Treated with Ruxolitinib and with a Current Diagnosis of Intermediate-2 or High-Risk Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

Trial Design

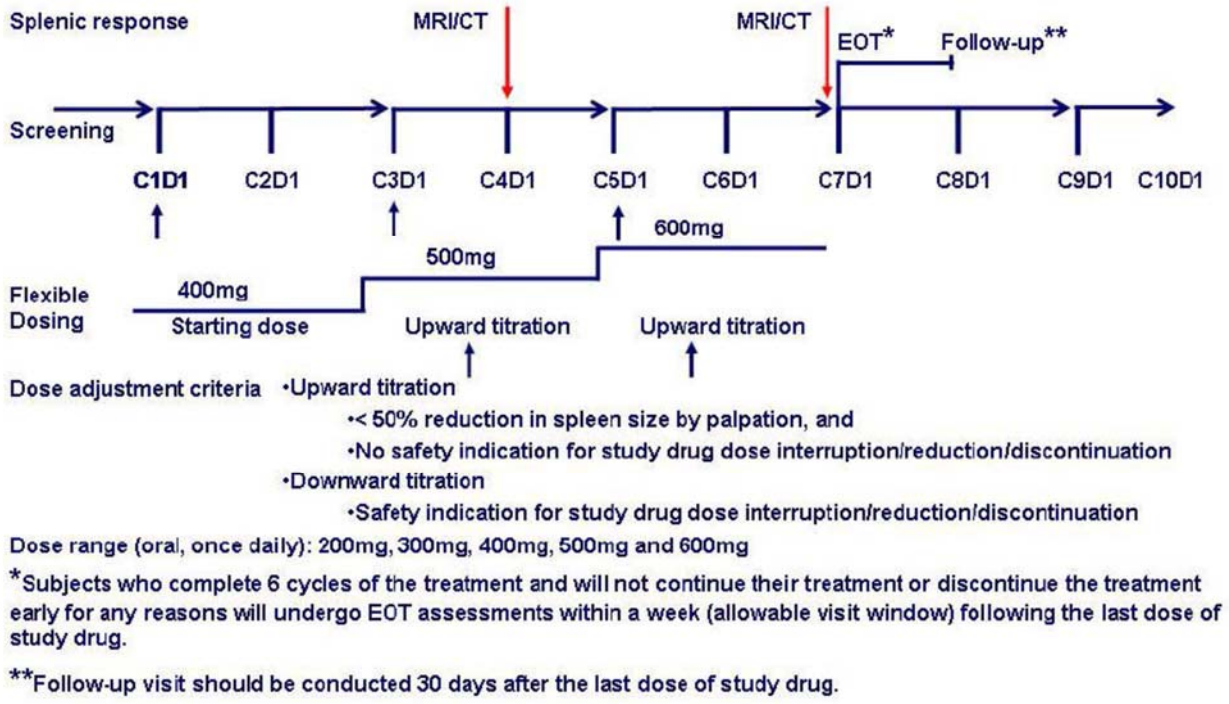
The study was a Phase 2, single arm, open-label, multicenter study of fedratinib in patients with intermediate-1 with symptoms, intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF who had been previously exposed to ruxolitinib for at least 14 days prior to enrollment.

The study was conducted by Sanofi. The study consisted of a screening period (1- to 28 days), followed by at least six 28-day cycles of treatment and a follow-up Visit was performed approximately 30 days following the last dose of fedratinib.

Eligible patients received 400 mg/day of fedratinib orally on Day 1 of Cycle 1. If there was lack of adequate splenic response (≥ 50% spleen size reduction by palpation compared to baseline) and there was no unacceptable drug toxicity the study drug dose was upward titrated in 100 mg/day increment up to maximum of 600mg/day only after the end of Cycles 2 and 4 within the first 6 cycles of the treatment. If there was toxicity, the study drug dose was downward titrated in 100mg/day decrements to a minimum of 200 mg/day. Patients who did not tolerate 200 mg dose must discontinue after 2 cycles at 200 mg.

Sanofi terminated the development of fedratinib on November 18, 2013. All subjects, including those previously discontinued from treatment, were given the option to receive thiamine supplementation for at least 90 days, and were followed for safety for 90 ± 3 days after initiation of thiamine supplementation.

Figure 8: Study Design ARD12181 (JAKARTA2)



Main eligibility Criteria:

Inclusion Criteria:

1. Adult patients with diagnosis of PMF or post-PV MF or post-ET MF, according to the 2008 World Health Organization (WHO) and IWG-MRT criteria
2. Subjects who previously received ruxolitinib treatment for PMF or post-PV MF or post-ET MF or PV or ET for ≥ 14 days (exposure of < 14 days is allowed for subjects who discontinued ruxolitinib due to intolerability or allergy) and discontinued the treatment for ≥ 14 days prior to the first dose of fedratinib.
3. Myelofibrosis classified as intermediate-2 or high-risk Dynamic International Prognostic Scoring System (DIPSS).
4. Spleen ≥ 5 cm below costal margin as measured by palpation.

Exclusion Criteria:

1. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of > 2 before the first dose of fedratinib at Cycle 1 Day 1.
2. The following laboratory values within 14 days prior to the initiation of fedratinib:
    a. Absolute neutrophil count (ANC) < 1.0 x 10^9/L
    b. Platelet count < 50 x 10^9/L
    c. Serum creatinine > 1.5 x upper limit of normal (ULN)
    d. Serum amylase and lipase > 1.5 x ULN
3. Subjects with known active (acute or chronic) hepatitis A, B, or C; and hepatitis B

and C carriers.
4. Aspartate aminotransferase or ALT ≥ 2.5 x ULN.
5. Total bilirubin:
    a. Excluded if ≥ 3.0 x ULN
    b. Patients with total bilirubin between 1.5 and 3.0 x ULN had to be excluded if the direct bilirubin fraction was ≥ 25% of the total
6. Subjects with prior history of chronic liver disease.
7. Life expectancy < 6 months.
8. Splenectomy.

Study Endpoints

Primary Endpoint: Spleen response rate (RR) defined as the proportion of subjects with a ≥ 35% SVR at end of Cycle 6 as measured by MRI/CT scan relative to baseline. The review of MRI/CT scan was performed by a central imaging laboratory.

Secondary Endpoints:

- Key secondary efficacy endpoint is symptom response rate (SRR), defined as the proportion of subjects with a ≥ 50% reduction in the total symptom score from baseline to the end of Cycle 6 using the modified myelofibrosis symptom assessment form (MFSAF) diary.
- Duration of spleen response as measured by MRI/CT scan: defined as the time from the date of the first response to the date of subsequent PD or death, whichever is earlier.
- Safety and tolerability as assessed by clinical, laboratory, electrocardiogram (ECG), and vital sign events; graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (v4.03)

Dose Modification: Dose Interruption and Dose Reduction for Toxicity
The dose of fedratinib was to be interrupted if patient experienced Grade 4 thrombocytopenia, or Grade 4 neutropenia and dosing could be resumed at 1 dose level lower if values returned to Grade ≤ 2. The dose of fedratinib should be interrupted if patient experienced Grade ≥ 3 ALT, AST or total bilirubin elevation, Grade ≥ 2 peripheral neuropathies, Grade ≥ 3 gastrointestinal toxicity, or fatigue that did not respond to therapeutic or supportive measures within 48 hours and dosing could be resumed at 1 dose level lower if the toxicity resolved to Grade 1. Any subject experiencing Grade 4 ALT, AST, or total bilirubin elevations, in the absence of other demonstrable cause (non-drug related), was to be withdrawn from study treatment.

If a dose was reduced for a given subject and the toxicity resolved for ≥ 1 cycle, the dose level could be re-escalated 1 dose level higher per cycle at the discretion of the investigator up the original dose. However, if a patient experienced a Grade 4 non-hematological toxicity and required dose reduction, subsequent upward dose titration

was not allowed.

Efficacy and Safety Assessments

Efficacy Assessment: Efficacy assessments by MRI/CT scan were performed at the End of Cycle 3 (Day 1 of Cycle 4), End of Cycle 6, and at the end of every 6 cycles thereafter for up to 2 years.

The assessment of symptoms response rate was based on the modified MFSAF questionnaire (Mesa, 2013), which included a TSS for key MF symptoms (night sweats, itching, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain).

Safety Assessment: Clinical safety was evaluated during the entire study based on the incidence of treatment emergent adverse events (TEAEs) and changes in clinical laboratory, peripheral blood smear, ECOG PS, ECG, and vital signs and by physical examinations.

Overall Survival: Overall survival (an exploratory endpoint) was defined as the time interval from the date of first dose to the date of death due to any cause. In the absence of confirmation of death before the analysis cutoff date, OS was to be censored at the last date the subject was known to be alive, or at the study cutoff date, whichever was earlier.

Statistical Analysis Plan:

Analysis population: The study populations were defined as follows:

- Intent-to treat (ITT) Population: all subjects enrolled.
- All Treated (AT): enrolled subjects who took ≥ 1 dose (even if partial) of study medication.
- 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.
- Myelofibrosis Symptom Assessment Form (MFSAF) Analysis Population: treated subjects with an evaluable baseline assessment of modified MFSAF TSS and ≥ 1 postbaseline evaluable assessment.
- Pharmacokinetics (PK) Population: subjects who received ≥ 1 dose of study drug and had evaluable drug concentration data.
- 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.

Protocol amendments:

There were 4 amendments to the original protocol, dated 20 Oct 2011:

1. Amendment #1 (Dated 23 Feb 2012): Added more frequent monitoring of liver function tests during the first 3 cycles of treatment.
2. Amendment #2 (Dated 29 Feb 2012): Provided explicit instructions on dose modifications in case Grade 4 ECG abnormalities were detected, and provided explicit instructions on ECG evaluations
3. Amendment #3 (Dated 28 Nov 2012): Increased the study sample size to 70 subjects and include subjects with intermediate – 1 with symptoms. in an attempt to provide sufficient statistical power (at least 90%) for testing response rate beyond a clinically important threshold: 10% RR; for this other JAK2 treatment-refractory population; in addition, the increased sample size was to allow sufficient evaluations for subgroups.
4. Amendment #4 (Dated 27 Nov 2013): Sanofi terminated the fedratinib development program on 18 Nov 2013. All subjects were permanently discontinued from further fedratinib treatment, and all subjects (including those previously discontinued from the study) were given the option to receive thiamine supplementation for 90 days and were to be followed for safety for the length of the Thiamine Supplementation Period.

Protocol Deviations

A total of 4 patients had important protocol deviations. All deviations were related to not meeting the inclusion 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.

Demographic:

Table 36 below summarizes the baseline demographics in JAKARTA-2 Study.

Table 36: Demographic Characteristics – ITT Population (JAKARTA-2)

Demographic Parameters	**Fedratinib 400 mg N=97 n (%)**
Sex	
Male	53 (55)
Female	44 (45)
Age	
Mean years (SD)	66.5 (8.1)
Median (years)	67
Min, max (years)	38, 83
Age Group	

≤ 65 years	41 (42)
> 65 years	56 (58)
≤ 75 years	84 (87)
> 75 years	13 (13)
Race	
White	92 (95)
Black or African American	1 (1)
Asian	4 (4)

Reviewer comments: The majority of patients were male with median age of 67 years.

Baseline Disease Characteristics
Disease characteristics at baseline are summarized in Table 37 below.

Table 37: Disease Characteristics at Baseline (JAKARTA-2)– ITT Population

Baseline Disease Characteristics	**Fedratinib 400 mg N=97 n (%)**
Type of Myelofibrosis	
Primary MF	53 (55)
Post-PV MF	25 (26)
Post-ET MF	19 (19)
Time Since Diagnosis of MF (years)	
Mean (SD)	6.1 (5.6)
Median	4.1
Min, max	0.3, 24.5
Risk Status	41 (42)
Intermediate 1 with symptoms	16 (16)
Intermediate-2	47 (49)
High Risk	34 (35)
JAK2 Mutational Profile	
Wild Type	29 (30)
Mutant	61 (63)
Missing	
Baseline spleen volume (mL)	**N=94**
Mean (SD)	3095 (1459)
Median	2894
Min, Max	737, 7815
Constitutional Symptoms[A]	
Yes	93 (96)
No	4 (4)

ECOG PS Score	
0	26 (27)
1	45 (46)
2	23 (24)
Missing	3 (3)
RBC Transfusion Dependence Status[B]	
Yes	14 (14)
No	83 (86)

[A] 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.
[B] Receiving ≥ 2 units/month of red blood cell transfusions over 3 months prior to first dose

Reviewer comments: The study population was 55% with primary MF with approximately 45% with intermediate-2 risk. The median time since MF diagnosis was 4 years which was shorter than that of patients in the 400 mg group in JAKARTA Study (5.7 years). The majority of patients had constitutional symptoms at baseline (~ 96%). The mean spleen volume was over 3000 mL.

JAKARTA-2 Study Results
Efficacy Results

The primary efficacy endpoint was the proportion of patients with ≥ 35% spleen volume reduction at end of cycle 6. A total of 30 patients in the ITT population (N=97) had a spleen volume reduction of >35%. The response rate is 30.9% (95% CI: 21.9, 41.1). The median duration of response was not reached for the responding patients.

The proportion of patients with a 50% or more reduction in the TSS at the end of cycle 6 in the MF-SAF analysis population of N=90 patients was 26.7% (95% CI: 17.9,37.0). In the absence of a control arm and the open label single arm design of the trial it is difficult to draw an inference in the interpretation of TSS reduction in PRO.

The Applicant provided the response status to the prior therapy of ruxolitinib in response to an information request sent to the Applicant. Of the 97 patients enrolled in the trial, 26 patients responded to ruxolitinib, 51 patients were non-responders to ruxolitinib and 20 patients had a non-evaluable response to ruxolitinib. Of the 51 patients who were refractory to ruxolitinib, only 42 patients completed 6 cycles of fedratinib therapy. A total of 16 patients had a response in these 42 patients, providing an estimated ORR of 38% (95%CI: 24, 54).

Table 38: Best Overall Spleen Response Rates to Fedratinib and to Prior ruxolitinib*

	Rux Non-Responders N=51	Rux Responders N=26	Non-Evaluable N=20	Overall N=97

Responders	16/51 31% (19,46)	10/26 38% (20, 59)	4/20 20% (6,44)	30/97 31 (22, 41)
Completed 6 cycles of fedratinib	42	23	15	80
ORR	16/42 38% (24,54)	10/23 43% (23,66)	4/15 27% (8,55)	30/80 38% (27,49)

[#] *Fedratinib response is based on reduction in spleen volume (measured by MRI/CT) from baseline (response defined as ≥50% reduction in spleen size per IWG-MRT*

[*] *Prior ruxolitinib response is based on reduction in spleen size (measured by palpation) from baseline (response defined as ≥50% reduction in spleen size per IWG-MRT.*

Source: Reviewer generated. ADSL.XPT, ADEFF.XPT, ADSUB.XPT datasets.

***Reviewer's comment**: The number of patients evaluable for a response (N=42) in the relapsed/refractory (R/R) patient population is small. In addition, the exposure duration to ruxolitinib is short increasing the difficulty in identifying the R/R patients.*

8.1.4 Integrated Review of Effectiveness

There was only one controlled efficacy study (JAKARTA) summitted in this application. Therefore, the Integrated Review of Effectiveness is substantially drawn from that study.

8.1.5 Integrated Assessment of Effectiveness

No integrated assessment for effectiveness was performed since the pivotal trial and supporting trial differed in design.

8.2 Review of Safety

8.2.1 Safety Review Approach

The overall safety evaluation in this application includes the safety data derived from 18 clinical trials encompassing the fedratinib clinical development program. The safety database included 807 subjects who received at least 1 dose of fedratinib including multiple doses (614 subjects) or single-dose (193 subjects) regimens. For labeling purposes, the main source of safety data will be derived from 9 clinical studies (JAKARTA, ARD11936, JAKARTA-2, ARD12042, ARD12888, TED12037, TED12015, INT12497, and TES13519), encompassing studies in 608 patients with primary or secondary myelofibrosis (MF), polycythemia vera (PV), essential thrombocythemia (ET), or solid tumors, who received more than one dose (ranging from 30 mg to 800 mg) of fedratinib as a single agent.

The primary focus of the safety in patients with primary or secondary myelofibrosis will be derived from the phase 3 pivotal randomized study EFC12153 (JAKARTA) and the

supporting phase 2 study ARD12181 (JAKARTA-2).

The safety risk of potential Wernicke encephalopathy will be analyzed using all patients exposed to fedratinib in clinical trials.

8.2.2 Review of the Safety Database

Overall Exposure

The overall safety was assessed in 807 subjects who received at least one dose (single dose or multiple doses) ranging from 30 mg to 800 mg/daily of fedratinib throughout the fedratinib clinical development program (18 clinical studies) including patients with primary or secondary myelofibrosis, polycythemia vera or essential thrombocythemia, and solid tumor. A total 614 subjects received multiple doses regimen and 193 subjects received a single-dose regimen. Nine studies of the fedratinib clinical development program used a multiple-dose design including 459 patients with PMF, post-PV MF, post-ET MF.

Two clinical studies conducted in patients with primary or secondary myelofibrosis (Study EFC12153, and Study ARD12181) are the primary source for the safety data included in this review for the proposed indication of primary or secondary MF, which comprise a total of 361 patients with primary or secondary myelofibrosis, including 71 rerandomized patients initially randomized to placebo arm in JAKARTA study (35 patients in the 400 mg and 36 patients in the 500 mg).

- Study EFC12153 (JAKARTA), a Phase 3 randomized, double-blind, placebo-controlled study in subjects with intermediate-2 or high-risk PMF, post-PV ET, or post-PV MF who were not previously exposed to a JAK2 inhibitor;
- Study ARD12181 (JAKARTA2), a Phase 2, single-arm, open-label study of fedratinib in subjects with intermediate-1 with symptoms, intermediate-2 or high-risk PMF, post-ET or post-PV MF previously exposed to ruxolitinib;

Table 39: Primary Safety in Subjects With Primary or Secondary MF (EFC12153, ARD12181)

Study	Study Description	Placebo N = 95	Fedratinib Dose Group (N)		
			400 mg N = 228	500 mg N = 133	All N = 361
EFC12153 JAKARTA	Phase 3, DB, controlled in newly diagnosed with primary or secondary MF	95	96	97	193
	Rerandomized patients	-	35	36	71
ARD12181 JAKARTA-2	Phase 2, open label, single arm in previously treated with ruxolitinib	-	97	-	97
Total subjects per group in primary Safety		**95**	**228**	**133**	**361**

Source: ISS/SCS Statistical Analysis Plan

Adequacy of the safety database:

The size of the safety database and duration of exposure were sufficient to characterize the safety of fedratinib. However, evaluation of long-term treatment with fedratinib on overall survival was limited, due to early study terminations.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

NDA 212327 was submitted as an electronic Common Technical Document (eCTD) and is organized following the FDA Guidance for Industry. The electronic submission has been verified and confirmed to be virus free using McAfee Security Virus Scan Enterprise Version 8.8.0.

The NDA 212327 submission was of adequate quality to allow for review of the safety data provided to support the application.

Categorization of Adverse Events

Treatment Emergent adverse events (TEAEs) were defined as AEs that developed or worsened in severity compared with baseline during the on-treatment period (or the post-crossover on-treatment period for placebo subjects who crossed over to fedratinib).

The on-treatment period was defined as the period from the date of the first dose of any study drug up to 30 days after the last dose of any study drug. For subjects in the

placebo arm who crossed over, the on-treatment period was the period from the date of first dose until the crossover date (i.e., date of first fedratinib administration). The post-crossover on-treatment period was the period from the date of first dose of study drug after crossover up to 30 days after the last dose of any study drug.

Adverse events were coded using MedDRA Version 20.1. The investigators graded the intensity of the AEs using NCI CTCAE Version 4.03.

Routine Clinical Tests

Clinical laboratory evaluations performed on all patients included hematology, peripheral blood smears, coagulation, biochemistry, complete liver function tests (LFTs), urinalysis, magnesium levels, and pregnancy tests (in women).

Laboratory tests were performed by local laboratories.

8.2.4 Safety Results

Study 12153 (JAKARTA):

Dose Exposure:

The mean time of exposure was 52 weeks for the 400 mg fedratinib group and 46 weeks for the 500 mg fedratinib group compared to 20 weeks for the placebo group. The median duration of exposure for the 400 mg fedratinib group was 62 weeks and 60 weeks for the 500 mg compared to 24 weeks in the placebo group.

At the time of study termination, 79 patients in the 400 mg group, 69 patients in the 500 mg group and 61 patients in the placebo group completed 6 cycles of treatment.

Table 40 summarizes the drug exposure during the study.

Table 40: Exposure by Treatment Group (All Treated Population, JAKARTA Study)

	Fedratinib 400 mg (N=96)	Fedratinib 500 mg (N=97)	Placebo (N=95)
Duration of exposure in weeks[1]			
Mean (SD)	52 (25.8)	46.4 (28.8)	19.8 (7.9)
Median (Min, Max)	62.1 (1, 91.9)	59.7 (0.9, 89)	24 (1.7, 43.7)
Number of Treatment Cycles Completed, n (%)			
Completed 3 Cycles	89 (93)	80 (83)	80 (84)
Completed 6 Cycles	79 (82)	69 (71)	61 (64)
Completed 9 Cycles	68 (71)	59 (59)	1 (1)
Completed 12 Cycles	62 (65)	57 (59)	0 (0)
Completed 15 Cycles	55 (57)	48 (49)	0 (0)
Completed 15 Cycles	29 (30)	24 (25)	0 (0)
Completed >18 Cycles	25 (26)	17 (18)	0 (0)
Actual Dose Intensity (mg/week)[2]			
Mean (SD)	2599 (312)	3012 (589)	3433 (195)
Median (Min, Max)	2765 (1420, 2800)	3254 (672, 3500)	3500 (2357, 3500)
Require 1-level dose reduction, n (%)	44 (46)	44 (45)	6 (6)
Require 2-level dose reduction, n (%)	11 (12)	16 (17)	0 (0)
Dose interruption of ≥ 7 consecutive days, n (%)	22 (23)	42 (43)	5 (5)

(1) Duration of exposure was defined as: last dose date - first dose date regardless of unplanned intermittent discontinuations + 1.
(2) Actual dose intensity is defined as the cumulative dose divided by the duration of exposure in terms of the number of weeks on treatment.

Source: Table 14.3.1.1.1 and Table 14.3.1.1.4

Review comments: The median time of exposure was similar between the 400 mg and the 500 mg groups. Approximately, 82% of patients in the 400 mg fedratinib group received at least 6 cycles and 62% received at least 12 cycles. Half of patients in the 400 mg and 500 mg groups received fedratinib for at least 15 cycles. Only one quarter of patients in the 400 mg and 18% of patients in the 500 mg group received more than 18 cycles.

The percentage of patients who required dose reduction was similar between the 400 mg and 500 mg groups (~45%). Only, 12% of patients in the 400 mg group required two dose reductions. Dose interruption for at least 7 consecutive days occurred at a lower

rate in the 400 mg group compared to the rate in the 500 mg group (23% vs 43%, respectively).

Crossover Safety Population (JAKARTA Study):
The median treatment exposure for patients who crossed over from placebo to fedratinib was similar (44 weeks) for the 400 mg (N=35) and 500 mg arms (N=36). Approximately, 80% of patients in the 400 mg and 67% of patients in the 500 mg arm completed at least 9 cycles.

The frequency of subjects in the Crossover Safety Population with ≥ 1 dose reduction was 74% in the 400 mg arm and 69% in the 500 mg arm. The percentage of patients in the 500 mg arm who had 2 dose reductions or dose interruptions for ≥ 7 days were higher compared with the 400 mg arm (11% versus 3% and 31% versus 11%, respectively).

Treatment Emergent Adverse Events and Adverse Reactions

During the treatment period 99% of fedratinib treated patients and 94% of placebo treated patients reported at least one treatment emergent adverse event (TEAE).

TEAEs that occurred during the entire treatment duration are summarized in Table 41 below.

Table 41: Overall Summary of TEAEs in the Arms for the Entire Treatment Duration (All Treated Population- JAKARTA Study)

	Fedratinib 400 mg N=96 n (%)	Fedratinib 500 mg N=97 n (%)	Placebo* N=95 n (%)
At least one TEAE	96 (100)	95 (98)	89 (94)
At least one Grade 3 or 4 TEAE	68 (71)	76 (78)	29 (31)
TEAE Leading to Death	5 (5)	8 (8.2)	6 (6)
Treatment-emergent Serious AE (SAE)	37 (39)	43 (44)	22 (23)
TEAE Leading to Permanent Treatment Discontinuation	26 (27)	35 (36)	8 (8)
TEAE Leading to Dose Reduction or Dose Interruption	43 (45)	65 (67)	14 (15)

*Placebo treated patients received treatment for maximum of 6 cycles.

Reviewer comments: Overall, the reported serious adverse events and Grade 3 or 4 adverse events were more common among patients in the 500 mg arm compared to the 400 mg arm. Also, the percentages of patients with adverse events leading to drug

discontinuation or dose reduction were higher in the 500 mg arm (36% and 67%) compared to the 400 mg arm (27% and 45%), respectively.

Treatment emergent adverse events that occurred in patients who crossed over from placebo to fedratinib are summarized in Table 42 below.

Table 42: Overall Summary of TEAEs After Crossover (Crossover Safety Population-JAKARTA Study)

	Placebo Crossed Over to	
	Fedratinib 400 mg N = 35 n (%)	Fedratinib 500 mg N = 36 n (%)
TEAE	34 (97)	36 (100)
Grade 3 or 4 TEAE	23 (66)	27 (75)
TEAE Leading to Death	1 (3)	1 (3)
Treatment-emergent SAE	13 (37)	13 (36)
TEAE Leading to Permanent Treatment Discontinuation	6 (17)	12 (33)
TEAE Leading to Dose Reduction or Dose Interruption	13 (37)	22 (61)

Reviewer comments: Grade 3 or 4 adverse events and TEAE leading to discontinuation or dose reduction or dose interruption were more common in patients who received 500 mg compared to 400 mg. However, the rates of TEAE, TEAEs leading to death were comparable between the two arms.

Deaths (JAKARTA Study)

The overall rate of death on study up to 6 cycles was lower in the 400 mg arm (7 (7%)) compared with the placebo and 500 mg arms (12 (13%) and 14 (14%), respectively).

The frequency of death that occurred during the entire treatment duration was higher in the 500 mg arm compared to the 400 mg arm (25% vs 16%, respectively).

Deaths that occurred up to 6 cycles and during the entire treatment duration are summarized in Table 43 below.

Table 43: Deaths occurring in JARKARTA Study (all treated population)

	Fedratinib		Placebo (N=95) n (%)
	400 mg (N=96)	500 mg (N=97)	

	n (%)	n (%)	
Death On study up to 6 cycles	**7 (7)**	**14 (14)**	**12 (13)**
Due to adverse reaction	1 (1)	4 (4)	4 (4)
Progressive disease	4 (4)	7 (7)	6 (6)
Other	2 (2)	3 (3)	2 (2)
Death that occurred during the entire treatment duration	**15 (16)**	**24 (25)**	**-**
Progressive disease	9 (9)	11 (11)	-
Due to adverse reaction	2 (2)	7 (7)	-
Other[a]	4 (4)	5 (5)	-
Death[b]	0	1 (1)	-

[a] Other primary causes of death = heart failure (2 subjects), and pneumonia and unknown cause (1 subject each) in the 400 mg arm and colon neoplasm (adenocarcinoma), complication post-transplant, multiorgan failure after infectious complications and bone marrow transplantation, sepsis/pneumonia/myelofibrosis, and unknown cause in the 500 mg arm (1 subject each).
[b] One additional death was reported by the investigator with the cause of death is "not collect" on the Death e-CRF.

Two deaths due to TEAEs were reported in the 400 mg arm during the entire treatment duration (1 with acute leukemia transformation and 1 with cardiogenic shock). Three subjects in the 400 mg group died from 1 acute leukemia, 1 end stage disease (DP), 1 cardiopulmonary arrest, disseminated intravascular coagulation, multiple organ dysfunction syndrome and hemorrhagic shock.

Reviewer comments: The overall death rate during the entire study duration was lower in the 400 mg group (16%) compared to the 500 mg group (25%) or the placebo group (13%). Death due to adverse reactions during the entire treatment duration was lower for the 400 mg group (2%) than for the 500 mg group (7%).

Death-Crossover Safety population

The overall death rate among subjects in placebo group who crossed over to fedratinib treatment was 5/35 (14%) of patients rerandomized to the 400 mg and 5/36 (14%) of patients rerandomized to the 500 mg. The primary causes of death among crossover groups were disease progression (3 subjects in the 400 mg arm and 1 subject in the 500 mg arm), adverse reaction in 1 subject in each arm, and other reason (4 subjects in the 400 mg arm and 3 subjects in the 500 mg group.

Reviewer comments: The overall death rate among subjects in placebo group who crossover to fedratinib treatment was similar between groups for those rerandomized to 400 mg as to those rerandomized to 500 mg.

Serious Adverse Events

Anemia, cardiac failure, and gastrointestinal (GI) toxicity were the most common

reported serious adverse events during the entire treatment duration.

Serious adverse events reported during entire on treatment duration are summarized in Table 44 below.

Table 44: Treatment-emergent SAEs Reported for 3 or More Subjects in Any Treatment Arm During Entire Treatment Duration (JAKARTA), by Primary SOC and PT (All Treated Population)

System Organ Class/ Preferred Term	**Fedratinib 400 mg N = 96**			**Fedratinib 500 mg N = 97**			**Placebo N = 95**		
	All Grades n (%)	Grades 3,4 n (%)	Grade 5 n (%)	All Grade n (%)	Grades 3,4 n (%)	Grade 5 n (%)	All Grade n (%)	Grades 3,4 n (%)	Grade 5 n (%)
Subjects With ≥ 1 Treatment-emergent SAE	**37 (39)**	**26 (27)**	**6 (6)**	**43 (44)**	**33 (34)**	**8 (8)**	**22 (23)**	**14 (15)**	**6 (6)**
Cardiac Disorders	**11 (12)**	**9 (9)**	**2 (2)**	**9 (9)**	**7 (7)**	**2 (2)**	**5 (5)**	**3 (3)**	**1 (1)**
Heart failure	6 (6)	5 (5)	0 (0)	5 (5)	4 (4)	1 (1)	3 (3)	2 (2)	0 (0)
Cardiac Arrhythmia	3 (3)	2 (2)	1 (1)	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Blood and Lymphatic System Disorders	**8 (8)**	**7 (7)**	**1 (1)**	**11 (11)**	**9 (9)**	**1 (1)**	**4 (4)**	**3 (3)**	**0 (0)**
Anemia	4 (4)	4 (4)	0 (0)	5 (5)	5 (5)	0 (0)	1 (1)	1 (1)	0 (0)
Gastrointestinal Disorders	**5 (5)**	**4 (4)**	**0 (0)**	**8 (8)**	**7 (7)**	**1 (1)**	**5 (5)**	**4 (4)**	**0 (0)**
Infections and Infestations	**11 (12)**	**5 (5)**	**0 (0)**	**15 (15)**	**15 (16)**	**14 (14)**	**5 (5)**	**3 (3)**	**2 (2)**
Pneumonia	4 (4)	2 (2)	0 (0)	3 (3)	4 (4)	4 (4)	2 (2)	1 (1)	1 (1)
Neoplasms Benign, Malignant, and Unspecified	**6 (6)**	**3 (3)**	**3 (3)**	**5 (5)**	**5 (5)**	**0 (0)**	**3 (3)**	**2 (2)**	**1 (1)**

Source: Table 14.3.2.10.2

Reviewer comments: Serious adverse events were reported in higher frequency in fedratinib treated groups compared to placebo group. However, serious adverse events were reported in less frequency in the 400 mg arm (39%) compared to the 500 mg arm (44%). The most common serious adverse events were heart failure, anemia, pneumonia and cardiac arrhythmia with similar incidence between the 400 mg and the 500 mg treated patients.

Serious Adverse Events – Crossover Safety Population

Serious adverse events reported in the crossover safety population are summarized by the primary SOC and PT in Table 45 below.

Table 45: SAEs by Primary SOC, PT Placebo Crossover Safety Population

System Organ Class/Preferred Term	Fedratinib 400 mg N = 35	Fedratinib 500 mg N = 36

	All Grades n (%)	Grades 3,4 n (%)	Grade 5 n (%)	All Grade n (%)	Grades 3,4 n (%)	Grade 5 n (%)
Subjects With ≥ 1 Treatment-emergent SAE	13 (37)	10 (29)	1 (3)	13 (36)	9 (25)	1 (3)
Cardiac Disorders	**2 (6)**	**1 (3)**	**0 (0)**	**1 (3)**	**1 (3)**	**0 (0)**
Heart failure	1 (1)	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)
Blood and Lymphatic System Disorders	**6 (17)**	**5 (14)**	**0 (0)**	**3 (8)**	**3 (8)**	**0 (0)**
Anemia	3 (8)	3 (8)	0 (0)	2 (6)	2 (6)	0 (0)
Gastrointestinal Disorders	**2 (6)**	**1 (3)**	**0 (0)**	**2 (6)**	**1 (3)**	**0 (0)**
Nausea and Vomiting	1 (3)	1 (3)	0 (0)	2 (6)	1 (3)	0 (0)
Infections and Infestations	**4 (8)**	**3 (9)**	**0 (0)**	**1 (3)**	**1 (3)**	**0 (0)**
Lower respiratory tract infection	2 (6)	2 (6)	0 (0)	1 (3)	1 (3)	0 (0)
Nervous System Disorders	**1 (3)**	**1 (3)**	**0 (0)**	**2 (6)**	**1 (3)**	**0 (0)**
Encephalopathy	0 (0)	0 (0)	0 (0)	2 (6)	1 (3)	0 (0)

Reviewer comments: The frequency of SAEs in placebo patients who received fedratinib after crossover was similar in the 400 and 500 mg arms (37% and 36%, respectively) and similar to those reported in the 400 mg and 500 mg arms in the randomized period. Anemia, lower respiratory tract infection, and nausea and vomiting were the most common SAEs.

Grade 3 or 4 adverse events

Grade 3 or 4 TEAEs reported during the entire treatment duration are summarized by worst NCI CTCAE toxicity grade in Table 46 below.

Table 46: Grade 3 or 4 TEAEs Reported for 2 or More patients during the Entire Treatment Duration, (All Treated Population, JAKARTA Study)

	Fedratinib 400 mg N = 96 n (%)	Fedratinib 500 mg N = 97 n (%)	Placebo N= 95 n (%)
Subjects With ≥ 1 Grade 3 or 4 TEAE	68 (71)	76 (78)	33 (34)
Anemia	43 (45)	40 (41)	7 (7)
Thrombocytopenia	11 (12)	18 (19)	6 (6)
Neutropenia	4 (4)	10 (10)	0 (0)
Vomiting	3 (3)	9 (9)	0 (0)
Fatigue	7 (7)	7 (7)	0 (0)
Lipase increased	4 (4)	7 (7)	1 (1)
Cardiac failure	6 (6)	2 (2)	2 (2)
Cardiac Arrhythmia	4 (4)	3 (3)	2 (2)
Pneumonia	2 (2)	5 (5)	1 (1)
Hyperkalemia	2 (2)	6 (6)	2 (2)
Diarrhea	5 (5)	5 (5)	0 (0)

Nausea	0 (0)	6 (6)	0 (0)
Sepsis	2 (2)	2 (2)	0 (0)
Asthenia	2 (2)	4 (4)	1 (1)
Hypertension	3 (3)	2 (2)	0 (0)
Atrial fibrillation	2 (2)	2 (2)	1 (1)
Aspartate aminotransferase increased	2 (2)	3 (3)	0 (0)
Alanine aminotransferase increased	2 (2)	3 (3)	0 (0)
Amylase increased	2 (2)	1 (1)	0 (0)
Hyponatremia	2 (2)	2 (2)	0 (0)
Hyperlipasemia	2 (2)	2 (2)	0 (0)
Bone pain	2 (2)	1 (1)	0 (0)

Source: Table 14.3.1.3.1 and Table 14.3.1.3.2

Reviewer comments: The rate of Grade 3 or 4 TEAEs was slightly higher in the 500 mg arm (78%) compared to the 400 mg arm (71%) and significantly higher than in the placebo arm (34%). The frequency of anemia was slightly higher in the 400 mg arm (45%) compared to the 500 mg arm (41%). The frequencies of thrombocytopenia and neutropenia were lower in the 400 mg arm compared to the 500 mg arm (12%, 4% vs 19%, 10%, respectively). The most common Grade 3 or 4 adverse events that occurred in the 400 mg arm were anemia, thrombocytopenia, fatigue and GI toxicity.

Grade 3 or 4 in Crossover safety population
The frequencies of Grade 3 or 4 TEAEs reported in the Crossover Safety Population are Summarized in Table 47 below.

Table 47: Grade 3 or 4 TEAE(s) Crossover Safety Population

	Fedratinib 400 mg N = 35 n (%)	Fedratinib 500 mg N = 36 n (%)
Subjects With ≥ 1 TEAE Grade 3 or 4	23 (66)	27 (75)
Anemia	14 (40)	17 (47)
Thrombocytopenia	8 (23)	10 (28)
Neutropenia	3 (9)	3 (8)
Alanine Aminotransferase Increased	0 (0)	3 (8)
Dizziness	2 (6)	1 (3)
Vomiting	0 (0)	2 (6)

Source: Table 14.3.1.10.2

Reviewer comments: Grade 3 or 4 adverse events reported in patients who crossover from placebo were consistent with those reported in patients who originally received

fedratinib. Anemia, thrombocytopenia and neutropenia were the most common Grade 3 or 4 TEAE.

Dropouts and/or Discontinuations Due to Adverse Effects

Treatment-emergent AEs leading to permanent treatment discontinuation during the entire treatment duration are summarized by primary SOC and PT in Table 48 below.

Table 48: TEAE Leading to Permanent Treatment Discontinuation by Primary SOC and PT during entire Treatment duration (All Treated Population, JAKARTA Study)

	Fedratinib 400 mg N = 96 n (%)	Fedratinib 500 mg N = 97 n (%)	Placebo N = 95 n (%)
Patients with ≥ 1 TEAE leading to discontinuation	26 (27)	35 (36)	8 (8)
Cardiac Disorders	**8 (8)**	**2 (2)**	**2 (2)**
Cardiac failure	3 (3)	1 (1)	2 (2)
Myocardial ischemia	2 (2)	0 (0)	2 (2)
Blood and Lymphatic System Disorders	**9 (9)**	**9 (9)**	**2 (2)**
Thrombocytopenia	4 (4)	6 (6)	0 (0)
Anemia	2 (2)	1 (1)	0 (0)
Neutropenia	0 (0)	2 (2)	0 (0)
Gastrointestinal Disorders	**6 (6)**	**10 (10)**	**0 (0)**
Diarrhea	2 (2)	2 (2)	0 (0)
Nausea	2 (2)	2 (2)	0 (0)
Vomiting	0 (0)	4 (4)	0 (0)
Investigation	**5 (5)**	**5 (5)**	**0 (0)**
Increased blood creatinine	2 (2)	2 (2)	0 (0)
Amylase increased	1 (1)	1 (1)	0 (0)
Lipase Increased	1 (1)	3 (3)	0 (0)
General Disorders	**1 (1)**	**2 (2)**	**0 (0)**
Fatigue	0 (0)	2 (2)	0 (0)

Source: Table 14.3.2.12.1 and Table 14.3.2.12.3

Reviewer comments: The rate of TEAEs leading to fedratinib treatment discontinuation was higher in the 500 mg arm compared to the 400 mg arm (36% vs 27%, respectively). The most common TEAEs leading to treatment discontinuation reported were thrombocytopenia, anemia, cardiac failure and GI toxicity.

Treatment-emergent Adverse Events Leading to Dose Reduction or Dose Interruption

Treatment-emergent AEs leading to dose reduction or dose interruption during the entire treatment duration is summarized by primary SOC and PT in Table 49 below.

Table 49: TEAE(s) Leading to Dose Reduction or Interruption by Primary SOC, PT and Grade (All Treated Population, JAKARTA Study)

System Organ Class/ Preferred Term	Fedratinib 400 mg N = 96		Fedratinib 500 mg N = 97		Placebo N = 95	
	All Grades n (%)	Grades 3,4 n (%)	All Grade n (%)	Grades 3,4 n (%)	All Grade n (%)	Grades 3,4 n (%)
Subjects With ≥ 1 TEAE leading to dose reduction or interruption	**43 (45)**	**22 (23)**	**65 (67)**	**57 (59)**	**14 (15)**	**12 (13)**
Gastrointestinal Disorders	**17 (18)**	**6 (6)**	**8 (8)**	**24 (25)**	**4 (4)**	**2 (2)**
Vomiting	10 (10)	3 (3)	11 (11)	7 (7)	0 (0)	0 (0)
Diarrhea	9 (9)	3 (3)	8 (8)	3 (3)	0	0
Nausea	9 (9)	0	6 (6)	4 (4)	0	0
Blood and Lymphatic System Disorders	**12 (13)**	**8 (8)**	**27 (28)**	**24 (25)**	**4 (4)**	**2 (2)**
Anemia	8 (8)	5 (5)	17 (18)	14 (14)	1 (1)	1 (1)
Thrombocytopenia	3 (3)	2 (2)	7 (7)	6 (6)	0	0
General Disorders and administration Site	**5 (5)**	**4 (4)**	**10 (10)**	**9 (9)**	**2 (2)**	**2 (2)**
Fatigue	3 (3)	3 (3)	5 (5)	5 (5)	0 (0)	0 (0)

Source: Table 14.3.2.13.1, Table 14.3.2.13.2 and Table 14.3.2.14.2

Reviewer comments: The percentage of patients who had dose reduction or dose interruption during the entire treatment duration was lower in the 400 mg arm (45%) compared to the 500 mg arm (67%). The most common TEAEs leading to dose reduction or interruption in the 400 mg arm were GI toxicity (vomiting, diarrhea and nausea), anemia, thrombocytopenia and fatigue.

Significant Adverse Events

Anemia and Red Blood Cell (RBC) Transfusion:

Grade 3 or 4 anemia and grade 3 or 4 anemia based on laboratory values was the most frequently reported hematologic abnormality during the randomization period and during the entire treatment duration.

Grade 3 or 4 anemia, Grade 3 or 4 anemia based on laboratory values and serious Grade 3 or 4 anemia reported during randomization period and during the entire study are summarized in Table 50 below.

Table 50: Grade 3 or 4 Anemia (All Treated Population, JAKARTA Study)

	During Randomization Period (Up to 6 cycles)			Entire Treatment Duration	
	Fedratinib 400 mg N = 96 n (%)	**Fedratinib 500 mg N = 97 n (%)**	**Placebo N= 95 n (%)**	**Fedratinib 400 mg N = 96 n (%)**	**Fedratinib 500 mg N = 97 n (%)**
Grade 3 or 4 Anemia Based on Laboratory Values	40 (42)	54 (56)	23 (24)	52 (54)	63 (65)
Grade 3 or 4 Anemia	30 (31)	25 (26)	7 (7)	44 (46)	41 (42)
Serious Grade 3 or 4 Anemia	2 (2)	5 (5)	1 (1)	4 (4)	5 (5)

Source: Table 14.3.2.16.1b, Table 14.3.2.16.1c, Table 14.3.2.16.1d, Table 14.3.2.16.2b, Table 14.3.2.16.2c, and Table 14.3.2.16.2d

Reviewer comments: The rates of grade 3 or 4 anemia and grade 3 or 4 anemia based on laboratory values during the randomization period were higher in the 400 mg arm compared to the placebo arm (31% vs 7% and 42% vs 24%, respectively). During the entire study period the frequencies of anemia based on laboratory values were higher in the 500 mg arm compared to the 400 mg arm (65% vs 54%). However, the frequency of anemia Grade 3 or 4 was slightly higher in the 400 mg arm compared to the 500 mg arm (46% vs 42%).

RBC Transfusions:
During entire treatment duration 59 (62%) patients in the 400 mg, 67 (69%) patients in the 500 mg arm and 31 (32%) patients in the placebo arm received RBC transfusion. The median number of RBC units transfused to patients in the 400 mg, 500 mg and placebo arms were 10, 14, 10 units, respectively.

The majority of patients (> 90%) in all groups were RBC transfusion independent at baseline. RBC transfusion conversion from transfusion independent to transfusion dependent (dependence was defined as receiving ≥ 2 units/month of RBC transfusion over 3 months) during the study, occurred in 25% (22/88) of patients in the 400 mg arm, 26% (24/92) of patients in the 500 mg arm and 12% (11/90) of patients in the placebo arm.

RBC transfusion conversion from RBC dependent at baseline to become transfusion independent reported in 7 of 8 (88%) patients in the 400 mg arm, 5 of 5 (100%) patients in the 500 mg and in 5 of 6 (83%) patients.

Reviewer comments: The rate of patients converted from transfusion dependent to transfusion independent was higher in patients treated with 400 or 500 mg fedratinib compared to placebo (25%, 26% vs 12%, respectively).

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events in ≥ 10% of subjects reported during the entire treatment duration are summarized by primary SOC and PT in Table 51 below.

Table 51: TEAEs Reported for at Least 10% of Subjects in Either Fedratinib Arm for the Entire Treatment Duration, by Primary SOC and PT (All Treated Population)

Primary System Organ Class by Preferred Term	Fedratinib 400 mg N = 96 n (%)	Fedratinib 500 mg N = 97 n (%)	Placebo N= 95 n (%)
Subjects With ≥ 1 any Grade TEAE	**96 (100)**	**95 (98)**	**89 (94)**
Gastrointestinal Disorders	**89 (93)**	**89 (92)**	**47 (50)**
Diarrhea	68 (71)	58 (60)	15 (16)
Nausea	64 (67)	51 (53)	15 (16)
Vomiting	44 (46)	54 (56)	5 (5)
Constipation	12 (13)	19 (20)	7 (7)
Blood and Lymphatic System Disorders	**62 (65)**	**59 (61)**	**23 (24)**
Anemia	53 (55)	47 (49)	13 (14)
Thrombocytopenia	16 (17)	22 (23)	8 (8)
Neutropenia	6 (6)	12 (12)	0 (0)
General Disorders and Administration Site Conditions	**52 (54)**	**41 (42)**	**32 (34)**
Fatigue	24 (25)	14 (14)	9 (10)
Peripheral edema	14 (15)	9 (9)	8 (8)
Asthenia	13 (14)	16 (17)	6 (6)
Infections and Infestations	**50 (52)**	**48 (50)**	**26 (27)**
Urinary tract infection	9 (9)	10 (10)	1 (1)
Investigations	**47 (49)**	**51 (53)**	**15 (16)**
Alanine aminotransferase increased	12 (13)	8 (8)	1 (1)
Weight increased	12 (13)	8 (8)	4 (4)
Blood creatinine increased	11 (12)	17 (18)	1 (1)
Aspartate aminotransferase increased	6 (6)	10 (10)	0 (0)
Weight decreased	5 (5)	12 (12)	5 (5)
Musculoskeletal and Connective Tissue Disorders	**41 (43)**	**23 (24)**	**20 (21)**
Muscle spasms	15 (16)	8 (8)	1 (1)
Bone pain	12 (13)	8 (8)	2 (2)
Pain in extremity	12 (13)	3 (3)	4 (4)
Respiratory, Thoracic, and Mediastinal Disorders	**40 (42)**	**33 (34)**	**18 (19)**

Cough	13 (14)	14 (14)	6 (6)
Dyspnea	11 (12)	12 (12)	6 (6)
Metabolism and Nutrition Disorders	**34 (35)**	**31 (32)**	**12 (13)**
Hyperkalemia	6 (6)	10 (10)	4 (4)
Nervous System Disorders	**32 (33)**	**29 (29)**	**9 (10)**
Dizziness	13 (14)	10 (10)	3 (3)
Headache	13 (14)	6 (6)	1 (1)

Source: Table 14.3.1.4.1 and Table 14.3.1.4.2

Reviewer comments: The TEAEs reported in ≥ 10% of patients during the entire treatment duration with at least 5% difference between the fedratinib and the placebo arms were GI toxicity (nausea, vomiting, diarrhea), anemia, thrombocytopenia, urinary tract infection, fatigue and asthenia, peripheral edema, liver enzymes increased (AST and ALT), muscle spasm, bone pain, pain in the extremity, cough, dyspnea, dizziness and headache. Most common hematological AEs in the 400 mg arm were anemia and thrombocytopenia. Most common nonhematological AEs reported in the 400 mg arm were diarrhea, nausea, vomiting, fatigue and asthenia.

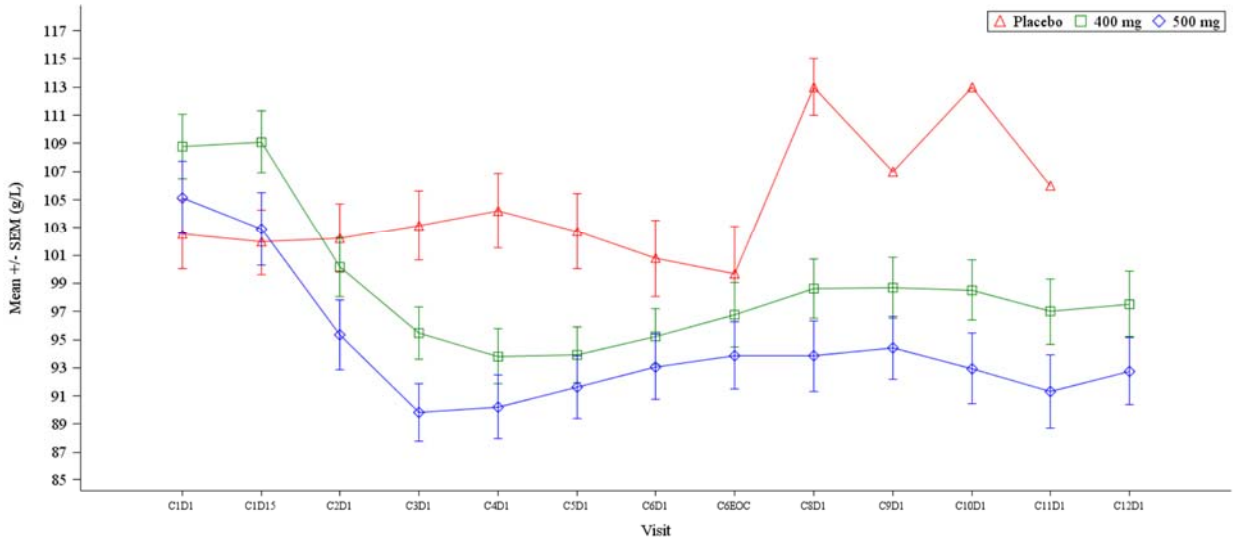
LABORATORY FINDINGS

The major laboratory findings for adverse events for fedratinib were anemia, thrombocytopenia, increased lipase or/and amylase, AST and ALT increased.

Hemoglobin level

Changes in mean Hb ± SEM as measured per visit for all subjects in the all treated population is shown in Figure 9.

Figure 9: Mean ± SEM Hemoglobin by Visit and Treatment Arm (All Treated Population)



Placebo	90	94	91	82	72	66	61	43	2	1	1	1	
400 mg	93	96	92	89	86	83	80	74	70	68	66	60	62
500 mg	91	93	85	81	75	71	69	67	62	59	56	52	55

Note: For the fedratinib 400 and 500 mg arms, only subjects initially randomized to the respective arms were included. For placebo subjects, only data before crossover were included. Three subjects received placebo past Cycle 6 due to rerandomization deviations at the site level.

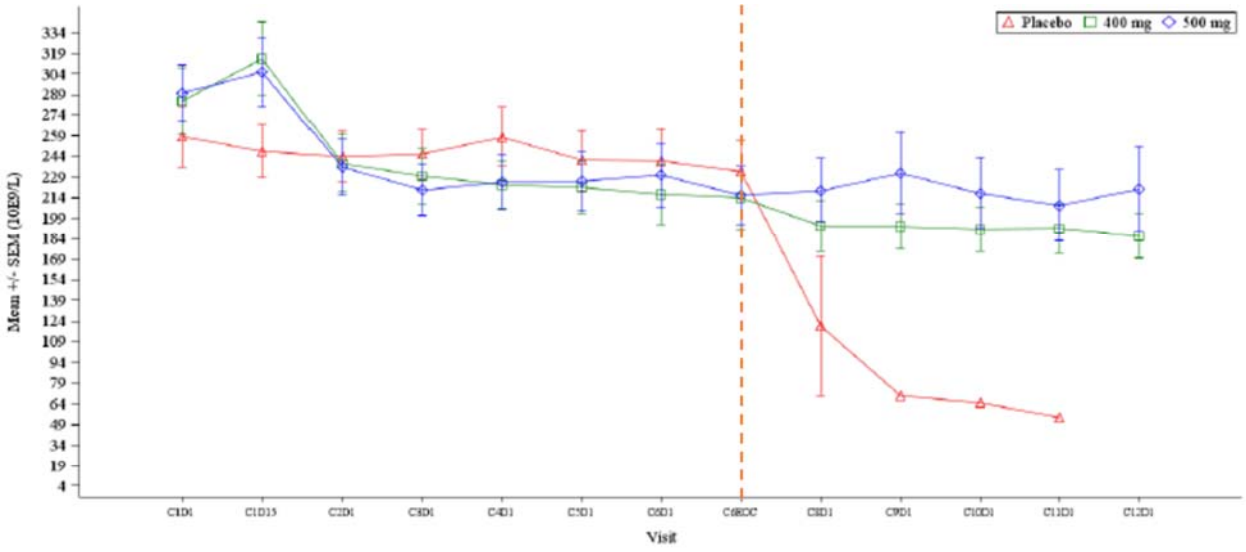
Source: Figure 14.3.4.1.1

Reviewer's comments: While, the mean hemoglobin level in the placebo arm remained stable up to 6 cycles, the fedratinib treatment arms associated with a decrease in hemoglobin levels over time with nadir reached after 12 to 16 weeks. However, a partial recovery in hemoglobin level was observed in both fedratinib treatment arms after 24 weeks (6 cycles) of treatment and extended to the rest of treatment duration.

Platelet count

Changes in mean platelet count ± SEM as measured per visit for all subjects in the All Treated Population showed that the mean platelet count in the placebo arm remained stable up to 6 cycles. The mean platelet counts in both fedratinib treatment arms showed a slight increase at the mid Cycle 1 followed by a steep decline in platelet count. The mean platelet count nadir occurred at 28 weeks (184 x 10^9/L) for the 400 mg arm and at 12 weeks (220 x 10^9/L) for the 500 mg arm. After Cycle 6, the mean platelet count remained stable in the 500 mg arm with slight decrease in 400 mg arm.

Figure 10: Mean ± SEM Platelet Count by Visit and Treatment Arm (All Treated Population)



Placebo	90	94	91	82	72	66	61	43	2	1	1	1	
400 mg	93	96	92	89	86	83	80	74	69	68	66	60	61
500 mg	91	93	85	81	75	71	69	67	62	59	56	52	56

Note: For the fedratinib 400 and 500 mg arms, only subjects initially randomized to the respective arms were included. For placebo subjects, only data before crossover were included. Three subjects received placebo past Cycle 6 due to rerandomization deviations at the site level.

Source: Figure 14.3.4.2.1

Reviewer's comment: Treatment with fedratinib was associated with a decrease in mean platelet counts with the mean nadir occurring in 28 weeks and remaining stable for almost for the entire study duration.

Effect of Platelet Transfusions on Platelet Count Abnormalities

During the entire treatment duration, platelet transfusions were received by 3 of 96 (3%) subjects in the placebo arm, 9 of 96 (9%) subjects in the 400 mg arm, and 12 of 97 (12%) subjects in the 500 mg arm. The median number of units of transfused platelets received by subjects in the placebo, 400 mg, and 500 mg arms were 2, 4, and 2 units, respectively.

White Blood Cell Count

Half of patients in the 400 mg and 500 mg group treated with fedratinib experienced any grade of WBC count decreased during the entire treatment duration. WBC Grade 3 decreased was reported in lower frequency among subjects in the 400 mg group compared to the 500 mg group (3% vs 14%). Grade 4 WBC decreased was reported during the entire treatment duration in similar rate in both fedratinib treated groups

(4%).

The rates of fedratinib-treated subjects with neutrophil count decreased during the entire treatment duration of all grade, grade 3 or grade 4 (37%, 5%, 5%, respectively) were lower in the 400 mg compared to the 500 mg arm (50%, 12%, 7%, respectively).

Clinically Significant Hepatic Laboratory Abnormalities

Alanine aminotransferase (ALT) increased:
The ALT all grade increased during the entire treatment duration was reported in higher frequency in the 400 mg arm (58%), compared to the 500 mg arm (49%). However, Grade 3 or 4 ALT increased was reported in similar rate in the 400 mg and 500 mg at 4%.

Aspartate aminotransferase (AST) increased:
The AST all grade increased during the entire treatment duration was reported in higher frequency in the 400 mg arm (64%), compared to the 500 mg arm (52%). Grade 3 or 4 AST increased reported in 2% of subjects in the 400 mg compared to 3% in the 500 mg arm.

Amylase and Lipase elevation

Lipase increased:
All grade and Grade 3 or 4 increased in lipase during the entire treatment duration were reported in 49% and 14%, respectively, of subjects in the 400 mg group compared to 40% and 10%, respectively, of subjects in the 500 mg group.

Blood Creatinine Increased
During the entire treatment duration all grades creatinine increased were reported in 74% of subjects in the 400 mg group and 77% in the 500 mg group. Grade 3 or 4 creatinine increased was reported in higher frequency in the 400 mg group compared to the 500 mg group, 6 (6%) vs 1 (1%).

Table 52: Subjects with Liver, Renal, and Pancreatic Abnormalities During the Entire treatment Duration (All Treated Population)

Laboratory Test	Fedratinib 400 mg		Fedratinib 500 mg		Placebo	
	All Grades n (%)	Grades 3,4 n (%)	All Grade n (%)	Grades 3,4 n (%)	All Grade n (%)	Grades 3,4 n (%)
	N = 96		N = 96		N = 94	
Alanine aminotransferase increased	**56 (58)**	**4 (4)**	**47 (49)**	**4 (4)**	**16 (17)**	**0 (0)**
Aspartate aminotransferase increased	**61 (64)**	**2 (2)**	**50 (52)**	**3 (3)**	**26 (28)**	**1 (1)**
Blood bilirubin increased	**37 (39)**	**3 (3)**	**31 (32)**	**1 (1)**	**38 (40)**	**2 (2)**
Alkaline phosphatase increased	**61 (64)**	**2 (2)**	**55 (57)**	**1 (1)**	**51 (54)**	**2 (2)**
	N = 96		N = 97		N = 95	
Creatinine Increased	**71 (74)**	**6 (6)**	**74 (77)**	**1 (1)**	**28 (30)**	**1 (1)**
Lipase increased	**47 (49)**	**13 (14)**	**38 (40)**	**10 (10)**	**6 (7)**	**2 (2)**
Serum amylase increased	**28 (29)**	**2 (2)**	**25 (26)**	**3 (3)**	**7 (7)**	**0 (0)**

Source: Table 14.3.4.11.2 and Table 14.3.4.13.1

VITAL SIGNS

Vial sign abnormalities were reported by investigators only if they were medically relevant (e.g., those that were symptomatic; led to permanent treatment discontinuation, dose delay, dose reduction, or dose interruption; or were considered serious).

Hypertension was reported as a TEAE during the entire on treatment duration in 1 subject in the placebo arm, 4 subjects in the 400 mg arm, and 6 subjects in the 500 mg arm. Grade 3 or 4 TEAE of hypertension was reported in 3 subjects in the 400 mg arm and 2 subjects in the 500 mg arm.

The frequencies of subjects with PCSAs in HR, SBP, and DBP during the entire on-treatment duration are summarized in Table 53 below.

Table 53: Vital Signs Abnormalities During the entire On-treatment duration (All Treated Population)

Vital sign	Fedratinib 400 mg N= 96 n (%)	Fedratinib 500 mg N= 97 n (%)	Placebo N= 95 n (%)
Heart Rate			
≤ 50 bpm and decrease from baseline ≥ 20 bpm	1 (1)	3 (3)	0 (0)
≥ 120 bpm and increase from baseline ≥ 20 bpm	0 (0)	2 (2)	2(2)
Systolic Blood Pressure			
≤ 95 mmHg and decrease from baseline ≥ 20 mmHg	4 (4)	3 (3)	6 (6)

≥ 160 mmHg and increase from baseline ≥ 20 mmHg	11 (12)	9 (9)	5 (5)
Diastolic Blood Pressure			
≤ 45 mmHg and decrease from baseline ≥ 10 mmHg	1 (1)	2 (2)	2 (2)
≥ 110 mmHg and increase from baseline ≥ 10 mmHg	1 (1)	0 (0)	1 (1)

Source: Table 14.3.5.1.1 and Table 14.3.5.1.2

Reviewer comments: The percentages of patients with heart rate, systolic blood pressure or diastolic blood pressure abnormalities were comparable between the fedratinib treatment arms. There were no apparent significant differences between the fedratinib treated groups and the placebo group.

STUDY 121881 (JAKARTA-2)

Dose Exposure:
Treatment was discontinued due to early study termination in 63 (65%) subjects. The median time of exposure was 24 weeks (6 Cycles). However, since the study was not designed to evaluate a dosing regimen, 33 patients had their dose titrated up to 500 mg (17 patients) and up to 600 mg (15 patients). One patient received a maximum dose of 800 mg.

Table 54 summarizes the extend of fedratinib exposure.

Table 54: Dose Exposure in JAKARTA-2 Study- AT Population

	Fedratinib 400 mg (N=97)
Duration of exposure in weeks	
Mean (SD)	28.1 (17.8)
Median (Min, Max)	24.4 (0.7, 79.4)
Number of Treatment Cycles Completed, n (%)	
0-3 Cycles	17 (18)
> 3-6 Cycles	32 (33)
> 6-9 Cycles	25 (26)
> 9-12 Cycles	9 (9)
> 12 Cycles	14 (14)
Actual Dose Intensity (mg/week)	
Mean (SD)	2691 (577)
Median (Min, Max)	2800 (1110, 3884)
Received a maximum dose of 500 mg, n (%)	17 (18)
Received a maximum dose of 600 mg, n* (%)	16 (16)
Require ≥ 1 level dose reduction, n (%)	38 (39)
Dose interruption of ≥ 7 consecutive days, n (%)	25 (26)

* One patient received a maximum dose of 800 mg.

Source: Table 14.3.1.1.1 and Table 14.3.1.1.2

Reviewer comments: Only half of patients in the JAKARTA-2 study were exposed to 6 cycles of fedratinib treatment. Approximately 40% of patients required at least one dose reduction. One third of patients received a fedratinib dose higher than the 400 mg.

DEATH
There were 7 deaths that occurred during the treatment period. Four patients died from disease progression and 3 deaths were due to adverse events. The fatal TEAEs were pneumonia, shock, and cardio-respiratory arrest.

Reviewer comments: The rates of adverse reactions leading to death were consistent with those in the JAKARTA trial.

Serious Adverse Events
There was a total of 33 (34%) patients who experienced serious adverse events. The most common SAEs were pneumonia in 4 (4%) patients and pleural effusion in 3 (3%) patients.

Grade 3 or 4 TEAE
A total of 61 (63%) subjects experienced Grade 3 or 4 TEAEs. Grade 3 or 4 TEAEs reported in 2 or more subjects are summarized by primary SOC and PT in Table 55 below.

Table 55: Grade 3 or 4 TEAEs Occurring in 3 or More Subjects in JAKARTA-2 Study - AT Population

System Organ Class/ Preferred Term	Fedratinib 400 mg N=97 n (%)
Subjects with ≥ 1 Grade 3 or 4 TEAEs	**61 (63)**
Blood and Lymphatic System Disorders	**45 (46)**
Anemia	37 (38)
Thrombocytopenia	21 (22)
Investigations	**20 (21)**
Hyperlipasemia	9 (9)
Alanine aminotransferase increased	3 (3)
Lymphocyte count decreased	3 (3)
Gastrointestinal disorders	**10 (10)**
Diarrhea	4 (4)
Abdominal pain	3 (3)
Respiratory, thoracic and mediastinal disorders	**5 (5)**
Pneumonia	4 (4)

Reviewer comments: The most common Grade 3 or 4 adverse reactions or laboratory abnormality reported in JAKARTA-2 trial were anemia, thrombocytopenia, hyperlipasemia, diarrhea, and pneumonia.

Common Adverse events
Treatment-emergent AEs occurring in at least 10% of subjects are summarized by primary SOC and PT in Table 56 below.

Table 56: TEAEs Occurring in ≥ 10% of Subjects by Primary SOC and PT - AT Population

System Organ Class/ Preferred Term	Fedratinib 400 mg N=97 n (%)
Subjects with ≥ 1 TEAE	**97 (100)**
Gastrointestinal Disorders	**81 (84)**
Diarrhea	60 (62)
Nausea	54 (56)
Vomiting	40 (41)
Constipation	20 (21)
Abdominal pain	12 (12)
Blood and Lymphatic System Disorders	**58 (60)**
Anemia	47 (49)
Thrombocytopenia	26 (27)
Infections and Infestation	**51 (53)**
Urinary tract infection	13 (13)
General Disorders and Administration Site Conditions	**46 (47)**
Fatigue or asthenia	24 (25)
Pyrexia	11 (11)
Nervous System Disorders	**35 (36)**
Headache	13 (13)
Dizziness	11 (11)
Respiratory, Thoracic and Mediastinal Disorders	**34 (35)**
Cough	13 (13)
Dyspnea	12 (12)
Skin and Subcutaneous Tissue Disorders	**33 (34)**
Pruritus	17 (18)

Reviewer comments: The most common adverse reactions reported in JAKARTA-2 trial were GI toxicity (diarrhea, nausea, vomiting), anemia, thrombocytopenia and fatigue. The rates of adverse reactions were consistent with those reported in the JAKARTA trial.

Electrocardiograms (ECGs)

Clinical significance of ECG abnormalities was determined by the investigator and reported on the e-CRF. Subjects with ≥ 1 abnormal ECG parameter during the on-treatment period, regardless of baseline status, are summarized in

Table 57: Patients with at Least 1 Abnormal ECG Parameter On Treatment up to 6 Cycles, Regardless of Baseline Status (All Treated Population)

	Fedratinib 400 mg N=96	Fedratinib 500 mg N=97	Placebo N=95
Normal, n (%)	27 (28)	27 (28)	29 (31)
Abnormal but clinically insignificant, n (%)	63 (66)	64 (66)	61 (64)
Abnormal and clinically significant, n (%)	6 (6)	6 (6)	5 (5)

Reviewer's comments: The percentage of patients with clinically significant abnormal ECG during randomization (up to 6 Cycles) was similar between fedratinib groups and placebo.

QT

A total of 7 patients (2 patients in the placebo arm, 2 patients in the 400 mg arm, and 3 patients in the 500 mg arm) had QTcF ≥ 500 msec during randomization period (up to 6 Cycles). Six patients (1 patient in the placebo arm, 2 patients in the 400 mg arm, and 3 patients in the 500 mg arm) had QTcF change from baseline (delta QTcF) > 60 msec, during treatment up 6 Cycles.

Immunogenicity

N/A

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Wernicke Encephalopathy

During fedratinib drug development, a safety signal of Wernicke encephalopathy (WE) was identified. According to published data, one case of WE and another case of encephalopathy of unknown origin were reported before data cutoff. Additional two cases of WE were reported after the database was locked. As a result, the FDA placed all

clinical trials of fedratinib on Complete Clinical Hold on November 15, 2013. The hold decision was made based on Sanofi preliminary reports that fedratinib may be associated with thiamine deficiency related adverse events, including 4 cases of Wernicke's encephalopathy (WE). Sanofi's analysis of these cases suggests that the causes of Wernicke's encephalopathy are multifactorial, including malnutrition, nausea, vomiting, renal dysfunction, and possibly linked to thiamine deficiency. Subsequently, Sanofi terminated all the clinical development for fedratinib on November 2013. All patients who discontinued fedratinib treatments entered a thiamine supplementation period.

WERNICKE'S ENCEPHALOPATHY (WE)*

* Author by Dr. Joohee Sul, MD

Wernicke's encephalopathy (WE) is an acute syndrome and important cause of acute delirium caused by thiamine (vitamin B1) deficiency. WE is an acute encephalopathy characterized by mental confusion, oculomotor dysfunction and ataxia (the classic triad of symptoms). Although patients can improve rapidly with thiamine administration, if left untreated progression to coma and death can occur. A chronic amnestic dementia characterized by severe memory loss with confabulation and lack of insight (Korsakoff's psychosis) may also develop. Therefore, rapid recognition of the condition and urgent thiamine replacement is critical to preventing neurologic morbidity. Although WE is most commonly associated with alcohol use, the condition may also occur in the setting of poor nutritional status, a myriad of conditions including hyperemesis, bariatric surgery, anorexia, and cancer. Based on autopsy studies suggest that WE under-recognized clinically. [6-8]

Pathophysiology

Thiamine is essential to the function of multiple cellular processes, including metabolic pathways, maintenance of cell membrane osmotic gradients, and production of neurotransmitters. The body's thiamine reserves are generally sufficient to support metabolic functions for 10-20 days. High-calorie and high-carbohydrate diets increase metabolic thiamine requirements. Thiamine deficiency is purported to lead to neuronal damage secondary to oxidative stress, impaired glucose metabolism, and NMDA excitotoxicity. As sites of high thiamine consumption, neurons in the periaqueductal gray matter, colliculi, medial thalami and mamillary bodies are especially susceptible to deficits,[9] accounting for the imaging changes found in these anatomic locations. Nutritional deficiency alone may not lead to WE, suggesting that multiple factors may be involved.[10] For example, abnormalities in transketolase, an enzyme that processes thiamine, may be abnormal in individuals who develop WE,[11,12] and genetic factors have been implicated as well.[13-15]

Clinical

Diagnosis of WE is generally based on clinical features and can be supported by imaging findings and thiamine levels. The hallmarks of WE are oculomotor signs, especially nystagmus and gaze palsies, which generally predate confusion or ataxia. The mental status changes of WE are characterized by disorientation and abulia (i.e., as seen with bithalamic strokes). Ataxia is generally appreciated when evaluating the gait and does not typically involve the extremities. Peripheral neuropathy can also occur, most often involving the lower extremities and contributing to ataxia. Other clinical findings include vestibular dysfunction and autonomic dysfunction. When these symptoms occur in the alcohol users, WE is readily identified; however, the syndrome rarely presents with the classic triad and as such is generally underdiagnosed. Chronic or subclinical thiamine deficiency may lead to symptoms of WE appearing sooner; therefore, it is essential to interrogate the past medical history for weight loss and alcohol use. Moreover, glucose metabolism is a thiamine-intensive process, and a large glucose infusion can shuttle any available thiamine into cells, triggering WE. Hence, the recommendation is to always administer thiamine for suspected cases of WE before or concomitant with any glucose.

The Caine criteria were developed to identify WE in patients with chronic alcohol use and is reported to have high sensitivity in making the diagnosis. Two of the following four elements should be present to consider a diagnosis: (1) dietary deficiencies, (2) oculomotor abnormalities, (3) cerebellar dysfunction, and (4) either an altered mental state or mild memory impairment. [16]

Table 58: The operational criteria for the clinical diagnosis of WE, as formulated by Caine *et al*

Symptom or sign	As evidenced by one or more of the following
Dietary deficiencies	– Undernutrition (body mass index <2 SD below normal) – A history of grossly impaired dietary intake – An abnormal thiamine status
Oculomotor abnormalities	– Ophthalmoplegia – Nystagmus – Gaze palsy
Cerebellar dysfunction	– Unsteadiness or ataxia – Abnormalities of past pointing – Dysdiadokokinesia – Impaired heel-shin testing
Either an altered mental state	– Disorientation in two of three fields – Confused – An abnormal digit span – Comatose
or	or
Mild memory impairment	– Failure to remember two or more words in the four-item memory test – Impairment on more elaborate neuropsychological tests of memory function

Notes: When two out of these four criteria apply, the clinical diagnosis of WE is made. The criteria are less sensitive in case of a co-occurring hepatic encephalopathy.
Abbreviation: WE, Wernicke encephalopathy.

Source: Arts NJ, et al, Neuropsychiatr Dis Treat 13:2875-2890, 2017 [17]

The diagnosis can be supported by imaging findings of focal abnormalities along midline structures. The classic changes seen on MRI are symmetric signal abnormalities in the bilateral thalami, mamillary bodies, tectal plate and periaqueductal gray matter, likely due to cytotoxic edema and local breakdown of the blood brain barrier. Chronic thiamine deficiency may also result in focal abnormalities in the cerebellum, midbrain, caudate nuclei, corpus callosum and cortex. Sensitivity of MRI is poor (53%), however, specificity appears to be high (93%). [18] In patients with altered mental status and bilateral, symmetric thalamic signal abnormalities on MRI, the differential diagnosis should include ischemia (artery of Percheron stroke or deep venous thrombosis), acute disseminated encephalomyelitis (ADEM) or infectious encephalitis. Decreased serum thiamine levels and urinary thiamine excretion may also support the diagnosis; however, serum levels may not accurately reflect levels in the central nervous system (CNS) or other tissues, and a normal thiamine level does not exclude WE. There is not a specific thiamine level at which WE will develop, and other factors such as impaired thiamine utilization may be implicated. An erythrocyte transketolase activity assay and blood pyruvate levels may be investigated; however, these tests may not be readily available.

WE in patients with cancer

There are multiple mechanisms by which patients with cancer may be at increased risk for WE. Any systemic illness resulting in an increased metabolic rate may lead to thiamine deficiency, including hypermetabolic states of malignancy. Patients with cancer may also be at risk of thiamine deficiency due to anorexia, vomiting, and poor absorption or nutrition. Atypical presentations, lack of a history of alcohol use and underlying comorbidities add to the challenge of diagnosing WE in this population. A systematic literature review by Isenberg-Grzeda et al investigated the frequency of cancer-related WE and identified 129 patients; 38 (30%) presented with the classic triad of symptoms while 22 (17%) patients went undiagnosed during their lifetime.[19] Autopsy studies have also revealed higher than expected neuropathologic changes indicative of WE. For example, in twenty-four patients with leukemia and lymphoma, eight patients were found to have post-mortem pathologic features of WE without an associated clinical diagnosis.[6]

In addition to the typical causes of thiamine deficiency, certain chemotherapeutic agents such as erbulozole, ifosfamide and fluoropyrimidine are associated with impaired metabolism, transport or utilization.[20-22] Although the mechanism by which these drugs may lead to thiamine deficiency is unclear, interference with thiamine transport/activation, or inhibition of the active form of the vitamin, thiamine phosphate, have been implicated. Blood levels of thiamine in these cases are unlikely to indicate the relative deficiency, even in patients with severe symptoms.

Treatment

WE is a medical/neurologic emergency that warrants immediate administration of thiamine. Rapid recognition and treatment are required to avoid the potential permanent devastating morbidity. Although there are no randomized trials to support a specific treatment regimen, it has been suggested that high doses of thiamine may be necessary to cross the blood–brain barrier (BBB). Both the Royal college of Physicians (RCP) and the European Federation of Neurologic Societies (EFNS) recommend high dose intravenous (IV) thiamine (200-500 mg IV tid). Thiamine diphosphate is a key factor in glucose metabolism, and a large glucose infusion can trigger WE in patients with subclinical thiamine deficiency. Hence, the recommendation is to always administer thiamine for suspected cases of WE before or concomitant with any glucose. Symptoms generally response quickly to thiamine replacement, with oculomotor findings resolving within hours and mental status changes within hours to days; so much so that a lack of a response to thiamine should challenge the diagnosis of WE. As with clinical signs and symptoms, resolution of imaging findings can occur rapidly with thiamine administration. [23]

Celgene evaluation of the risk of WE

The current sponsor, Celgene, evaluated the possible association of thiamine deficiency and the development of WE in fedratinib-treated patients. The entire clinical database from 18 clinical studies was searched by the applicant for all subjects being treated with fedratinib or in blinded fedratinib studies reporting any signs or symptoms (e.g., mental status changes, ophthalmologic abnormalities and cerebellar findings) that could be associated with WE.

The applicant stated that the search identified 132 subjects with at least 1 TEAE that could be associated with WE in subjects who received fedratinib. No subjects who received placebo in JAKARTA had events suggestive of WE. However, there were 4 subjects out of 95 subjects received placebo with 1 Grade 1 or 2 event of a possible sign or symptom associated with WE and no Grade 3 or 4 events, and review of the cases did not confer any suggestion of WE.

Eight subjects with potential WE were initially identified among more than 600 subjects who were enrolled and treated in all fedratinib clinical trials (including 539 subjects with MPN and 75 subjects with solid tumors). These subjects were identified as having neurological symptoms that could be compatible with a diagnosis of WE.

Of these 132 subjects treated with fedratinib who had at least one TEAE possibly suggestive of WE:

- There were 86 reported have a single, Grade 1 or 2 nonserious event with no other findings that would suggest a diagnosis of WE.
- There were 28 subjects with more than one TEAEs possibly associated with WE:
    - 19 subjects experienced 2 Grade 1 or 2 events,
    - 5 subjects with 3 Grade 1 or 2 events, and
    - 4 subjects with 4 Grade 1 events that could be associated with WE.

  Review of these cases showed self-limited isolated events or events without a temporal relationship to fedratinib that would not suggest a diagnosis of WE
- There were 10 subjects who had Grade 3 or 4 events that were identified as not having a constellation of signs or symptoms that could be compatible with a diagnosis of WE.
- Eight cases were identified as having signs and symptoms suggestive of WE.

According to the applicant among the 8 subjects treated with fedratinib who had neurological symptoms suggestive of WE and had diagnosis of either WE or encephalopathy, there were 4 subjects identified in the Phase 3 pivotal study in patients with MF (JAKARTA), and the other 4 subjects were enrolled in other fedratinib studies (Studies ARD11936, ARD12042, ARD12181, and TES13519). For these 8 subjects the Applicant concluded that: 1 subject was determined not to have WE and 1 subject was diagnosed by consensus of experts as WE and for the remaining 6 subjects, the data

were inconclusive or did not support a diagnosis of WE. The applicant stated that all 7 cases of 1 definite and 6 potential WE occurred in subjects receiving 500 mg fedratinib at the time of experiencing neurological symptoms. There was no contribution of alcohol suspected in these subjects. Chronic nausea, vomiting, and weight loss resulting in malnutrition as well as severe diarrhea in the absence of thiamine supplementation are recognized causes of thiamine deficiency, which can lead to WE. The applicant added that all cases had pre-existing malnutrition, weight loss, and/or significant GI adverse events that were not adequately controlled as well as other risk factors that may have contributed to thiamine deficiency. A thiamine level was normal for 1 subject and not obtained for any other subjects at the time of symptoms. In one case, the subject had stopped fedratinib for 2 weeks and was only treated with IV fluids prior to the onset of symptoms. Two subjects continued receiving fedratinib treatment while their neurological symptoms improved. The analysis suggested that the potential causes of WE in these subjects treated with fedratinib were multifactorial, including malnutrition, nausea, vomiting, and diarrhea.

The Applicant stated that the data suggests that the potential WE events were not due to a direct pharmacologic effect of fedratinib on thiamine absorption or processing but could rather be a consequence of poor control of well-known fedratinib-associated GI AEs (diarrhea, nausea, and vomiting). Furthermore, the use of fedratinib does not appear to increase the risk of WE compared to the historical rates that have been reported in the general population and in MPN subjects. Thiamine deficiency, and therefore WE, is a preventable and treatable condition if recognized early and if thiamine replacement therapy is initiated in a timely manner.

FDA Review of the potential risk of WE

The FDA in consultation with the Division of Neurology Products (consult review completed by Dr. Steven Dinsmore) and the Oncology Center for Excellence (consult review completed by Dr. Joohee Sul) reviewed the safety database for fedratinib from 18 clinical studies to evaluate the safety signal of encephalopathy.

According to Dr. Dinsmore, the search of fedratinib's safety database identified 8 cases with diagnosis of encephalopathy or WE. The patient ages ranged from 62 to 77 years. Seven cases were reported in women and 1 case in male. The cases were identified in wide geographic regions (US, Europe, Middle east and Asia). In six cases patients had either primary or secondary MF, 1 case with PV and 1 subject had head and neck cancer. The time on fedratinib until symptoms were described was between two and thirteen cycles. Seven 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 metastatic head and neck cancer and severe malnutrition who had a fatal outcome. In one case, a male patient (b) (6) is

clinically least supported with diagnosis of WE, patient had no MRI report adjudicated as consistent with WE, and his case was confounded by likely hepatic encephalopathy (concomitant portal hypertension and liver dysfunction). The term of "core cases of WE" will refer to the 7 cases which does not include the potential hepatic encephalopathy case.

Table 59 summarized the cases of WE.

Table 59: Core Cases of Wernicke encephalopathy (WE), (All Treated Population)

Patient ID/ Demographic	Patient 1 (b) (6)	Patient 2 (b) (6)	Patient 3 (b) (6)	Patient (b) (6)	Patient 5 (b) (6)	Patient 6 (b) (6)	Patient 7 (b) (6)	Patient 8 (b) (6)
Study	EFC12153	EFC12153	EFC12153	EFC12153	ARD12181	TES13519	ARD11936	ARD12042
Country	France	Korea	Israel	Brazil	Spain	Belgium	US	Spain
Indication	Post-PV MF	Primary MF	Post-PV MF	Primary MF	Post-PV MF	H&N Cancer	Primary MF	PV
Age	76	71	77	63	62	67	70	67
Gender	female	female	female	female	male	female	female	female
Dose (mg/day)	500	500	500	500	400	500	500	500
Cycle of WE event	2	11 (after cross over)	3	3 (after cross over)	10	2	11	9
First Dose	(b) (6)							
Last dose								

Source: Consult's Reviewer (Dr. Dinsmore)

The time to onset of WE diagnosis seen in the 7 Core WE Cases is widely dispersed over the fedratinib treatment timeline. The most rapid time to onset occurs after 44 days while the most prolonged occurs at study day 529 as seen in Figure 11**Error! Reference source not found.** below. The time to onset of WE appears to lack a consistent temporal relationship to the start of fedratinib treatment which may suggest a complex underlying mechanism.

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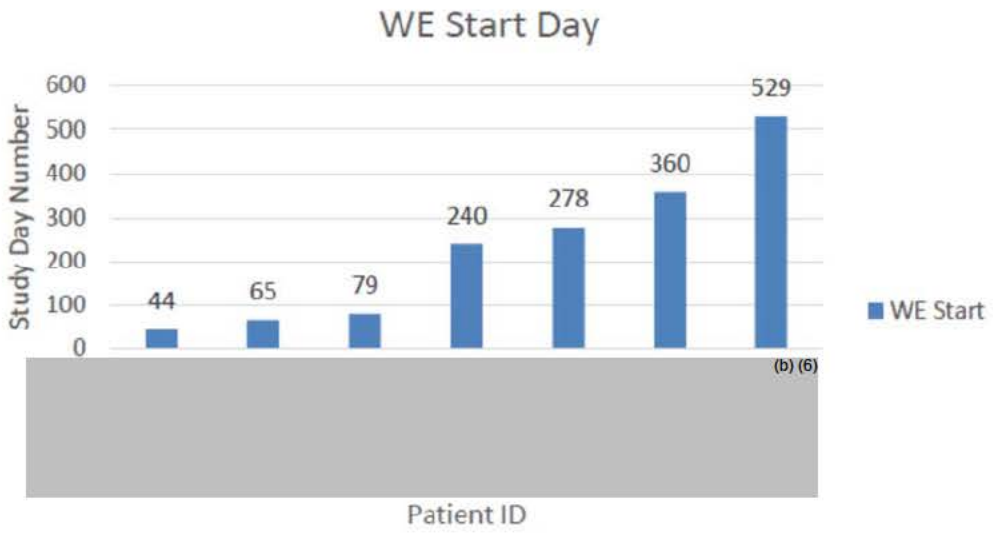
Figure 11: Time to Onset of WE After the Start of fedratinib Treatment



Source: Consult's Reviewer (Dr. Dinsmore)

According to Dr. Dinsmore, based on the assessment of the relationship between nutritional challenge (body weight decreased and the nutritional status metrics (albumin, globulin and serum protein)) and development of WE, evidence of a substantial nutritional challenge was identified in 5 of the 7 core cases. In two cases the evidence of nutritional challenge as a cause of critical thiamine depletion is weak and opens the possibility that there is a contribution by fedratinib to the dysfunction of thiamine economy leading to a WE event.

The assessment of imaging (MRI) findings revealed that in 5 cases the changes are consistent with WE (hyperintensities in the medial thalamus bilaterally, mamillary bodies and periaqueductal gray matter on FLAIR image sequence), and in 2 cases the imaging appears to be negative.

The assessment of response to thiamine treatment suggests that there is a clear temporal relationship between thiamine treatment and resolution of the WE event as evident by complete resolution of the symptoms upon receiving thiamine supplementation in 3 cases. The evidence for benefit of thiamine has strongest support in the profile of case (b) (6), where an MRI performed on study day 50 had diagnostic features of WE. The patient received thiamine on study day 51. An MRI was repeated on study day 67, and the high signal lesions in the bilateral medial thalamus, mamillary bodies, and periaqueductal gray matter had resolved.

Dr. Dinsmore concluded that 7 of the cases have valid diagnoses of Wernicke's Encephalopathy. The totality of information in the NDA submission supports the conclusion that there is a clear risk of WE and of the broader spectrum of thiamine

deficiency disorders; these include partial expressions of encephalopathy and peripheral nervous system dysfunction.

Dr. Sul stated that based on the review of reported 8 cases of potential WE, Dr. Sul assessed the five (5) patients have a clinical presentation consistent with WE, including imaging findings that are striking for symmetric midline abnormalities that are typical if not pathognomonic for WE. For all cases, the Caine criteria were applied, albeit with major limitations owing to the absence of complete clinical histories. Underlying risk factors such as weight loss, anorexia, nausea, and vomiting occurred variably and not all cases of potential WE transpired in the setting of a clear nutritional deficiency. However, given that the thiamine transport rather than absolute deficiency may be implicated in the cause of WE, these cases may have occurred in patients with normal or borderline thiamine reserves.

Dr. Sul concluded that, although the Applicant contends that the incidence of WE in fedratinib program is comparable to the incidence in the general population, there were no such cases identified in patients enrolled to receive placebo. In addition, although it is also likely that WE is underdiagnosed in patients with cancer, WE does not appear to be a commonly identified adverse drug reaction (ADR) reported across all oncology clinical trials. Finally, inhibition of thiamine function by chemotherapeutic agents has been proposed as a mechanism for chemotherapy related WE and a similar mechanism may be implicated in these cases, despite the Applicant's contention that the data are not supportive. Regardless of whether these cases meet the clinical criteria for WE, they do qualify as cases of serious encephalopathy occurring disproportionately in patients receiving fedratinib compared with patients receiving placebo.

Reviewer's comments: I agree with Dr. Dinsmore's and Dr. Sul's conclusions that although, the totality of clinical evidence in some of these cases may not meet the full clinical criteria for WE diagnosis, these cases qualify and support a diagnosis of serious encephalopathy associated with fedratinib treatment. The relationship between the development of encephalopathy and thiamine deficiency not fully apparent, due to lack of thiamine level measurement in most of the cases (only in 1 case were the thiamine level was normal). However, in most of the cases thiamine replacement suggested of at least partial recovery.

This clinical reviewer disagrees with the Applicant's conclusion that "the data suggests that the potential WE events were not due to a direct pharmacologic effect of fedratinib on thiamine absorption or processing but could rather be a consequence of poor control of well-known fedratinib-associated GI AEs (diarrhea, nausea, and vomiting)," due the following finding: 1) There was no cases reported in patients who received placebo, 2) In two cases patients crossover from placebo and developed WE after receiving 3 and 11 cycles of fedratinib, 3) Not all cases associated with significant GI toxicities or weight loss. Available data did not provide sufficient clinical evidence to conclude whether the

potential risk of encephalopathy including WE associated with fedratinib treatment is resulted from direct effect of the drug or due to synergy with other factors.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant used patient-reported outcome (PRO) instruments in the pivotal trial (JAKARTA) and the supporting trial (JAKARTA-2). The submission did not include a PRO evidence dossier(s) for review. However, the Applicant seeks PRO-related labeling claims for the secondary endpoints (the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0) for the respective studies.

We consulted the Clinical Outcome Assessment (COA) staff seeking input PRO data submitted and the applicant's proposed PRO language in Section 14 of the label. The COA consult review completed by Christopher St. Clair concludes the following:

- The modified MFSAF v2.0 includes concepts that are content relevant to MF patients based on literature and discussion with Clinical. This review concludes that the modified MFSAF v2.0 is adequate to support labeling of efficacy data from JAKARTA provided that the symptoms assessed by the instrument are clearly described in the label.
- (b) (4)

For future medical product development, sponsors should consider using the most recent version of the MFSAF (version 4.0), which includes a fatigue assessment. Additionally, sponsors should carefully consider the study design and its effect on PRO data interpretation. FDA recommends that if a claim of treatment benefit is sought, there is a clear endpoint definition and formal statistical testing with adjustment for multiplicity, as well as an appropriate pre-specified statistical analysis plan (SAP) with a plan to control the type 1 error rate. In the SAP, there should be details on the statistical analysis methods, procedures for handling missing values, justification for the endpoint definition and procedures for what constitutes meaningful within-patient change.

Reviewer comments: I agree with the COA consult's reviewer conclusion that the modified MFSAF v2.0 includes content and concepts relevant to patients with MF and adequate to support labeling. I also agree with the COA consult reviewer's recommendations for future medical product development in patients with MF to use

MFSAF (version 4.0).

8.2.7 Safety Analyses by Demographic Subgroups

Safety subgroup analyses were performed by age (65 years or less vs older than 65 years, 75 years or less vs older than 75 years), sex, race, baseline ECOG PS, baseline platelet count, baseline hemoglobin, and prior use of hydroxyurea.

The median treatment duration in each subgroup in the 400 mg and 500 mg were summarized in Table 60 below.

Table 60: Subgroup Exposure During the Entire Treatment Duration (All Treated Population)

Subgroup	Population	N	Fedratinib 400 mg		Fedratinib 500 mg	
			n	Duration Weeks	n	Duration Weeks
	All Treated	**288**	**96**	**62**	**97**	**60**
Age at baseline	≤ 65 years	154	61	61	49	62
	> 65 years	134	35	64	48	50
	≤ 75 years	262	86	61	87	61
	> 75 years	26	10	63	10	27
Sex	Male	169	54	61	61	63
	Female	119	42	63	36	43
Race	White	256	86	61	81	56
	Asian	27	8	62	14	67
	Black	4	1	63	2	15
Baseline ECOG PS	0	103	41	64	31	67
	≥ 1	185	55	61	66	47
Baseline Platelet count	< 100 x 10^9/L	47	14	55	15	48
	≥ 100 x 10^9/L	241	82	62	82	60
Baseline Hemoglobin level	≤ 10 g/dL	132	33	64	52	63
	> 10 g/dL	156	63	61	45	55
Prior Use of Hydroxyurea	Yes	182	69	61	59	61
	No	106	27	64	38	55

ECOG = Eastern Cooperative Oncology Group; n = number of subjects with data; N = total number subjects in subgroup; PS = performance status

Reviewer comments: The median duration of exposure in the 400 mg arm in the following subgroups, age, sex, race, baseline ECOG score, baseline Hg and prior history to hydroxyurea was similar to the overall population. The only exception was the median

exposure in patients with platelet count < 100 x 10^9/L was shorter than that in overall population. In the 500 mg arm, the median exposure was shorter in subgroups of age >65 years, female, ECOG ≥ 1 and platelet counts < 100 x 10^9/L compared to the overall population.

TEAEs by Age – Entire Treatment Duration

Age groups ≤ 65 versus > 65 years: The table below summarized the differences in frequency of most common adverse events by age group of 65 years or younger versus older than 65 years.

Table 61: TEAEs with at least 7% differences in frequencies between Age Subgroup ≤ 65 vs > 65 Years in any fedratinib arms during the entire on-treatment duration (All Treated Population)

Preferred Term	Fedratinib 400 mg		Fedratinib 500 mg	
	≤ 65 Years N= 61 n (%)	>65 Years N= 35 n (%)	≤ 65 Years N= 49 n (%)	>65 Years N= 48 n (%)
Anemia	32 (53)	21 (60)	25 (51)	22 (46)
Fatigue	12 (20)	12 (34)	2 (4)	12 (25)
Diarrhea	40 (66)	28 (80)	42 (86)	32 (67)
Nausea	38 (62)	26 (74)	26 (53)	25 (52)
Thrombocytopenia	13 (21)	3 (8)	12 (25)	10 (21)

Reviewer comments: The frequency of anemia, fatigue, diarrhea adverse events were more common in the age group of 65 years or older. However, thrombocytopenia was more common among age group of 65 years or younger in patients who received 400 mg of fedratinib.

Serious Adverse Events:

During the entire treatment duration: The frequency of serious adverse events in patients who received 400 mg and age group of older than 65 years compared to those in age group of 65 years or younger (46% vs 37%). Serious adverse events of pneumonia in patients who received 400 mg fedratinib were reported more frequently in age of 65 years or younger compared to those who are older than 65 years (7% vs 0%). However, SAE of cardiac failure in patients who received 400 mg of fedratinib reported in 3/35 (9%) of subjects in age group of older than 65 years compared to 2/61 (3%) of subjects in age group of 65 years or younger.

Grade 3 or 4 TEAEs:
During the entire treatment duration: Grade 3 or 4 TEAEs in the 400 mg reported in 77% of patients in the age group of older than 65 years compared to 67% of patients in age group of 65 years or younger.

8.2.8 Specific Safety Studies/Clinical Trials

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Refer to nonclinical review.

Human Reproduction and Pregnancy

There were no reports of pregnancy in subjects with MF or in healthy subjects who received fedratinib. However, there was 1 report of pregnancy in 35-year-old subject with ET (Study ARD12042) who reported an ectopic pregnancy on Day 418 who was receiving 200 mg of fedratinib. Fedratinib was interrupted, and the subject underwent surgical evacuation of retained products of conception. Patients recovered on Day 460.

Pediatrics and Assessment of Effects on Growth

This drug was not studied in pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose was reported for 6 patients in the fedratinib development program. In 3 patients no adverse events were reported and other 3 patients no serious ≤ Grade 2 adverse events were reported.

There does not appear to be a drug abuse potential.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There are no postmarketing data since fedratinib is not approved in any country. There was no safety update reported by the Applicant since no patients received fedratinib since the full clinical hold.

Expectations on Safety in the Postmarket Setting

The applicant is planning to conduct (b) (4)

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8.2.11 Integrated Assessment of Safety

Overall, 807 subjects received fedratinib in the pooled clinical studies throughout fedratinib clinical development, including 459 patients with myeloproliferative neoplasm.

8.3 Statistical Issues

The JAKARTA trial was part of the clinical trials put on hold due to the safety concerns with Wernicke's Encephalopathy. As a result, there is insufficient follow-up data to provide an estimate of the long-term benefits of drug in terms of overall survival and progression free survival.

8.4 Conclusions and Recommendations

The recommendation of regular approval of fedratinib for the treatment of patients with intermediate-2 to high risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis is primarily based on efficacy data from JAKARTA study in patients with intermediate-2 to high risk primary or secondary myelofibrosis.

The primary endpoint is spleen response (≥ 35% reduction in spleen volume at week 24 confirmed by MRI/CT 4 weeks later). The key secondary endpoint is symptom response (≥ 50% reduction in total symptom score).

JAKARTA trial: The primary endpoint was achieved by 35 of 96 patients (37% [95%CI, 27%-46%]) in the fedratinib 400 mg group compared to 1 of 96 patients (1% [95% CI, 0%-13%]) in the placebo group. JAKARTA met its primary endpoint which showed a statistically significant difference in spleen response rate in two-sided log-rank test ($p < 0.0001$) in favor of fedratinib 400 mg compared to placebo. The duration of spleen response was 18.2 months. The key secondary endpoint of total symptoms response also, showed a statistically significant favoring fedratinib.

The secondary endpoint of symptoms response rate was achieved in 36 of 89 (40%) patients in the fedratinib 400 mg group compared to 7 of 81 (8.6%) patients in the placebo group. The fedratinib 400 mg showed statistically significant difference compared to placebo ($p < 0.0001$).

The efficacy results in JAKARTA trial showed a clinically meaningful and statistically significant improvement of the primary endpoint of spleen response rate and key secondary endpoint of symptoms response rate in patients with intermediate-2 or high-risk MF who are treated with fedratinib compared to placebo.

Results from the supporting trial (JAKARTA-2) were consistent with efficacy results from JAKARTA. Both trials showed significant improvement in the primary endpoint of spleen volume reduction and key secondary endpoint of total symptoms score reduction with fedratinib treatment.

The safety of fedratinib was evaluated among 608 patients who received multiple doses of fedratinib as a single agent (ranging from 30 mg to 800 mg) in 9 clinical studies (JAKARTA, ARD11936, JAKARTA2, ARD12042, ARD12888, TED12037/ TED12015, INT12497, and TES13519) in patients with myelofibrosis polycythemia vera (PV) and essential thrombocythemia (ET), or solid tumors, including 459 patients with myelofibrosis. A total of 358 of the 608 (59%) patients were exposed for 6 months or longer and 237 (39%) were exposed for 12 months or longer.

The most common adverse reactions including laboratory abnormalities were diarrhea, nausea, anemia, vomiting, fatigue, thrombocytopenia, and constipation.

Wernicke's Encephalopathy (WE): Serious and fatal encephalopathy, including Wernicke's encephalopathy, occurred in fedratinib treated patients. Serious cases were reported in 1.3% (8/608) of patients treated with fedratinib in clinical trials and 0.16% (1/608) of cases were fatal.

The safety of fedratinib 400 mg was evaluated during randomization period in the JAKARTA trial in 96 patients who received 400 mg fedratinib daily and was compared to 95 patients who received placebo. Key eligibility criteria included adult patients with intermediate-2 or high-risk primary MF or post-PV MF or post-ET MF with splenomegaly, platelet count ≥50 x 10^9/L, and no splenectomy. Patients received fedratinib at 400 mg daily (n=96) or placebo (n=95). Among patients receiving fedratinib, 82% were exposed for more than 6 months and 65% for more than one year. Patients had a median duration of exposure to fedratinib 400 mg daily of 15.5 months compared with placebo where patients were treated for 6 months or until disease progression after which patients were allowed to crossover to active treatment. Notable safety observations adverse reactions are:

- Serious adverse reactions occurred in 21% of fedratinib-treated patients. Serious adverse reactions in ≥2% of patients receiving fedratinib 400 mg daily included cardiac failure (5%) and anemia (2%). Fatal adverse reactions of cardiogenic shock occurred in 1% of patients receiving fedratinib 400 mg daily.

- Permanent discontinuation due to an adverse reaction occurred in 14% of patients receiving fedratinib. Most frequent reasons for permanent discontinuation in 2% or more of patients receiving included cardiac failure (3%), thrombocytopenia, myocardial ischemia, diarrhea, and increased blood creatinine (2% each).

- Dosage interruptions due to an adverse reaction occurred in 30% of patients who received fedratinib. Most adverse reactions requiring dosage interruption in >3% of patients who received fedratinib included anemia, diarrhea, nausea, and vomiting.

- The most common adverse reactions including laboratory abnormalities (reported in ≥ 20%) were diarrhea, nausea, vomiting, and fatigue/asthenia.

- Grade 3 or 4 ALT, AST, or Total Bilirubin (TBL) Elevation: Elevations of ALT and AST (all grades) occurred in 43% and 40%, with Grade 3 in 1% and 0%, respectively, of fedratinib- treated patients. The median time to onset of any grade transaminase elevation was approximately 1 month, with 75% of cases occurring within 3 months. One patient developed hepatic failure with Grade 4 elevations of ALT, AST, and bilirubin at a dose of 300 mg.

- Amylase and Lipase Elevation: Grade 3 or higher amylase and/or lipase elevations developed in 2% and 10%, respectively, of fedratinib-treated patients. The median time to onset of any grade amylase or lipase elevation was 15 days, with 75% of cases occurring within 1 month of starting treatment. One patient developed pancreatitis in the fedratinib clinical development program (n=608) and pancreatitis resolved with treatment discontinuation.

The long-term safety was limited due to early termination of fedratinib development. Only 24 patients received fedratinib for 24 cycles or more. The analysis on those patients did not identified any new adverse reaction.

From clinical perspective the safety profile of fedratinib was shown to be manageable by dose modifications and monitoring for the risk of encephalopathy. However, the reviewer recommends including a Boxed Warning in the label regarding the risk of encephalopathy including Wernicke's encephalopathy (WE). The Warning should include assessment of thiamine prior to start fedratinib, periodically during treatment, and as clinically indicated. Patients should be monitored for signs or symptoms of encephalopathy during treatment.

The efficacy and safety data from the JAKARTA study and the pooled safety data support a favorable benefit risk profile for fedratinib for the treatment of patients with intermediate-2 to high risk primary or secondary MF.

Laura Fernandes, PhD
Statistical Reviewer

Jingjing Ye, PhD
Statistical Team Leader

Saleh Ayache, MD
Primary Clinical Reviewer

Kathy Robie Suh, MD, PhD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held.

10 Pediatrics

Fedratinib was granted an Orphan Drug Designation under FDA Act 526 for the treatment of secondary and primary myelofibrosis on May 18, 2009. Therefore, this application is exempt from the requirement of the Pediatric Research Equity Act (PREA).

11 Labeling Recommendations

11.2 Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Boxed Warning	(b) (4)	Warning for encephalopathy including WE
Section 1	INREBIC® is indicated for the treatment of adult patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) (b) (4) .	INREBIC® is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).
Sections (b) (4)	–	Added dose modifications for patients using concomitant strong CYP3A4 inhibitors.,
Section (b) (4)	–	Added dose modification in patients with severe renal impairment (creatinine clearance (CLcr) 15 mL/min to 29 mL/min
Section 5	(b) (4) - -	The risk of encephalopathy including WE was moved to Section 5.1 Added hepatic toxicity (section 5.4) Added Amylase and Lipase elevation (Section 5.5)
Section 14	Clinical Studies	(b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

To communicate the risk of encephalopathy, including Wernicke's encephalopathy, I recommend that an addition of the Box Warning, assess the thiamine level prior and during treatment with fedratinib, monitoring and management of GI toxicity and monitoring patients for early sign and symptoms of WE may be adequate to mitigate the risk. In addition, I recommend the applicant should be required to establish a "targeted pharmacovigilance" collection of data of all cases of encephalopathy including WE to further assess the safety signal and it is association with fedratinib treatment.

No risk evaluation and mitigation strategies (REMS) is recommended.

13 Postmarketing Requirements and Commitment

Due to insufficient follow-up of patients on JAKARTA and JAKARTA2 trials to establish the long-term safety outcome of patients treatment with fedratinib, I recommend that the following post-marketing requirement:

1. Conduct a randomized, concurrently controlled clinical trial comparing fedratinib 400 mg once daily to best available therapy in patients with DIPSS-intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib. The trial will enroll a sufficient number of patients to ensure that at least 150 subjects are treated with at least 6 cycles of fedratinib and are followed for at least 3 years from first dose, or until death. The protocol should include measures to assess and manage adverse events of nausea, diarrhea, vomiting, thiamine deficiency, and encephalopathy at baseline and during the trial. The final protocol must be agreed upon with the Agency.

The following clinical pharmacology trials will be required under FDAAA:

2. Conduct a clinical pharmacokinetic trial to determine an appropriate dose of fedratinib to minimize toxicity in subjects with severe hepatic impairment. Design and conduct the trial in accordance with the FDA guidance for industry entitled, *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.

3. Conduct a clinical trial to evaluate the effect of coadministration of a dual CYP2C19 and CYP3A4 inhibitor on the pharmacokinetics and safety of a single dose of fedratinib. Design and conduct the trial in accordance with the FDA guidance for industry entitled, *Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications.* In addition, conduct physiologically based pharmacokinetic (PBPK) modeling using data from the clinical trial to determine an appropriate dose of fedratinib in patients dosed with fedratinib at steady state and coadministered with multiple doses of dual CYP2C19 and CYP3A4 inhibitor in accordance with FDA guidances for industry entitled, *In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies* and *Physiologically Based Pharmacokinetic Analyses – Format and Content*.

4. Conduct a clinical trial to evaluate the effect of single dose of fedratinib on the single dose pharmacokinetics and safety of sensitive substrates of P-gp, BCRP, MATE-1/2K, and OCT2 transporters. Design and conduct the trial in accordance with the FDA guidance for industry entitled, *Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications.*

The following postmarketing commitment will be subject to reporting requirements under Section 506B:

1. Conduct a clinical pharmacokinetic trial to determine an appropriate dose of fedratinib when fedratinib is coadministered with and without multiple doses of strong and moderate CYP3A4 inducers. Design and conduct the trial in accordance with the FDA guidance for industry entitled, *Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications.*

14 Division Director (DHOT)

Haleh Saber, PhD
Deputy Division Director

15 Division Director (OCP)

Nam Atiqur Rahman, PhD
Division Director

16 Division Director (OB) Comments

Rajeshwari Sridhara, PhD
Division Director

17 Division Director (Clinical) Comments

Associate Division Director (Deisseroth) Summary Review of NDA 212327
(This section is based in part on the reviews of Drs. Saleh Ayache and Kathy Robie Suh.)

Background: On January 3, 2019, Impact Biomedicines, Inc, and Celgene submitted NDA 212327 in which they requested marketing approval of fedratinib (Inrebic) for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. This request was based on Study EFC121153 (Jakarta), a phase 3 randomized double-blind placebo-controlled trial in which 289 patients with intermediate-2 or high-risk primary or secondary myelofibrosis were randomized (1:1:1) to placebo, or to 400 or 500 mg daily oral fedratinib in capsules. The primary efficacy endpoint was the proportion of subjects with ≥ 35% of spleen volume reduction (SVR) at the end of cycle 6 (EOC6) assessed by MRI/CT scans and confirmed 4 weeks later. The key secondary endpoint was the percentage of patients with a ≥ 50% reduction of the total symptom score (TSS) from baseline to EOC6 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v 2.0.

Efficacy Results: The analysis of the primary endpoint in the Jakarta trial showed that 36.5% of the 96 patients receiving 400 mg of fedratinib daily exhibited ≥ 35% SVR whereas only 1% of the 96 patients given placebo showed a ≥ 35% SVR at the EOC6 ($p<0.0001$). The median duration of the SVR was 18.2 months. The analysis of the key secondary endpoint showed that 40.4% of the 89 patients given 400 mg daily of fedratinib exhibited a ≥ 50% reduction of the TSS at the EOC6 whereas only 8.6% of the 81 patients given placebo showed such a change ($p<0.0001$). The baseline TSS for the 400 mg po qd fedratinib arm and the placebo arm were 17.50 and 15.45 respectively out of a possible maximum score of 60.

Safety Results: The primary safety endpoint in the Jakarta trial was a comparison of the 96 patients on the 400 mg fedratinib arm with the 95 patients on the placebo arm. The median duration of exposure on the 400 mg fedratinib arm was 15.5 months compared to 6 months on the placebo arm. Deaths due to adverse reactions was 5% on the 400 mg fedratinib arm and 8.2% on the placebo arm. The safety review of Dr. Saleh Ayache states that “the TEAEs reported in ≥ 10% of patients during the entire treatment duration with at least 5% difference

between the fedratinib and the placebo arms were GI toxicity (nausea, vomiting, diarrhea), anemia, thrombocytopenia, urinary tract infection, fatigue and asthenia, peripheral edema, liver enzymes increased (AST and ALT), muscle spasm, bone pain, pain in the extremity, cough, dyspnea, dizziness, and headache. The most common adverse reactions were diarrhea, nausea, anemia, vomiting, fatigue, thrombocytopenia and constipation.

Encephalopathy with Fedratinib: Serious and fatal cases of encephalopathy, including Wernicke's encephalopathy (WE) may have occurred in up to 7/608 patients treated with fedratinib. There were no patients with encephalopathy reported on the placebo arm of the Jakarta trial. WE was associated with the 500 mg daily dose of fedratinib, with treatment-emergent AEs of GI origin and with baseline malnutrition. The Applicant hypothesized that these factors led to thiamine deficiency and then to WE. The Applicant has hypothesized that the risk of WE associated with fedratinib can be mitigated by: 1. monitoring patients for thiamine deficiency and for signs and symptoms of WE, 2. monitoring patients for GI toxicity and management of these side effects, and 3. thiamine supplementation.

PMRs and PMCs: PMR #1. Conduct a randomized controlled trial comparing fedratinib at 400 mg/day with BAT for ability to assess and manage adverse events of nausea, vomiting, diarrhea, thiamine deficiency and encephalopathy at baseline and during the trial; PMR #2. Conduct a PK trial to determine the dose of fedratinib for severe hepatic impairment; PMR #3: DDI study to assess effect of co-administration of CYP2C19 and CY3A4 on PK and safety of fedratinib; PMR #4: Effect of single dose of fedratinib on P-gp, BCRP, MATE-1/2K, and OCT2 transporters; and PMC #1: PK trial to identify appropriate dose of fedratinib when it is co-administered with strong inducers of CYP3A4.

Benefit Risk Discussion: Analysis of the Jakarta trial suggests that the administration of 400 mg of fedratinib po qd increases the percentage of patients exhibiting a clinically meaningful reduction of the SVR (with a median duration of 18.2 months) and TSS that offsets the adverse reactions associated with fedratinib which can be managed by dose adjustments. PMR #1 will study the optimal ways to monitor and manage the risk of encephalopathy with fedratinib therapy.

Regulatory Recommendation: This Supervisory Associate Division Director agrees with the recommendation of the reviewers for approval of fedratinib for the following indication: adult patients with intermediate-2 or high-risk primary or

secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director

18 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Richard Pazdur, MD
Acting Director

19 Appendices

19.2 References

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19.3 Financial Disclosure

Covered Clinical Study (Name and/or Number): EFC12153, ARD12181, ARD11936, ARD12888, ARD 12042, TED12037, TED12015, BEX12257, TDU12620, FED12258, INT12497, INT12893, INT12894, BDR12462, ALI13451, POP13450, POP13449 and TES13519

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 892		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 40 Investigators		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.4 Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

19.5 OCP Appendices (Technical documents supporting OCP recommendations)

19.5.1 General Information

Table 63: Listing of clinical pharmacology studies

Study Type	Study Number	Formulation	Study Description
Single Dose Studies	BEX12257	Powder	Single dose (200 mg) ADME study in healthy subjects
	TDU12620	Initial, 1A1	Single dose ascending study (10-680 mg) in healthy subjects
Bioavailability and Food Effect	ALI13451	1B1	Food effect study in healthy Subjects
	FED12258	1A1	Food effect study (100 & 500 mg) in healthy Subjects
	BDR12462	1B1	BE study 500 mg tablet vs. 500 mg capsules
Drug-Drug Interaction Studies	INT12893	1A1	Drug-drug interaction study with strong CYP3A inhibitor, ketoconazole in healthy Subjects
	INT12894	1B1	PPI study in healthy Subjects

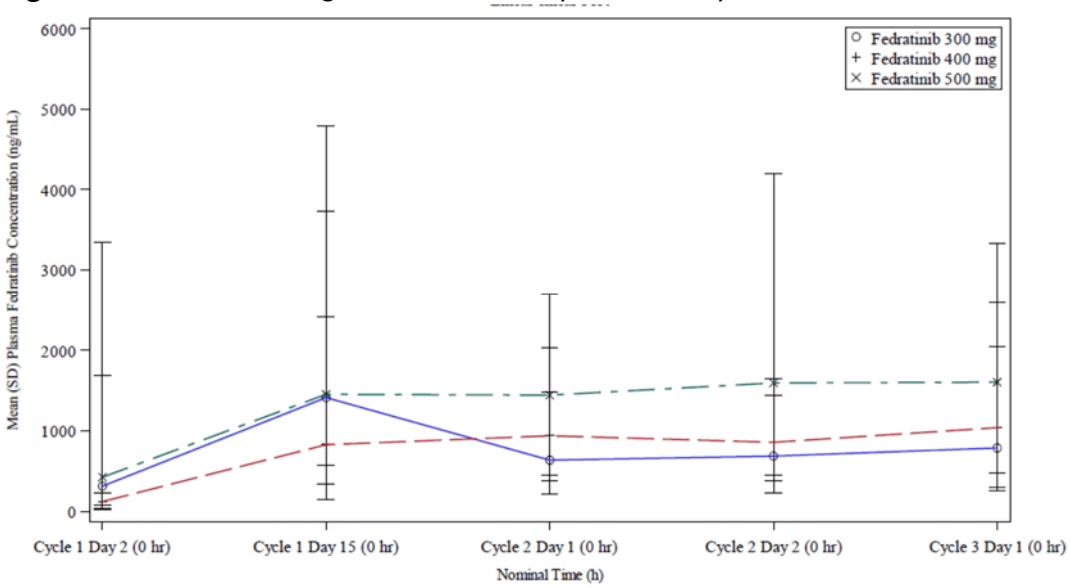
	INT12497	1A1	DDI cocktail study (CYP3A, 2C19, 2D6) in solid tumors
Thorough QT	TES13519	1B1	Multiple 500 mg doses of fedratinib in solid tumors.
Organ Impairment	POP13449	1B1	Single dose renal impairment study in healthy subjects
	POP13450	1B1	Single dose hepatic impairment study in healthy subjects
Multiple Dose in Patients	TED12037	Initial	Phase 1 study in MF (30-800 mg QD)
	TED12015	Initial	Phase 1/2 study in MF (Japanese) (30-800 mg QD)
	ARD11936	1A1	Phase 2 study in MF at 300, 400 & 500 mg QD.
	ARD12042	1A1	Phase 2 study in PV or ET (100-600 mg QD)
	ARD12888	1B1	Phase 2 study in MF (300, 400, & 500 mg QD)
	ARD12181	1A1	Phase 2 study of in ruxolitinib-treated MF (400 mg)
	EFC12153	1B1	Phase 3, placebo-controlled randomized study in MF (400 & 500 mg QD)

Initial = initial formulation (10, 40, 200 mg), 1A1 = new strengths (50, 100 mg), 1B1 = (b) (4) (100 mg), & 1C1 = to-be-marketed (same as 1B1 but with ink printing), ADME = absorption, distribution, metabolism, and excretion, BA = bioavailability, CYP = cytochrome P450, PD = pharmacodynamic, P-gp = P-glycoprotein, PK = pharmacokinetic, QD=once-daily.
Source: Clinical Pharmacology Summary, Module 2.7.2

Single and Multiple Dose Pharmacokinetics, and Dose Proportionality

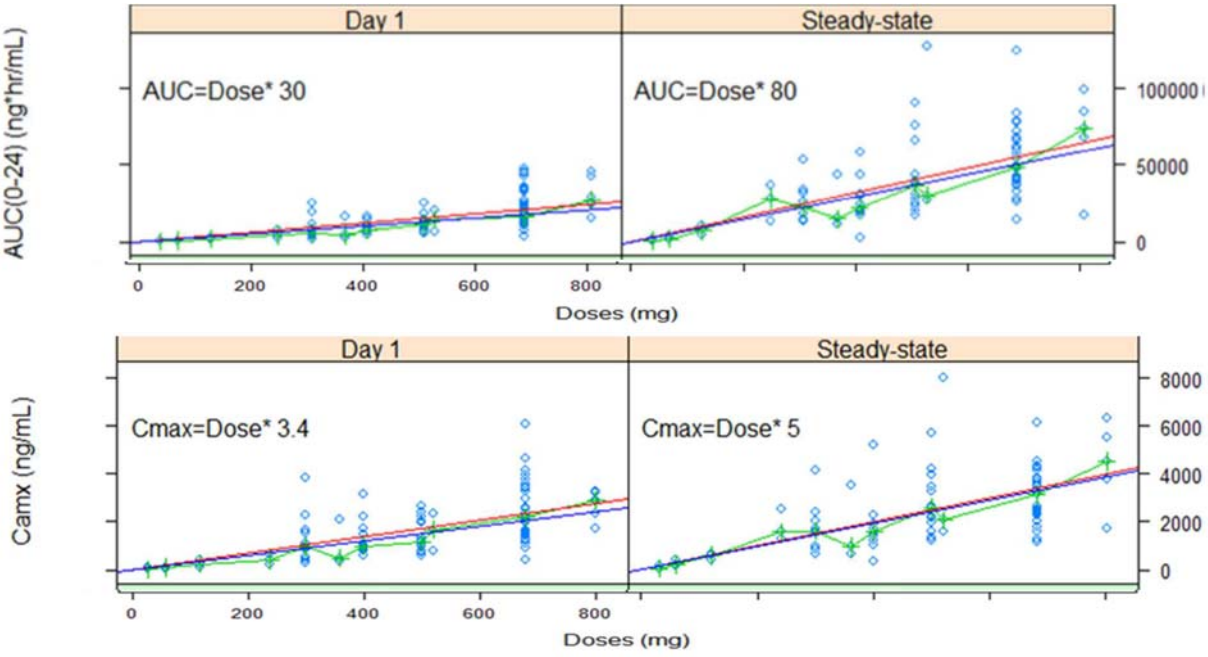
Following once daily fedratinib dosing in patients with MF in Study ARD11936, steady state was achieved by Day 15 (Figure 12). Fedratinib PK was greater than dose proportional between 30 mg and 800 mg after a single dose and at steady state (Cycle 2, Day 1) following once daily dosing in patients with MF(Figure 13). At 300 mg to 500 mg once daily, the PK was approximately dose proportional (Table 64). In addition, population PK analysis indicated that the increase in fedratinib AUC was dose proportional at ≥200 mg in patients (Appendix 19.5.7.1). This was also supported by observed data between 240 to 800 mg once daily in patients with MF. There was up to 3- to 4-fold accumulation of fedratinib exposure at steady state at 300 mg to 500 (Table 64).

Figure 12: Fedratinib trough concentrations by visit in Study ARD11936



Source: Figure 14, Study ARD11936

Figure 13: Box plots of geometric mean AUC (top) and Cmax (bottom) between 5 and 600 mg after single dose (left) and multiple dose (right) in patients with myelofibrosis



Source: Figures 34 & 35 of SCP

The PK parameters after 400 mg once daily administration in patients with MF are listed in Table 64.

Table 64: Dose proportionality of fedratinib PK in patients with myelofibrosis in Study ARD11936

	Once daily dosing		
PK Parameter	**300 mg** (n=10)	**400 mg** (n=10)	**500 mg** (n=11)
$AUC_{0\text{-}24hr}$, ng·h/mL	7016 (101)	9133 (33)	9982 (55)
C_{max}, ng/mL	1065 (91)	1294 (47)	1267 (55)
$AUC_{0\text{-}tau}$, ng·h/mL*	22371 (56)	26870 (43)	38712 (61)
C_{max}, ng/mL*	1534 (66)	1804 (49)	2539 (52)
Racc	3.2	2.9	3.9
* at C2D1. From Tables 36 & 37, ARD11936			

Inter-subject variability

Following a single dose of 400 mg in patients with MF, the inter-patient variability (%CV) of fedratinib under fasted conditions for fedratinib Cmax was 47% to 49% and $AUC_{0\text{-}inf}$ was 33 to 43% (Table 64) under fasted state. The variability under fed and fasting conditions in healthy subjects were similar (Table 66).

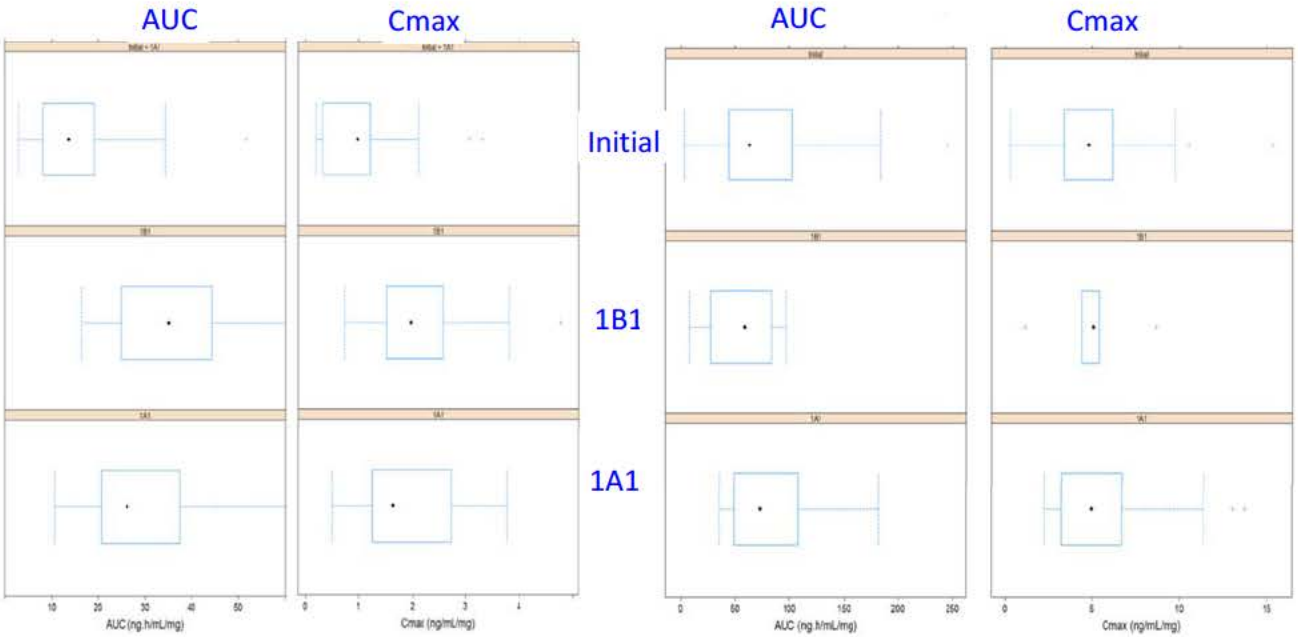
19.5.2 Absorption, Distribution, and Elimination

Absorption

Fedratinib is rapidly absorbed in the fasted state with a median time to peak concentration (Tmax) of 3 hour (range 2 to 4 hours) following a 400 mg oral once daily in patients with MF.

Comparability of Formulations APPEARS THIS WAY ON ORIGINAL

Figure 14: Comparison of dose normalized pharmacokinetic exposure for formulations Initial, 1A1, and 1B1 in healthy subjects (left) and patients with myelofibrosis (right) following a single oral dose



The left and right edges of the box represent the 25th and the 75th percentiles, respectively. Whiskers indicate the maximum and minimum, respectively. The black dots represent the median. The blue circles represent the outliers.
Source: Figures 2 & 6, FEDR-MPK-003P

The AUC and Cmax results from the initial, 1A1, and 1B1 clinical formulations were compared in healthy volunteer and patient studies (Figure 14). The mean dose normalized AUC and Cmax were comparable between formulations in patients (Figure 14, right). The mean dose normalized AUC in healthy volunteers appears similar for 1A1 and 1B1 formulations, but were lower for intial+1A1, however, the variability overlapped Figure 14, left).

Also, addition of formulation (the relative impact of the initial formulation and formulation 1A1 on formulation 1B1) as a covariate in the final population PK model indicated the impact of formulation on the PK of fedratinib was not clinically meaningful (Appendix 19.5.7.1). The results indicated that patients receiving the initial formulation and formulation 1A1 had 15% higher and 23% lower V2/F, respectively, compared with patients receiving formulation 1B1. The magnitude of changes in V2/F by formulation were <30%, and there was no effect on AUC.

Food Effect

Food had no effect on fedratinib exposure (Table 65). In the randomized clinical trial, INREBIC was administered without food. The Applicant recommended administration of INREBIC with or without food.

The effect of food on fedratinib PK was evaluated in the following two, single dose (2x 20 mg) studies in healthy subjects using the 1A1 and 1B1 capsule formulations:

- Study ALI13451: open label, 3-sequence, 3-period, 3-treatment, single dose (500 mg), crossover study with a 14-day washout between periods in 18 healthy subjects. Treatments included high-fat meal, low-fat meal and fasted conditions, and blood samples for PK were collected over 168 hour in all periods.
- Study FED12558: open-label, randomized, 2-sequence, 2-period, 2-treatment crossover study with a minimum 7-day washout between treatments, conducted in 2 cohorts in healthy subjects (n=9 in Cohort 1 and n=8 in Cohort 2). Cohort 1 tested 100 mg and Cohort 2 tested 500 mg. High fat meal was used in both cohorts. PK were collected over 168 hour in both periods

A high-calorie, high-fat meal (total 815 calories: 52% from fat, 33% from carbohydrate and 15% from protein) was used in Studies ALI13541 and FED12558, consistent with the recommendations in the Food Effect FDA Guidance for Industry (2002). Food was administered within 30 minutes prior to study drug administration. A low-fat meal (total 162 calories: 6% from fat, 78% from carbohydrate and 16% from protein) was also used in Study ALI13541

Table 65: Point estimates and 90% confidence intervals of pharmacokinetic parameters with a high-fat meal or a low-fat meal.

Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	C_{max} (ng/mL)	Fed/Fast
Study FED12558 (n=9)			
Fed-Hi vs Fast (100 mg, 1B1)	0.96 (0.85 to 1.08)	0.86 (0.72 to 1.02)	1.33
Study FED12558 (n=8)			
Fed-Hi vs Fast (500 mg, 1B1)	1.24 (0.89 to 1.74)	1.14 (0.97 to 1.33)	2.00
Study ALI13451 (n=12-18)			
Fed-Lo vs Fast (500 mg, 1A1)	1.22 (0.92 to 1.62)	1.12 (0.83 to 1.49)	0.80
Fed-Hi vs Fast (500 mg, 1A1)	0.94 (0.78 to 1.12)	0.91 (0.72 to 1.16)	1.60
Fed-Hi: High fat meal, Fed-Lo: Low fat meal, and Fast: fasted state			

Administration of a single 100 mg or 500 mg dose of fedratinib with a high-fat, high-calorie meal in healthy subjects resulted in 4 to 24% change in $AUC_{0\text{-}inf}$ and 8 to 14% change in C_{max} (Table 65). The median T_{max} with food was delayed by a median of 0.5 to 2 hours compared to fasted conditions (Table 66). With a low fat meal at single dose of 500 mg, the $AUC_{0\text{-}inf}$ increased by 22% and Cmax increased by 12% (Table 65).

Compared to fasted conditions (67%), the incidence of gastrointestinal toxicity was reduced in subjects taking a high-fat meal (17%) but was only slightly lower in subjects taking a low-fat meal (59%). Particularly, the incidence of nausea (6% vs. 56%), vomiting (0% vs. 33%) and diarrhea (6% vs. 28%) was reduced with a high-fat meal compared to fasted subjects, however, was only slightly lower with a low fat meal compared to the fasted subjects (47% vs. 56%, 29% vs. 33%, and 24% vs. 28%).

Table 66: Pharmacokinetic parameters of a single dose of fedratinib with a high-fat meal and low-fat meal.

PK parameter (unit)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max}† (hr)	$T_{1/2}$ (hr)
Study FED12558 (n=8, 9)				
Fasted (100 mg, 1B1)	2500 (34)	161 (48)	1.5 (0.5, 3)	86 (31)
Fed (100 mg, 1B1)	2610 (37)	144 (44)	2 (1.5, 6)	108 (58)
Fasted (500 mg, 1B1)	17000 (37)	1060 (36)	2 (1, 4)	86 (21)
Fed (500 mg, 1B1)	22300 (28)	1120 (30)	4 (3, 4)	76 (29)
Study ALI13451 (n=34, n=13)				
Fasted (500 mg, 1A1)	17400 (29)	1090 (42.3)	2.5 (1, 6)	75 (23)
Fed-Lo (500 mg, 1A1)	25700 (38)	1560 (40.2)	2 (1, 4)	72 (20)
Fed-Hi (500 mg, 1A1)	21700 (31)	1040 (32.3)	4 (2 - 6)	71 (42)

†median (min, max),
Source: Study FED12558, ALI13451

Distribution:

Fedratinib is 92% bound to human plasma proteins in vitro, including alpa-1 acid glycoprotein. Fedratinib was 96 to 98% bound ex vivo based on Studies POP13449 and 13450.

Mean radioactivity concentration ratios between blood and plasma ranged from 0.615 to 0.753 up to 16 hours postdose.

The volume of distribution (V/F) at steady state in patients with MF was 1770 L (Appendix 19.5.7.1).

The volume of distribution (V/F) after single dose at 300 mg and 500 mg in healthy subjects was 2620 L (21% CV) and 1190 L (22% CV), respectively.

Elimination

The fedratinib time-concentration profile exhibited a rapid decline in concentrations within 24 hours followed by a prolonged decline. In dose escalation study in healthy subjects, the mean (%CV) terminal half-life ($t_{1/2}$) of fedratinib was 62 hours (30%) and 78 hours (10%), and the mean (%CV) CL/F was 46 L/h (23%) and 21 L/h (14%) at single dose of 300 mg and 500 mg, respectively.

In patients with MF, the terminal $t_{1/2}$ of fedratinib was 114 hours at steady state, and the mean (%CV) apparent oral CL/F of fedratinib 13 L/h (51%) with CL/F independent of dose at doses ≥ 200 mg based on population PK analysis (Appendix 19.5.7.1). The effective half-life was 41 hours based on 3-fold accumulation at steady state with daily dosing (T½eff = tau*ln2 / ln[Rac/(Rac-1)])

Metabolism

In plasma, the parent drug was the main circulating compound, representing on average 80% (73.8% to 84.9%) of radioactivity AUC over 12 hours.

Two circulating metabolites were detected in plasma, the predominant metabolite SAR317981, was the pyrrolidone derivative of unchanged drug, accounting for ~ 9% of the radioactivity AUC. This metabolite was approximately 2-fold less active than the parent compound in vitro. The second circulating metabolite, SAR318031, N-butyric acid derivative of SAR317981, was detected in only 1 subject, and represented 6% of radioactivity AUC.

In vitro studies in native human hepatocytes and liver microsomes indicate that CYP3A4 (up to 77%), CYP2C19 (up to 20%), and FMO3 (up to 33%) appear to be the predominant isoforms responsible for the metabolism of fedratinib (MIH0888, PDM-07-101348-028) while CYP1A2, 2C8, 2C9, 2D6, FMO1 have a low contribution (<5%). In vitro studies using recombinant CYP and FMO isoforms indicate that among recombinant CYP3A and FMO isoforms, CYP3A4 and FMO3 were the major contributors for fedratinib metabolism.

Excretion

An open-label, mass balance study (BEX-12257) was conducted in healthy volunteers (n=6) with a single oral dose (200 mg) of fedratinib [^{14}C] oral solution. PK samples were collected up to 336 hours in blood and plasma. Urine samples were collected from pre-dose, and 12 to 24 hour intervals up to 336 hours. The excretion of radioactivity in feces was monitored at predose on Day 1 and up to 336 hours.

The radioactivity in the feces was 77% ± 7% in the urine was 5% ± 1% and of the total dose. Unchanged fedratinib accounted for 23% of the total dose in feces and 3% of the total dose in urine. Recovery was 82% in the mass balance study.

19.5.3 In Vivo Drug Interaction Studies

There is an increased risk of infections in patients with MF. For this reason, majority of patients with MF are prescribed anti-infectives, including azole anti-fungals. About 30% of patients had infections in Studies EFC12153 and ARD12181, and anti-infectives were coadministered in about 50% of patients in the fedratinib treated arms. A dedicated *in vivo* study, and simulations using physiologically based population PK (PBPK) model were submitted to evaluate the potential interaction of fedratinib with strong and moderate CYP3A4 modulators, and dual CYP2C19 and CYP3A4 inhibitors.

Strong CYP3A4 inhibitor increased single dose (300 mg) fedratinib exposures up to 3-fold (Table 67), and multiple doses of 400 mg fedratinib was predicted to increase fedratinib exposure at steady state by 2-fold (Appendix 19.5.6). Moderate CYP3A4

inhibitors was predicted to increase fedratinib exposure at steady state by less than 20% (Appendix 19.5.6).

Based on the above findings it will be recommended in the labeling to use concomitant medications that do not have strong CYP3A activity, and if unavoidable, the INREBIC dose be reduced to 200 mg once daily when coadministered with strong CYP3A inhibitor. No dose adjustment will be recommended for moderate CYP3A4 inhibitors.

No dedicated DDI study was conducted and PBPK model was not sufficient to assess the effects of strong or moderate CYP3A4 inducers and dual CYP2C19 and CYP3A4 inhibitors (Appendix 19.5.6). Therefore, it will be recommended that patients avoid the use of INREBIC with drugs that are strong and moderate inducers of CYP3A4 and dual CYP2C19 and CYP3A4 inhibitors in the labeling.

Drug-Drug Interactions

Effects on Fedratinib

Effect of Strong CY3A Inhibitors

Dose reduction is required with the co-administration of strong CYP3A4 inhibitors.

DDI Studies:
The effect of ketoconazole (a strong CYP3A4 inhibitor), on fedratinib PK was evaluated in an open-label, fixed sequence, 2-treatment, single dose, crossover study (INT12893) with a 15-day washout between periods in 14 healthy subjects. Two cohorts (n=7/cohort) were used: single dose of 50 mg in Cohort 1 and 300 mg in Cohort 2. Fedratinib alone was administered in Period 1 under fasting conditions. In Period 2, all subjects received 200 mg BID of ketoconazole (under fed conditions) from Days 1 to 14 and a single dose of fedratinib (under fasting conditions) was co-administered on Day 6. The blood samples for PK were collected at predose and up to 168 hours post dose in Day 1 of Period 1 and Day 6 of Period 2.

Table 67: Point estimates and 90% confidence intervals of pharmacokinetic parameters in the presence of strong CYP3A inhibitor

Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	C_{max} (ng/mL)	Glas+drug/Glas
Study INT12893 (n=7/cohort)			
Fedratinib+Keto vs Keto (50 mg)	3.85 (2.89 to 5.12)	1.85 (1.62 to 2.11)	1.0
Fedratinib+Keto vs Keto (300 mg)	3.06 (2.46 to 3.80)	1.93 (1.18 to 3.17)	0.8
Keto=ketoconazole Source:			

Table 68: Pharmacokinetics of fedratinib in the presence of strong CYP3A inhibitor

PK parameter (unit)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max}† (hr)	$T_{1/2}$ (hr)
Study INT12893 (n=7/cohort)				
Fedratinib (50 mg)	1290 (29)	72 (28)	1.5 (0.5, 2)	112 (31)
Fedratinib+Keto (50 mg)	5190 (38)	132 (42)	1.5 (1, 4)	131 (32)
Fedratinib (300 mg)	6460 (55)	379 (59)	3 (1.5, 3)	77 (17)
Fedratinib+Keto (300 mg)	25000 (40)	741 (46)	2.5 (1, 4)	95 (21)
†median (min, max) Source:				

Effect of Other Enzyme Modulators:

Fedratinib is also metabolized by CYP2C19 and FMO3 in vitro.

Effect of Gastric Acid Reducing Agents

There was no effect of acid reducing agents on fedratinib exposure (Table 69).

The effect of acid reducing agents was evaluated in the following studies:

- Study INT12894: open-label, 2-treatment cross-over study in 17 healthy subjects receiving a single dose of fedratinib (500 mg) on Day 1 of Period 1. In Period 2, subjects received 40 mg QD pantoprazole on Day 1-7 under fasting conditions (except of Day 7) and a single dose of fedratinib (500 mg) on Day 7. Eleven subjects withdrew, 9 due to vomiting after fedratinib administration. Ondansteron (8 mg) was administered prior to fedratinib dosing in 10 replacement subjects. The blood samples for PK were collected at predose and up to 168 hours post dose on Day 1 of Period 1 and Day 7 of Period 2.

Table 69: Point estimates and 90% confidence intervals of pharmacokinetic parameters in the presence of proton pump inhibitors

Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)	Glas+drug/Glas
Study INT12894 (n=17) -PPI			
No PPI vs PPI (500 mg, GEN-1)	1.15 (1.04 to 1.27)	1.09 (0.95 to 1.25)	1.0
PPI=pantoprazole			

Table 70: Pharmacokinetics of fedratinib in the presence of proton pump inhibitors

PK parameter (unit)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max}† (hr)	$T_{1/2}$ (hr)
Study INT12894 (n=17)				
Fedratinib (500 mg, GEN-1)	13200 (38)	683 (34)	3 (1.5-6)	74 (43)
Fedratinib + PPI (500 mg, GEN-	15100 (32)	754 (32)	3 (1.5-6)	69 (38)
†median (min, max)				

Effect of Fedratinib

On CYP3A, CYP2C19 and CYP2D6 substrates:

There was a 4-fold, 3-fold, and 2-fold increase in exposures of CYP3A4 (midazolam), CYP2C19 (omeprazole), and CYP2D6 (metoprolol) substrates, respectively, with multiple doses of fedratinib (Table 71).

Study INT12497 was an open-label study with 2 segments. Segment 1 was a 1-sequence, 2-period, 2-treatment crossover study.

Patients (n=16) with solid tumors were administered a single oral dose cocktail of omeprazole (20 mg), metoprolol (100 mg), and midazolam (2 mg) used as probe substrates for CYP2C19, CYP2D6, and CYP3A4 activities, respectively, without fedratinib on Day -1 or with fedratinib on Day 15, under fasting conditions (no food for 8 hours before and 2 hours after dose). Subjects received 500 mg QD fedratinib from Day 1 to Day 15 while fasted (at least 1 hour before or 2 hours after a meal). The majority of patients were also administered 8 mg ondansetron hydrochloride with fedratinib. Patients progressed to Segment 2 on Day 16 of the study, at the Investigator's discretion. Blood samples were collected for assessment of omeprazole, metoprolol, midazolam, and fedratinib plasma concentrations at predose on Day -1, Day 14, and at predose and up to 24 hours after dosing on Day 15 of Segment 1.

Table 71: Point estimates and 90% confidence intervals of pharmacokinetic parameters of omeprazole, metoprolol, and midazolam in the presence and absence of fedratinib

Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)	Glas+drug/Glas
Study INT12497 (n=13-16)			
Midazolam + Fedratinib vs. Fedratinib	3.84 (2.62 to 5.63)	1.82 (1.49 to 2.21)	1.0
Omeprazole + Fedratinib vs. Fedratinib	2.82 (2.26 to 3.53)	1.12 (0.81 to 1.53)	2.0
Metorolol + Fedratinib vs. Fedratinib	1.77 (1.27 to 2.74)	1.60 (1.25 to 2.05)	1.0

Fedr.=fedratinib

Table 72: Pharmacokinetics of midazolam, omeprazole, and metoprolol in the presence and absence of fedratinib

PK parameter (unit)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)	T_{max}† (hr)	$T_{1/2}$ (hr)
Study INT12497 (n=13-16)				
Omeprazole (20 mg)	1590 (79)	475 (52)	2 (1, 4)	2.0 (53)
Omeprazole (20 mg) + Fedratinib	4690 (60)	537 (47)	4 (2, 10)	3.6 (46)
Metoprolol (100 mg)	731 (62)	135 (51)	2 (1, 3)	3.4 (30)
Metoprolol (100 mg) + Fedratinib	1180 (64)	199 (48)	2 (1, 4)	3.2 (49)
Midazolam (2 mg)	42 (73)	13 (51)	0.5 (0.5, 1)	5.2 (39)
Midazolam (2 mg) + Fedratinib	148 (25)	24 (34)	0.5 (0.3, 2)	12.7 (57)
Fedratinib (500 mg QD) on Day 15	59300 (63%)	4040 (55%)	3 (1,24)	--

†median (min, max)

On CYP Inhibition In vitro:
Fedratinib shows time dependent inhibition of CYP3A and CYP2C19 (R2 ≥1.25) and inhibits 2D6 (R1 ≥1.02) but not CYP1A, CYP2B6, CYP2C8, CY P2C9, or CYP2E1 in vitro (Table 73) at clinically relevant concentrations per the current FDA DDI guidance (2017).

Table 73: IC_{50} and calculated R_1 values for fedratinib inhibition of CYP activities in human liver microsomes

CYP Enzyme	Substrate	Fedratinib IC_{50} (µM)	Positive Control	R_1 value $1+(I_{max,u}/K_i)$	R2= $(K_{obs}+K_{deg})/K_{deg}$
CYP1A2	Phenacetin	>100	Furafylline, α-Naphthoflavone	<1.02	--
CYP2B6	Bupropion	>100	Sertraline	<1.02	--
CYP2C8	Paclitaxel	100.8	Montelukast	<1.02	--
CYP2C9	Tolbutamide	52.2	Sulfaphenazole	<1.02	--
CYP2C19	S-Mephenytoin	>100	Tranylcypromine	--	6
CYP2D6	Dextromethorphan	20.2, >25	Quinidine	~1.02	---
CYP3A	Midazolam Testosterone	3 , >25 3	Ketoconazole	≤1.1	77

I_{max} at steady state =1995 ng/mL or 3.8 µM. Fraction unbound = 0.045, $I_{max,u}$=0.171 µM
$K_i = IC_{50}/2$ for competitive inhibition for those CYP enzymes without an experimental K_i value
Kobs= (Kintact x 50 x Imax,u)/(Ki + 50 x Imax,u)
Kdeg = 0.00048/min (CYP3A) & 0.00045/min (CYP2C19) (Drug Metab Dispos. 2013; 41(7): 1414-24).
Kintact=0.0335/min, and Ki=112 µM of fedratinib for CYP2C19, and Kintact=0.0430/min, and Ki=1.57 µM of fedratinib for CYP3A
Source: MIH0887, PDM-07-101348-024

On CYP Induction In vitro:
1 to µM of fedratinib induced CYP3A mRNA but net effect was inhibition of CYP3A enzyme activity (midazolam as substrate) in vitro.

On Transporter Inhibition In vitro:
Fedratinib has the potential to inhibit P-gp and BCRP (I_{gut}/IC_{50} ≥10), MATE1 and MATE-2K ($I_{max,u}/IC_{50}$ >0.02), and OCT2 ($I_{max,u}/IC_{50}$ >0.1) in vitro at clinically relevant concentrations per the current FDA DDI guidance (2017) (Table 74). Based on the results of the static model (R ~1.1, Table 74) and exploratory PBPK analysis suggesting no significant interaction potential with repaglinide (Appendix 19.5.6, Q7), drug interaction with substrates of OATP1B1 and OATP1B3 may not be clinically significant.

Table 74: IC_{50} and calculated R values for fedratinib inhibition of transporters

Transporter	Substrate	Fedratinib IC_{50} (µM)	I_{gut}/IC_{50}	$I_{max,u}/IC_{50}$	1+ $((f_{u,p} \times I_{in,max})/IC_{50})$ [b]
P-gp	Digoxin, vinblastin	10.1, 11.2	302	--	--
BCRP	Methotrexate	29.9	102	--	--
OCT1	Tetraethylammonium	6.06	--	<0.1	--
OCT2	Metformin	0.78	--	0.222	--
OAT1	p-Aminohippuric acid	>100	--	<0.1	--
OAT3	Estrone 3–sulfate	>100	--	<0.1	--
MATE1	Metformin	0.352	--	0.492	--
MATE2K	Tetraethylammonium	0.227	--	0.763	--
OATP1B1	Estradiol-17beta-glucuronide	16.4	--	--	1.07
OATP1B3	Cholecystokinin-Octapeptide	9.51	--	--	1.13

I_{gut}=Dose/250 mL = 1.6 mg/mL = 3050 µM, Imax = 3.8 µM or 2000 ng/mL, Imax,u=0.171 µM
[b] $I_{in,max}$ = Imax + (Fa x Fg x Ka x Dose)/Qh/R_B = 27 µM
Where $f_{u,p}$ = 0.045 (SCP), Fa=1, Fg=1, Ka=1.57/hr = 0.026/min (FEDR- MPK-001), Dose=400 mg, Qh= 1450 mL/min, and R_B=0.62 (SCP),
Source: Report AIV0208, TRI0013, TRI0014, CYP1800-R1a, TRE0075, CYP1800-R1b,

Substrates of Fedratinib

Transporters:

Fedratinib is a substrate of P-gp in vitro. Greater than 2-fold uptake of Fedratinib was observed in P-gp-expressing cells, and efflux ratio (ER) in the presence of a P-gp inhibitor decreased to <50% of the ER in the absence of inhibitor per the current FDA DDI guidance (2017) (Table 75).

Table 75: Evaluation of fedratinib as substrate of transporters in vitro

CYP Enzyme	Inhibitor	Fedratinib		Control Probes	Control Probes	
		Efflux or Uptake Ratio$^{\Delta}$	% Inhibition		Efflux or Uptake Ratio$^{\Delta}$	% Inhibition
P-gp/BCRP*	Cyclosporine CP-100256	14§ (5 µM)	88%§	Digoxin	24	95%
P-gp*	PSC833	33§ (5 µM)	82%§	Digoxin		
BCRP*	KO134	14 (5 µM)	23% §	Estrone sulfate	2.6	62%
OATP1B1†	Rifampicin	0.89 – 1.1 (1-10 µM)	--	E17ßG	72	94%
OATP1B3†	Rifampicin	1.1 – 1.3 (1-10 µM)		CCK8	22.5	93%
BSEP‡	Ketoconazole	0.9 – 1.0 (1 & 100 µM)	--	Taurocholic acid	19	94%
MRP2‡	MK571	0.9 – 1.3 (1 & 10 µM)		Estradiol-17β-glucuronide	5.3	63%

§Per FDA DDI guidance, substrate if efflux ratio ≥2 in P-gp or BCRP expressing cells and % inhibition >50%
$^{\Delta}$Per FDA DDI guidance, substrate if overexpressing/wild-type uptake ratio ≥2 and % inhibition >50%
Source: *TRS0006, †TRE0075, ‡CYP1800-R1a

Fedratinib is not a substrate of BCRP, MRP2, OATP1B1, OATP1B3 in vitro. Less than 2-fold uptake of fedratinib was observed in BCRP, MRP2, OATP1B1, OATP1B3 -expressing cells compared to those in wild-type cells, and inhibited ER by >50% in the presence of a transport inhibitor.

19.5.4 Specific Populations

No dose adjustment is recommended for age (20-94 years), sex, race or ethnicity (234 White, 16 Black, 9 Asian, and 11 Hispanic), body weight (43.5 to 145.6 kg), mild hepatic impairment (HI) and mild to moderate renal impairment (RI) as these factors did not affect the PK of fedratinib (Appendix 19.5.7.1).

Renal Impairment

A lower starting dose of 200 mg is recommended for patients with severe RI (CLcr 15 to <30 mL/min). A lower starting dose is not recommended for patients with mild (CLcr 60 to 89 mL/min) or moderate (CLcr 30 to <60 mL/min) RI based on safety assessment and PK. However, frequent monitoring of AEs and dose adjustment based on AEs are recommended for patients with moderate RI due to increase in fedratinib exposure.

5% of the administered dose is recovered in urine, with 3% as unchanged drug.

POP13449 was an open-label study conducted sequentially, based on renal function as measured by the Cockcroft-Gault (CG) method. Eight subjects with severe RI, 8 subjects with moderate RI and 13 healthy control subjects matched with gender, age (≤ 50 years old or > 50 years old), and body weight (within 15%) were administered a single 300 mg dose of fedratinib in fasted conditions (no food for 10 hours before and 2 hours after dosing). Blood samples were collected up to 264 hours postdose for total fedratinib concentrations, and up to 48 hours postdose for fedratinib unbound concentrations. The subjects with mild RI were not enrolled. The classification of renal function groups based on CLcr was not per the FDA renal impairment (2010) guidance. Upon reclassification of renal function groups based on FDA guidance, 5 subjects had to be reclassified: one subject was reclassified from severe RI to end stage renal disease (ESRD), and 4 subjects were reclassified from normal renal function to mild RI (CLcr 60 to <90 mL/min). Of the subjects with normal renal function (CLcr ≥90 mL/min), 6 and 5 subjects were used as matched controls for moderate and severe RI cohorts, respectively. Table 76 indicates that $AUC_{0\text{-}inf}$ increased by 1.5-fold with moderate RI (CLcr 30 to 59 mL/min) and 1.9-fold with severe RI (CLcr 15 to 29 mL/min) compared to their matched controls (CLcr ≥90 mL/min).

In addition, population PK analysis including patients with mild (CLcr 60 to <90 mL/min: n=194) moderate (n=109) and severe RI (n=3), showed that CLcr (as surrogate for renal function) was a significant covariate. There was a trend towards reduction in fedratinib CL/F with RI severity, which was in line with the results of the dedicated RI study (Appendix 19.5.7.1). However, the increase in exposure estimated by population PK analysis (Appendix 19.5.7.1) in patients with moderate and severe RI were 14% and 27% lower, respectively, compared to those in the dedicated RI study (Table 76). Only 3 patients with severe RI were included in the in population PK analysis.

Table 76: Point estimates and 90% confidence intervals of pharmacokinetic parameters of fedratinib

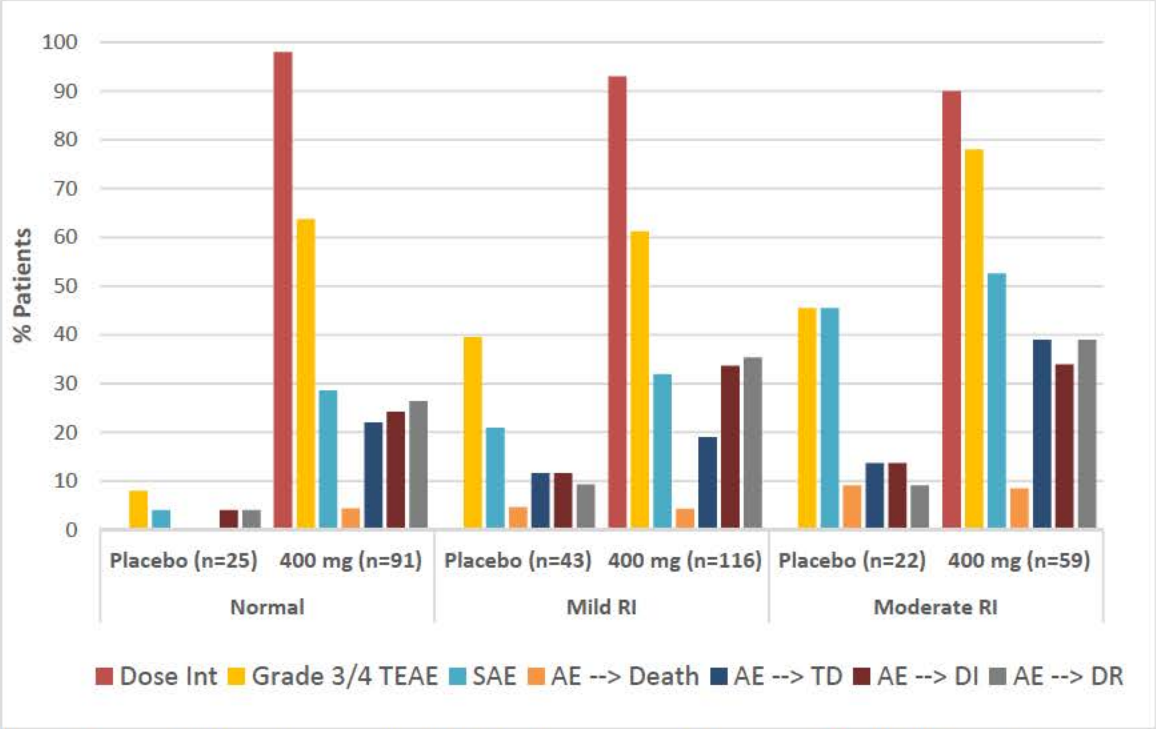
Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	C_{max} (ng/mL)	RI/Normal
Study POP13449 (n=7-9)			
Moderate RI vs. Matched Control	1.51 (0.86, 2.63)	1.39 (0.89 to 2.18)	0.75
Severe RI vs. Matched Control	1.87 (1.20, 2.92)	1.75 (1.21 to 2.52)	0.66

Table 77: Pharmacokinetics of fedratinib in moderate and severe hepatic impairment, and matched controls

PK parameter (unit)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	$AUC_{0\text{-}t}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max}† (hr)	$T_{1/2}$ (hr)
Study B1371014 (n=17)					
Matched Control	9514 (9)	4376 (8)	631 (13)	3 (2, 3)	139 (37)
Moderate RI	14380 (66)	6275 (58)	880 (66)	2.25 (1.5, 3)	110 (19)

Matched Control	9751 (24)	4594 (35)	699 (37)	3 (1.5, 3)	109 (21)
Severe RI	18275 (52)	8080 (40)	1227 (34)	2 (1, 4)	141 (31)
†median (min, max)					

Figure 15: Safety summary of renal impairment (RI) in the fedratinib and placebo groups from patients with MF in Trials EFC12153, ARD12181, ARD11936, ARD12181, and ARD12888 (All treated population)



Dose int= mean relative dose intensity (%), AE= adverse event, SAE=serious AE, AE→TD =treatment discontinuation due to AEs, AE→DI = dose interruption due to AEs, AE→DR = dose reduction due to AEs
Source: Tables IR052019.1.1 and 2.2, Response to IR, 5/20/19

The clinical trials with fedratinib did not require dose adjustment for patients with primary or secondary MF with RI. The summary of drug exposure from the clinical trials indicated that the relative dose intensity was similar in patients with mild and moderate RI compared to patients with normal renal function (Figure 15). The safety summary from the clinical trials indicated that incidence of total AEs, serious AEs, and dose interruptions or reductions due to AEs were similar in patients with moderate RI at 400 mg compared to those administered placebo, or in patients with mild RI at 400 mg or patients with normal renal function groups at 400 mg (Figure 15). Although the incidence of Grade 3/4 AEs, and drug discontinuations due to AEs were higher in patients with moderate RI at 400 mg compared to those administered placebo, or in patients with mild RI or normal renal function at 400 mg, the adverse events were manageable by dose modifications for toxicity in the trials. There were only 3 patients with severe RI at 400 mg in the clinical trials.

Therefore, it will be recommended to reduce dose to 200 mg in patients with severe RI. No dose reduction will be proposed with moderate renal impairment, however, due to potential for increased exposure, it will be recommended that patients with pre-existing moderate RI are frequently monitored for AEs, and if necessary, dose modified based on adverse reactions.

Hepatic Impairment

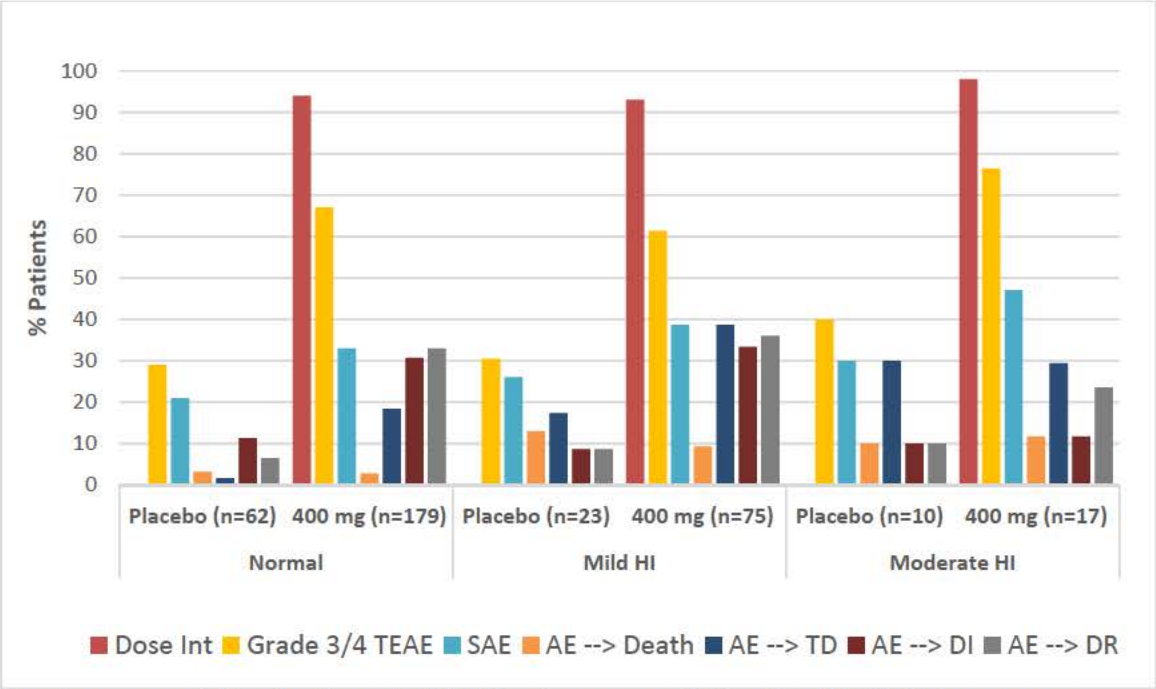
A lower starting dose is not recommended for patients with mild to moderate HI based on the available PK, and safety data. The effect of severe HI on PK of fedratinib has not been evaluated, and there is no safety and efficacy data in this population.

A dedicated HI study (POP13450) evaluated the PK and tolerability of single fedratinib (300 mg) in mild HI (Child-Pugh A: n=8) and matched subjects with normal hepatic function (n=8). Blood samples were collected up to 264 hours and 48 hours for total and unbound concentrations, respectively. The $AUC_{0\text{-}inf}$ was unchanged (1.07: 90% CI 0.74, 1.54) and Cmax increased by 14% (90% CI: 0.89, 1.46) in mild HI compared to subjects with normal hepatic function. The geometric mean (%CV) of $AUC_{0\text{-}t}$ was 10900 (26%) versus 9320 (47%) ng>h/mL and C_{max} was 807 (30%) versus 650 (35%) ng/mL in mild HI versus normal hepatic function.

The effect of HI on PK evaluated with 320 patients with normal renal function, 115 patients with mild HI, & 17 patients with moderate HI, by population PK analysis, indicated that HI was not a significant covariate (Appendix 19.5.7.1). However, no patients with severe HI were evaluated. In addition, safety of fedratinib in patients with mild HI was comparable to patients with normal hepatic function (Figure 16).

The clinical trials with fedratinib did not require dose adjustment for patients with primary or secondary MF with HI. The summary of drug exposure from the clinical trials indicated that the relative dose intensity was similar in patients with mild and moderate HI compared to patients with normal hepatic function at 400 mg (Figure 16). The safety summary from the clinical trials indicated that although the incidence of Grade 3/4 and serious AEs were higher in patients with moderate HI, the incidence of dose modifications were similar or lower in patients with moderate HI compared to those administered placebo or in patients with normal hepatic function at 400 mg (Figure 16). Therefore, PK, dose exposure, and safety assessment of patients with primary or secondary MF in the fedratinib clinical trials indicated similar relative dose intensity and similar incidence of serious AEs and manageable Grade 3 or 4 AEs at 400 mg in patients with the moderate HI versus mild HI or normal hepatic function groups at 400 mg.

Figure 16: Safety summary of hepatic impairment (HI) in fedratinib and placebo groups from patients with MF in Trials EFC12153, ARD12181, ARD11936, ARD12181, and ARD12888



Dose int= mean relative dose intensity (%), AE= adverse event, SAE=serious AE, AE→TD =treatment discontinuation due to AEs, AE→DI = dose interruption due to AEs, AE→DR = dose reduction due to AEs
Source: Tables IR052019.1.2, and 2.2, Response to IR, 5/20/19

19.5.5 Summary of Bioanalytical Method Validation and In-Study Performance

Method Validation

The Applicant used a liquid-liquid extraction with tandem mass spectrometric detection (LC/MS/MS) for quantitation of fedratinib in human plasma. Two bioanalytical sites were used for the estimation of fedratinib in human plasma. The bioanalytical methods were validated as described in Table 78.

Table 78: Method validation parameters

Validation Parameters	**8242554**	**AD-08-101348-019/MC07B-0264; AD-09-101348-052/MC07B-0265**
Facility	(b) (4)	(b) (4)
Analyte	Fedratinib	
Internal Standard (IS)	d^9-fedratinib	
Detection	LC/MS/MS	
Extraction	Liquid-liquid	
Range	1 to 1000 ng/mL	1 to 1000 ng/mL
Quality Controls	1, 3, 50, 800 ng/mL	1, 3, 30, 800 ng/mL
Inter/Intra-assay Precision	≤7%	≤6%

Inter/Intra-assay Accuracy	≤ 5%	≤ 10%
Dilution	5000 ng/mL (1:100)	800 (10x), 2000 (10x, 100x),
Dilution Accuracy & Precision	<2%	<9% and <6%
Stock stability for fedratinib	6 hrs at RT 46 days at -10°C to -30°C	105 days at -10°C to -30°C 6 hrs at RT
Stock stability for IS	6 hrs at RT	
Bench-top stability	25 hours at RT	28 hours at RT
Refrigerated stability	2 hours on ice	
Long-term Stability*	• 422 days at -20°C • 401 days at -70°C	• 30 days at -20°C &-70°C • 367 days at -70°C
Freeze-Thaw Stability	5 cycles at -20°C and -70°C	3 cycles
Reinjection stability:	110 hours at 2°C to 8°C	79 hours at 5°C
Hemolysis	No effect (A&P: <6%)	
Whole blood stability	2 hrs at RT & wet ice 24 hrs at RT	
Assay used in Clinical Studies	FED12558, ALI13541, BDR12462, TDU12620, BEX12257, POP13449, POP13450, INT12893, INT 12894, INT12497, ARD11936, ARD12042, ARD12888, ARD12181, EFC12153, TES13159	TED12037

†Addendum 1, ‡Addendum 2, RT=room temperature,

Fedratinib long-term frozen stability at -10°C to -30°C failed at 445 and 700 days of storage.

Cross-Validation

The two bioanalytical methods were cross-validated. QCs at 2, 5, 10, 20, 50, 200, 500 & 800 ng/mL were prepared at (b) (4) and analyzed at (b) (4). The precision and accuracy at the two bioanalytical sites were <10%.

In-Study Assay Performance:

In Studies FED12558, ALI13541, TED12037, POP13449, NT12893, INT 12894, ARD11936, ARD12042, ARD12181, EFC12153, and TES13159, the precision and accuracy was ≤8%. The precision and accuracy for dilution QCs were higher but were <13%. Majority (≥ 90%) of the analytical runs in the studies were successful. The incurred sample reanalysis (ISR) was performed in selected studies, and were within acceptable limits (≥67% of samples within 20% different).

The study samples were reported as handled within the validated storage and handling conditions (i.e., 422 days at -20°C or 401 days at -70°C):

19.5.6 Physiologically-based Pharmacokinetic (PBPK) Modeling Review

EXECUTIVE SUMMARY

The objective of this review is to evaluate the adequacy of the Applicant's PBPK report (DMPK-2852) titled "PBPK Modeling to Predict Drug-Drug Interactions between Fedratinib and Cytochrome P450 Modulators, Cytochrome P450 Substrates, and Transporter Substrates" to support the intended uses. Specifically, the Applicant applied the PBPK modeling approach to:

(1) evaluate the effect of coadministration of itraconazole (strong CYP3A4 inhibitor), ketoconazole (strong CYP3A4 inhibitor), ritonavir (strong CYP3A4 inhibitor), clarithromycin (strong CYP3A4 inhibitor), erythromycin (moderate CYP3A4 inhibitor), diltiazem (moderate CYP3A4 inhibitor), fluconazole (strong CYP2C19 and moderate CYP3A inhibitor), fluvoxamine (moderate CYP3A4 inhibitor and strong CYP2C19 inhibitor), efavirenz (moderate CYP3A4 inducer), or rifampin (strong CYP3A4 and CYP2C19 inducer) on the PK of fedratinib;

(2) evaluate the effect of coadministration of fedratinib on the PK of repaglinide (CYP2C8 substrate), and warfarin (CYP2C9 substrate).

(3) evaluate the effect of coadministration of fedratinib on the PK of metformin (OCT and MATE substrate), rosuvastatin (BCRP and OATP1B1/3 substrate), and digoxin (P-gp substrate).

The Division of Pharmacometrics has reviewed the original PBPK report, the amendment to the report, supporting modeling files, and the Applicant's response to FDA request for information dated 11 March 2019, and concluded the following:

- The PBPK model of fedratinib is adequate to predict the fedratinib PK profile in healthy volunteers and target cancer population.
- PBPK analyses are adequate to predict the magnitude of the effects of strong and moderate CYP3A4 inhibitors on fedratinib exposure at steady-state. The model predicted that a strong CYP3A4 inhibitor (such as itraconazole, ketoconazole and ritonavir) may increase fedratinib exposure by approximately 2-fold; while no significant interaction is predicted with a moderate CYP3A4 inhibitor (such as erythromycin and diltiazem) at steady-state. The PBPK analyses are adequate to support labeling language for fedratinib interaction with strong or moderate CYP3A4 inhibitors.
- The current PBPK analyses are not adequate to estimate the effects of a dual strong CYP3A4 and CYP2C19 inhibitor on fedratinib PK, because the contribution of CYP2C19 to fedratinib metabolism had not been established.
- The current PBPK analyses are not adequate to estimate the effects of a dual strong CYP3A4 and CYP2C19 inducer or a CYP3A4 inducer on fedratinib PK. There is uncertainty on estimating the clinical CYP3A4 (and CYP2C19) net activity due to the complex DDI potential of fedratinib.
- PBPK analyses predicted that an interaction between fedratinib 400 mg QD and a CYP2C9 substrate (such as warfarin) or a CYP2C8 substrate (such as repaglinide) is

unlikely to be relevant. (b) (4)

- PBPK analyses were inadequate to evaluate fedratinib effects on the PK of digoxin (P-gp substrate), metformin (OCT and MATE substrate), and rosuvastatin (BCRP and OATP1B1/3 substrate) due to the limitations identified in the substrate PBPK models.

BACKGROUND

Fedratinib proposed dosing regimen is 400 mg once daily (QD) as 4 x 100-mg capsules. After single dose (SD) administration of fedratinib, median Tmax was 2-3 hours. Fedratinib exposure (Cmax and AUC) was approximately dose-proportional following single-dose in healthy subjects, and multiple-dose in patients with MF at the 300 mg-500 mg dose range (ARD11936 and FEDR-MPK-001). Following multiple 400 mg QD administration in MF patients, there were approximately 3-fold accumulation in plasma (ARD11936). The total variability (%CV) of PK parameters was higher than 50% in patients (FED12258). Fedratinib showed high plasma protein binding, mainly to alpha-1 acid glycoprotein (LPR1082).

The isoforms CYP3A4, CYP2C19, CYP2D6, FMO1 and FMO3 contribute to the oxidative metabolism of fedratinib (PDM-07-101348-028). Based on the human ADME study (BEX12257, MEH0082), unchanged fedratinib was the major drug-related moiety in plasma with no major circulating metabolites.

Fedratinib was determined to be a time-dependent inhibitor (MIH0887) and inducer of CYP3A4 in vitro (IHH0014). Clinically, there was a 4-fold increase in the AUC of the index CYP3A4 substrate midazolam with concomitant administration of fedratinib 500 mg QD (INT12497). Fedratinib was determined to be a substrate and inhibitor of P-gp in vitro (AIV0208). Fedratinib was also an inhibitor of the transporters MATE1, MATE2-K, OCT1, OCT2, BCRP, OATP1B1, and OATP1B3 in vitro (TRI0013 and TRE0075).

METHODS

PBPK model structure and development

The PBPK analyses were performed using the population-based PBPK software Simcyp® (V17R1, Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). The fedratinib PBPK model was developed based on in vitro, human ADME study (BEX12257) and clinical PK data. Briefly, a first-order absorption model and a minimal PBPK model were utilized to describe fedratinib PK. The first-order absorption rate (ka value =0.22 1/h) was estimated using compartmental PK modeling of PK data in healthy subjects administered 500 mg SD fedratinib (TDU12620, BDR12462, FED12258, ALI13451). The fraction absorbed (fa) was estimated to be around 0.65 based on mass balance and metabolic profiling studies (BEX12257 and MEH0082). In vitro Caco-2 permeability data (AIV0208) under different drug concentrations and pH values were used to estimate the human intestinal effective permeability (Peff human 2.55 x 10^{-4} cm/s) value and the

hybrid intestinal blood flow parameter (Q_{Gut}=6.5 L/h). The unbound fraction in enterocytes (fu_{Gut}) was assumed equal to 1.

The unbound fraction in plasma (fup=0.05) and blood to plasma concentration ratio (B/P=0.7) values were determined in vitro (LPR1082). Fedratinib was mainly bound to alpha-1 acid-glycoprotein (LPR1082). The distribution parameters (Vss, Vsac, and Q) were estimated using compartmental PK modeling from 500 mg SD fedratinib (TDU12620, BDR12462, FED12258, and ALI13451).

The enzyme kinetics (CLint) for CYP3A4, CYP2D6, CYPC19 were estimated using the retrograde approach, based on the percentage contribution for each enzyme from in vitro human hepatocytes (MIH0888) and oral clearance. The initial clearance value (CL/F=27.2 L/h) was estimated using compartmental PK modeling (500 mg SD fedratinib, Studies TDU12620, BDR12462, FED12258, and ALI13451). The clearance, together with Vss, Vsac and Q values, were refined via sensitivity analysis to derive values that allowed recovery of the observed dose-normalized AUC in healthy-subjects. The model-predicted contribution of CYP isoenzymes (fm) to the systemic clearance were estimated to be around 72%, 11%, and 1.4% for CYP3A4, CYP2C19 and CYP2D6, respectively, for single dose fedratinib. The CLR value was estimated to be 1.67 L/h, based on the human ADME data (BEX12257). A non-specific systemic clearance was assigned in the model (CLadd=0.67 L/h) to account for other liver enzymes (i.e., FMOs)/systemic excretion).

The CYP interaction parameters, reversible inhibition for CYP2C8 and CYP2C9, and time-dependent inhibition for CYP3A4 and CYP2C19, were estimated based on in vitro data (human liver microsomes) (MIH0887). The CYP3A4 induction effect was determined using human hepatocytes (IHH0014). The kinetic data were calibrated against rifampin. The inhibition constants towards the transporters OCT1, OCT2, MATE1, MATE2-K, BCRP, OATP1B1, OATP1B3, and P-gp were determined in vitro (IC_{50} values converted to Ki using the Cheng-Prusoff equation).

Although fedratinib was determined to be a P-gp substrate in vitro, intestinal efflux was considered irrelevant. The intestinal P-gp efflux is likely to be saturated (above 100 µM, i.e. 52.5 µg/mL) following 400 mg dose of fedratinib (1600 µg/mL estimated by 400 mg/250mL) based on in vitro data. In the therapeutic dose range of 300 mg to 500 mg, fedratinib Cmax was approximately dose proportional in healthy subjects and patients with MF. Furthermore, the amount of radioactive fedratinib dose in the feces in first 24 hours was minor (less than 10%) (BEX12257), suggesting fedratinib was well absorbed and intestinal efflux did not limit its absorption. Based on this assessment, intestinal P-gp kinetics was not incorporated into the model.

Simulations were performed using the default healthy volunteer and “Sim-Cancer” virtual population models (software’s library, V17). Simulations were conducted in the

fasted state as food had no significant effect on fedratinib exposure (ALI13451). The default compound models (software's library, V17), for the perpetrators ketoconazole, itraconazole, ritonavir, clarithromycin, erythromycin, fluconazole, diltiazem, fluvoxamine, efavirenz and rifampin; and for the substrates midazolam, repaglinide, warfarin, digoxin, rosuvastatin and metformin were used in the PBPK simulations for the respective DDIs.

PBPK model verification

The performance of fedratinib PBPK model to predict fedratinib PK profile after single and multiple dose administration in healthy volunteers and patients with MF was evaluated by comparison of simulated and observed clinical PK data (TDU12620, INT12894 and ARD11936). The clinical DDI fedratinib-ketoconazole (INT12893) was used to verify the contribution of CYP3A4 to the disposition of fedratinib; while the clinical DDI fedratinib-midazolam (INT12893) was used to verify the CYP3A4 interaction parameters (time-dependent inhibition and induction) and their effect on fedratinib disposition at steady-state.

The PBPK simulations and respective study designs conducted for model development, verification and application are listed in Table 79.

Table 79: PBPK simulations (N) and respective study design used for fedratinib model

#	Trials x N	Study	Fedratinib Dosing Regimen	Perpetrator/ Victim	Dosing Regimen	Duration	PBPK Model Objective
1	10x10	TDU12620, BDR12462 FED12258, ALI13451 INT12893	500 mg SD	NA	NA	7 days	Development
2	10x10	TDU12620	300 mg SD	NA	NA	7 days	Verification
3	10x10	INT12894	500 mg SD	NA	NA	7 days	Verification
4	10x10	ARD11936	300 mg, 400 mg, and 500 mg QD	NA	NA	29 days	Verification
5	10x6	INT12893	300 mg SD on Day 6	Ketoconazole	200 mg BID for 14 days	14 days	Verification
6	10x13	INT12497	500 mg QD for 15 days	Midazolam	2 mg SD on Day 15	15 days	Verification
7	10x6	NA	400 mg SD and QD on Days 6-20	Ketoconazole	200 mg BID and 400 mg QD for 20 days	20 days	Application
8	10x6	NA	400 mg SD and QD on Days 6-20	Itraconazole	200 mg BID Day 1, 200 mg QD Days 2-20	20 days	Application
9	10x6	NA	400 mg SD and QD on Days 6-20	Ritonavir	100 mg BID for 20 days	20 days	Application
10	10x6	NA	400 mg SD and QD on Days 6-20	Clarithromycin	500 mg BID for 20 days	20 days	Application
11	10x6	NA	400 mg SD and QD on Days 6-20	Erythromycin	500 mg TID for 20 days	20 days	Application
12	10x6	NA	400 mg SD and QD on Days 6-20	Diltiazem	120 mg BID for 20 days	20 days	Application
13	10x10	NA	400 mg QD on Days 10-25	Repaglinide	0.25 mg SD on Day 15	25 days	Application
14	10x10	NA	400 mg QD on Days 10-25	Warfarin	15 mg SD on Day 15	25 days	Application

NA: Not applicable. (Source: Table 3 from the Amendment to PBPK report; Table 5 from Original PBPK report)

PBPK model application

The Applicant applied the verified fedratinib PBPK model to prospectively evaluate the following:

- Effect of coadministration of ketoconazole (strong CYP3A4 inhibitor), itraconazole (strong CYP3A4 inhibitor), ritonavir (strong CYP3A4 inhibitor), clarithromycin (strong CYP3A4 inhibitor), erythromycin (moderate CYP3A4 inhibitor), diltiazem (moderate CYP3A4 inhibitor), fluconazole (strong CYP2C19 and moderate CYP3A4 inhibitor), fluvoxamine (strong CYP2C19 inhibitor and weak CYP3A4 inhibitor), efavirenz (moderate CYP3A4 inducer), or rifampin (strong CYP3A4 and CYP2C19 inducer) on the PK of fedratinib;
- Effect of coadministration of fedratinib on the PK of repaglinide (CYP2C8 substrate) and warfarin (CYP2C9 substrate);
- Effect of coadministration of fedratinib on the PK of metformin (OCT and MATE substrate), rosuvastatin (BCRP and OATP1B1/3 substrate), and digoxin (P-gp substrate).

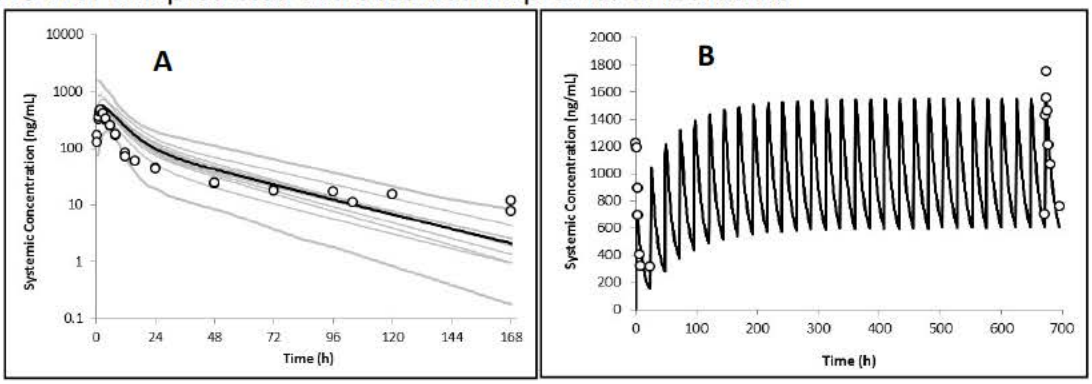
RESULTS

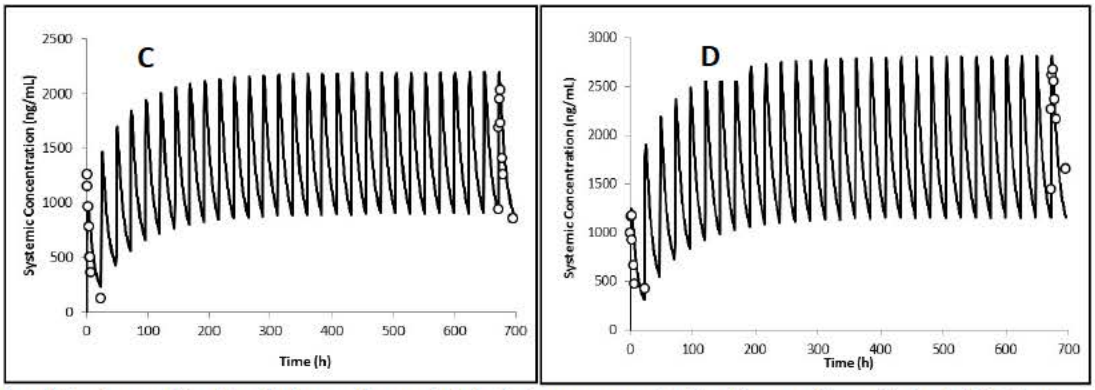
Q1. Can PBPK analyses provide a reasonable description of the PK of fedratinib?

Yes, PBPK simulations reasonably described the PK profile of fedratinib following single dose administration in healthy subjects, and multiple dose in patients with MF (Table 79, simulations #2-4). Comparison of observed PK profile versus PBPK predicted are shown in Figure 17.

PBPK simulations were conducted using both the healthy subjects and cancer population models. There was reasonable agreement between PBPK predicted and observed exposures in healthy volunteer PK data as well as patient PK data. Overall, the predicted geometric mean values for AUC (AUCinf or AUCtau) and Cmax were within 2-fold of the observed value in Table 80.

Figure 17: PBPK predicted and observed PK profiles of fedratinib





PBPK predicted mean (lines) and observed mean (circles) plasma concentration-time profiles of fedratinib following (A) a single oral dose of fedratinib 300 mg in healthy subjects (Study TDU12620). The solid black line is the mean data for the simulated population and the gray lines are the mean values for 10 simulated trials; (B) 300 mg QD in MF patients (Study ARD11936); (C) 400 mg QD in MF patients (Study ARD11936), and (D) 400 mg QD in MF patients (Study ARD11936). (Source: Simulation output files)

The PBPK predicted PK parameters for fedratinib using the aged-matched healthy subject population model fairly predict the observed data in patients given fedratinib 300- 500 mg dose levels (AP26113-11-101). The predicted geometric mean Cmax and AUC values were within 40% of the observed data (Table 80). Considering the variability (%CV) in the pharmacokinetics of the fedratinib, the healthy subjects PBPK model were considered adequate to predict the PK profile of fedratinib for patients with MF.

Table 80: Comparison of PBPK predicted and observed Mean (SD) [Geometric Mean] Cmax and AUC values of fedratinib

Fedratinib Dosing Regimen	Study Subjects	Observed		Virtual Subjects	Predicted		Pred / Obs Ratio	
		Cmax (ng/mL)	AUC (ng.hr/mL)		Cmax (ng/mL)	AUC (ng.hr/mL)	Cmax	AUC
300 mg SD	Healthy	521 (189) [497]	6730 (1990) [6530]	Healthy	656 (404) [551]	5770 (9950) [8560]	1.1	1.3
500 mg SD	Healthy	[683]	[13200]	Healthy	1130 (693) [950]	18800 (11100) [16100]	1.4	1.2
300 mg QD day1	patients with MF	1380 (1060) [1070]	9460 (7770) [7020]	*Healthy	810 (580) [644]	8780 (5042) [7471]	0.60	1.1
				Cancer	984 (574) [832]	11100 (4800) [10100]	0.78	1.4
300 mg QD SS	patients with MF	1800 (1120) [1530]	25300 (14100) [22400]	*Healthy	1723 (1096) [1403]	23601 (14838) [19024]	0.92	0.85
				Cancer	2240 (1230) [1930]	33600 (17200) [29300]	1.2	1.3
400 mg QD day1	patients with MF	1430 (754) [1290]	9610 (3450) [9130]	*Healthy	1106 (750) [890]	12579 (6803) [10792]	0.69	1.2
				Cancer	1390 (837) [1170]	16200 (7150) [14700]	0.91	1.6
400 mg QD SS	patients with MF	2020 (1250) [1800]	29100 (13500) [26900]	*Healthy	2418 (1453) [2007]	34159 (20247) [28122]	1.1	1.1
				Cancer	3250 (1780) [2810]	50800 (25700) [44300]	1.6	1.7
500 mg QD day 1	patients with MF	1420 (710) [1270]	11300 (6060) [9980]	*Healthy	1434 (1038) [1132]	16306 (9158) [13876]	0.89	1.4
				Cancer	1820 (1240) 1490	21400 (10700) [19100]	1.2	1.9
		2830 (1370)	44500 (24900)	*Healthy	3089 (1923)	43347 (25661)	1.0	0.92

500 mg QD SS	patients with MF	[2540]	[38700]		[2552]	[35781]		
				Cancer	4280 (2540) [3650]	66900 (36300) [57900]	1.4	1.5

Data are presented as Mean (SD) [Geometric mean]. Predicted/Observed Ratio of geometric means. *The Reviewer conducted the simulations using the Healthy North European Caucasian volunteer population model to allow coverage of the age range of the clinical study (50-82 years). SD: single dose; QD: repeated once-daily dosing; Day 1 Cycle 1 and SS (steady-state) Cycle 2 Day 1; AUC_{inf} for SD, AUC_{0-24h} for QD. (Source: Simulation output file -Reviewer's analysis. Tables 1 and 2 of Amendment PBPK_final report).

At the therapeutic dose of 400 mg QD, the predicted accumulation ratio (Rac=geo mean of AUC_{0-24h} Cycle1 Day 1/ AUC_{0-24h} Cycle 2 Day 1) for fedratinib was 2.6-fold compared to the observed ratio of 2.9 (ARD11936).

Q2. Does PBPK analyses predict the effect of a CYP3A4 modulator on the PK of fedratinib?

Yes. PBPK simulations reasonably predicted the clinically observed DDI between fedratinib and ketoconazole in healthy volunteers given a single dose of 300 mg fedratinib and repeated doses of 200 mg BID ketoconazole (Table 79, simulation #5). The predicted geometric mean PK parameters (Cmax, AUC, and ratios) for fedratinib were within 50% of the observed values (Table 81). These results suggest that fedratinib PBPK model provide a reasonable estimate of the metabolic contribution of CYP3A4 at single-dose in vivo.

Table 81: Comparison of observed and predicted Cmax and AUC values of fedratinib (300 mg SD) in the absence and presence of ketoconazole (200 mg BID)

Treatment	Cmax (ng/mL)		AUCinf (ng.h/mL)		Cmax Ratio (90%CI)		AUCinf Ratio (90%CI)	
	Pred	Obs	Pred	Obs	Pred	Obs	Pred	Obs
Control	529	379	8550	6460	2.09	1.93	3.17	3.06
with KTZ	1100	741	27100	25000	(1.98-2.21)	(1.18-3.17)	(2.91-3.45)	(2.46-3.80)

PK data are presented as geometric means. Cmax ratio and AUC ratio were expressed as with inhibitor/without inhibitor. Observed values (N=6-7) from study INT12893. (Source: Table 8 of Amendment PBPK_final report).

Q3. Does PBPK analyses predict the effect of fedratinib on a sensitive CYP3A4 substrate?

Yes. Fedratinib showed time-dependent inhibition and induction potential towards CYP3A4 in vitro. Clinically, there was a 4-fold increase in the AUC of the index CYP3A4 substrate midazolam with concomitant administration of fedratinib 500 mg QD (INT12497). PBPK simulations (Table 79, simulation #6) reasonably estimated the magnitude of this drug interaction. The predicted geometric mean Cmax and AUC ratios were within 10% of the observed data (Table 82). These results suggested that CYP3A4 interaction parameters in fedratinib PBPK model provided a reasonable estimate of the net effect of CYP3A4 inactivation and induction in vivo.

Table 82: Comparison of observed and predicted ratios for Cmax and AUC of midazolam (2 mg SD) in the presence of fedratinib (500 mg QD)

Cmax ratio (90%CI)		AUClast Ratio (90%CI)		AUCinf Ratio (90%CI)	
Predicted	**Observed**	**Predicted**	**Observed**	**Predicted**	**Observed**
2.02 (1.95-2.10)	1.82 (1.49-2.2)	3.62 (3.34-3.92)	4.01 (3.19-5.05)	4.26 (3.87-4.69)	3.84 (2.62-5.63)

PK data are presented as geometric means. Cmax and AUC ratio were expressed as with fedratinib/without fedratinib. Observed values (N=13-16) from study INT12497. (Source: Simulation output file, Table 9 of Amendment PBPK_final report).

Q4. Can PBPK analyses be used to estimate the effects of CYP3A4 inhibitors on fedratinib PK?

Yes. The DDI liabilities of fedratinib as a victim of strong and moderate inhibitors of CYP3A4 were estimated by PBPK analyses (Table 79, simulations #7-12). Predicted fedratinib exposure at single-dose and steady state in the presence of CYP3A4 inhibitors are summarized in Table 83.

At single-dose, PBPK analyses show that the drug interaction effect in terms of predicted geometric mean ratios for AUCinf were around 3-fold with strong CYP3A4 inhibitors and around 1.6-1.9-fold with moderate CYP3A4 inhibitors.

Compared with the single-dose scenario, PBPK analyses predicted lower interaction magnitudes following repeated doses of fedratinib in presence of CYP3A4 inhibitors. At steady-state, the predicted geometric mean ratios for $AUC_{tau,ss}$ were around 2-fold with strong CYP3A4 inhibitors and approximately 1.1-1.2-fold with moderate CYP3A4 inhibitors. These predictions are in line with the reduced contribution of CYP3A4 metabolism to fedratinib clearance at steady-state due to the net effect of CYP3A4 auto-inhibition.

Table 83: PBPK predicted Cmax and AUC ratios for fedratinib (400 mg) in the presence of CYP3A4 inhibitors at single-dose and steady-state

Perpetrator		Fedratinib 400 mg SD		Fedratinib 400 mg QD	
Class	**Dosing Regimen**	**Cmax Ratio (90% CI)**	**AUCinf Ratio (90% CI)**	**Cmax Ratio (90% CI)**	**AUCtau,ss Ratio (90% CI)**
CYP3A4 strong inhibitor	Ketoconazole 200 mg BID	2.05 (1.95-2.17)	3.02 (2.78-3.28)	1.78 (1.68-1.88)	2.02 (1.88-2.16)
CYP3A4 strong inhibitor	Ketoconazole 400 mg QD	2.08 (1.97-2.20)	2.88 (2.65-3.12)	1.74 (1.66-1.84)	1.95 (1.82-2.08)
CYP3A4 strong inhibitor	Ritonavir 100 mg BID	1.92 (1.83-2.01)	2.84 (2.63-3.06)	1.51 (1.46-1.56)	1.67 (1.60-1.73)
CYP3A4 strong inhibitor	Itraconazole 200 mg BID	2.21 (2.06-2.37)	3.19 (2.93-3.46)	1.84 (1.73-1.96)	2.14 (1.98-2.30)
CYP3A4 strong inhibitor	Clarithromycin 500 mg BID	1.73 (1.65-1.80)	2.09 (1.96-2.22)	1.27 (1.25-1.29)	1.30 (1.27-1.32)
CYP3A4 moderate inhibitor	Erythromycin 500 mg TID	1.58 (1.52-1.65)	1.85 (1.73-1.97)	1.15 (1.13-1.17)	1.18 (1.15-1.20)
CYP3A4 moderate inhibitor	Diltiazem 120 mg BID	1.52 (1.46-1.58)	1.62 (1.55-1.69)	1.11 (1.10-1.13)	1.13(1.11-1.14)

Data are presented as population geometric mean values for exposure ratios (AUC and Cmax) expressed as the fold change in the in the presence versus absence of a perpetrator. (Source: Simulation output files).

Q5. Can PBPK analyses be used to estimate the effects of a dual CYP3A4/CYP2C19 inhibitor on fedratinib PK?

No. There are uncertainties of using PBPK analyses to estimate the interaction effect of a dual CYP2C19 and CYP3A4 inhibitor on the PK of fedratinib. Firstly, the contribution of CYP2C19 to fedratinib metabolism has not been verified. Secondly, fedratinib is a time-dependent inhibitor of CYP2C19, as demonstrated by the interaction effect of increased exposure of omeprazole (2.8-fold) in cancer patients (INT12497). Therefore, there is a potential for auto-inhibition of CYP2C19. The current time-dependent inhibition parameters for CYP2C19 in fedratinib model underpredicted the interaction effect on omeprazole as a CYP3A4 and CYP2C19 substrate (predicted AUCR 1.5 vs observed AUCR 2.8).

Q6. Can PBPK analyses be used to estimate the effects of CYP3A4 and CYP3A4/CYP2C19 inducers on fedratinib PK?

No. There are uncertainties of using PBPK analyses to estimate the interaction effect of a strong dual CYP3A4 and CYP2C19 inducer (such as rifampin), and a moderate CYP3A4 inducer (such as efavirenz), on the PK of fedratinib. There is low confidence on predicting the clinical CYP3A4 (and CYP2C19) net activity resulting from the interplay of five different counteracting interaction mechanisms, namely induction of CYP3A4 and CYP2C19 by rifampin, and induction of CYP3A4 and inactivation of CYP2C19 and CYP3A4 by fedratinib. A clinical DDI study investigating the effects of rifampin and efavirenz on the PK of fedratinib is planned.

Q7. Can PBPK analyses be used to estimate the effects of fedratinib on CYP2C8 and CYP2C9 substrates?

Yes. PBPK DDI simulations were conducted between repeated doses of fedratinib (400 mg QD) and single dose of repaglinide (CYP2C8 substrate) or warfarin (CYP2C9 substrate) in healthy volunteer population (Table 79, simulations #13 and 14).

For repaglinide, the drug interaction effect in terms of predicted geometric mean (90% CI) ratios for Cmax and AUCinf were 1.28 (1.25-1.30) and 1.46 (1.41-1.51), respectively. The Applicant used repaglinide as a sensitive CYP2C8 substrate. However, repaglinide is also an OATP1B1 substrate. DDI simulations considered the fedratinib interaction effect on CYP2C8, CYP3A4 and OATP1B1.The default repaglinide PBPK model (software's library, v17) has been verified with clinical DDI data with gemfibrozil (CYP3A, CYP2C8 and OATP inhibitor), and clinical PK data collected in polymorphic population for OATP1B1. Approximately 2-fold increase in repaglinide AUC were reported when repaglinide is co-administrated with clinical OATP1B1 inhibitors such as cyclosporine and rifampin (DDI query using the University of Washington database). Reviewer noted the repaglinide PBPK model has not been verified with the DDI studies with cyclosporine and rifampin. As exploratory analysis, the reviewer conducted sensitivity analysis by

varying fedratinib Ki values for CYP2C8 and OATP1B1. The SA results suggested minor impact on predicted AUC ratio over the tested ranges (10- to 25-fold lower values). PBPK simulations suggested that fedratinib has no significant interaction potential with repaglinide.

For warfarin, the drug interaction effect in terms of predicted geometric mean (90% CI) ratios for Cmax and AUCinf were 1.00 (1.00-1.00) and 1.00 (1.00-1.00), respectively. To investigate the uncertainty around the CYP2C9 Ki value (=26.1 µM), a 10-fold lower Ki value was also tested. The predicted ratios (90% CI) for warfarin Cmax and AUCinf were 1.01 (1.01-1.01) and 1.04 (1.04-1.04), respectively. The reviewer conducted further sensitivity analysis concluding that ≤25% increase in warfarin exposure is expected with up to 75-fold lower CYP2C19 Ki value than the measured in vitro value. PBPK simulations suggested that an interaction between fedratinib and warfarin is unlikely to be clinically significant.

Q8. Can PBPK analyses be used to estimate the effects of fedratinib on drug-transporter substrates?
No. Limitations were found in the default metformin library model that precluded its used as an OCT and MATE substrate for estimation of the effect of fedratinib. Current in-house analysis of the metformin PBPK model demonstrated metformin model could not capture the full spectrum of clinical DDI effects reported in the literature. For example, the model under-predicted the effects of cimetidine and pyrimethamine on metformin at a dose level of 500 mg. There is also a concern that the metformin model may under-estimate the MATE-mediated clearance. Therefore, PBPK analyses could not be used to estimate the effects of fedratinib on an OCT and MATE substrate.

Similarly, there are concerns about the default digoxin library model that precluded its used as a P-gp substrate. The digoxin model does not incorporate P-gp elimination in the kidney. Further, there is an uncertainty in translating in vitro Ki to in vivo Ki towards P-gp. Therefore, PBPK analyses could not be used to estimate the effects of fedratinib on a P-gp substrate.

There are also concerns about the default rosuvastatin library model that precluded its used as a BCRP and OATP1B1/3 substrate. Although rosuvastatin PBPK model can describe the rosuvastatin SD and MD PK, and the interaction effect when co-administered with a single dose of 600 mg rifampicin (an inhibitor for multiple transporters); the model underpredicted the magnitude of interaction with cyclosporine (a prototypical inhibitor of BCRP/OATP1B1). Therefore, PBPK analysis could not be used to estimate the effects of fedratinib on a BCRP/OATP1B1/3 substrate.

CONCLUSIONS
In summary, the fedratinib PBPK model is adequate to predict the fedratinib PK in healthy volunteers and patients with MF.

PBPK analyses are adequate to predict the magnitude of the effects of strong and moderate CYP3A4 inhibitors on fedratinib exposure at steady-state. The model predicted that a strong CYP3A4 inhibitor (such as ketoconazole) may increase fedratinib exposure by approximately 2-fold; while no significant interaction is predicted with a moderate CYP3A4 inhibitor (such as erythromycin and diltiazem) at steady-state. The PBPK analyses are adequate to support labeling language for fedratinib interaction with strong and moderate CYP3A4 inhibitors.

The current PBPK analyses are not adequate to estimate the effects of a dual CYP3A4 and CYP2C19 inhibitor on fedratinib PK because the contribution of CYP2C19 to fedratinib metabolism has not been established.

The current PBPK analyses are not adequate to estimate the effects of a dual CYP3A4 and CYP2C19 inducer or a CYP3A4 inducer on fedratinib PK. There is uncertainty on estimating the clinical CYP3A4 (and CYP2C19) net activity due to the complex DDI potential of fedratinib.

PBPK analyses predicted that an interaction between fedratinib 400 mg QD and a CYP2C9 substrate (such as warfarin) or a CYP2C8 substrate (such as repaglinide) is unlikely to be clinically significant. The PBPK analyses are adequate to support labeling language for fedratinib interaction with substrates for CYP2C8 or CYP2C9.

PBPK analyses could not be used to estimate the effects of fedratinib on substrates for drug transporters (namely, OCT1/2, MATE1/2-K, P-gp, BCRP and OATP1B1/3) because of limitations identified in the substrate PBPK models of metformin, digoxin and rosuvastatin.

19.5.7 Pharmacometric Review

19.5.7.1 Population PK Analysis

Summary of Analysis Dataset

Population PK analysis was conducted based on 3442 evaluable fedratinib plasma concentrations in 452 patients from 6 trials (TED12037, ARD11936, ARD12042, ARD12181, ARD12888 and EFC12153). Study design, subject populations, dosing regimens, treatment duration, and PK sampling plan of the 6 clinical trials are summarized in **Table 84**.

Summary statistics of the continuous and categorical covariates that were evaluated in the population PK analysis are shown in Table 85 **Table 85** and Table 86, respectively. The patients had a median (range) age of 65 (20, 95) years, and were primarily White (88%). There were 146 (32.0%), 197 (43.2%), 109 (23.9%) and 4 (0.9%) patients with normal renal

function, mild renal impairment, moderate renal impairment and severe renal impairment, respectively, according to their creatinine clearance calculated using the Cockcroft-Gault Equation. There were 320 (70.8%) patients with normal hepatic function, 115 (25.4%) patients with mild hepatic impairment and 17 (3.8%) patients with moderate hepatic impairment, and no patient with severe hepatic impairment based on NCI-ODWG criteria. There were no co-medication records in the population PK dataset.

Final PK Model

Population PK model was developed using NONMEM® Version 7.3.0 with first-order conditional estimation with interaction method (FOCE INTER). Model comparisons were based on the objective function value (OFV), goodness-of-fit (GOF) plots, visual predictive check (VPC) and precision in parameter estimates. A difference in OFV > 3.84, 6.63, and 10.83 (df = 1) between 2 nested models is significant at $p < 0.05$, 0.01, 0.001, respectively.

The PK of fedratinib was best characterized by a two-compartment model with first order absorption rate constant (ka) incorporating a lag time, and linear elimination. The inter-individual variability (IIV) associated with the PK parameters was estimated as log-normally distributed with a non-zero covariance on apparent clearance (CL/F), apparent central volume of distribution (V_2/F) and ka. Covariate analysis identified 5 covariates, including polycythemia vera (PV) on both V2/F and CL/F, body weight (WT) on V_2/F, creatinine clearance (CLcr) on CL/F and dose on V2/F. The equations to describe parameter-covariate relationships for fedratinib CL/F and V_2/F are provided below:

$$CL/F_{TV} = 13 * 1.54\ (if\ Diagnosis = PV) * \left(\frac{CLcr}{78.3}\right)^{0.294} \quad (1)$$

$$V2/F_{TV} = 311 * \left(\frac{WT}{70.1}\right)^{0.727} * 1.87\ (if\ Diagnosis = PV) * \left(\frac{Dose}{400}\right)^{-0.279} \quad (2)$$

The final fedratinib PK model parameter estimates, along with the corresponding estimates of precision (95% CI) from Bootstrap are presented in **Table 87**. The goodness-of-fit plots for the final fedratinib PK model are presented in Figure 18. The prediction-corrected visual predictive check (pcVPC) (**Figure 19**) illustrated the prediction percentiles and 95% confidence interval (CI) around the prediction percentiles of simulated concentrations overlaid on the observed fedratinib concentrations and 5th and 95th percentiles of observed fedratinib concentrations. The unexplained biases in CL/F and V_2/F when plotted against identified covariates observed with the base model was eliminated in the final model (**Figure 20**).

Table 84: Studies Included in the Population Pharmacokinetic Analysis of Fedratinib

Study Number(s)	Phase	Design	Doses/Treatment	Study Drug Dosage Form & Meal Status	Population (Number randomized)	PK Sample Collection
TED12037 (MF-TG101348-001)	1	Open-label, dose-escalation study evaluating the safety, tolerability, PK, and PD of orally administered TG101348 (fedratinib)	**Phase 1 (Dose Escalation):** 30, 60, 120, 240, 360, 520, 680, 800, or higher (depending on patient) mg/day QD **Phase 2 (Dose Confirmation):** a cohort of ≤ 30 additional subjects were treated at the MTD *each treatment cycle was 28 days with ≤ 6 cycles for duration of study	Study drug was administered orally on an empty stomach (1 hour before or 2 hours after meals)	Patients with PMF, post-PV-MF, or post-ET-MF (N = 59)	**Cycle 1:** Day 1, 28: pre-dose and 0.5, 1, 2, 4, 8, 28 h post-dose. Day 2, 29 dosing was delayed until after the last PK sample on Days 1 and 28, respectively. If intra-subject dose escalation occurred, trough PK samples were obtained at the end of dose cycle with higher dose.
ARD11936	2	Randomized, open-label, dose-ranging study of the efficacy and safety of orally administered SAR302503 (fedratinib)	300, 400, or 500 mg/day QD in consecutive 28-day cycles for approximately 10 months	Study drug was administered orally on an empty stomach (1 hour before or 2 hours after meals)	Patients with intermediate-2 or high risk PMF, post-PV-MF, or post-ET-MF with splenomegaly (N = 31)	**Cycle 1:** Day 1: pre-dose and 1, 2, 3, 4, 6, 8 h post-dose; Day 2: pre-dose; Day 15: pre-dose **Cycle 2:** Day 1: pre-dose and 1, 2, 3, 4, 6, 8 h post-dose; Day 2: pre-dose **Cycle 3:** Day 1: pre-dose
ARD12181 (JAKARTA2)	2	Open-label, single arm study	**Cycles 1, 2:** 400 mg/day QD **Cycles 3, 4:** • Upward titration: max of 500 mg/day QD • Downward titration: min of 200 mg/day QD **Cycles 5, 6:** • Upward titration: max of 600 mg/day QD • Downward titration: min of 100 mg/day QD if still taking drug *dosing regimens are flexible; can upward then downward titrate, etc. **cycles = 28 days; duration of study ≥ 6 months	Study drug was administered orally on an empty stomach (1 hour before or 2 hours after meals)	Patients previously treated with ruxolitinib and with a current diagnosis of intermediate or high risk PMF, post-PV-MF, or post-ET-MF (N = 97)	**Cycle 1, 2:** Day 1: pre-dose and 0.5-2, 2.5-4 h post-dose **Cycle 4:** Day 1: pre-dose

Study Number(s)	Phase	Design	Doses/Treatment	Study Drug Dosage Form & Meal Status	Population (Number randomized)	PK Sample Collection
EFC12153 (JAKARTA)	3	Randomized, double-blind, placebo-controlled, 3-arm study	**Initial:** 400, 500 mg or matching PBO QD for ≥ 6 consecutive 28-day cycles **PBO Arm & Crossover:** PBO arm may crossover to 400 or 500 mg QD when they have either completed 6 cycles treatment or had experience disease progression.	Study drug was administered orally on an empty stomach (1 hour before or 2 hours after meals)	Patients with intermediate-2 or high risk PMF, post-PV-MF, or post-ET-MF with splenomegaly (N = 289)	**Cycles 1, 2:** Day 1: pre-dose and up to 4 hours post-dose
ARD12042	2	Randomized, open-label study	100, 200 or 400 mg QD for ≥ 8 consecutive 28-day cycles	Study drug was administered orally on an empty stomach (1 hour before or 2 hours after meals)	Patients with PV or ET who are resistant to or intolerant to hydroxyurea (N = 81)	**Cycle 1:** Day 1: pre-dose and 1, 2, 3, 4, 6 and 8 hours post-dose; Day 2: pre-dose; Day 15: pre-dose. **Cycle 2:** Day 1: pre-dose and 1, 2, 3, 4, 6 and 8 hours post-dose; Day 2: pre-dose. **Cycle 3:** Day 1: pre-dose.
ARD12888	2	Randomized, open-label study	300, 400 or 500 mg QD for ≥ 1 consecutive 28-day cycles	Study drug was administered orally on an empty stomach (1 hour before or 2 hours after meals)	Japanese patients with intermediate-2 or high risk PMF, post-PV-MF, or post-ET-MF with splenomegaly (N=8)	**Cycle 1:** Day 1: pre-dose and 1, 2, 3, 4 and 8 hours post-dose; Day 2: pre-dose; Day 8: pre-dose; Day 15: pre-dose. **Cycle 2:** Day 1: pre-dose and 1, 2, 3, 4 and 8 hours post-dose; Day 2: pre-dose. **Cycle 3:** Day 1: pre-dose.

MF = Myelofibrosis; PMF = Primary myelofibrosis; PV = Polycythemia vera; ET = Essential thrombocythemia; QD = once daily; PBO = placebo; PK = pharmacokinetics; PD = pharmacodynamics; MTD = maximum tolerated dose

Source: FEDR-MPK-001, Population PK Analysis Report, Tables 1 and 2.

Table 85: Summary Statistics for the Continuous Covariates Evaluated in the Formal Covariate Assessment

Study	11936	12037	12042	12153	12181	12888	Total
No. of Subjects	31	52	78	186	97	8	452
Age (year)							
No.	31	52	78	186	97	8	452
Mean	61.77	64.67	59.04	63.74	66.52	66.13	63.54
Median	63	65	63	64	67	66	65
SD	12.24	10	14.75	9.45	8.14	6.69	10.76
Min	36	43	19[a]	39	38	53	19[a]
Max	83	85	95	86	83	76	95
Body Weight (kg)							
No.	30	52	78	184	96	8	448
Mean	73.82	72.99	76.22	68.62	73.55	53.47	71.58
Median	71.88	75.05	73.7	68	73	53.35	70.05
SD	13.88	13.39	18.38	12.21	12.89	4.97	14.23
Min	46	48.2	44	39.5	47	48	39.5
Max	109.09	105.2	135.1	102.5	105.7	60.7	135.1
Body Height (cm)							
No.	31	52	77	182	93	8	443
Mean	168.74	170.01	168.85	168.64	169.77	160.98	168.94
Median	167.6	170.9	168	169	170	161	169
SD	9.9	7.42	10.6	9.36	9.47	4.81	9.42
Min	152.2	152.4	149.2	148	149	152.8	148
Max	193.9	182	193.4	192	195	168	195
Time since Diagnosis (year)							
No.	29	52	78	185	97	8	449
Mean	3.45	5.62	8.47	4.48	6.15	3.64	5.58
Median	1.23	3.18	8.41	2.29	4.08	1.03	3.46
SD	4.8	5.94	6.38	5.28	5.59	4.53	5.77
Min	0	0.06	0	0.04	0.31	-0.06	-0.06
Max	18.27	25.75	31.92	25.88	24.53	11.1	31.92
Albumin (g/L)							
No.	30	52	77	184	97	8	448
Mean	41.77	39.44	42.55	41.17	39.36	39.75	40.83
Median	42	39	43	41	40	39.5	41
SD	4.38	4.06	3.73	4.57	4.52	5.39	4.49
Min	31	27	34	25	28	33	25
Max	49	47	53	52.8	50	48	53
Study	11936	12037	12042	12153	12181	12888	Total
No. of Subjects	31	52	78	186	97	8	452

Alanine transaminase (IU/L)							
No.	31	52	78	186	97	8	452
Mean	21.42	24.29	23.05	20.77	22.21	16.75	21.85
Median	21	18	18.5	17.45	18	15	18
SD	8.44	22.69	13.84	12.38	14.71	10.43	14.43
Min	9	8	8	2	3	6	2
Max	40	159	86	74.1	97	40	159
Aspartate transaminase (IU/L)							
No.	31	52	78	185	97	8	451
Mean	32.48	30.63	24.94	28.03	30.41	24	28.54
Median	32	26	24	25	27	21.5	26
SD	10.94	19.64	9.04	15.97	16.06	11.9	15.24
Min	7	8	6	6	11	12	6
Max	59	138	56	173.8	106	46	173.8
Bilirubin (umol/L)							
No.	31	52	78	186	97	8	452
Mean	14.12	13.65	10.02	15.64	14.90	15.07	14.17
Median	11.97	11.97	8.68	13.68	13	11.54	11.97
SD	8.15	6.22	5.27	8.64	7.95	7.56	7.91
Min	5.13	6.84	1.54	4.79	3.42	8.38	1.54
Max	47.88	32.49	25.48	55.3	48.2	27.36	55.3
Creatinine Clearance (mL/min)							
No.	31	52	78	186	97	8	452
Mean	83.57	75.98	93.36	77.84	77.81	68.79	80.53
Median	78.96	79	89.72	76.44	76.97	72.5	78.46
SD	30.42	28.56	32.88	24.95	22.85	21.94	27.40
Min	37.42	32.2	32.53	20.06	38.24	37	20.06
Max	157.28	148.2	181.45	158.38	142.04	105.2	181.45

SD = Standard deviation

[a] Due to change in age calculation from preliminary source dataset to final source dataset, age of three subjects increased by one year. One of the change was from 19 to 20 years old, which led to the change in minimum age from 19 to 20 years old.

Source: FEDR-MPK-001, Population PK Analysis Report, Table 5.

Table 86: Summary Statistics for the Categorical Covariates

Study	11936	12037	12042	12153	12181	12888	Total
No. of Subjects (%)	**31 (6.9)**	**52 (11.5)**	**78 (17.3)**	**186 (41.2)**	**97 (21.5)**	**8 (1.8)**	**452**
Gender							
Male	16 (3.5)	29 (6.4)	35 (7.7)	110 (24.3)	53 (11.7)	6 (1.3)	249 (55.1)
Female	15 (3.3)	23 (5.1)	43 (9.5)	76 (16.8)	44 (9.7)	2 (0.4)	203 (44.9)
Race							
White	27 (6.0)	46 (10.2)	72 (15.9)	162 (35.8)	92 (20.4)	0 (0)	399 (88.3)
Black	2 (0.4)	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)	0 (0)	7 (1.5)
Asian	2 (0.4)	3 (0.7)	5 (1.1)	22 (4.9)	4 (0.9)	8 (1.8)	44 (9.7)
Other	0 (0)	2 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.4)
Ethnicity							
Unknown	31 (6.9)	1 (0.2)	78 (17.3)	186 (41.2)	97 (21.5)	8 (1.8)	401 (88.7)
Hispanic/ Latino	0 (0)	2 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.4)
NonHispanic/ NonLatino	0 (0)	49 (10.8)	0 (0)	0 (0)	0 (0)	0 (0)	49 (10.8)
NCI-ODWG Liver Function Classification							
Normal	18 (4.0)	39 (8.6)	68 (15.0)	122 (27.0)	67 (14.8)	6 (1.3)	320 (70.8)
Mild	12 (2.7)	12 (2.7)	10 (2.2)	54 (11.9)	25 (5.5)	2 (0.4)	115 (25.4)
Moderate	1 (0.2)	1 (0.2)	0 (0)	10 (2.2)	5 (1.1)	0 (0)	17 (3.8)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ECOG Score							
0	11 (2.4)	15 (3.3)	48 (10.6)	70 (15.5)	26 (5.8)	4 (0.9)	174 (38.5)
1	15 (3.3)	29 (6.4)	28 (6.2)	98 (21.7)	45 (10.0)	3 (0.7)	218 (48.2)
2	5 (1.1)	8 (1.8)	2 (0.4)	18 (4.0)	23 (5.1)	1 (0.2)	57 (12.6)
6	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.7)	0 (0)	3 (0.7)
Diagnosis							
Primary MF	18 (4.0)	39 (8.6)	0 (0)	120 (26.5)	53 (11.7)	2 (0.4)	232 (51.3)
Post PV MF	8 (1.8)	10 (2.2)	0 (0)	47 (10.4)	25 (5.5)	1 (0.2)	91 (20.1)
Post ET MF	5 (1.1)	3 (0.7)	0 (0)	19 (4.2)	19 (4.2)	5 (1.1)	51 (11.3)
PV	0 (0)	0 (0)	45 (10.0)	0 (0)	0 (0)	0 (0)	45 (10.0)
ET	0 (0)	0 (0)	33 (7.3)	0 (0)	0 (0)	0 (0)	33 (7.3)

NCI-ODWG = National Cancer Institute Organ Dysfunction Working Group; ECOG = Eastern Cooperative Oncology Group (Score: 0 = Fully active; 1 = Restricted in physically strenuous activity; 2 = Ambulatory; 6 = Unknown)

Source: FEDR-MPK-001, Population PK Analysis Report, Table 4.

Table 87: Parameter Estimates from the Final Population Pharmacokinetic Model for Fedratinib

Parameter	Parameter Estimates	Bootstrap median (95% CI)[a]	
Fixed effects			
TVKA, h^{-1}	1.57	1.64	(1.34 – 2.05)
TVV2/F, L	311	313	(282 – 343)
TVCL/F, L/h	13.0	13.1	(12.4 – 13.9)
TVV3/F, L	1460	1470	(1190 – 1790)
TVQ/F, L	45.2	45.2	(38.5 – 52.9)
TVALAG1, h	0.265	0.265	(0.264 – 0.321)
PV on V2/F [b]	1.87	1.85	(1.40 – 2.42)
Weight on V2/F [b]	0.727	0.733	(0.383 – 1.10)
Dose on V2/F [b]	-0.279	-0.279	(-0.502 – -0.0672)
PV on CL/F [c]	1.54	1.51	(1.23 – 1.96)
CLcr on CL/F [c]	0.294	0.297	(0.157 – 0.441)
Random effects			
Inter-Individual variability			
ω^2, KA	1.07	1.09	(0.728 – 1.54)
ω^2, V2/F	0.383	0.371	(0.247 – 0.510)
ω^2, CL/F	0.255	0.250	(0.176 – 0.352)
$COV_{V2/F-CL/F}$	0.197	0.193	(0.145 – 0.249)
Residual variability			
σ^2 (Log additive)	0.201	0.194	(0.159 – 0.264)

ALAG1 = absorption lag time; CI = confidence interval; CL/F = apparent clearance; COV = covariance; CLcr = creatinine clearance; KA = absorption rate constant; PV = polycythemia vera; Q/F = apparent intercompartmental clearance; TV = typical value; V2/F = apparent volume of distribution of central compartment; V3/F = apparent volume of distribution of peripheral compartment

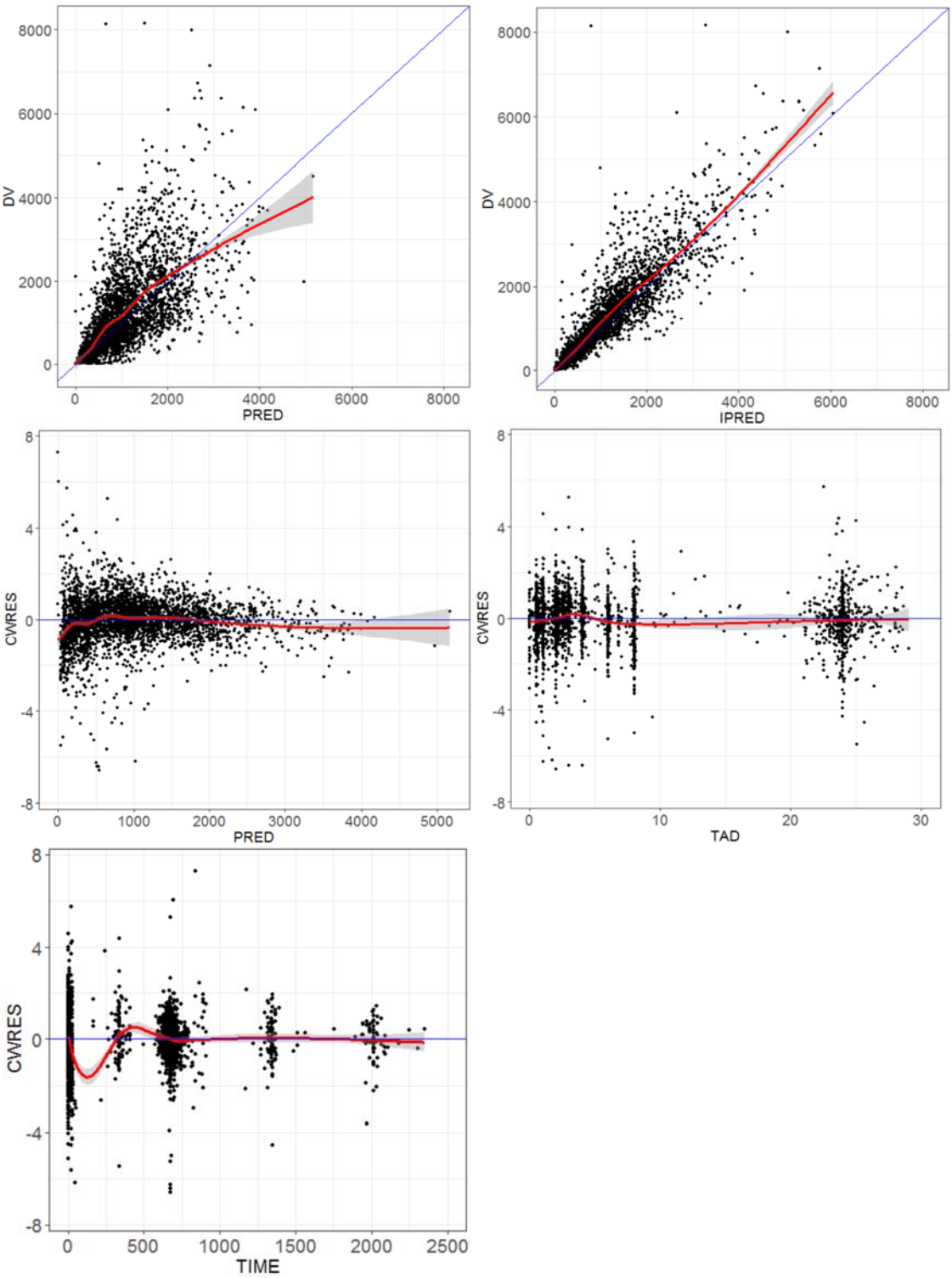
[a] Bootstrap confidence interval values are taken from bootstrap calculation (484 successful out of a total of 500 bootstrap replicates).

[b] $V2/F\ (L) = 311*1.87(\text{if Diagnosis=PV})*(\text{Weight}/70.1)^{0.727}*(\text{Dose}/400)^{-0.279}$

[c] $CL/F\ (L/h) = 13.0*1.54(\text{if Diagnosis=PV})*(\text{CLcr}/78.3)^{0.294}$

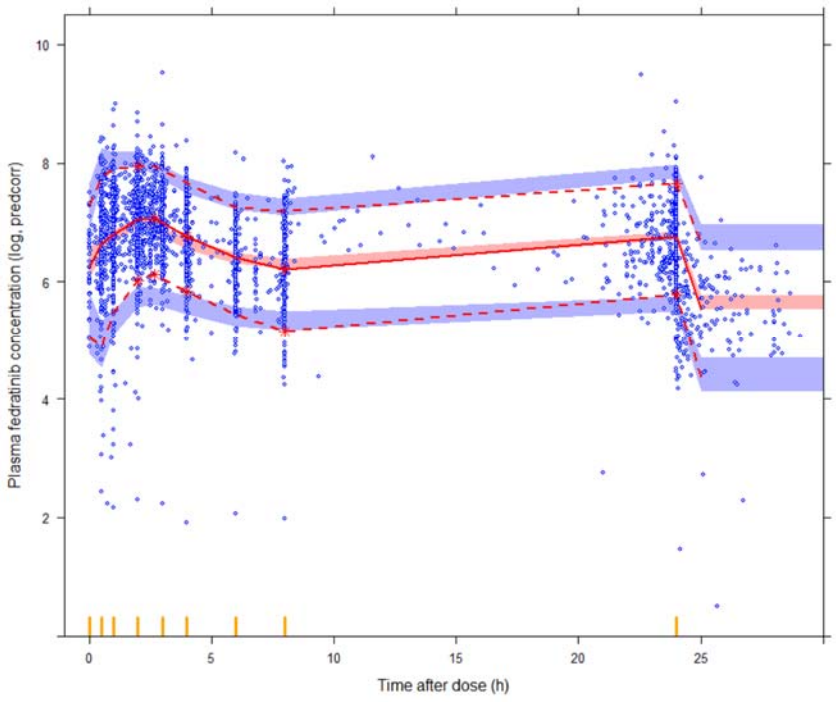
Source: FEDR-MPK-001, Population PK Analysis Report, Table 8.

Figure 18: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model for Fedratinib.



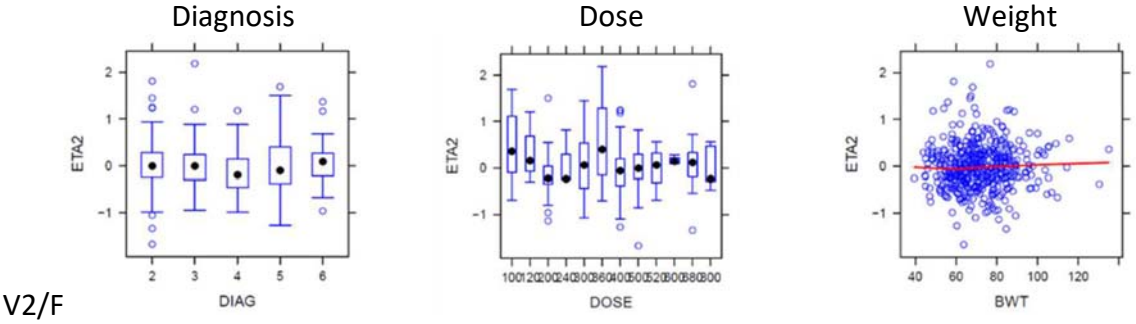
Source: FEDR-MPK-001, Population PK Analysis Report, Figures 8, 9, 10, 11, and 12.

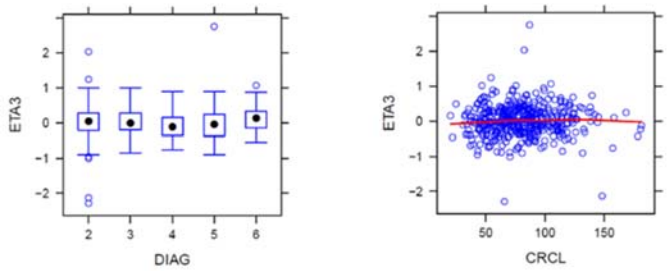
Figure 19: Prediction-Corrected Visual Predictive Check for the Time Profiles of Fedratinib.



Source: FEDR-MPK-001, Population PK Analysis Report, Figure 15.

Figure 20: Unexplained Variabilities in CL/F and V_2/F Plotted Against the Identified Significant Covariates in the Final PopPK Models.





CL/F

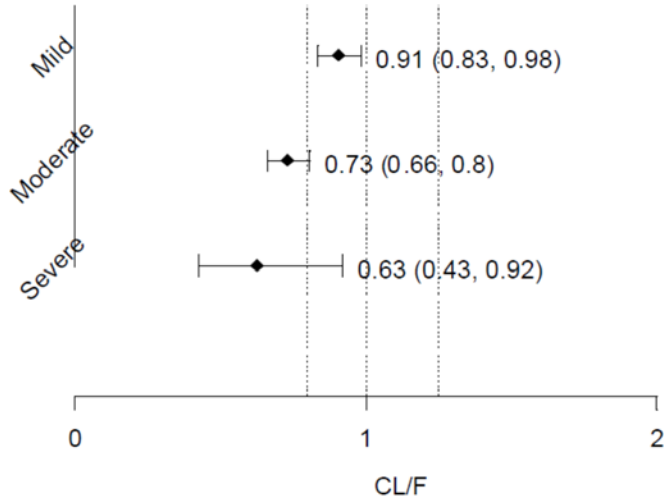
Diagnosis: 2 = Primary MF; 3 = Post PV MF; 4 = Post ET MF; 5 = PV; 6 = ET

Source: FEDR-MPK-001, Population PK Analysis Report, Figures 13 and 14.

Statistically Significant Covariates

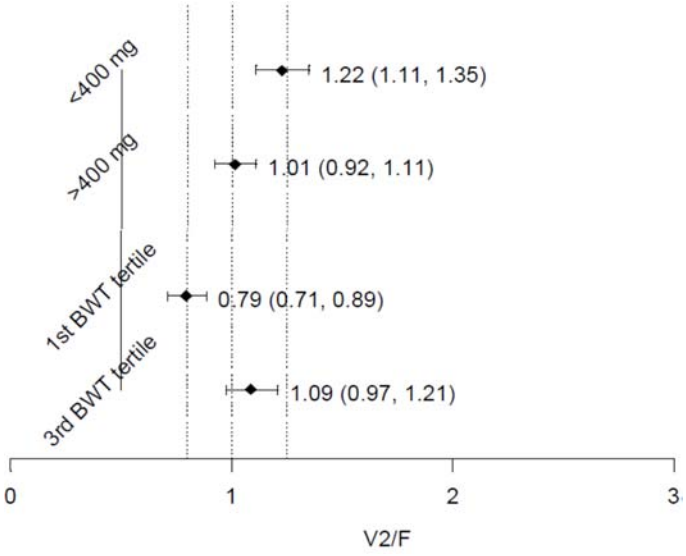
As shown in **Figure 21**, the typical steady-state AUC (dose divided by CL/F) in MF patients with mild (60 ≤ CLcr < 90 mL/min) and moderate (30 ≤ CLcr < 60 mL/min) renal impairment were 10% and 37% higher than that in MF patients with normal renal function (CLcr ≥90 mL/min). Due to the statistical significance of the effect of weight and dose on V_2/F (**Figure 22**), the C_{max} of fedratinib would increase slightly more than dose proportional and would be inversely correlated to body weight. Given that the magnitude of change in V_2/F by body weight was less than 30%, and it does not affect AUC, body weight was not identified as a clinically relevant covariate, and thus no dose adjustment is required based on body weight.

Figure 21: Forest Plot of Renal Impairment on Fedratinib CL/F.



Source: FEDR-MPK-001, Population PK Analysis Report, Figure 6.

Figure 22: Forest Plot of Fedratinib Dose and Body Weight on Fedratinib V2/F.



Source: FEDR-MPK-001, Population PK Analysis Report, Figure 7.

Individual Exposure Measures for Fedratinib

Based on individual Bayesian estimates of CL/F and the nominal starting dose, $AUC_{0\text{-}24,ss}$ of fedratinib was calculated and summarized by study (**Table 88** and **Table 89**) to be used as exposure metric for E-R analyses.

Table 88: Geometric Mean (CV%) $AUC_{0\text{-}24,ss}$ of Fedratinib in Patients with MF at Doses of 300 – 500 mg by Study

Study	11936			12153		12181
Dose	300 mg (N = 10)	400 mg (N = 10)	500 mg (N = 11)	400 mg (N = 91)	500 mg (N = 94)	400 mg (N = 97)
$AUC_{0\text{-}24,ss}$ (ng*h/mL)	23049.93 (66.2)	27448.70 (44.8)	39848.69 (65.0)	30217.25 (34.5)	39903.72 (43.9)	33500.33 (41.1)

$AUC_{0\text{-}24,ss}$ = area under the concentration-time curve from time zero to 24 hours after dosing at steady state; CV = coefficient of variation; MF = myelofibrosis

Source: FEDR-MPK-001, Population PK Analysis Report, Table 9.

Table 89: Geometric Mean (CV%) $AUC_{0\text{-}24,ss}$ of Fedratinib in Patients with PV/ET at 400 mg Dose in Study 12042

Study: Dose	12042: 400 mg	
Diagnosis	PV (N = 20)	ET (N = 11)
$AUC_{0\text{-}24,ss}$ (ng*h/mL)	23898.30 (51.5)	27361.38 (19.7)

$AUC_{0\text{-}24,ss}$ = area under the concentration-time curve from time zero to 24 hours after dosing at steady state; CV = coefficient of variation; ET = essential thrombocythemia; PV = polycythemia vera

Source: AC220-PMx002, Exposure-Response Analysis Report, Table 33.

Applicant's Conclusions

- PK of fedratinib was adequately described by a two-compartment model with first-order absorption incorporating a lag time and first-order elimination.
- From 200 mg to 600 mg, the fedratinib AUC exposure increased proportionally with dose.
- Patients with PV had 1.87-fold larger V_2/F and 1.54-fold larger CL/F as compared to patients with MF.
- Dose and body weight are statistically significant covariates on V_2/F, but none of these covariates is clinically relevant requiring no dose adjustment.
- CLcr is a statistically significant covariate on CL/F, and MF patients with mild and moderate renal impairment had 10% and 37% increase in fedratinib exposure, respectively.
- Age, gender, race and liver function were not statistically significant covariates affecting fedratinib PK exposure.

Reviewer's Comments: *The Applicant's population PK model appears adequate to describe the observed concentration-time profile of fedratinib following the administration of fedratinib ranged from 100 to 800 mg QD in patients with primary MF, post PV MF, post ET MF, PV or ET. Therefore, the PK model is acceptable to generate post-hoc exposure metrics, e.g. $AUC_{0\text{-}24,SS}$ and $AUC_{C1\text{-}C6}$ of fedratinib for exposure-response analyses for efficacy and safety measurements. Based on population PK analysis, the terminal $t_{1/2}$ of fedratinib was 114 hours and the mean Vd/F was 1770 L at steady state in patients with MF.*

Covariate analysis revealed that the fedratinib exposure was not significantly altered by Age (20 years to 95 years), race (White, Black, Asians), sex, body weight (40 kg to 135 kg), mild [total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin 1 to 1.5 times ULN and any AST] or moderate (total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment, mild renal impairment (CL_{CR} ≥60 mL/min to <90 mL/min as estimated by Cockcroft-Gault equation), thus no dose adjustment is needed for the above-mentioned specific populations. In addition, per the Agency's request, the Applicant also evaluated the effect of the different formulations on the PK of fedratinib. The results showed that formulation was a significant covariate on V_2/F but not on CL/F. Patients receiving the initial formulation and formulation 1A1 had 15% higher and 23% lower V2/F, respectively, compared with patients receiving formulation 1B1. However, the impact of formulation on the PK of fedratinib was considered to be not clinically meaningful, as there was no effect of formulation on AUC.

19.5.7.2 Exposure-Response for Efficacy

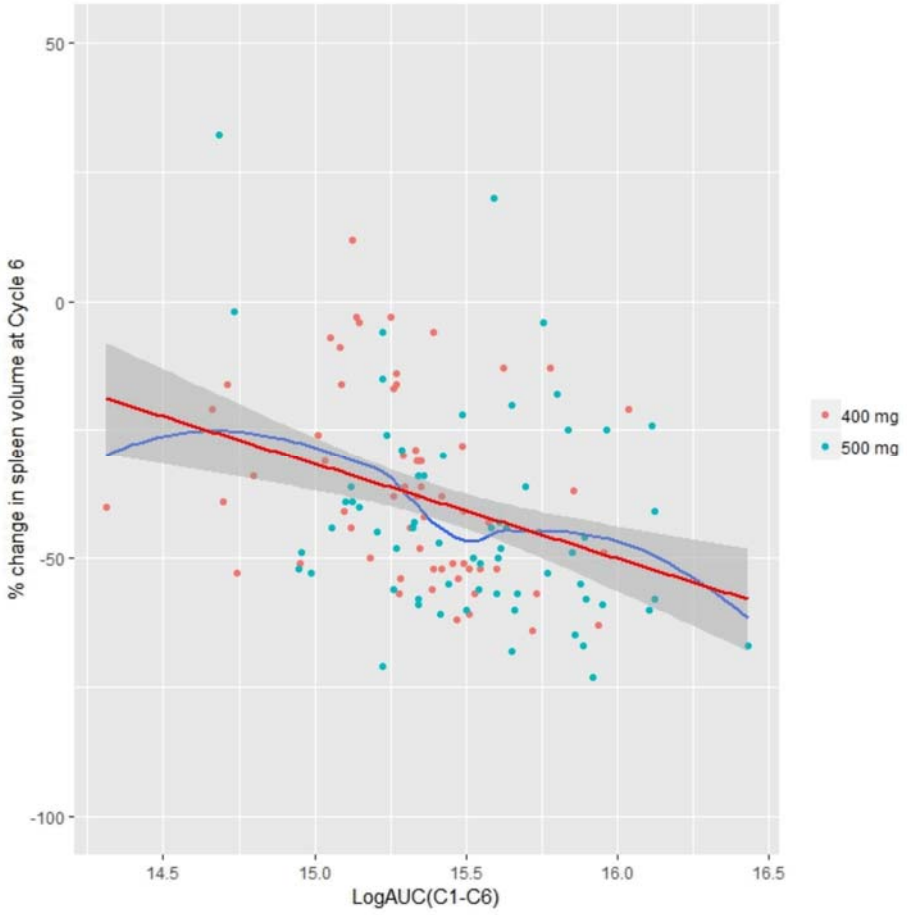
The fixed dosing regimens of fedratinib 400 mg QD and 500 mg QD were used in the registrational trial EFC12153, while a titrated fedratinib dosing regimen was used in supportive trial ARD12181. Patients in study ARD12181 received an initial fedratinib dose of 400 mg/day on Cycle 1 Day 1,

and the fedratinib dose was titrated upwards in 100 mg/day increments up to maximum of 600 mg/day, after End of Cycles 2 and 4 based on a lack of adequate spleen response (≥ 50% spleen size reduction by palpation compared with baseline) and no unacceptable drug toxicity. As the exposure-response (E-R) relationships would be confounded by the different dose regimens if using the pooled data from the two trials, the E-R analyses were conducted separately for each trial using different PK exposure metrics for the following efficacy endpoints, i.e., spleen volume response, spleen volume percent change, and total symptom score response.

Trial EFC12153

The E-R analyses showed a linear correlation between percent change in spleen volume at the End of Cycle 6 versus cumulative log-transformed AUC from Cycle 1 to Cycle 6 ($LogAUC_{C1-C6}$), indicating the spleen volume reduction increases as the fedratinib exposure increases (**Figure 23**). In addition, the logistic regression analyses also showed that fedratinib PK exposure was a statistically significant factor affecting SVR and TSSR (Table 90). The positive slopes of $LogAUC_{C1-C6}$ suggested that the probability of spleen volume response increases as the fedratinib PK exposure increases.

Figure 23: Locally Weighted Scatterplot Smoothing and Fitting Curve from Linear Regression of Percent Change in Spleen Volume from Baseline at End of Cycle 6 vs $LogAUC_{C1-C6}$ from Trial EFC12153



The blue line is the locally weighted scatterplot smoothing line. The red line is the fitting curve from linear regression model, and the grey shaded area represents the 95% confidence band from linear regression.
Source: Response to FDA Request for Information on 03/13/2019, Figure 1.

Table 90: Model Summary of Incidence of ≥35% SVR and TSSR versus PK Exposure from Trial EFC12153

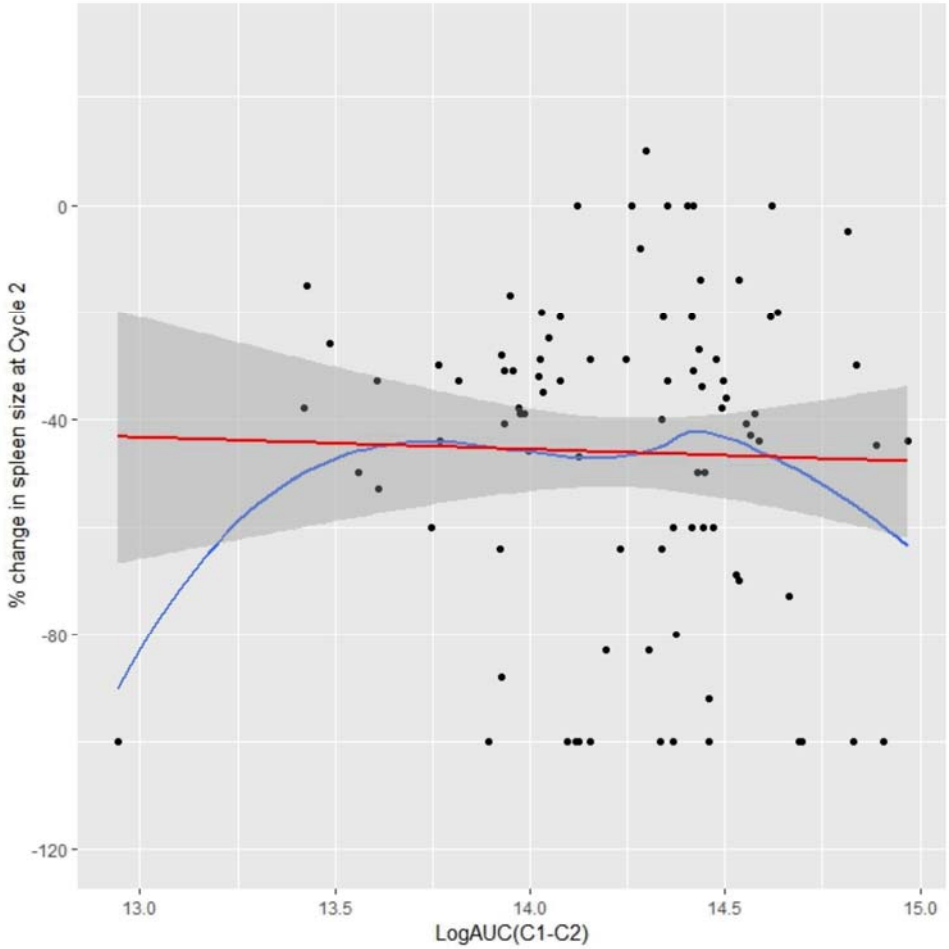
Model	Parameter	Estimate	Std.err	p-value	95% Confidence Interval	
SVR	Intercept	-30.9	6.50	<.0001	-44.8	-19.3
	Slope of $LogAUC_{C1-C6}$	2.02	0.424	<.0001	1.26	2.93
TSSR	Intercept	-14.3	5.35	0.0073	-25.9	-4.81
	Slope of $LogAUC_{C1-C6}$	0.869	0.348	0.0125	0.247	1.62

Source: Response to FDA Request for Information on 03/13/2019, Tables 2 and 3.

Trial ARD12181

As the E-R analysis might be confounded by the dose titration algorithm in Trial ARD12181, predicted cumulated AUC from Cycle 1 to 2 (AUC_{C1-C2}) before dose escalation was used as the exposure metric for the E-R analysis. The E-R analyses showed a flat E-R relationship between percent change in spleen volume at the End of Cycle 2 and $LogAUC_{C1-C2}$ (**Figure 24**). In addition, the logistic regression analyses also showed that fedratinib PK exposure was not a statistically significant factor affecting SVR and TSSR (Table 91). However, the E-R relationships in Trial ARD12181 is not definitive due to: 1) narrow exposure range, 2) the response had not reached steady state at the End of Cycle 2; and 3) the use of palpation for measurement of spleen size in Cycles 1 and 2 is more subjective as opposed to MRI/CT in Trial EFC12153.

Figure 24: Locally Weighted Scatterplot Smoothing and Fitting Curve from Linear Regression of Percent Change in Spleen Size (by Palpation) from Baseline at End of Cycle 2 versus $LogAUC_{C1-C2}$ from Trial ARD12181.



The blue line is the locally weighted scatterplot smoothing line. The red line is the fitting curve from linear regression model, and the grey shaded area represents the 95% confidence band from linear regression.

Source: Response to FDA Request for Information on 03/13/2019, Figure 2.

Table 91: Model Summary of Incidence of ≥50% SVR and TSSR versus PK Exposure from Trial ARD12181

Model	Parameter	Estimate	Std.err	p-value	95% Confidence Interval	
SVR	Intercept	-3.49	8.55	0.684	-20.8	13.1
	Slope of $LogAUC_{C1-C6}$	0.206	0.600	0.731	-0.959	1.42
TSSR	Intercept	-14.3	9.21	0.119	-33.5	2.97
	Slope of $LogAUC_{C1-C6}$	0.966	0.644	0.134	-0.247	2.30

Source: Response to FDA Request for Information on 03/13/2019, Tables 5 and 6.

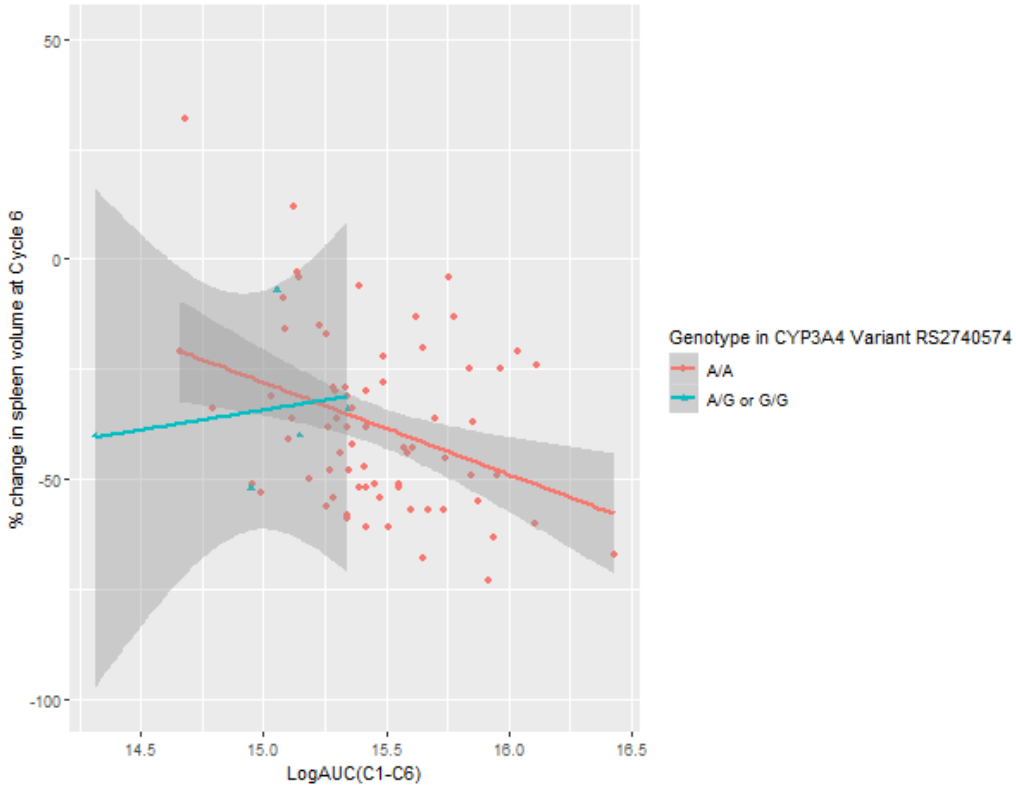
Reviewer's Comments: *The applicant's exposure-response analyses for efficacy are acceptable. The slope was 2.02 (2% increase in ≥35% SVR for every unit of increase in log exposure) based on the linear model in Trial EFC12153 . Based on the slope and the mean difference in exposure between the two doses, only a 0.1% additional increase in ≥35% SVR at EOC6 is predicted at 500 mg versus 400 mg. This is due to the considerable overlap in exposure observed between the two doses (**Figure 2**) due to higher incidence of dose modifications (51 %) due to AEs at the 500 mg dose in Trial EFC12153.*

19.5.7.3 Impact of CYP3A4 Genotype on Exposure-Efficacy Relationship in Study EFC12153

The reviewers conducted the following independent analysis to evaluate the impact of CYP3A4 genotype on fedratinib exposure and the exposure-efficacy relationship in patients with MF who were naïve to ruxolitinib treatment in study EFC12153. There were two single nucleotide polymorphisms (SNPs) in CYP3A4: RS2740574 and RS4986910, associated with fedratinib PK exposure.

For CYP3A4 variant RS2740574, 5/8 (62.5%) patients with genotype "A/G" or "G/G" and 71/100 (71%) patients with genotype "A/A" had data on fedratinib AUC and percentage change in spleen volume at Cycle 6. Patients with genotype "A/G" or "G/G" (n = 5) tended to have lower AUC_{C1-C6} (3317 ± 1089 mg·h/L vs. 5477 ± 1989 mg·h/L), and less percentage change in spleen volume at Cycle 6 (-34.6% ± 16.8% vs. -37.5% ± 20.0%), as compared to patients with genotype "A/A" (n = 71). The E-R relationships for percentage change in spleen volume at Cycle 6 in patients with CYP3A4 variant RS2740574 genotype "A/G" or "G/G" and patients with genotype "A/A" are presented in **Figure 25**. The difference in E-R relationship in these two subpopulations may be driven by patient ID=(b) (6) with genotype "A/G", 14.3 of $logAUC_{C1-C6}$ and -40% change in SV at cycle 6. In addition, the E-R relationships are also confounded by the imbalance in demographics and disease status at baseline between two subpopulations (**Table 92**).

Figure 25: The Exposure-Response Relationships for Percentage Change in Spleen Volume at Cycle 6 in Patients with Different CYP3A4 Variant RS2740574 Genotypes in Study EFC12153



Source: Reviewer's analysis.

Table 92: Demographics and Disease Status at Baseline in Patients Different CYP3A4 Variant RS2740574 Genotypes in Study EFC12153.

	CYP3A4 variant RS2740574	
	A/G or G/G (n=5)	A/A (n=71)
Mean (SD) Age, year	66.4 (12.3)	62.1 (9.2)
Mean (SD) Weight, kg	68.4 (6.3)	71.0 (11.8)
Mean (SD) Height, kg	167.9 (3.6)	170.3 (10.0)
Sex		
Female	2 (40.0%)	27 (38.0%)
Male	3 (60.0%)	44 (62.0%)
Race		
Asian	0 (0.0%)	7 (9.9%)
Black or African American	1 (20.0%)	1 (1.4%)
Other	0 (0.0%)	1 (1.4%)
White	4 (80.0%)	62 (87.3%)

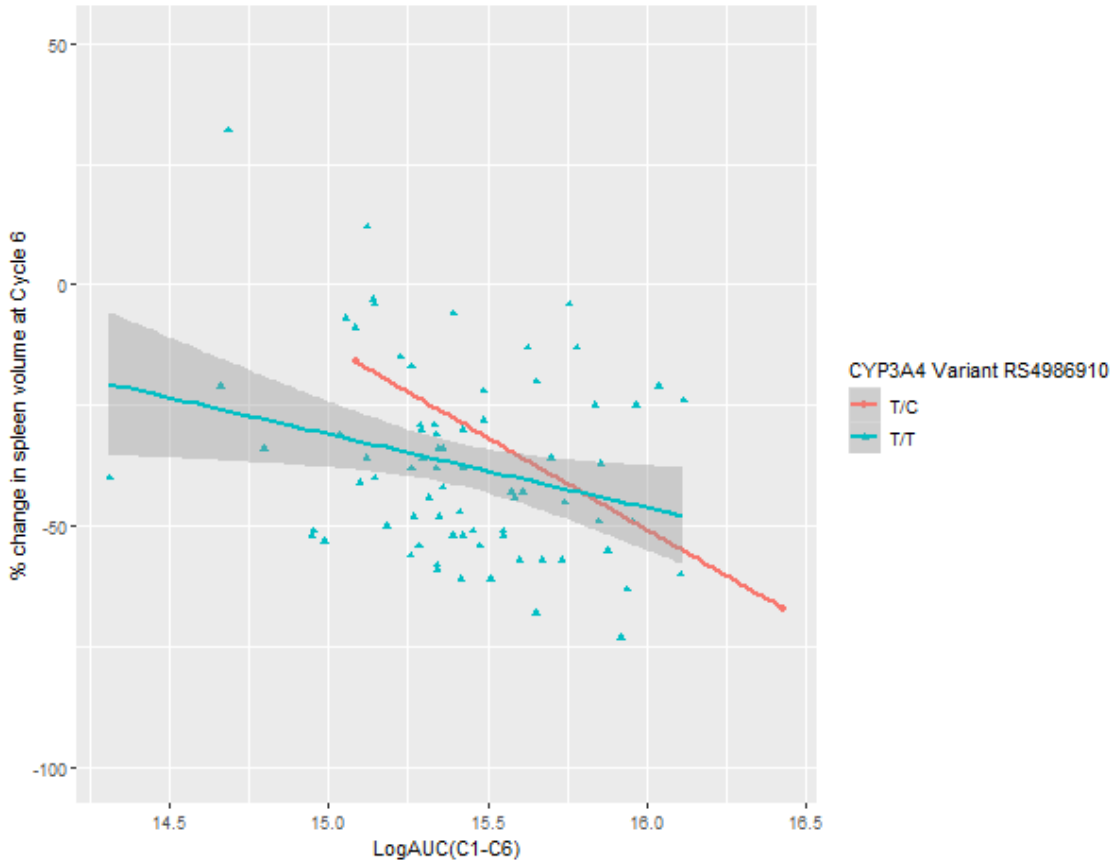
Type of Myelofibrosis		
Post-essential thrombocythemia	0 (0.0%)	5 (7.0%)
Post-polycythemia Vera MF	3 (60.0%)	18 (25.4%)
Primary MF	2 (40.0%)	48 (67.6%)
Risk Group		
High risk	3 (60.0%)	29 (40.8%)
Intermediate level 2	2 (40.0%)	42 (59.2%)
Baseline Platelet Count Group		
50 - < 100 x 10^9/L	1 (20.0%)	12 (16.9%)
100 - < 200 x 10^9/L	0 (0.0%)	20 (28.2%)
>= 200 x 10^9/L	4 (80.0%)	39 (54.9%)
Baseline Hemoglobin		
< 10g/dL	2 (40.0%)	27 (38.0%)
>= 10g/dL	3 (60.0%)	44 (62.0%)
Baseline ECOG Performance Status		
Unknown		
0	2 (40.0%)	25 (35.2%)
1	2 (40.0%)	39 (54.9%)
2	1 (20.0%)	7 (9.9%)
Baseline RBC Transfusion Dependence		
No	5 (100.0%)	68 (95.8%)
Yes	0 (0.0%)	3 (4.2%)
Baseline Hepatic Function		
Unknown	2 (20%)	0 (0.0%)
Normal	2 (40.0%)	47 (66.2%)
Mild	2 (40.0%)	17 (23.9%)
Moderate	0 (0.0%)	7 (9.9%)
Baseline Renal Function		
Normal	1 (20.0%)	27 (38.0%)
Mild	2 (40.0%)	34 (47.9%)
Moderate	2 (40.0%)	10 (14.1%)
JAK2 Mutational Profile		
Unknown	0 (0.0%)	2 (2.8%)
Mutant	5 (100.0%)	49 (69.0%)
Wild	0 (0.0%)	20 (28.2%)

Source: Reviewer's analysis.

For CYP3A4 variant RS4986910, 2/2 (100%) patients with genotype "T/C" and 74/106 (70%) patients with genotype "T/T" had data on fedratinib AUC and percentage change in spleen volume at Cycle 6. patients with genotype T/C (n=2) seems to have higher AUC_{C1-C6} (8613 ± 7125 mg·h/L vs. 5246 ± 1778 mg·h/L), and slightly greater percentage change in spleen volume at Cycle 6 (-41.5% ± 36.1% vs. -37.2% ± 19.6%) as compared to patients with genotype T/T (n = 74).

However, the results should be interpreted with caution due to the limited patients with genotype T/C in CYP3A4 variant RS4986910 and other potential confounders. In addition, a definitive E-R relationship cannot be established for patients with genotype T/C due to the limited sample size (**Figure 26**).

Figure 26: The Exposure-Response Relationship for Percentage Change in Spleen Volume at Cycle 6 in Patients with Different Genotype in CYP3A4 Variant RS4986910 in Study EFC12153



Source: Reviewer's analysis.

Overall, dose adjustment is not recommended for patients with genotype "A/G" or "G/G" in CYP3A4 variant RS2740574 or patients with genotype "T/C" in CYP3A4 variant RS4986910, given the lack of informative fedratinib PK exposure and definitive exposure-response relationships in these specific populations.

19.5.7.4 Dose/Exposure-Response for Safety

Dose-Response for Safety

Based on safety pool datasets from Trials EFC12153, ARD12181, and ARD11936, dose-response analyses were conducted for the following safety measurements, TEAEs at Grade ≥3, treatment-emergent SAEs, TEAEs Leading to permanent treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to dose interruption, anemia at Grade ≥3, and thrombocytopenia at Grade ≥3, using actual dose levels when the adverse events occurred. In general, the odds of experiencing an event in any of the 7 categories of safety measurements were higher at 500 mg than 400 mg (**Table 93**), which support the starting dose of 400 mg QD from a safety perspective.

Table 93: Odds Ratio Estimates and Confidence Intervals of Safety measurements at 500 mg vs. 400 mg

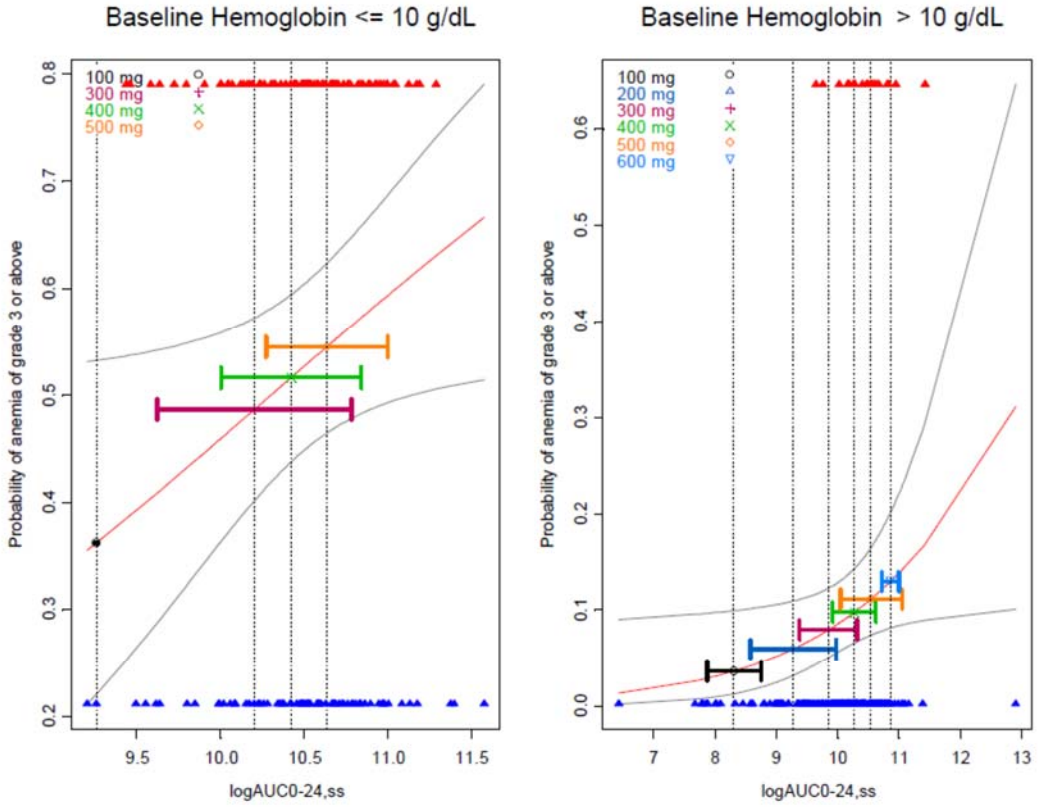
	Estimate	95% Confidence Interval
TEAEs at Grade ≥3	2.67	1.26 - 5.64
Treatment-Emergent SAEs	3.49	1.85 - 6.58
TEAEs Leading to Permanent Treatment Discontinuation	3.65	1.82 - 7.32
TEAEs Leading to Dose Reduction	2.47	1.48 - 4.12
TEAEs Leading to Dose Interruption	3.04	1.69 - 5.46
Anemia at Grade ≥3	1.58	0.91 - 2.73
Thrombocytopenia at Grade ≥3	1.50	0.73 - 3.05

Source: Response to FDA Information Request on 3/13/2019, Tables 7, 8, 9, 10, 11, 12 and 13.

Exposure-Response for Safety

A total of 404 patients from four Phase 2 studies (ARD12181, ARD11936, ARD12042 and ARD12888) and one Phase 3 study (EFC12153), who had both post-hoc estimated PK exposures ($AUC_{0\text{-}24,ss}$) from the final population PK model and safety measurements were included in the exposure-safety analysis. The $AUC_{0\text{-}24,ss}$ at the nominal starting dose was selected for exposure-safety analysis because: 1) 73% of the patients experienced dose reduction or interruption while only 11% patients experienced dose escalations from the nominal starting dose, thus the $AUC_{0\text{-}24,ss}$ at the starting dose generally represented the maximal daily exposure at steady state; and 2) other PK exposure parameters, e.g., $C_{max,ss}$ and $C_{trough,ss}$ of the nominal starting dose were highly correlated with $AUC_{0\text{-}24,ss}$. Applicant's logistic regression of exposure-safety analyses suggested that the increasing fedratinib exposure increases probability of anemia at Grade ≥3 (**Figure 27**), thrombocytopenia at Grade ≥3 (Figure 28), diarrhea at any grade (Figure 29), nausea and vomiting at any grade (**Figure 30**), any TEAEs at Grade ≥3 (Figure 31), treatment-emergent SAEs (Figure 32), TEAE Leading to permanent treatment discontinuation (**Figure 33**), and TEAE leading to dose reduction (**Figure 34**), except for TEAE leading to dose interruption, which is independent of the fedratinib steady-state AUC exposure. In addition, the baseline hemoglobin contributed to a higher incidence of anemia at Grade ≥3 (**Figure 27**) and any TEAEs at Grade ≥ 3 (Figure 31), while platelet count also contributed to a higher incidence of thrombocytopenia at Grade ≥3 (Figure 28) and any TEAEs at Grade ≥ 3 (Figure 31).

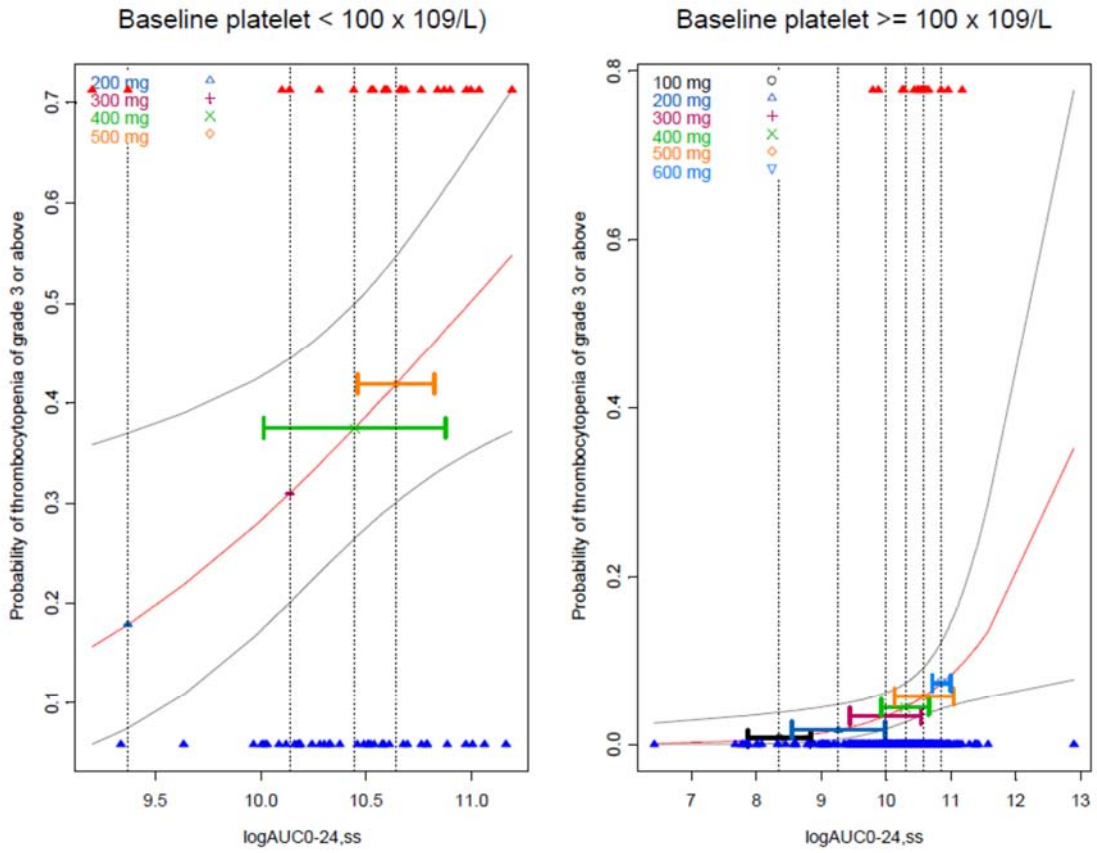
Figure 27: Logistic Model of Probability of Anemia of Grade 3 or Above Versus $LogAUC_{0\text{-}24,ss}$.



$logAUC_{0\text{-}24,ss}$ = 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.

Source: FEDR-MPK-002, Exposure-Response Analysis Report, Figure 13.

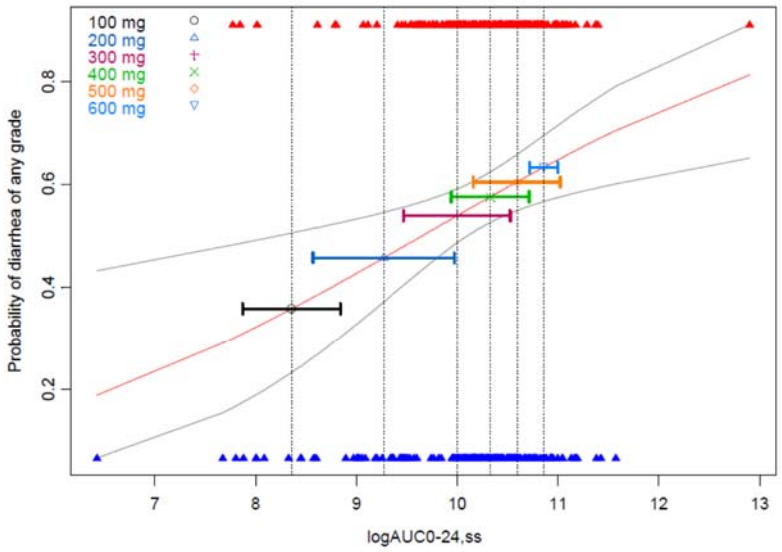
Figure 28: Logistic Model of Probability of Thrombocytopenia of Grade 3 or Above Versus LogAUC0-24,ss.



$logAUC_{0\text{-}24,ss}$ = 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.

Source: FEDR-MPK-002, Exposure-Response Analysis Report, Figure 16.

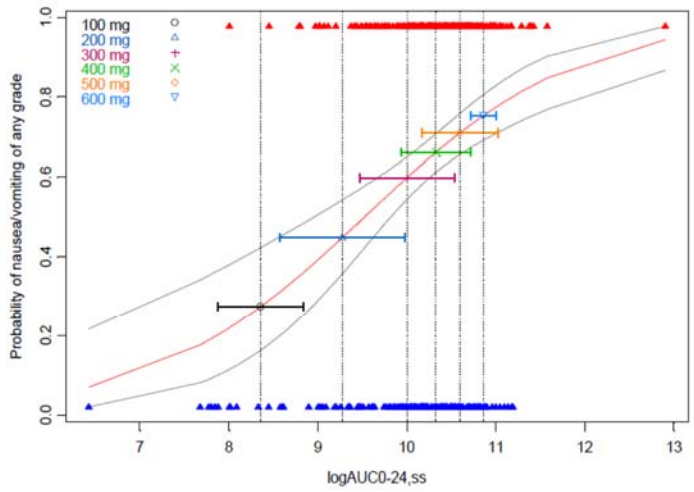
Figure 29: Logistic Model of Probability of Diarrhea of Any Grade Versus LogAUC0-24,ss.



$logAUC_{0\text{-}24,ss}$ = 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.

Source: FEDR-MPK-002, Exposure-Response Analysis Report, Figure 14.

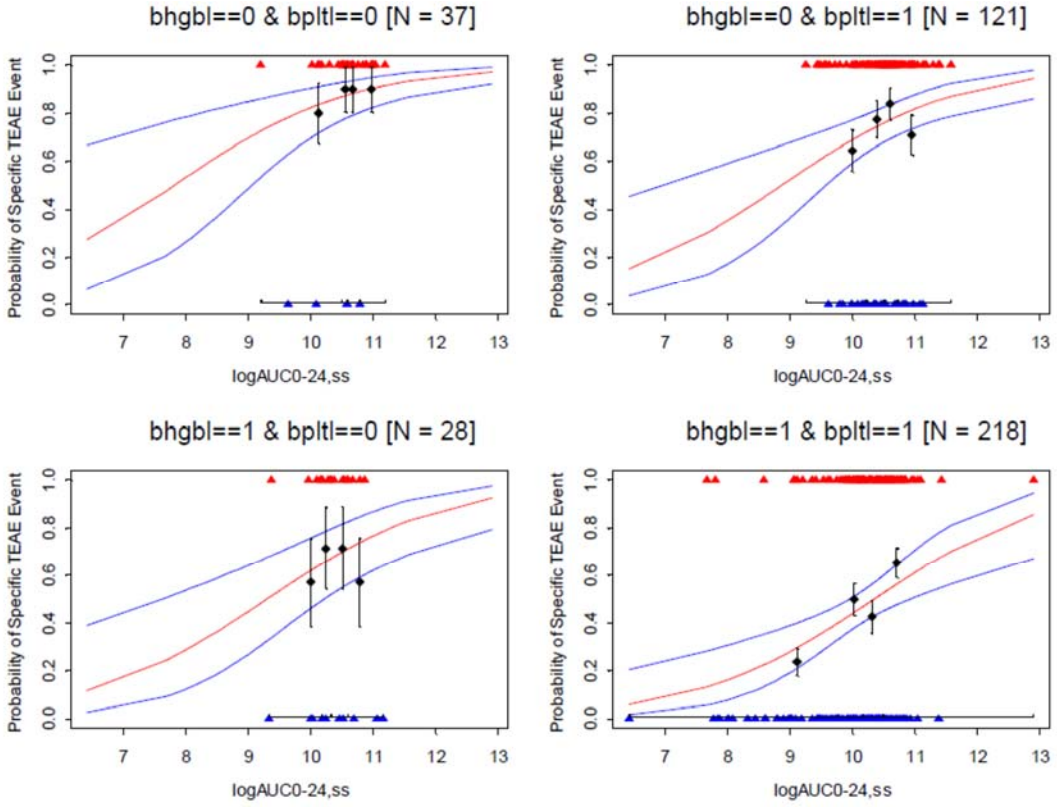
Figure 30: Logistic Model of Probability of Nausea/Vomiting of Any Grade Versus $LogAUC_{0\text{-}24,ss}$.



$logAUC_{0\text{-}24,ss}$ = 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.

Source: FEDR-MPK-002, Exposure-Response Analysis Report, Figure 15.

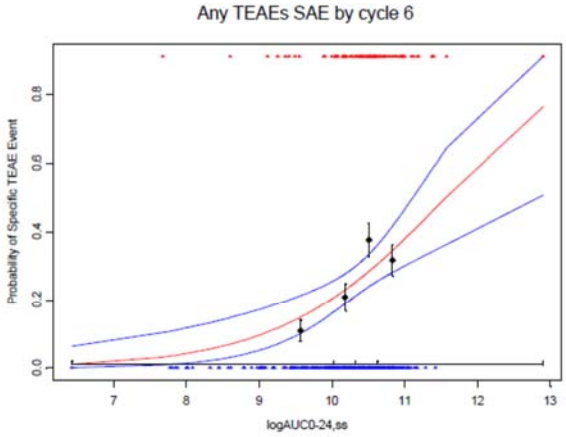
Figure 31: Logistic Model of Probability of Any TEAE at Grade ≥ 3 Versus LogAUC0-24,ss.



bhgbl==0: baseline hemoglobin level ≤ 10 g/L
bhgbl==1: baseline hemoglobin level > 10 g/L
bpltl==0: baseline platelet count < 100 x 10^9/L
bpltl==1: baseline platelet count ≥ 100 x 10^9/L
The red line is the model predicted probability and the two blue lines are the 95% confidence bands from logistic regression. The four solid black diamonds with vertical error bars represent the observed probability (mean with standard deviation) at the 1st, 2nd, 3rd and 4th quartile of $logAUC_{0\text{-}24,\ ss}$. The red triangles on the top represent responders (i.e., patients who had a TEAE Grade ≥ 3) and the blue triangles at the bottom represent non-responders (i.e., patients who did not have a TEAE Grade ≥ 3).

Source: Response to FDA Request for Information Dated 03/04/2019, Figure 2.

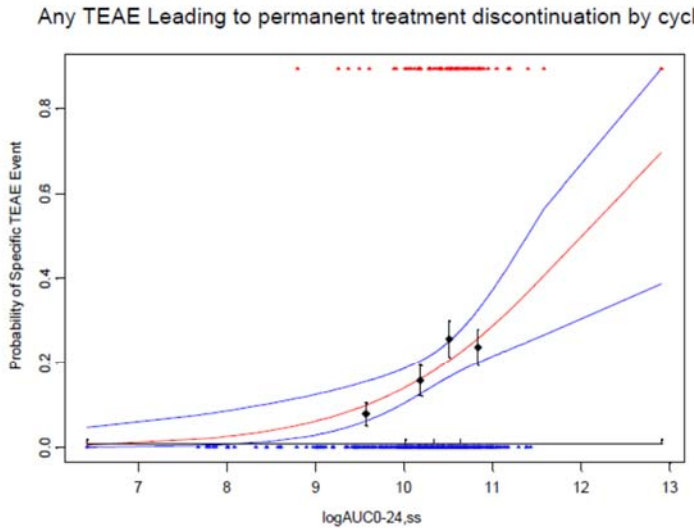
Figure 32: Logistic Model of Probability of Any Treatment-Emergent SAE Versus LogAUC0-24,ss.



The red line is the model predicted probability and the two blue lines are the 95% confidence bands from logistic regression. The four solid black diamonds with vertical error bars represent the observed probability (mean with standard deviation) at the 1st, 2nd, 3rd and 4th quartile of $logAUC_{0\text{-}24,ss}$. The red triangles on the top represent responders (i.e., patients who had a treatment-emergent SAE) and the blue triangles at the bottom represent non-responders (i.e., patients who did not have a treatment-emergent SAE).

Source: Response to FDA Request for Information Dated 03/04/2019, Figure 3.

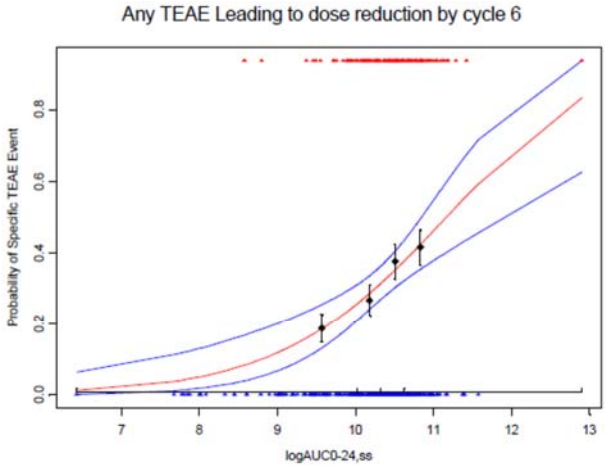
Figure 33**:** Logistic Model of Probability of Any TEAE Leading to Permanent Treatment Discontinuation Versus $LogAUC_{0\text{-}24,ss}$.



The red line is the model predicted probability and the two blue lines are the 95% confidence bands from logistic regression. The four solid black diamonds with vertical error bars represent the observed probability (mean with standard deviation) at the 1st, 2nd, 3rd and 4th quartile of $logAUC_{0\text{-}24,ss}$. The red triangles on the top represent responders (i.e., patients who had a TEAE leading to permanent treatment discontinuation) and the blue triangles at the bottom represent non-responders (i.e., patients who did not have a TEAE leading to permanent treatment discontinuation).

Source: Response to FDA Request for Information Dated 03/04/2019, Figure 4.

Figure 34: Logistic Model of Probability of Any TEAE Leading to Dose Reduction Versus Log$AUC_{0\text{-}24,ss}$.



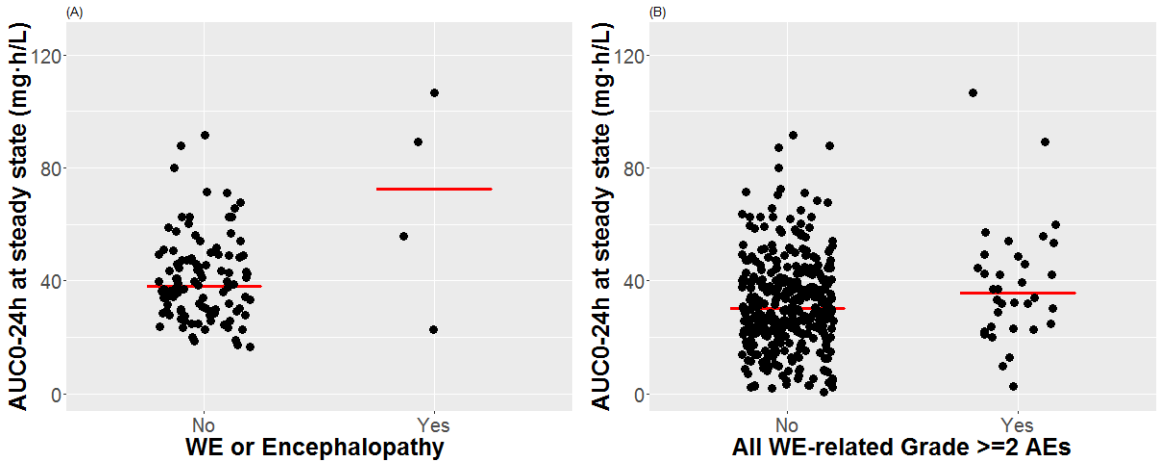
The red line is the model predicted probability and the two blue lines are the 95% confidence bands from logistic regression. The four solid black diamonds with vertical error bars represent the observed probability (mean with standard deviation) at the 1st, 2nd, 3rd and 4th quartile of $logAUC_{0\text{-}24,ss}$. The red triangles on the top represent responders (i.e., patients who had a TEAE leading to dose reduction) and the blue triangles at the bottom represent non-responders (i.e., patients who did not have a TEAE leading to dose reduction).

Source: Response to FDA Request for Information Dated 03/04/2019, Figure 5.

Reviewer's Comments: *The applicant's dose/exposure-response analyses for safety measurements indicated the proposed dosing regimen of 400 mg QD is generally associated with lower risk of TEAEs compared to 500 mg QD. In addition, the reviewer also conducted independent E-R analysis to assess the relationship between fedratinib exposure and potential WE or encephalopathy, or Grade ≥2 AEs related to WE. The results indicated that patients with WE or encephalopathy (n=4) tended to have higher $AUC_{0\text{-}24,SS}$ (68.5 ± 37.2 mg·h/L) than patients without WE or encephalopathy (44.1 ± 37.9 mg·h/L) when on fedratinib 500 mg QD (n = 107) (*

Figure 35*A). Similarly, patients with Grade ≥2 AEs related to WE (n=16) tended to have slightly higher $AUC_{0\text{-}24,SS}$ (42.2 ± 26.0 mg·h/L) compared to those in patients without Grade ≥2 AEs related to WE (33.1 ± 24.4 mg·h/L) when on fedratinib any dose (n = 388) (Figure 35B). But overall, the association was not clear between fedratinib exposure and potential WE or encephalopathy, or Grade ≥2 AEs related to WE, given 1) the limited number of WE or encephalopathy cases, 2) largely overlapping range of exposure in patients with/without WE or Grade ≥2 AEs related to WE, and 3) potential confounders which were imbalanced between the two subpopulations (**Table 94**).*

Figure 35: Comparison of Fedratinib Exposure between (A) Patients with and without WE or Encephalopathy on Fedratinib 500 mg QD, and (B) Patients with and without Grade ≥2 AEs Related to WE on Fedratinib Any Dose.



Source: Reviewer's analysis.

Table 94: Demographics and Disease Status at Baseline in Patients with or without WE or Encephalopathy on Fedratinib 500 mg QD and Patients with or without Grade ≥2 AEs Related to WE on Fedratinib Any Dose.

	WE or encephalopathy		Grade ≥2 AEs related to WE	
	Yes (n=4)	No (n=107)	Yes (n=16)	No (n=388)
Age, year Mean (SD)	72.5 (4.8)	64.4 (9.6)	68.4 (5.7)	63.2 (11)
Weight, kg Mean (SD)	60.5 (9.8)	69.2 (13.3)	68.2 (11.2)	71.5 (14.5)
Height, kg Mean (SD)	158.3 (7.4)	168.3 (9.5)	167.5 (10.6)	168.8 (9.6)
Sex				
Female	4 (100.0%)	38 (35.5%)	8 (50.0%)	174 (44.9%)
Male	0 (0.0%)	69 (64.5%)	8 (50.0%)	214 (55.1%)
Race				
Asian	0 (0.0%)	18 (16.8%)	1 (6.2%)	40 (10.3%)
Black or African American	0 (0.0%)	2 (1.9%)	0 (0.0%)	6 (1.6%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
White	4 (100.0%)	87 (81.3%)	15 (93.8%)	341 (87.9%)
Type of Myelofibrosis				
ET	1 (25.0%)	0 (0.0%)	1 (6.2%)	32 (8.2%)
PV	0 (0.0%)	0 (0.0%)	1 (6.2%)	44 (11.3%)
Post-ET	0 (0.0%)	12 (11.2%)	4 (25.0%)	44 (11.3%)
Post-PV MF	2 (50.0%)	24 (22.4%)	7 (43.8%)	76 (19.6%)
Primary MF	1 (25.0%)	71 (66.4%)	3 (18.8%)	192 (49.5%)
Risk Group				
Unknown	0 (0.0%)	0 (0.0%)	2 (12.5%)	76 (19.6%)

High risk	3 (75.0%)	53 (49.5%)	7 (43.8%)	138 (35.6%)
Intermediate level 1	0 (0.0%)	0 (0.0%)	1 (6.2%)	15 (3.9%)
Intermediate level 2	1(25.0%)	54 (50.5%)	6 (37.5%)	159 (41.0%)
Baseline Platelet Count Group				
< 50 x 10^9/L	0 (0.0%)	1 (0.9%)	0 (0.0%)	4 (1.0%)
50 - < 100 x 10^9/L	0 (0.0%)	14 (13.1%)	3 (18.8%)	58 (14.9%)
100 - < 200 x 10^9/L	1 (25.0%)	28 (26.2%)	3 (18.8%)	96 (24.7%)
>= 200 x 10^9/L	3 (75.0%)	64 (59.8%)	10 (62.5%)	230 (59.3%)
Baseline Hemoglobin				
< 10g/dL	3 (75.0%)	57 (53.3%)	8 (50.0%)	147 (37.9%)
>= 10g/dL	1 (25.0%)	50 (46.7%)	8 (50.0%)	241 (62.1%)
Baseline ECOG Performance Status				
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.8%)
0	1 (25.0%)	36 (33.6%)	7 (43.8%)	153 (39.4%)
1	2 (50.0%)	60 (56.1%)	7 (43.8%)	184 (47.4%)
2	1 (25.0%)	11 (10.3%)	2 (12.5%)	48 (12.4%)
Baseline RBC Transfusion Dependence				
Unknown	1(20.0%)	2 (1.9%)	2 (12.5%)	82 (21.1%)
No	3(75.0%)	97 (90.6%)	12 (75.0%)	278 (71.7%)
Yes	0 (0.0%)	8 (7.5%)	2 (12.5%)	28 (7.2%)
Baseline Hepatic Function				
Unknown	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.3%)
Normal	2 (50.0%)	79 (73.8%)	7 (43.8%)	277 (71.4%)
Mild	2 (50.0%)	24 (22.4%)	8 (50.0%)	95 (24.5%)
Moderate	0 (0.0%)	3 (2.8%)	1 (6.2%)	15 (3.9%)
Baseline Renal Function				
Unknown	0 (0.0%)	2 (1.9%)	0 (0.0%)	8 (2.1%)
Normal	0 (0.0%)	25 (23.4%)	2 (12.5%)	126 (32.5%)
Mild	0 (0.0%)	54 (50.5%)	8 (50.0%)	167 (43.0%)
Moderate	3 (75.0%)	25 (23.4%)	5 (31.2%)	84 (21.6%)
Severe	1 (25.0%)	1 (0.9%)	1 (6.2%)	3 (0.8%)
JAK2 Mutational Profile				
Unknown	1 (25.0%)	7 (6.5%)	2(12.5%)	100 (25.8%)
Mutant	3 (75.0%)	79 (73.8%)	14(87.5%)	206 (53.1%)
Wild	0 (0.0%)	21 (19.6%)	0 (0.0%)	82 (21.1%)

ET: Essential thrombocythemia; PV: Polycythemia Vera.
Source: Reviewer's analysis.

19.6 Additional Clinical Outcome Assessment Analyses

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNIFER J LEE
08/15/2019 08:38:07 AM

SALEH AYACHE
08/15/2019 09:08:00 AM

PEDRO L DELVALLE
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CHRISTOPHER M SHETH
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HALEH SABER
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SRIRAM SUBRAMANIAM
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LIANG LI
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MANUELA GRIMSTEIN
08/15/2019 09:24:52 AM

OLUSEYI A ADENIYI
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LIAN MA
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YUCHING N YANG
08/15/2019 09:52:47 AM

ROSANE CHARLAB ORBACH
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GUOXIANG SHEN
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NAM ATIQUR RAHMAN
08/15/2019 10:04:32 AM
I concur.

JINGJING YE on behalf of LAURA L FERNANDES
08/15/2019 10:29:58 AM

JINGJING YE
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RAJESHWARI SRIDHARA
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KATHY M ROBIE SUH
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ALBERT B DEISSEROTH
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RICHARD PAZDUR
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