

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212327Orig1s000**

**OTHER REVIEW(S)**

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** July 25, 2019

**To:** Jennifer Lee, PharmD, Senior Regulatory Health Project Manager,  
Division of Hematology Products (DHP)  
  
Virginia Kwitkowski, Associate Director for Labeling, DHP

**From:** Robert Nguyen, PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for INREBIC (fedratinib) capsules, for oral use

**NDA:** 212327

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In response to DHP's consult request dated February 20, 2019, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the original NDA submission for Inrebic.

**PI:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Jennifer Lee) on July 10, 2019, and are provided below.

**Medication Guide:** A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on July 18, 2019.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/  
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ROBERT L NGUYEN  
07/25/2019 11:59:39 AM

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy

**PATIENT LABELING REVIEW**

Date: July 18, 2019

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
  
Robert Nguyen, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): INREBIC (fedratinib)

Dosage Form and Route: Capsules, for oral use

Application Type/Number: NDA 212327

Applicant: Celgene Corporation

## 1 INTRODUCTION

On January 3, 2019, Celgene Corporation, submitted for the Agency's review an original New Drug Application (NDA 212327) for INREBIC (fedratinib) capsules, for oral use, a New Molecular Entity (NME), for the proposed indication of the treatment of intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis [REDACTED] (b) (4) [REDACTED].

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on February 20, 2019 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for INREBIC (fedratinib) capsules, for oral use.

## 2 MATERIAL REVIEWED

- Draft INREBIC (fedratinib) MG received on January 3, 2019 and received by DMPP and OPDP on July 10, 2019.
- Draft INREBIC (fedratinib) Prescribing Information (PI) received on January 3, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 10, 2019.
- Approved JAKAFI (ruxolitinib) comparator labeling dated May 24, 2019.

## 3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

## 4 CONCLUSIONS

The MG is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
07/18/2019 01:59:42 PM

ROBERT L NGUYEN  
07/18/2019 02:03:15 PM

LASHAWN M GRIFFITHS  
07/18/2019 02:07:07 PM

Neuro-oncology Consult  
Reviewer: Joohee Sul, MD  
Requesting Division: Division of Hematology Products (DHP)  
Product: Fedratinib  
RE: Analysis of encephalopathy cases associated with fedratinib  
NDA 212327  
IND 078286

The Division of Hematology Products (DHP) has requested a review of multiple reported cases of possible Wernicke's encephalopathy associated with fedratinib administration.

### WERNICKE'S ENCEPHALOPATHY

Wernicke's encephalopathy (WE) is clinically important syndrome of acute delirium caused by thiamine (vitamin B1) deficiency. The classic triad of symptoms includes confusion, oculomotor dysfunction and ataxia. Although patients can improve rapidly with thiamine administration, if left untreated progression to coma and death can occur. A chronic amnesic 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, the clinical diagnosis of WE appears to be lower compared with the post-mortem diagnosis determined by neuropathological features, suggesting that the condition is underdiagnosed.<sup>1-3</sup>

#### *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,<sup>4</sup> 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.<sup>5</sup> For example, abnormalities in transketolase, an enzyme that processes thiamine, may be abnormal in individuals who develop WE,<sup>6,7</sup> and genetic factors have been implicated as well.<sup>8-10</sup>

#### *Clinical*

Diagnosis of WE is generally based on clinical features, and can be supported by imaging findings and thiamine levels. The hallmark 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.<sup>11</sup>

Symptom or sign	As evidenced by one or more of the following
Dietary deficiencies	<ul style="list-style-type: none"> <li>- Undernutrition (body mass index &lt;2 SD below normal)</li> <li>- A history of grossly impaired dietary intake</li> <li>- An abnormal thiamine status</li> </ul>
Oculomotor abnormalities	<ul style="list-style-type: none"> <li>- Ophthalmoplegia</li> <li>- Nystagmus</li> <li>- Gaze palsy</li> </ul>
Cerebellar dysfunction	<ul style="list-style-type: none"> <li>- Unsteadiness or ataxia</li> <li>- Abnormalities of past pointing</li> <li>- Dysdiadokokinesia</li> <li>- Impaired heel-shin testing</li> </ul>
Either an altered mental state	<ul style="list-style-type: none"> <li>- Disorientation in two of three fields</li> <li>- Confused</li> <li>- An abnormal digit span</li> <li>- Comatose</li> </ul>
or	or
Mild memory impairment	<ul style="list-style-type: none"> <li>- Failure to remember two or more words in the four-item memory test</li> <li>- Impairment on more elaborate neuropsychological tests of memory function</li> </ul>

**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<sup>12</sup>

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%).<sup>13</sup> 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.<sup>14</sup> 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.<sup>1</sup>

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.<sup>15-17</sup> 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 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 respond 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.<sup>18</sup> Appendix 1 includes a table summarizing the published recommendations for diagnosis, therapy and prevention of WE.<sup>19-21</sup>

## FEDRATINIB

Fedratinib is an oral Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3) that has been studied in patients with myelofibrosis (MF) and polycythemia vera (PV). The proposed indication for fedratinib is as follows:

Fedratinib is indicated for the treatment of intermediate or high-risk primary or secondary MF [REDACTED] (b) (4).

The proposed dose of fedratinib is 400 mg once daily. There have been eighteen (18) clinical studies conducted with fedratinib, and 807 patients or healthy volunteers have received  $\geq 1$  dose of fedratinib, with 614 subjects receiving multiple doses and 451 patients with intermediate or high-risk MF receiving fedratinib across five (5) clinical trials. Two studies are intended to support the proposed indication of fedratinib:

- EFC12153, JAKARTA (n=289): A randomized, double-blind, placebo-controlled study in subjects with intermediate or high-risk primary MF with splenomegaly
- ARD12181, JAKARTA2 (n=97): A single-arm study in subjects with intermediate or high-risk MF previously exposed to ruxolitinib (ARD12181, JAKARTA2).

### *Regulatory history*

Please see clinical review of NDA 212327 for full history

- June 13, 2007: Pre-IND meeting with TargeGen, Inc. for TG101348 (fedratinib), to discuss development of TG101348 in patients with primary and secondary MF
- October 25, 2007: IND 78286 submitted
- April 28, 2009: Fast Track Designation request for TG101348 for treatment of MF
- May 25, 2010: End of phase 1 meeting to discuss a randomized placebo-controlled study of TG101348 in patients with primary and secondary MF, intended to support registration
- September 20, 2010: IND amendment to transfer the IND to Sanofi-Aventis U.S., Inc.
- May 23, 2011: Request for SPA of clinical protocol EFC12153, 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."
- July 29, 2011: SPA resubmission incorporating FDA comments/recommendations
- September 11, 2011: Clinical protocol EFC12153 received SPA from FDA
- February 21, 2012: Proposal to amend clinical protocols to incorporate safety measures based on SAE of grade 4 elevated LFT
- June 27, 2013: Pre-NDA meeting
- November 11, 2013: Sanofi submitted an information amendment describing four cases of WE or encephalopathy
- November 13, 2013: IND 078286 was placed on Complete Clinical Hold for several reported cases of WE and heart failure (by teleconference)

- November 21, 2013: Sanofi informed FDA that they no longer intend to submit the NDA as planned
- November 15, 2016: Sanofi informed FDA of change of sponsor to Impact Therapeutics, Inc
- May 11, 2017: Consult completed by Division of Neurology Products (DNP) to evaluate the sponsor's position that the observed cases of WE were due to nutritional challenge, primarily nausea and vomiting while on fedratinib therapy, possibly with a component of preexisting nutritional depletion in some cases. DNP concluded that the information presented in the submission was insufficient to differentiate whether nutritional challenge or a primary fedratinib effect was the basis for the occurrence of WE.
- May 16, 2017: Impact requested a type A meeting to discuss conditions for removing the clinical hold
- July 19, 2017: Complete response to clinical hold containing additional data including long form case narratives and event timelines for each case, with neurology/neuroradiology expert analysis for each of the eight reports.
- August 16, 2017: Follow-up consult from DNP concluding that "The available data has not substantially advanced the diagnostic certainty of all WE cases to the desired level of precision"
- December 1, 2017: Breakthrough Therapy Designation request for fedratinib for the treatment of MF
- February 23, 2018: Letter informing FDA that Impact Biomedicines became a wholly owned subsidiary of Celgene Corporation
- January 3, 2019: NDA 212327 submitted.

#### SUMMARY OF ENCEPHALOPATHY CASES

The Complete Response to Clinical Hold received July 20, 2017 formed the primary basis for this review. Please see Appendix 2 for a tabular summary of the cases.

The Applicant reported eight (8) potential cases of WE occurring throughout the development program. It is worth noting that the original sponsor (Sanofi) received the first safety reports for WE occurring in two patients (on Study EFC12153 and Study TES13159). These reports prompted a retrospective review of the clinical database to investigate for additional cases. A total of eight cases were collated and submitted for review.

Of the cases described, this reviewer assessed that 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 transporter 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.

Thiamine transporter 1 and 2 (THTR 1 and 2) are transport proteins that ferry thiamine into cells; inhibition of THTR 1 leads to megaloblastic anemia and THTR 2 leads to a Wernicke's like

encephalopathy. There are in vitro data suggesting that fedratinib interferes with thiamine uptake and transport via inhibition of THTR 2 (and to a lesser degree THTR 1).<sup>22,23</sup> However, the Applicant contends that these studies do not represent the true effect of fedratinib on thiamine transport, and report that an independent study was conducted using the same cell lines as the published studies, but with human serum to improve physiological relevance and to account for protein binding. The Applicant reports that in this study, fedratinib at concentrations up to 30 µM had no effect on THTR 1 and had an observed IC<sub>50</sub>>30µM for THTR 2 (higher than the exposure observed for any patient in the fedratinib studies). The Applicant reports that these findings are consistent with results from an alternate study of chronic exposure of fedratinib in rats.<sup>24</sup>

#### 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.

#### RECOMMENDATIONS:

This reviewer agrees with the proposal to consider a (b) (4) boxed warning for WE. Although assessment of thiamine levels may not be helpful, they should nevertheless be routinely collected. Management of potential WE and prevention in vulnerable populations should follow published guidelines, summarized in Appendix 1. Practitioners should also be aware that there is a risk of adverse reactions associated with infusion of B vitamins. Furthermore, the impact of vitamin supplementation on cancer outcomes is unclear and this should be considered in the risk/benefit assessment.

1. Agree with boxed warning describing WE. Would consider modifying the language to identify serious encephalopathy rather than WE as the adverse drug reaction of interest. Designating a warning for WE specifically may serve to only highlight those cases where the "classic triad" of symptoms is present.

(b) (4)

3. Recommend all patients with suspected encephalopathy undergo brain MRI as part of the evaluation.
4. Recommend the Applicant capture key information that may assist with characterizing any potential encephalopathy including:
  - a. Social history including alcohol use

- b. Nutritional history including recent weight loss and dietary changes (e.g., fad diets)
  - c. Concomitant medications including supplements/herbals
- 5. Recommend careful neurological evaluation, specifically oculomotor and gait examination to monitor for possible signs/symptoms that may predate encephalopathy.
- 6. Further investigation into differences in thiamine transport genes may be considered.

## APPENDIX 1

Table: Published recommendations for diagnosis, therapy and prevention of Wernicke's encephalopathy

	<b>DIAGNOSIS</b>	<b>THERAPY</b>	<b>PREVENTION</b>
<b>EFNS<sup>19</sup></b>	<ul style="list-style-type: none"> <li>• Maintain high suspicion in all conditions that could lead to thiamine deficiency</li> <li>• Apply the Caine criteria</li> <li>• Measure thiamine level before administration of thiamine (HPLC analysis)</li> <li>• Use MRI to support the diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>• Thiamine 200 mg TID (IV preferred over IM) before any carbohydrate</li> <li>• Continue thiamine until no further clinical improvement</li> </ul>	<ul style="list-style-type: none"> <li>• Post-bariatric surgery: parenteral thiamine supplementation; follow-up thiamine levels for at least 6 months</li> <li>• Prophylactic parenteral thiamine (200 mg) before carbohydrates in all subjects with a risk condition managed in the ER</li> </ul>
<b>RCP<sup>20</sup></b>	<ul style="list-style-type: none"> <li>• None specified</li> </ul>	<ul style="list-style-type: none"> <li>• Oral thiamine is not recommended</li> <li>• Thiamine: 500 mg IV (Pabrinex) TID for 3 days, discontinue if no response</li> <li>• Magnesium and phosphate supplementation also recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Thiamine (Pabrinex): 250 mg IV TID for 3-5 days</li> </ul>

EFNS: European Federation of Neurological Societies; RCP: Royal College of Physicians; HPLC: high-performance liquid chromatography; IV: intravenous; IM: intramuscular; TID: three times daily; ER: emergency room; Pabrinex: Ampoules no. 1 and no. 2 contain: Vitamin B1 (thiamine) 250 mg; Vitamin B2 (riboflavin) 4 mg; Vitamin B6 (pyridoxine) 50 mg; Nicotinamide 160 mg; Vitamin C (ascorbic acid) 500 mg

1. Galvin R, Brathen G, Ivashynka A, et al: EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol 17:1408-18, 2010
2. Thomson AD, Cook CC, Touquet R, et al: The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and Emergency Department. Alcohol Alcohol 37:513-21, 2002

APPENDIX 2

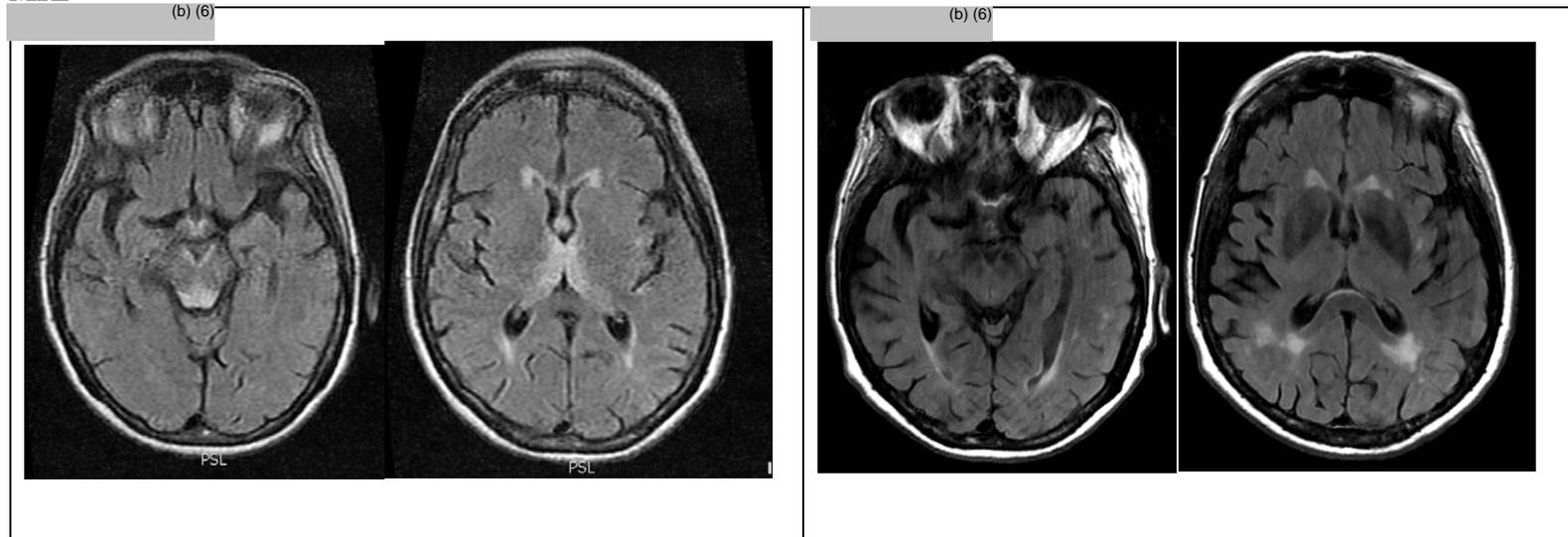
Tabular summary of cases of encephalopathy

APPEARS THIS WAY ON ORIGINAL

Patient ID: (b) (6)  
 Age/Gender: 76/F  
 Indication: Post-PV MF, high risk  
 Protocol: EFC12153

ECOG	Risk factors	First dose	Last dose	Onset	Clinical signs/symptoms	Thiamine?	Outcome
2	Weight loss Severe malnutrition Nausea/vomiting: Gr 2 (b) (4) Gr 3 (b) (4)			(b) (6)	Complained of confusion and fall at home on admission. Exam showed confusion, axial ataxia, up beating nystagmus, normal reflexes. Seizures on (b) (6).	Yes	(b) (6) confused, Glasgow 15 discharged resolved with cognitive function deficits

**MRI**



**MRI:** T2/FLAIR abnormalities in the periaqueductal gray, bilateral medial thalami, consistent with WE that are resolved on MRI dated (b) (6). Also present are diffuse non-specific white matter changes.

**Caine criteria:** 4/4

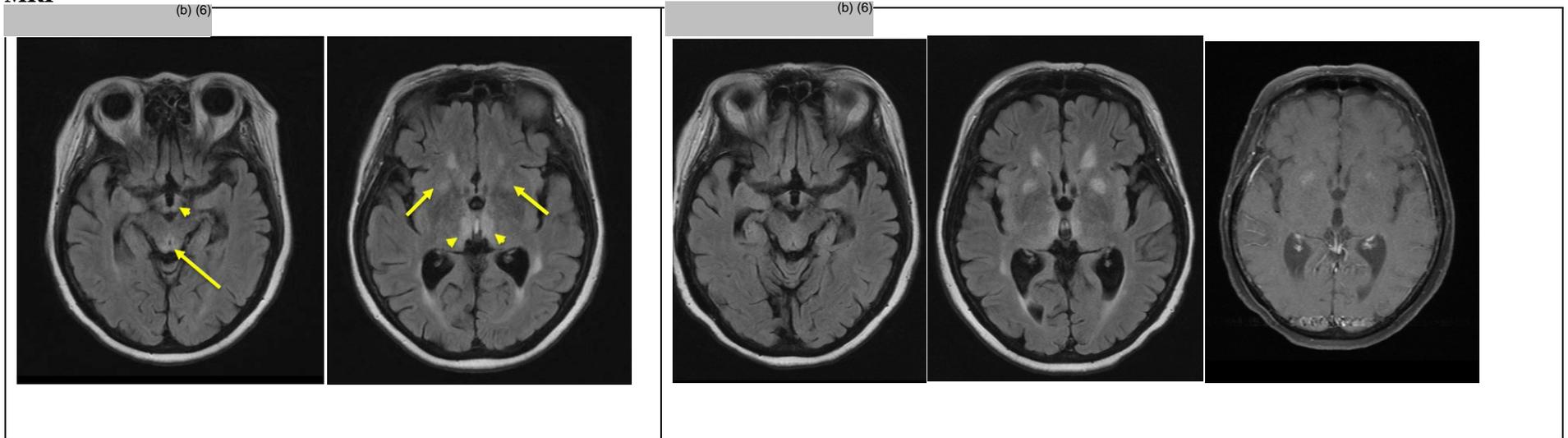
**Summary:** The case appears to be consistent with WE based on clinical history and imaging findings. The patient had pre-disposing factors such as significant nutritional decline prior to start of study drug. It is unclear whether thiamine supplementation was effective in improving symptoms, and the route of administration of thiamine is not stated (oral vs. IV). The patient appears to have persistent mental status changes (possible Korsakoff's syndrome?)

Patient ID: (b) (6)  
 arm  
 Age/Gender: 70/F  
 Indication: PMF, high risk  
 Protocol: EFC12153

\*crossover from placebo

ECOG	Risk factors	First dose	Last dose	Onset	Clinical signs/symptoms	Thiamine?	Outcome
1	Grade 2 vomiting: (b) (6)			(b) (6)	Drowsy, stuporous, hyponatremia	Yes (b) (6)	Symptoms resolved after thiamine, multivitamin and electrolyte replacement. Encephalopathy considered resolved (b) (6)

**MRI**



**MRI:** Symmetric, increased FLAIR hyperintensities in the periaqueductal gray, bilateral medial thalami and bilateral basal ganglia on initial MRI, with persistence of findings in the thalami and basal ganglia on follow-up imaging. It appears a post-gadolinium MRI was done that revealed enhancement in the basal ganglia.

**Caine criteria:** 1/4

**Summary:** This case does not appear consistent with WE based on the clinical description, although the imaging findings are suggestive. This does represent a case of serious encephalopathy that could be related to multiple factors. Hyponatremia and cardiac failure may have contributed to the development of encephalopathy.

Patient ID: (b) (6)

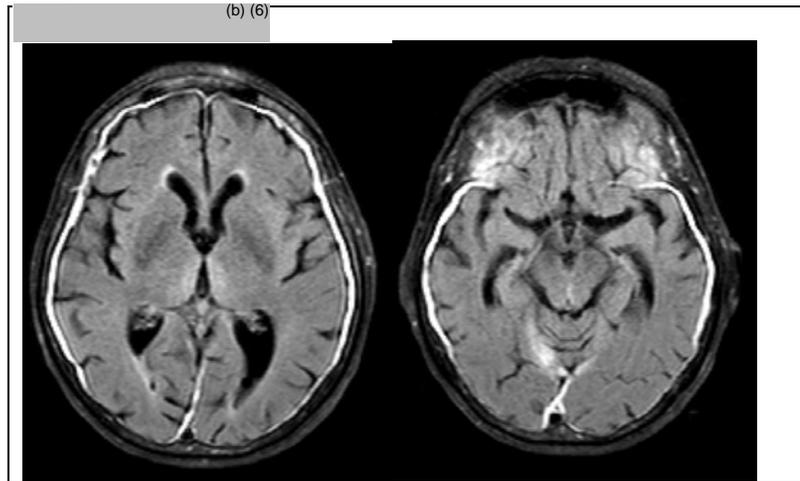
Age/Gender: 77/F

Indication: PPV-MF, high risk

Protocol: EFC12153

ECOG	Risk factors	First dose	Last dose	Onset	Clinical signs/symptoms	Thiamine?	Outcome
1	Chronic renal failure Nausea/vomiting: Gr 3: (b) (6) Gr 3: (also diarrhea gr 3)			(b) (6)	Admitted with depressed level of consciousness, in acute renal failure with mild hyponatremia. Right hemiparesis and decreased sensation.	Yes	Slow improvement, not oriented to place and time. (b) (6): Event considered resolved.

### MRI



**MRI:** Diffuse, symmetric dural hyperintensities, non-specific faint increased bithalamic FLAIR signal

**Caine criteria:** 1/4

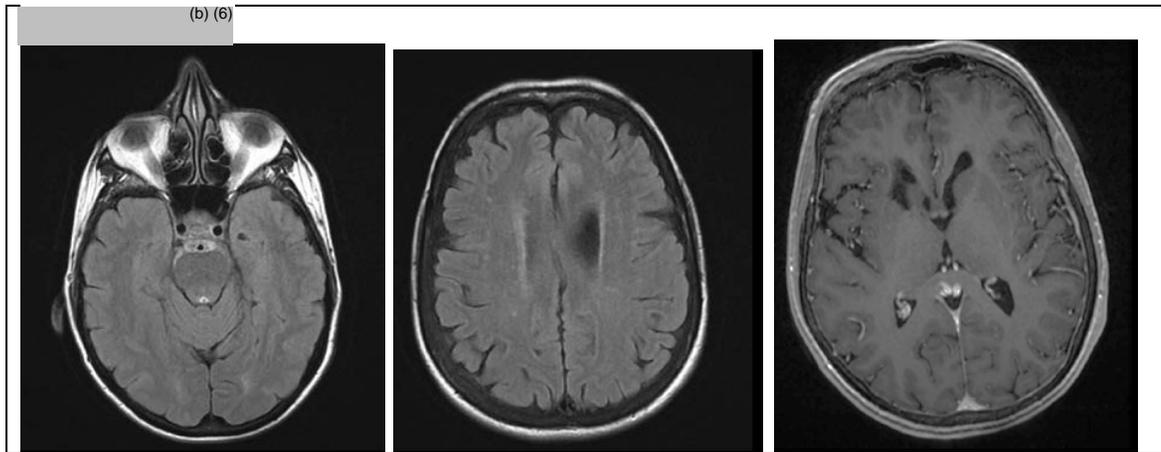
**Summary:** This case does not appear consistent with WE, based on the clinical history and imaging findings. However, this does represent a case of serious encephalopathy that could be multifactorial. The N/V/D were reported resolved on October 10, 2012; however, it is unclear the degree to which they resolved. It is also not clear what date the thiamine was administered or the route of administration; however, there appears to be a lag in resolution of symptoms. Transketolase assay indicated normal thiamine levels (14%) on (b) (6).

Patient ID: (b) (6)  
 Age/Gender: 63/F  
 Indication: PMF, intermediate level 2  
 Protocol: ECF12153

\*crossover from placebo arm

ECOG	Risk factors	First dose	Last dose	Onset	Clinical signs/symptoms	Thiamine?	Outcome
2	Nausea/vomiting Grade 1:3/4 - (b) (6)	(b) (6)	(b) (6)	(b) (6)	Paresthesias reported on (b) (6). Presented on (b) (6) with dizziness and diplopia, MRI at that time was considered not clinically significant. Seizure on (b) (6). Symptoms included confusion, ataxia, cognitive deficit without memory loss. (b) (6): Patient had nystagmus, ataxia, and cognitive impairment and was hospitalized for IV thiamine.	Yes, oral and IV	(b) (6): Neurological consultation noted that symptoms greatly improved after the IV thiamine replacement. On (b) (6), the patient is reported as recovering; however, with persistent dizziness. (b) (6) MRI reported to have no changes.

**MRI**



**MRI:** Non-specific changes, right frontal horn encephalomalacia, possibly due to prior infarct

**Caine criteria:** 3/4

**Summary:** This case appears to be consistent with WE, based on the clinical findings of diplopia, ataxia and cognitive deficits. The patient is reported to have significant improvement in symptoms after IV thiamine. Although the patient had a history of vestibular neuritis, this had been reportedly stable for 10 years. The only MRI available for review in this package is from (b) (6).

Patient ID: (b) (6)  
 Age/Gender: 62/M  
 Indication: PPV-MF, intermediate level 2  
 Protocol: ARD12181

ECOG	Risk factors	First dose	Last dose	Onset	Clinical signs/symptoms	Thiamine?	Outcome
0	Upper GI hemorrhage Esophageal varices			(b) (6)	Slight forgetfulness for the past 24-48 hours, examination revealed the patient was in good condition, oriented and without encephalopathy. On (b) (6) 3 the patient received IV thiamine: thiamine was at 529.72 nmol/L (normal range 113.05-293.93 nmol/L)	Yes Oral and IV	Event considered resolved on (b) (6)

**MRI**



**MRI:** Non-specific white matter changes in the peri-aqueductal region, as well as peri-ventricular white matter changes, likely secondary to microvascular disease

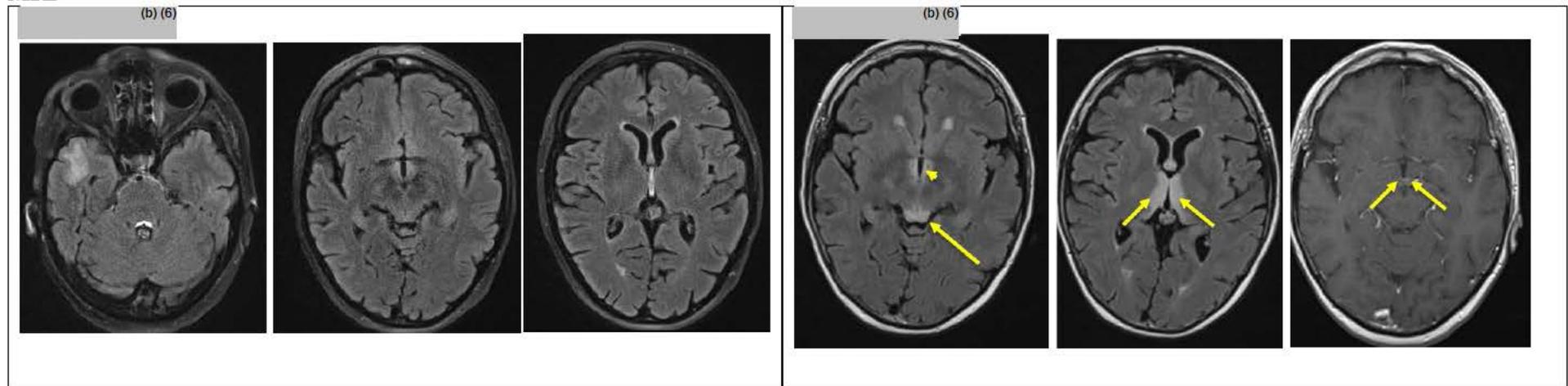
**Caine criteria:** 1/4

**Summary:** This case does not appear consistent with WE. It is not clear that the patient had significant encephalopathy clinically.

Patient ID: (b) (6)  
 Age/Gender: 67/F  
 Indication: Head and neck cancer  
 Protocol: TES13519

ECOG	Risk factors	First dose	Last dose	Onset	Clinical signs/symptoms	Thiamine?	Outcome
1	Brain metastases (b) (6): grade 2 anorexia (b) (6): grade 3 anorexia, grade 1 vomiting History of alcohol use			(b) (6)	(b) (6): patient received accidental overdose (non-serious). (b) (6): MRI identified new perilesional edema at temporal right pole associated with pre-existing brain metastases. (b) (6): Reported confusion, nystagmus, ataxia (b) (6): Epilepsy	Not reported	Patient died (b) (6)

**MRI**



**MRI:** (b) (6) MRI reveals hyperintensity in the right temporal pole. MRI from (b) (6) reveals bilateral, symmetric hyperintensities in the colliculi, mammillary bodies, medial thalami.

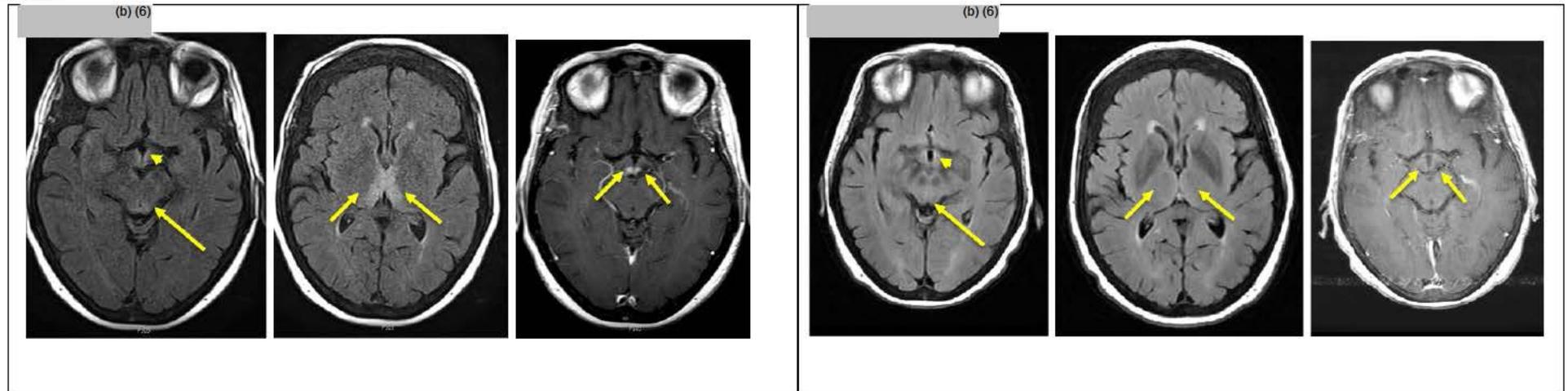
**Caine criteria:** 4/4

**Summary:** This case appears to be consistent with WE. The clinical features and MRI findings are suggestive of a non-infectious encephalopathy.

Patient ID: (b) (6)  
 Age/Gender: 70/F  
 Indication: PMF, high risk  
 Protocol: ARD11936

ECOG	Risk factors	First dose	Last dose	Onset	Clinical signs/symptoms	Thiamine?	Outcome
1	Weight loss			(b) (6)	(b) (6): grade 2 cerebral ischemia (stroke) reported with altered mental status, seizure. Impaired numerical and cognitive skills, memory deficit, nystagmus, diplopia and decreased strength on the right side; persistent memory deficits. MRI revealed subacute stroke in the left fronto-parietal cortex. (b) (6): grade 2 cerebral ischemia, possible WE considered.	Yes Oral	(b) (6): Cognitive function improved

**MRI**



**MRI:** Symmetric hyperintensities in the bilateral medial thalami and mammillary bodies. These findings appear to be improved on the follow-up MRI.

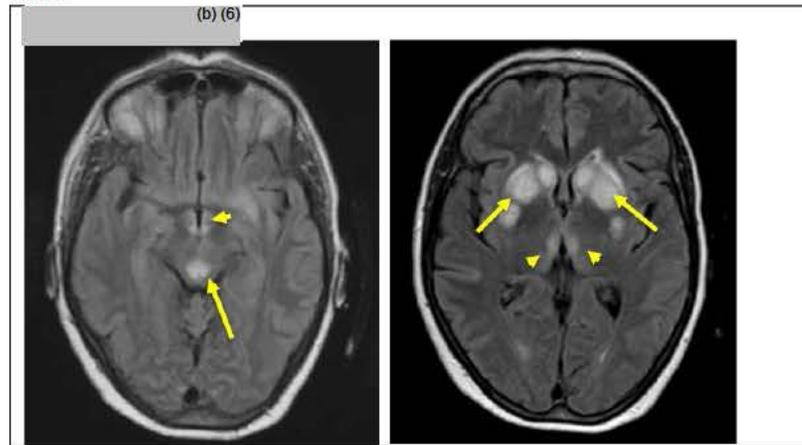
**Caine criteria:** 2/4

**Summary:** This case appears to be consistent with WE, although the presentation is somewhat confounded by reports of subacute cerebral infarcts. The images available for review do not clearly demonstrate changes consistent with cortical infarcts; however, there are changes consistent with WE.

Patient ID: (b) (6)  
 Age/Gender: 67/F  
 Indication: Essential thrombocytopenia  
 Protocol: ARD12042

ECOG	Risk factors	First dose	Last dose	Onset	Clinical signs/symptoms	Thiamine?	Outcome
0				(b) (6)	Diplopia with episodic memory disorder, repetitive language, and apraxia. (b) (6) Grade 3 encephalopathy leading to hospitalization. (b) (6) MRI reported as abnormal	Yes Oral?	Considered resolved on (b) (6)

**MRI**



**MRI:** Symmetric, bilateral hyperintensities in the periaqueduct, medial thalami, medial basal ganglia.

**Caine criteria:** 2/4

**Summary:** This case appears to be consistent with WE. The imaging findings are not consistent with a vertebrobasilar stroke, as suggested.

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## CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

<b>COA Tracking ID:</b>	C2019061
<b>NDA Number/Referenced IND:</b>	NDA 212327/IND 078286
<b>Sponsor/Applicant:</b>	Impact Biomedicines, Inc. (Celgene)
<b>Established Name/Trade Name:</b>	INREBIC (fedratinib) oral capsules
<b>Indication:</b>	For the treatment of intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) (b) (4)
<b>Meeting Type/Deliverable:</b>	Advice letter to Division
<b>Review Division:</b>	Division of Hematology Products
<b>Clinical Reviewer</b>	Saleh Ayache
<b>Clinical Team Leader (TL):</b>	Kathy Robie Suh
<b>Review Division Project Manager:</b>	Jennifer Lee
<b>COA Reviewer:</b>	Christopher St. Clair
<b>COA TL:</b>	Selena Daniels
<b>COA Associate Director:</b>	Elektra Papadopoulos
<b>Date Consult Request Received:</b>	February 20, 2019
<b>Date COA Review Completed:</b>	July 11, 2019

*Please check all that apply:*       Rare Disease/Orphan Designation  
 Pediatric

### A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 212327 for INREBIC (fedratinib) oral capsules. The proposed indication is for the treatment of intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) (b) (4).

The applicant used patient-reported outcome (PRO) instruments in two pivotal trials:

- Study NCT01523171 (JAKARTA-2): a multicenter, open-label, single-arm phase 2 clinical trial in patients who were previously exposed to ruxolitinib
- Study NCT01437787 (JAKARTA): a randomized, double-blind, placebo-controlled, phase 3 clinical trial in patients who were not previously exposed to a JAK2 inhibitor (i.e., treatment-naïve)

The PRO instruments included in Studies JAKARTA and JAKARTA-2 are shown in Table 1.

**Table 1. PRO Instruments Included in Studies JAKARTA and JAKARTA-2**

COA Name	Concept(s)	Endpoint Position <sup>1</sup>	Copy of COA
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<sup>1</sup> Please see Section B.2.3 of this COA review for the complete endpoint hierarchy.

Modified Myelofibrosis Symptom Assessment Form v2.0 (MFSAF v2.0; PRO)	MF-related symptoms	Secondary	Appendix A
EQ-5D-3L (PRO)*	Health status	Exploratory (JAKARTA only)*	Appendix B
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 v3.0 (EORTC QLQ-C30; PRO)*	General cancer symptoms and impacts; treatment-related symptoms	Exploratory (JAKARTA-2 only)*	Appendix C

*\*Note: EQ-5D was only included in the phase 3 study (JAKARTA), and EORTC QLQ-C30 was only included in the phase 2 study (JAKARTA-2).*



(b) (4)

The review 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<sup>2</sup>), which includes a fatigue assessment. Additionally, sponsors should carefully consider the study design and its effect on PRO data interpretation. We recommend 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

<sup>2</sup> Gwaltney et al 2017. Development of a harmonized patient-reported outcome questionnaire to assess myelofibrosis symptoms in clinical trials. *Leuk Res.* 2017 Aug;59:26-31. doi: 10.1016/j.leukres.2017.05.012. Epub 2017 May 12.

for the endpoint definition and procedures for what constitutes meaningful within-patient change. We recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss COA endpoint strategy to ensure the selected instruments are fit-for-purpose and are well-defined and reliable for the contexts of use prior to initiation of pivotal studies.

## **B. CLINICAL OUTCOME ASSESSMENT REVIEW**

### **1 BACKGROUND AND MATERIALS REVIEWED**

#### Regulatory Background:

- TargeGen submitted an Investigational New Drug (IND) application to the United States (US) Food and Drug Administration (FDA) on 24 Oct 2007 for the compound now known as fedratinib, and initiated the first-in-human (FIH) Phase 1 dose-escalation study in myelofibrosis subjects (MF-TG101348-001, later renamed TED12037) on 05 Feb 2008, followed by a Phase 1/2 long-term extension study on 22 Jul 2008 (MF-TG101348-002, later renamed TED12015).
- Sanofi (previous sponsor) acquired TargeGen; the IND was transferred to Sanofi on 21 Sep 2010. Sanofi subsequently embarked on a full clinical development program for fedratinib. On 18 Nov 2013, Sanofi decided to terminate the fedratinib clinical development program after the US FDA placed a clinical hold on all studies being conducted under the IND on 15 Nov 2013 due to concerns of Wernicke’s encephalopathy (WE) and heart failure.
- Impact Biomedicines, Inc. (formerly known as “Impact Therapeutics, Inc”; also referred to as “Impact”) acquired fedratinib from Sanofi; the IND was transferred to Impact on 17 Nov 2016. A Type A meeting was held with FDA on 16 May 2017 to discuss lifting the clinical hold. At that meeting, FDA recommended that Impact perform a detailed review of all data regarding possible WE and cardiomyopathy cases and evaluate thiamine levels in subjects on fedratinib therapy. On 19 Jul 2017, Impact submitted this information to the Agency concluding that while cases of WE were reported in subjects treated with fedratinib, the subjects also had considerable predisposing factors that are known to lead to WE in any population. Impact also concluded that based on preclinical data fedratinib does not have an effect on thiamine receptor function, and therefore, does not cause WE. The FDA concluded on 18 Aug 2017 that Impact provided the necessary documentation to remove the clinical hold.
- Celgene acquired Impact and the compound, fedratinib; the IND was transferred to Celgene on 13 Feb 2018. Celgene-Impact had a pre-NDA meeting with FDA on 10 May 2018. At that meeting, FDA recommended and Celgene-Impact agreed that a (b) (4) Medication Guide would be submitted as part of the NDA to mitigate the risks of WE.
- Previous advice on the clinical outcome assessments (COA) was limited as there was insufficient information regarding the Myelofibrosis Symptom Assessment Form (MFSAF) in 2010. Since then, the modified MFSAF version 2.0 has been previously accepted and labeled in myelofibrosis (Jakafi®; NDA 202192).

Previous COA Reviews:

- AT 2010-023 IND 78286 MFSAF (myelofibrosis, sx relief)\_DDOP

Disease Background:

Primary myelofibrosis (PMF) is a chronic myeloproliferative disorder characterized by a clonal proliferation involving pluripotent hematopoietic stem cells and clonal cell-derived cytokines. As a consequence typically patients present with cytopenias (anemia, thrombocytopenia, leucopenia) and/or variable degrees of thrombocytosis or leukocytosis, debilitating constitutional symptoms, such as weight loss, fatigue, night sweats, pruritus and cough as well as extramedullary hematopoiesis resulting in marked splenomegaly. PMF usually affects patients with advanced age but reports on young people do exist. Current approved drug therapy for PMF such as erythropoiesis stimulating agents or hydroxyurea have not been shown to influence survival and are often used for palliative purposes only. Allogeneic stem cell transplantation, which is so far the only curative option, carries high mortality and morbidity and is precluded by age, poor performance status (PS) and co-morbidities

Investigational Product:

SAR302503 (previously referred to as TG101348) is a protein kinase inhibitor, selective JAK2 inhibitor, which is being developed as an orally available treatment for myelofibrosis (MF). In vitro, SAR302503 shows dose-dependent inhibition of JAK2-induced proliferation and induction of apoptosis in human erythroid leukemia cells at concentrations associated with inhibition of phosphorylation of the JAK2 substrate, STAT5.

Other materials reviewed:

- Phase 3 protocol for Study EFC12153 (JAKARTA; amended version dated November 27, 2013)
- Phase 2 protocol for Study ARD12181 (JAKARTA-2; dated October 20, 2011)
- Clinical study report for Study INCB 18424-351 (COMFORT-I for ruxolitinib; dated April 27, 2011)

## 2 CONTEXT OF USE

### 2.1 Clinical Trial Population

The target population for Studies NCT01437787 (JAKARTA) and NCT01523171 (JAKARTA-2) were adults (age  $\geq 18$  years) with intermediate or high-risk MF, Eastern Cooperative Oncology Group (ECOG) Performance Status  $\leq 2$ , enlarged spleen size, and life expectancy  $\geq 6$  months. Additionally, JAKARTA-2 required all subjects to be resistant or intolerant to prior ruxolitinib therapy.

A complete list of the inclusion and exclusion criteria is summarized in the clinical study protocols for JAKARTA and JAKARTA-2.

**Reviewer's comment(s):**

- *This reviewer confirmed with Clinical (March 25, 2019) that the populations for JAKARTA and JAKARTA-2 were similar to the population in COMFORT-I for Jakafi® (ruxolitinib). The*

major difference is that all patients in JAKARTA-2 were previously exposed to (and failed) ruxolitinib therapy, whereas JAKARTA did not require patients to be previously exposed to ruxolitinib.

- Note that there were no inclusion/exclusion criteria based on symptomatology (i.e., no criterion based on MFSAF score). Based on discussion with Clinical, this is not an issue as patients would need to be symptomatic at baseline to be considered as a responder based on the pre-specified responder analysis.

## 2.2 Clinical Trial Design

Table 2 describes the clinical trial designs of Studies JAKARTA and JAKARTA-2.

**Table 2.** Clinical Trial Designs for Studies JAKARTA and JAKARTA-2

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3 (JAKARTA)	<input type="checkbox"/> Single arm <input type="checkbox"/> Open label <input checked="" type="checkbox"/> Double-blind <input checked="" type="checkbox"/> Randomized <input checked="" type="checkbox"/> Placebo-/Vehicle-controlled <input type="checkbox"/> Active comparator-controlled <input type="checkbox"/> Cross-over <input checked="" type="checkbox"/> Multinational <input type="checkbox"/> Non-inferiority	24 weeks	Yes
Phase 2 (JAKARTA-2)	<input checked="" type="checkbox"/> Single arm <input checked="" type="checkbox"/> Open label <input type="checkbox"/> Double-blind <input type="checkbox"/> Randomized <input type="checkbox"/> Placebo-/Vehicle-controlled <input type="checkbox"/> Active comparator-controlled <input type="checkbox"/> Cross-over <input checked="" type="checkbox"/> Multinational <input type="checkbox"/> Non-inferiority	24 weeks	Yes

Refer to the clinical trial protocols for JAKARTA and JAKARTA-2 for more details on the clinical trial designs.

### Reviewer's comment(s):



(b) (4)

## 2.3 Endpoint Position, Definition, and Assessment Schedule

Tables 3-4 describe the intended placement of the COA in the endpoint hierarchy, including the endpoint definitions and assessment schedules for Studies JAKARTA and JAKARTA-2.

**Table 3.** Endpoint Position, Definition, and Assessment Schedules for Study JAKARTA

Endpoint Position	Assessment	Concept	Endpoint Definition	Assessment Frequency
Primary	Magnetic resonance imaging (MRI) or computed tomography (CT) scan	Reduction in spleen size	Proportion of patients with $\geq 35\%$ reduction in volume of spleen size at the end of Cycle 6, and confirmed 4 weeks thereafter	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Monthly <input checked="" type="checkbox"/> <b>Other: Screening, Day 1 of Cycle 4, End of Cycle 6, and beginning of every 6 cycles thereafter for up to 2 years</b> <input checked="" type="checkbox"/> Assessment at cross-over or early discontinuation
Secondary <input checked="" type="checkbox"/> Multiplicity adjusted	Modified MFSAF v2.0 (PRO)	Symptom response rate	Proportion of patients with $\geq 50\%$ reduction from baseline to the end of Cycle 6 in the total symptom score	<input checked="" type="checkbox"/> <b>Other: Screening, 7 days prior to Day 1 of Cycles 1 through 6, End of Cycle 6, end of treatment, and 30-day post-treatment follow-up</b> <input checked="" type="checkbox"/> Assessment at cross-over or early discontinuation
Exploratory <input type="checkbox"/> Multiplicity adjusted	EQ-5D-3L (PRO)	Health status	No specified endpoint. Analyses include frequency and proportion with 95% CI, descriptive summary statistics, change from baseline	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Monthly <input checked="" type="checkbox"/> <b>Other: Day 1 of Cycle 1, End of Cycle 6, end of treatment, and 30-day post-treatment follow-up</b> <input checked="" type="checkbox"/> Assessment at cross-over or early discontinuation

**Table 4.** Endpoint Position, Definition, and Assessment Schedules for Study JAKARTA-2

Endpoint Position	Assessment	Concept	Endpoint Definition	Assessment Frequency
Primary	Magnetic resonance imaging (MRI) or computed tomography (CT) scan	Reduction in spleen size	Proportion of patients with $\geq 35\%$ reduction in volume of spleen size at the end of Cycle 6, and confirmed 4 weeks thereafter	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Monthly <input checked="" type="checkbox"/> <b>Other: Screening, Day 1 of Cycle 4, End of Cycle 6, and beginning of every 6 cycles thereafter for up to 2 years</b> <input checked="" type="checkbox"/> Assessment at cross-over or early discontinuation
Secondary <input checked="" type="checkbox"/> Multiplicity adjusted	Modified MFSAF v2.0 (PRO)	Symptom response rate	Proportion of patients with $\geq 50\%$ reduction from baseline to the end of Cycle 6 in the total symptom score	<input checked="" type="checkbox"/> <b>Other: Screening, Days 1 and 15 of Cycle 1, Day 1 of Cycles 2-6, End of Cycle 6</b> <input checked="" type="checkbox"/> Assessment at cross-over or early discontinuation
Exploratory <input type="checkbox"/> Multiplicity adjusted	EORTC QLQ-C30 v3.0 (PRO)	General cancer symptoms and impacts; treatment-related symptoms	No specified endpoint. Analyses include frequency and proportion with 95% CI, descriptive summary statistics, change from baseline	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Monthly <input checked="" type="checkbox"/> <b>Other: Day 1 of Cycles 1-6, End of Cycle 6, end of treatment, and 30-day post-treatment follow-up</b> <input checked="" type="checkbox"/> Assessment at cross-over or early discontinuation

**Reviewer's comment(s):**

- *This reviewer confirmed with Clinical (March 25, 2019) that the modified MFSAF v2.0 endpoint definition is similar to the one used in the COMFORT-I trial for Jakafi®. However, the modified MFSAF v2.0 diary was administered at different times and the TSS was calculated using different time points in JAKARTA compared to COMFORT-I:*
  - *In JAKARTA, the modified MFSAF v2.0 diary was completed once daily for the week prior to Day 1 of each treatment cycle (i.e., the last week of every treatment cycle) and at the End of Cycle 6. The TSS score for End of Cycle 6 was calculated using the*

mean of 7 days of symptom scores prior to the End of Cycle 6, with fewer than 5 days of data being counted as missing.

- In COMFORT-I, the modified MFSAF v2.0 diary was completed daily throughout the entire study (baseline to Week 24). The TSS score for Week 24 was calculated using the mean of 28 days of symptom scores prior to the Week 24 visit, with fewer than 20 days of data being counted as missing. Refer to section 12.2.2.1 of the COMFORT-I protocol for more information.

Based on discussion with Clinical and Biostatistics, product labeling will include a statement describing the administration schedule for the modified MFSAF v2.0 diary in JAKARTA.

- The applicant additionally included the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) as an exploratory endpoint assessment in JAKARTA and JAKARTA-2. The MPN-SAF contains fatigue items, whereas the modified MFSAF v2.0 does not. Because fatigue is a core symptom of MF, future studies should consider using an MF-specific assessment that includes a fatigue item(s) (e.g., the MFSAF v4.0<sup>2</sup>). For an individual claim of fatigue improvement, sponsors should consider a separate fatigue assessment (e.g., a PROMIS<sup>®</sup> Fatigue short form). See additional reviewer's comments in section B.3 of this review.

(b) (4)

## 2.4 Labeling or promotional claim(s) based on the COA

The applicant proposed the following targeted COA-related labeling claims:

### **Primary or Secondary Myelofibrosis (MF)**

(b) (4) included the proportion of patients with a 50% or greater reduction in Total Symptom Score (TSS) from baseline to the End of Cycle 6 as measured by the modified Myelofibrosis Symptoms Assessment Form (MFSAF) v2.0 diary. [...]

The modified MF-SAF included 6 key MF associated symptoms: night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. The symptoms were measured on a scale from 0 (absent) to 10 (worst imaginable).

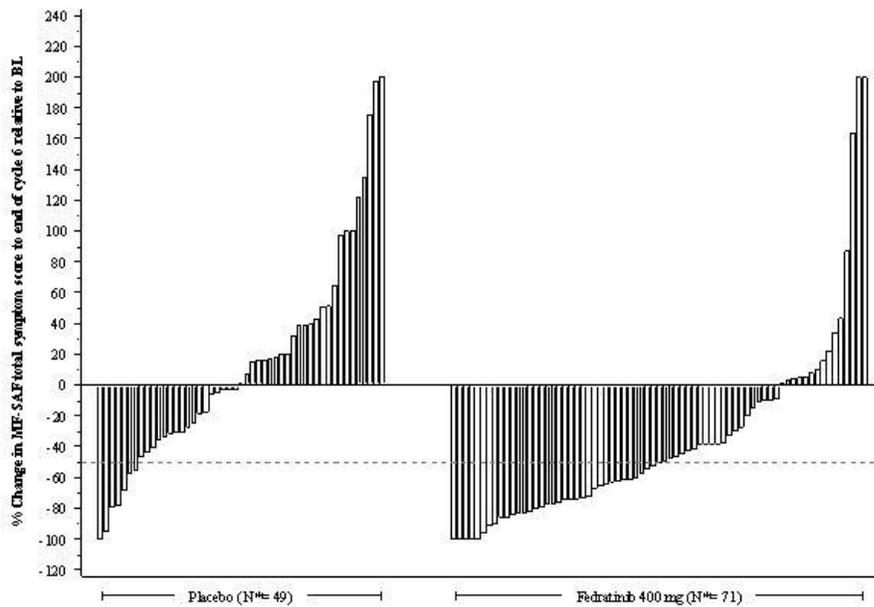
The proportion of patients with a 50% or greater reduction in TSS was 40.4% in the INREBIC 400 mg group and 8.6% in the placebo group (Table 9).

**Table 9: Improvement in Total Symptom Score in Patients with Myelofibrosis in the Phase 3 Study, JAKARTA**

	<b>INREBIC 400 mg</b> (N=89) n (%)	<b>Placebo</b> (N=81) n (%)
Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score at the End of Cycle 6	36 (40.4)	7 (8.6)
p-value	<i>p</i> <0.0001	

Figure 2 shows the percent change in Total Symptom Score from baseline at the End of Cycle 6 for each patient.

**Figure 2: Percent Change from Baseline in Total Symptom Score at End of Cycle 6 for Each Patient in Phase 3 Study, JAKARTA**



(b) (4)

- *As stated in the reviewer’s comments* [redacted] (b) (4)  
[redacted]  
[redacted] (b) (4)  
[redacted]
- *As stated in the reviewer’s comments under Section B.2.3 of this review, JAKARTA and COMFORT-I (the pivotal trial for Jakafi®) both used the modified MFSAF v2.0, but the instrument was administered at different times and the TSS was calculated using different time points. Based on discussion with Clinical and Biostatistics, product labeling will include a statement describing the administration schedule of the modified MFSAF v2.0 diary in JAKARTA.*
- [redacted] (b) (4)
- *The applicant* [redacted] (b) (4)  
[redacted] *item of the MFSAF. This reviewer recommends using the term “itching” for all references to item 2 of the MFSAF, as this is consistent with the language used in the labeling for Jakafi®, which also used the modified MFSAF v2.0 diary.*
- *The applicant uses* [redacted] (b) (4)  
[redacted] *this reviewer recommends using the same terminology that is used in the Jakafi® label, which is to refer to the instrument as the “modified MFSAF v2.0.”*
- *The statement,* [redacted] (b) (4)  
[redacted]  
[redacted] *This reviewer recommends that the data for all endpoints is reported consistently throughout the product label.*

### 3 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the COAs are summarized in Table 5.

**Table 5.** Concepts of Interest for COAs Included in Studies JAKARTA and JAKARTA-2

COA name	Concept(s)
Modified MFSAF v2.0	MF-related symptoms (night sweats, itching, abdominal discomfort, early satiety, pain under left ribs, bone/muscle pain)

The applicant did not submit a conceptual framework for the modified MFSAF v2.0. However, a conceptual framework was generated based on the instrument on its face (Table 6).

**Table 6.** Conceptual framework of the Modified MFSAF v2.0

Item	General Concept
Item 1: Night sweats	MF-related symptoms
Item 2: Itching	
Item 3: Abdominal discomfort	
Item 4: Early satiety	
Item 5: Pain under left ribs	
Item 6: Bone/muscle pain	

**Reviewer’s comment(s):**

- *Based on discussion with Clinical, the concepts included in the modified MFSAF v2.0 are clinically relevant for the target population, with the caveat that the modified MFSAF v2.0 does not include a fatigue assessment. Fatigue is a core symptom of MF, and therefore future studies should consider using an MF-specific assessment that includes a fatigue item(s) (e.g., the MFSAF v4.0<sup>2</sup>). For an individual claim of fatigue improvement, sponsors should consider a separate fatigue assessment (e.g., a PROMIS<sup>®</sup> Fatigue short form).*
- *As noted in the reviewer’s comments under Section B.2.3 of this review, the MPN-SAF includes fatigue items. However due to endpoint positioning (exploratory endpoint in JAKARTA and JAKARTA-2) and data interpretability issues (e.g., suboptimal assessment schedule, missing data, problematic scoring) it is not adequate to support labeling claims.*

## 4 CLINICAL OUTCOME ASSESSMENT(S)

### Modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0

The modified MFSAF v2.0 is a 6-item PRO instrument designed to assess core MF-related symptoms, which include:

- Night sweats
- Itching (pruritus)
- Abdominal discomfort
- Filling up quickly when you eat (early satiety)
- Pain under ribs on left side
- Bone or muscle pain

Each item is rated on an 11-point numeric rating scale (NRS) from 0 (“absent”) to 10 (“worst imaginable”). Patients are instructed to respond to items based on how each symptom affected them at their worst moment over the past 24 hours. A copy of the modified MFSAF v2.0 is provided in Appendix A.

## 5 SCORING ALGORITHM

### Modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0

The MFSAF is scored by summing the scores for each of the 6 items to form a Total Symptom Score (TSS). The TSS ranges from 0 to 60, with higher scores indicating greater symptom severity.

**Reviewer’s comment(s):**

- For the modified MFSAF v2.0, total symptom score (TSS) was calculated for each day only if a response was present for all 6 items; patients without responses for all items were considered missing. The TSS used in analysis was the average of daily scores for each item over the 7 days before each cycle. Weekly averages were only calculated for patients with data from at least 5 out of 7 days before each cycle; patients with fewer than 5 days of data were considered missing. Refer to Section 9.7.1.2.6.2. of the JAKARTA study report for more information.
- In the intent-to-treat population analysis, only patients with a non-zero baseline MFSAF TSS were included.

## 6 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- Literature review and/or publications
- Documentation of expert input
- Qualitative study protocols and interview guides for focus group or patient interviews
- Chronology of events for item generation, modification, and finalization (item tracking matrix)
- Synopsis of qualitative findings
- Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- Quantitative summary report with evidence to support item retention and scoring
- Transcripts (if available)

Table 7 documents the adequacy of the content of the modified MFSAF v2.0.

**Table 7.** Review of Content Validity for the Modified MFSAF v2.0

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<input checked="" type="checkbox"/> Literature <input type="checkbox"/> Clinical input e.g. discussion with clinical reviewer	
Content validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional	<input checked="" type="checkbox"/> The item concepts are relevant/important to target patient population and appropriate to the study design and objectives	<ul style="list-style-type: none"><li>• Mesa et al 2009<sup>3</sup></li><li>• Mesa et al 2013<sup>4</sup></li></ul>

<sup>3</sup> Mesa et al 2009. The Myelofibrosis Symptom Assessment Form (MFSAF): an evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. Leuk Res. 2009 Sep;33(9):1199-203. doi: 10.1016/j.leukres.2009.01.035. Epub 2009 Feb 27.

<sup>4</sup> Mesa et al 2013. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2013 Apr 1;31(10):1285-92. doi: 10.1200/JCO.2012.44.4489. Epub 2013 Feb 19.

	<p>information is needed</p> <p><input type="checkbox"/> No</p>	<p><input type="checkbox"/> The instrument is comprehensive with respect to the concept (i.e., does not omit important content)</p> <p><input checked="" type="checkbox"/> Target sample for qualitative research is appropriate.</p> <p><input checked="" type="checkbox"/> Studied sample for qualitative research adequately represents the target patient population</p> <p><input checked="" type="checkbox"/> Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives</p> <p><input checked="" type="checkbox"/> Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity)</p> <p><input checked="" type="checkbox"/> COA is culturally adapted and adequately translated</p> <p><input checked="" type="checkbox"/> Descriptive statistics (if available) support content relevance</p> <p><input checked="" type="checkbox"/> Other (see Reviewer's comments)</p>	<ul style="list-style-type: none"> <li>• Gwaltney et al 2017<sup>2</sup></li> </ul>
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**Reviewer's comment(s):**

- *The content validity of the MFSAF in this context of use is well-documented in the literature; additional qualitative evidence is not necessary in this context of use. However, as noted previously in the reviewer's comments under Sections B.2.3 and B.3, fatigue is a core symptom of MF which is not assessed in the modified MFSAF v2.0. However, the modified MFSAF v2.0 has been previously accepted in previous applications (Jakafi®). For future studies, sponsors should consider using the most recent version of the MFSAF (version 4.0<sup>2</sup>), which includes a fatigue assessment. For an individual claim of fatigue improvement, sponsors should consider a separate fatigue assessment (e.g., a PROMIS® Fatigue short form).*

## 7 OTHER MEASUREMENT PROPERTIES

To date, the following information has been submitted (check all that apply):

- Literature review and/or publications
- Quantitative analysis synopsis
- Full quantitative analysis plan
- Quantitative summary report with evidence to support reliability, construct validity, ability to detect change and scoring

Table 8 documents the adequacy of the other measurement properties of the Modified MFSAF v2.0.

**Table 8.** Review of Other Measurement Properties for the Modified MFSAF v2.0

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Reliability	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input type="checkbox"/> Internal consistency reliability estimates in acceptable range (e.g., Cronbach’s $\alpha > 0.70$ ) <input checked="" type="checkbox"/> Test-retest reliability (or intra-rater reliability) estimates in acceptable range (e.g., ICC $\geq 0.70$ ) <input type="checkbox"/> Inter-rater reliability estimates in acceptable range <input type="checkbox"/> Other (see Reviewer’s comments)	<ul style="list-style-type: none"> <li>Mesa et al 2013<sup>Error!</sup> Bookmark not defined.</li> </ul>
Construct validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> Relationship to other assessments with similar concepts is as expected <input type="checkbox"/> Relationship to other assessments with dissimilar concepts is as expected <input type="checkbox"/> COA differentiates between clinically distinct groups (i.e., known groups validity) <input type="checkbox"/> COA scores are related to a known gold standard assessment of the same concept <input type="checkbox"/> Other (see Reviewer’s comments)	<ul style="list-style-type: none"> <li>Mesa et al 2009<sup>3</sup></li> <li>Mesa et al 2013<sup>Error!</sup> Bookmark not defined.</li> </ul>
Ability to detect change	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> COA can identify differences in scores over time in individuals or groups who have changed with respect to the concept <input type="checkbox"/> Other (see Reviewer’s comments)	<ul style="list-style-type: none"> <li>Mesa et al 2011<sup>5</sup></li> </ul>

**Reviewer’s comment(s):**

- The other measurement properties of the MFSAF in this context of use are well-documented in the literature, and the modified MFSAF v2.0 has already been used to support labeling for Jakafi®. Additional quantitative evidence is not necessary in this context of use.*

## 8 INTERPRETATION OF SCORES

To date, the following information has been submitted (check all that apply):

- Anchor-based analyses
- Anchor-based empirical cumulative distribution function (eCDF) curves

<sup>5</sup> Mesa et al 2011. Evaluating the serial use of the Myelofibrosis Symptom Assessment Form for measuring symptomatic improvement: performance in 87 myelofibrosis patients on a JAK1 and JAK2 inhibitor (INCB018424) clinical trial. *Cancer*. 2011 Nov 1;117(21):4869-4877. doi: 10.1002/cncr.26129. Epub 2011 Apr 8.

- eCDF study arm curves (Treatment vs. Placebo/Active Comparator)
- Anchor-based probability density function (PDF) curves
- PDF study arm curves (Treatment vs. Placebo/Active Comparator)
- Qualitative support for meaningful change (e.g., patient input)

Table 9 documents the adequacy of the score interpretability of the modified MFSAF v2.0.

**Table 9.** Review of Score Interpretability for the Modified MFSAF v2.0

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input type="checkbox"/> Appropriate global anchor scales were included for anchor-based analyses <input type="checkbox"/> Threshold(s) for within-patient meaningful change identified (anchor-based methods) <input checked="" type="checkbox"/> Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) <input type="checkbox"/> Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) <input type="checkbox"/> Other (see Reviewer’s comments)	CDF curves: <ul style="list-style-type: none"> <li>• JAKARTA study report, figures 13-19</li> </ul>

**Reviewer’s comment(s):**

- *The applicant did not include patient-reported global impression scales (e.g., Patient Global Impression of Severity [PGIS] and/or Patient Global Impression of Change [PGIC]) in Studies JAKARTA and JAKARTA-2. Generally, this would present a potential challenge to determining meaningful change in an instrument. However, the responder definition selected by the applicant (50% reduction from baseline) for the modified MFSAF v2.0 has been previously accepted by the Division in other applications to constitute a meaningful change (Jakafi®; NDA 202192)*
- *In the JAKARTA study report, the applicant included CDF curves comparing modified MFSAF v2.0 scores for the fedratinib 400 mg, fedratinib 500 mg, and placebo arms. CDF curves were included for change in weekly TSS at End of Cycle 6, and change in each of the individual symptom scores at End of Cycle 6. Clear separation can be seen between the treatment and placebo arms in the TSS analysis, and in the analyses of individual symptom scores for abdominal discomfort, bone or muscle pain, early satiety, and pain under ribs on left side. There is not clear separation between study arms for the analysis of itching score, and there is separation between all three study arms for the analysis of night sweats score.*

**D. APPENDICES**

Appendix A: Modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0



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CHRISTOPHER ST. CLAIR  
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SELENA R DANIELS  
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ELEKTRA J PAPADOPOULOS  
07/18/2019 09:32:42 AM

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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: July 12, 2019  
Requesting Office or Division: Division of Hematology Products (DHP)  
Application Type and Number: NDA 212327  
Product Name and Strength: Inrebic (fedratinib) capsules, 100 mg  
Applicant/Sponsor Name: Impact Biomedicines, Inc., a wholly owned subsidiary of Celgene Corporation (Impact-Celgene)  
FDA Received Date: July 12, 2019  
OSE RCM #: 2019-231-1  
DMEPA Safety Evaluator: Stephanie DeGraw, PharmD  
DMEPA Team Leader: Hina Mehta, PharmD

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## 1 PURPOSE OF MEMORANDUM

Impact-Celgene submitted the revised container label for Inrebic (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review<sup>a</sup> and via email communication.<sup>b</sup> We reviewed the label to determine if it is acceptable from a medication error perspective.

## 2 CONCLUSION

The revised container label is acceptable from a medication error perspective. We have no additional recommendations at this time.

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<sup>a</sup> Ogbonna, C. Label and Labeling Review for Inrebic (fedratinib) NDA 212327. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 10. RCM No.: 2019-231.

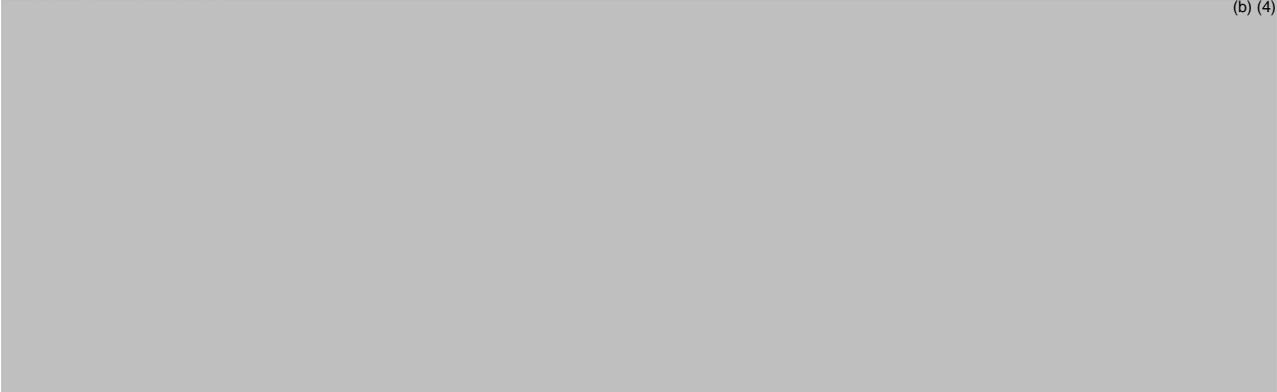
<sup>b</sup> Lee, J. Fedratinib - Container Labeling Email. NDA 212327. 2019 JUL 2.

<https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805020af&showAsPdf=true>

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JULY 12, 2019

Container Label

(b) (4)



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STEPHANIE L DEGRAW  
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HINA S MEHTA  
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## CLINICAL INSPECTION SUMMARY

<b>Date</b>	June 13, 2019
<b>From</b>	Anthony Orenca M.D., F.A.C.P., GCPAB Medical Officer Min Lu, M.D., M.P.H. GCPAB Acting Team Leader, Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
<b>To</b>	Saleh Ayache, M.D., Medical Officer Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader Ann Farrell, M.D., Director Jennifer Lee, Pharm.D., Regulatory Project Manager Division of Hematology Products
<b>NDA</b>	212327
<b>Applicant</b>	Impact Biomedicines, Inc., a wholly-owned subsidiary of Celgene Corporation
<b>Drug</b>	Fedratinib
<b>NME</b>	Yes
<b>Therapeutic Classification</b>	Selective JAK2 protein kinase inhibitor
<b>Proposed Indication</b>	Treatment of intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (b) (4)
<b>Consultation Request Date</b>	February 6, 2019 (Priority Review)
<b>Summary Goal Date</b>	June 15, 2019
<b>Action Goal Date</b>	August 16, 2019
<b>PDUFA Date</b>	September 3, 2019

### 1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

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.

## 2. BACKGROUND

Fedratinib (SAR302503 [previously referred to as TG101348]) is a selective JAK2 inhibitor. The sponsor proposes Fedratinib as an oral treatment for myelofibrosis. The sponsor conducted a single study (Protocol EFC12153) to evaluate the safety and efficacy of fedratinib.

### Study Protocol EFC12153

Protocol EFC12153 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm study of 2 doses of fedratinib in subjects 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. Following an initial 28-day screening period, eligible subjects were randomized (1:1:1) to receive either 400 or 500 mg/day fedratinib or matching placebo orally, once a day for at least 6 consecutive 28-day cycles. Eligible subjects from all treatment arms were re-randomized by Interactive Voice Response System (IVRS).

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

The study was conducted in 94 active study centers in 24 countries. A total of 289 subjects were randomized: 96 in the placebo arm, 96 in the fedratinib 400 mg arm, and 97 in the fedratinib 500 mg arm. A total of 288 study subjects were treated: 95 in the placebo arm, 96 in the fedratinib 400 mg arm, and 97 in the fedratinib 500 mg arm. The first study patient was enrolled on December 22, 2011. The last study subject completed the study on June 25, 2014.

### Rationale for Site Selection

The CDER Division of Hematology Products requested inspection of three study sites -two international sites and one domestic clinical site for inspection, based on enrollment of large numbers of study subjects in these three sites. Further, there were insufficient domestic site data to assess the clinical trial site data quality and conduct of this investigative study.

## 3. RESULTS (by site):

Name of Clinical Investigator/Address	Protocol #/ Site #/ # Subjects Enrolled	Inspection Dates	Classification
Animesh Pardanani, M.D. Mayo Clinic 200 SW 1st St. Rochester, MN 55905	EFC12153  Site #840008  13 subjects	March 4 - 8, 2019	VAI

<b>Name of Clinical Investigator/Address</b>	<b>Protocol #/ Site #/ # Subjects Enrolled</b>	<b>Inspection Dates</b>	<b>Classification</b>
Emanuil Gheorghita, M.D. Str Calea Bucuresti nr 25-27 Brasov, Romania	EFC12153  Site #642003  6 subjects	May 20 - 23, 2019	*NAI
Kazimierz Kuliczkowski, M.D. Str ul. Pasteura 4 Wroclaw, Dolnoslaskie 50- 367, Poland	EFC12153  Site #616003  6 subjects	May 13 - 17, 2019	*NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

\* Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

**Clinical Investigator****1. Animesh Pardanani, M.D.**

A total of 17 subjects were screened and 13 subjects were enrolled. Four subjects did not complete the study due to the following reasons: three patients withdrew consent to participate and one study subject had an adverse event. Nine patients completed the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for patient informed consent documentation, primary study endpoint assessment, adverse event and serious adverse event reporting. A comprehensive audit of the inclusion and exclusion criteria for patient enrollment was evaluated at this site inspection. The primary efficacy endpoint was performed by an independent committee. The FDA audit verified that the images were sent to the central imaging lab for blinded data evaluation. All imaging reports and evidence of submission to the central lab were available and verifiable at this clinical study site. There were no limitations during conduct of the clinical site inspection.

At the conclusion of the inspection, a Form FDA 483 was issued, in part, due to failure to conduct the investigation according to the study protocol, specifically related to delayed serious adverse event reporting. For example:

- (1) Subject (b) (6) (on fedratinib treatment) with a Grade 4 anemia SAE was reported six days later to the sponsor.
- (2) Subject (b) (6) (on fedratinib treatment) with a Grade 3 hematoma SAE was reported four days later to the sponsor.

Dr. Pardamani responded adequately to the 483 observations in a letter dated March 22, 2019. The site has planned and will institute corrective actions in response to the above regulatory deficiencies.

Although the above findings are regulatory violations, the findings are unlikely affect the overall reliability of safety and efficacy data from the site.

## **2. Emanuel Gheorghita, M.D.**

A total of seven subjects were screened and six subjects were enrolled. Four subjects completed Treatment Cycle 6 of the clinical investigation. One subject discontinued from the study due to withdrawal of consent and another patient discontinued due to an adverse event.

For this inspection, a complete review of all regulatory documentation at the study site was performed, including the source records for all the subjects enrolled at the site prior to the data lock. The records reviewed included medical records, ECG reports and notes, regulatory binder documents, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for the six screened and enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for eligibility, adverse events, and serious adverse event reporting. Source documents for the clinical spleen examination data used, to support MRI data for the primary efficacy study endpoint were assessed at the study site. The primary efficacy endpoint measurements and evaluations were conducted by independent review at a central site. There was no under-reporting of adverse events noted during this site audit. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

## **3. Kazimierz Kulickowski, M.D.**

A total of seven subjects were screened and six subjects were enrolled. Four subjects completed Treatment Cycle 6 of the clinical investigation. One patient discontinued from the study due to withdrawal of consent to participate in the study and another study subject discontinued due to disease progression.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for the six screened and enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for eligibility, adverse events, and serious adverse event reporting. Source documents for the clinical spleen examination data used, to support MRI data for the primary efficacy study endpoint were also evaluated at the study site. The primary efficacy endpoint measurements and assessments were adjudicated by an independent review committee. There was no under-reporting of adverse events noted during this site audit.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

*{See appended electronic signature page}*

Anthony Orenca, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Min Lu, M.D., M.P.H.  
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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.  
Branch Chief, Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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LABEL AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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Date of This Review:	May 10, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212327
Product Name and Strength:	Inrebic (fedratinib) capsule, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Impact Biomedicines, Inc., a wholly owned subsidiary of Celgene Corporation (Celgene)
FDA Received Date:	January 3, 2019
OSE RCM #:	2019-231
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

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## 1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested DMEPA to review the Prescribing Information (PI) and container label for areas of vulnerability that may lead to medication errors.

On January 3, 2019, Impact Biomedicines, Inc submitted 505(b) original NDA 212327 for Inrebic (fedratinib) capsules. The proposed indication is for the treatment of intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (b) (4).

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the proposed Prescribing Information (PI) and container label for areas of vulnerability in regards to medication error.

We identified areas of concern in the PI and container label that should be revised to improve the clarity of the information presented.

We provide recommendations for the Division in Section 4.1, and recommendations for Impact Biomedicines, Inc., a wholly owned subsidiary of Celgene Corporation (Celgene) in Section 4.2 to address these deficiencies.

## 4 CONCLUSION & RECOMMENDATIONS

We determined that the proposed PI and container label are vulnerable to confusion that can lead to medication errors. We provide recommendations for the Division in Section 4.1, and recommendations for Impact Biomedicines, Inc., a wholly owned subsidiary of Celgene Corporation (Celgene) in Section 4.2 to address these deficiencies to be implanted prior to the approval of NDA 212327.

#### 4.1 RECOMMENDATIONS FOR THE DIVISION

##### A. Highlights of Prescribing Information

###### 1. Dosage and Administration Section

- a. Add the statements "Modify dosage for toxicity." to ensure this important information is not missed as there are several dosage modifications that may need to be considered. In addition, add "with or without food" for clarity. Revise to "400 mg once daily with or without food. Modify dosage for toxicity (2.1, 2.2., 2.3, 2.4, 2.5)".

##### B. Full Prescribing Information

###### 1. Dosage and Administration Section

- a. In (b) (4) of Section 2.2, consider replacing the symbols "≥", and "≤" with their intended meanings to prevent misinterpretation and confusion per [ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations](#).

###### 2. Dosage Forms and Strengths

- a. To improve readability, between the numerical dose and unit of measure remove the "-" in "100-mg" i.e. change from "100-mg" to "100 mg".

###### 3. How Supplied/Storage and Handling Section

- a. To improve readability, between the numerical dose and unit of measure. remove the "-" in "100-mg" i.e. change from "100-mg" to "100 mg".

#### 4.2 RECOMMENDATIONS FOR IMPACT BIOMEDICINES, INC., A WHOLLY OWNED SUBSIDIARY OF CELGENE CORPORATION (CELGENE)

We recommend the following be implemented prior to approval of this NDA 212327:

##### A. Container Labels

1. The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

2. As currently presented, the location of the lot and expiration date is not defined. Please confirm location of the lot and expiration date. In addition, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date, per [Draft Guidance: Container and Carton](#), April 2013 (lines 493-507).
3. Decrease the prominence of the statement “Rx Only” and debold it to avoid confusion and medication error per [Draft Guidance: Container and Carton](#), April 2013 (lines 146-149).
4. Remove the (b) (4) to avoid confusion and medication error since the (b) (4)
5. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.<sup>1</sup> The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling.
6. Per 21 CFR 208.24(d) for products with medication guide a statement should be prominently displayed on the principal display panel. Thus, we recommend adding “Dispense the enclosed Medication Guide to each patient” prominently on the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Inrebic received on January 3, 2019 from Impact Biomedicines, Inc., a wholly owned subsidiary of Celgene Corporation (Celgene).

Table 2. Relevant Product Information for Inrebic	
Initial Approval Date	N/A
Active Ingredient	fedratinib
Indication	is indicated for the treatment of intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) [REDACTED] (b) (4) [REDACTED].
Route of Administration	oral
Dosage Form	capsule
Strength	100 mg
Dose and Frequency	400 mg (four capsules) once daily
How Supplied	Reddish brown, opaque size 0 capsule, printed with "FEDR 100 mg" in white ink. <ul style="list-style-type: none"> <li>• 120-count bottles of 100-mg capsules (NDC 59572-720-12)</li> </ul>
Storage	Store below 86°F (30°C).

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>a</sup> along with postmarket medication error data, we reviewed the following Inrebic labels and labeling submitted by Impact Biomedicines, Inc., a wholly owned subsidiary of Celgene Corporation (Celgene).

- Container label received on January 3, 2019
- Prescribing Information (Image not shown) received on January 3, 2019  
<\\cdsesub1\evsprod\nda212327\0001\m1\us\proposed.docx>

### G.2 Label and Labeling Images



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<sup>a</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**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.**  
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/s/  
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HINA S MEHTA  
05/10/2019 06:28:31 PM

Division of Neurology Products Consult Memo

NDA	212237
SD#	1
Sequence Number	0001
Sponsor	IMPACT BIOMEDICINES INC
Drug	fedratinib
Proposed Indication	the treatment of intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) <span style="float: right;">(b) (4)</span>
Material Submitted	NDA submission
Correspondence Date to DHP	1/3/2019
Date Received by DNP	2/20/2019
Date Review Completed	5/1/19
Reviewer	Steven Dinsmore, DO

**Glossary**

ADAE	ADaM xpt dataset
Core WE Cases (Wernicke's Encephalopathy)	This phrase is used through the review document to identify the potential Wernicke's encephalopathy in 7 patients where the mission of the consult is to assess the strength of the diagnosis. These emerged during the fedratinib IND and resulted in clinical hold on 11/15/13
CTCAE	Common Terminology Criteria for Adverse Events
IND	Investigation new drug application
ISS	Integrated summary of safety
MRI	Magnetic resonance image
Nutritional challenge	The phrase nutritional challenge events will be used in the document to identify 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.
Nutritional Status Metrics	Serum albumin, globulin and protein
OL	Open label
PN	Peripheral nerve (nervous)
SAE	Serious adverse event
TTO	Time to onset
WE	Wernicke's Encephalopathy
WE event	Occurrence of the adverse event of Wernicke's encephalopathy
WE-like	Include WE-PN occurrence that are not diagnosed as WE but indicate CNS dysfunction not otherwise explained and / or peripheral nervous system adverse events

WE-PN	Composite MedDRA Term Query composed of all preferred terms in 3 SMQ's including Noninfectious encephalitis (SMQ), Noninfectious encephalopathy/delirium (SMQ), Peripheral neuropathy (SMQ) and the following 8 terms from the Ocular motility disorders (SMQ)- Extraocular muscle disorder, Eye movement disorder, Gaze palsy, Ocular dysmetria, Oculogyric crisis, Ophthalmoplegia, Vestibular nystagmus, and Diplopia.
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## I. Introduction

During drug development (IND 078286), a signal for Wernicke's encephalopathy emerged associated with fedratinib treatment. The IND was put on Complete Clinical Hold on 15 November 2013, after several cases of possible Wernicke's encephalopathy (from this point identified as WE) were reported to FDA. In March of 2017, the sponsor requested a Type A meeting to discuss removal of the clinical hold. The full clinical hold was removed on 18 August 2017 with a statement from FDA that "questions remain regarding the clinical adverse event findings documented in your trials and what further steps need to be taken to mitigate risk." An initial consult was performed by DNP to evaluate the sponsor's argument that the observed cases of WE were due to nutritional challenge, primarily nausea and vomiting while on fedratinib therapy, perhaps with a component of pre-existing nutritional depletion in some cases. Two consults were performed by DNP as the available information on the potential case of Wernicke's encephalopathy expanded. The conclusion of the consult evaluation was that "The strength of the signal is very uncertain. This is due to the inability to extract in sufficient detail from the available data the clinical features of WE and the potentially confounding instances of nutritional challenge and medical background issues that may deplete thiamine." An additional issue of concern was the potential for fedratinib to have a primary effect on the cellular thiamine economy via inhibition of the individual human thiamine transporter (hTHTR2).

The product has now been submitted as NDA 212327 for marketing approval. DHP has submitted a consult requesting reassessment of the original reports of Wernicke's encephalopathy in light of the broader information package provided in the NDA to determine if these cases indicate a clear risk of WE or WE-like encephalopathy. In addition, DHP is requesting comment on whether the data suggest an increased risk of other neurotoxicity.

## II. Consult Questions

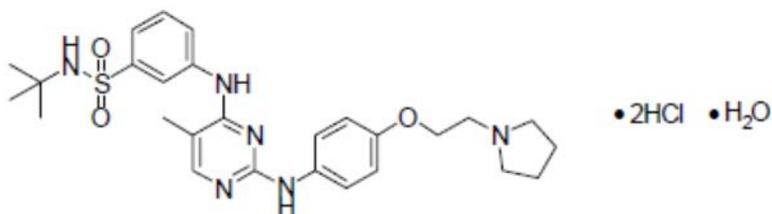
- a. Review the cases and any other relevant information in the NDA submission to provide any additional input regarding the potential risk of WE and comment on whether the cases represent clear risk of WE or WE-like encephalopathy.
- b. Comment on whether any data suggest an increased risk of neurotoxicity with fedratinib. This NDA application contains (b) (4)

## III. Fedratinib Chemistry

- Generic Name: Fedratinib
- Chemical name: N-tert-butyl-3-[(5-methyl-2-[1]pyrimidin-4-yl)amino]benzene-1-sulfonamide-hydrogen chloride-water (1/2/1)
- Molecular formula: C<sub>27</sub>H<sub>36</sub>N<sub>6</sub>O<sub>3</sub>S, 2 HCl, H<sub>2</sub>O
- Molecular weight: 615.62 (dihydrochloride monohydrate), 524.68 (free base)

- Chemical Structure

Figure 1 fedratinib Structural Formula



#### IV. Pharmacology

##### a. History and Mechanism of Action

Fedratinib is a potent, small molecule kinase inhibitor of wild type and mutationally activated Janus kinase 2 (JAK2) and FMS-like tyrosine (FLT) kinase 3 (FLT3). Fedratinib inhibits dysregulated JAK2 signaling that drives the pathogenesis of myeloproliferative neoplasms (MPNs), including myelofibrosis and polycythemia vera. In patient-derived cell lines expressing JAK2V617F and cells engineered to express WT JAK2 or JAK2V617F, fedratinib reduced phosphorylation of STAT3/STAT5, inhibited cell proliferation, and increased apoptosis.

#### V. Fedratinib NDA Safety Evaluation Package

The Summary of Clinical Safety (SCS) provides safety results in support of a New Drug Application (NDA) for the use of fedratinib for:

- the treatment of patients with primary or secondary (post-polycythemia vera [post-PV] or post-essential thrombocythemia [post-ET]) myelofibrosis (MF), or

(b) (4)

The proposed dosing regimen is fedratinib 400 mg orally once daily taken in 28-day cycles continuously until PD or unacceptable toxicity.

The overall evaluation of safety is derived from the 18 clinical studies encompassing the fedratinib clinical development program, 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 doses (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 [2]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 a former sponsor.

- VI. Approach to Review: Review strategy will be covered in 4 headings described in this section. Each major approach heading will have a dedicated outline section in the document to follow that will expand on the individual areas of assessment.
- a. **SEARCH TERMS:** Create a broad query of MedDRA terms to test the controlled and open label dataset of the NDA submission for the presence and frequency of Wernicke encephalopathy and peripheral neuropathy terms. This will be identified as the WE-PN query through the review document (see [glossary](#) and [Appendix 1, Composite WE-PN Query Terms](#))
    - i. **Nutritional Challenge:** this a key concept in the review because events that disrupt dietary intake will reduce thiamine availability. The purpose of characterizing a key identifier (consistently identified as “nutritional challenge”) is to simplify expression of this concept for ease of discussion and presentation throughout the review document. Preferred terms that will be included under the core term “nutritional challenge” will include “nausea”, “vomiting”, “decreased appetite”, “weight decreased”, “abnormal loss of weight”. Although abdominal pain appears frequently in the ISS ADAE dataset (200 entries from 120 patients) it was not considered a core nutritional challenge term because it is unclear to what degree this experience will suppress food intake.
  - b. **Core WE Cases:** In this section, the strength of the 7 Wernicke’s Encephalopathy diagnoses will be reevaluated.

In the original IND consultations, there were 8 WE cases reported. One report, patient 012181-(b) (6) is the clinically least supported, had no MRI report adjudicated as consistent with WE, and is confounded by likely hepatic encephalopathy; this patient will remain in the [Appendix 2, Core Case Master Table](#) but will not be included for further discussion in [section VII](#), or WE Cases from the IND Development Interval. Throughout the document, the term “Core WE Cases” will be used to identify the remaining 7 WE reports of interest.

The diagnostic conclusions of the Core WE Cases will be reassessed, creating a comprehensive set of data for each patient in a master table ([Appendix 2, Core Case Master Table](#)). This table is a comprehensive assembly and display of relevant data for each case of potential WE. The metrics of interest that will be captured and collated in the table and for narrative discussion in [section VII](#) are identified in the following outline entries:

- i. **WE-PN** term frequency, this acronym is used throughout the document to refer to the composite query described in (a) “search terms” above and identified in [Appendix 1, Composite WE-PN Query Terms](#). See the rationale for WE-PN query below.
- ii. Baseline medical history, possible contribution to thiamine depletion
- iii. Time to onset of the WE event from start of study drug treatment
- iv. Nausea and vomiting frequency
  1. Alignment of nutritional challenge terms with the WE event
  2. Alignment of weight change with the WE event
- v. Baseline BMI and weight change during the study interval
- vi. Nutritional parameter trend over the study timeline by examination of serum albumin, globulin and protein.

- vii. Update 8 core case master table to show the alignment of all relevant WE diagnostic metrics. This will include study days of Nausea, Vomiting, CTCAE grade of events, weight percent change from baseline where proximal to the WE event date. Body weight trendlines are also created for each patient and presented in [Appendix 3 Weights by Study Day, Core WE Cases](#)
- viii. Show the temporal relationship of WE-PN preferred terms, captured in the ISS ADAE dataset when they are temporally related to the WE event date.
  - ix. Reassess the integrated diagnostic conclusions, of 7 WE reports that exclude the hepatic encephalopathy case, in the 8 core case master table (see [Appendix 2, Core Case Master Table](#)) based on the summation of clinical, nutritional, AE events and MRI diagnostic conclusions (see IND 78286 Meeting Background Briefing Materials, 3/14/2017, SD # 329, seq # 0310)
  - x. Examine for evidence that the WE syndrome is reversible with thiamine treatment by assessing time to treatment response and available clinical data.
- c. **WE-PN TERM CONTROLLED DATA**, Section VIII: Examine the controlled data from study EFC12153 for differential occurrence of WE-PN terms between the PBO and fedratinib 400mg and 500mg treatment groups.
  - i. Distribution of WE-PN terms by treatment arm
  - ii. Distribution of Nausea and Vomiting preferred terms by treatment arm
- d. **WE-PN TERM OPEN LABEL**, Section IX: Examine the open label data from studies ARD11936, ARD12042, ARD12181, ARD12888, EFC12153, INT12497, TED12037, TES13519 for the frequency of WE-PN terms and clusters of these terms within individual patients that potentially signal a case of WE (ISS ADSL SAFFL=Y, n=632).
  - i. Examine narratives of patients with WE-PN terms that were SAE's
    - 1. Age, profile of AE's that may indicate more severe underlying illness
    - 2. Identify if clinical features are present in the narrative presentations that are supportive of a WE event
  - ii. Examine the overall profile of AE from patients in OL treatment that had a cluster of 3 or more WE-PN terms for features that are consistent with a WE event
    - 1. Relevant AE's in close temporal proximity on the study timeline
    - 2. TTO from study drug initiation
    - 3. Assess the patient's age and profile of AE's that may indicate more severe underlying illness
  - iii. There will also be a sampling of the overall AE profile from patients that had 2 WE-PN terms. However, this examination was limited by time constraints and included 7 of the 18 patients in this category, see [Table 10](#).
  - iv. Examine the frequency of WE-PN terms in the OL population
  - v. Examine the toxicity grade of WE-PN terms in the OL population for WE and PN terms
  - vi. Examine for evidence that the WE syndrome is reversible with thiamine treatment by examination of the frequency of WE-PN terms post thiamine treatment.
    - 1. All patients where fedratinib and thiamine treatment overlap in the ISS ADAE dataset will be identified.
- e. Determine if there are additional cases, derived from the WE-PN assessment of clustered terms in the ISS ADAE dataset, as characterized in "WE-TERM OPEN LABEL", in section d above.

- f. **Thiamine Depletion:** Examine the medical literature relevant to nonclinical evidence for interference in cellular thiamine economy as well as the characteristics of thiamine depletion in vulnerable populations (including oncology patients, intensive care unit, hyperemesis gravidarum, and the elderly) to inform the potential for thiamine depletion in the fedratinib treatment population.
- g. Evaluate for additional neurotoxicity
  - i. Examination of the frequency of adverse events and SAEs in the SOC “Nervous System Disorders” will be performed; although there is no comparison population, the EFC12153 PBO population is explored but n and exposure time are small.

#### Rationale for WE-PN Term Query

Wernicke’s encephalopathy and beriberi are caused by the same underlying deficiency of thiamine. Clinical terms relevant to Wernicke’s encephalopathy must capture preferred terms relevant to encephalopathy and peripheral neuropathy. Three MedDRA SMQ’s as well as 8 terms from a 4<sup>th</sup> SMQ were compiled to create a broad set of relevant terms to capture any terms in the controlled and open label adverse event datasets that could be associated with WE or beriberi peripheral nerve adverse events. The following SMQ’s were selected: Noninfectious encephalitis (SMQ), Noninfectious encephalopathy/delirium (SMQ), Peripheral neuropathy (SMQ) and 8 terms from the Ocular motility disorders (SMQ). These terms are Extraocular muscle disorder, Eye movement disorder, Gaze palsy, Ocular dysmetria, Oculogyric crisis, Ophthalmoplegia, Vestibular nystagmus, and Diplopia. This resulted in a composite query of 330 terms shown in [Appendix 1](#). This composite query will be identified as “WE-PN” throughout the document.

#### VII. Core WE Cases from the IND Development Interval and Presented in the NDA Package

Eight potential cases of WE were reported during the fedratinib IND. These reports were reviewed as part of three consults from DHP on 3/14/17, 7/20/17, and 10/3/17. The information available at that stage of review was more fragmented and less complete. The diagnostic conclusions of these 8 original WE reports are reassessed with the greater detail available from the NDA full clinical study datasets. The data sources used for the reassessment include the ISS ADaM ADAE, ADSL, ADVS, ADLB, and ADCM from the ISS Analysis Dataset Legacy in eCTD module 5.3.5.3. The ADAE dataset was utilized to identify and extract the study day of nutritional challenge events as well as the WE adverse events (including the CTCAE grade and whether the event was an SAE. The ADVS dataset was utilized to extract the BMI and body weight values through the study timeline. The ADLB dataset was used to examine those metrics useful for evaluation of nutritional status across the study timeline while the ADCM dataset was used to identify the initiation of thiamine treatment. As needed, these same dataset titles were examined in the individual ADaM study modules rather than in the pooled ISS data module. The individual WE patient narratives presented in the ISS were reviewed as well as the same patient narratives from the individual source study reports when necessary to check for greater granularity of content. One patient, 012181-(b) (6) is judged to have mental status change due to hepatic encephalopathy and will not be discussed further in the assessment of potential cases, see [Appendix 2, Core Case Master Table](#). The following analysis is directed at assessing the strength of the WE diagnosis in the 7 remaining Core WE Cases.

The ISS ADAE dataset is examined for WE-PN term entries from the 7 (remaining) potential cases of WE. Four of eight patients have terms captured by the WE-PN Query, see [Table 1](#).

*Table 1 WE-PN Terms Identified in the ISS ADAE Dataset from the Core WE Patients.*

CORE SUBJECT ID	preferred term
011936- (b) (6)	Memory impairment
011936- (b) (6)	Neuropathy peripheral
012153- (b) (6)	Paraesthesia
012153- (b) (6)	Encephalopathy
012181- (b) (6)	Encephalopathy

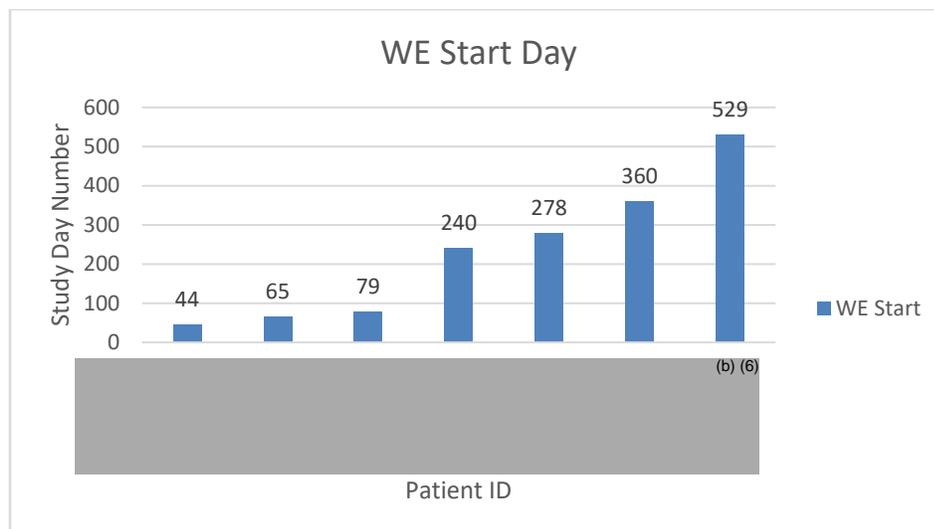
Reviewer Comment: The ADAE dataset captures relevant terms from 3 of 7 patients judged to have a positive diagnosis of WE. Diagnosis could not be established based on adverse event entries alone but required clinical narratives and MRI brain imaging. This informs the limitation of identifying WE based on the full OL dataset without additional information including clinical narratives.

The baseline medical history is captured for the 7 potential WE cases from the ADMH dataset of each individual clinical study. The purpose was to examine for terms consistent with pre-existing challenge to thiamine economy. Overall these data did not identify conditions that would clearly establish a thiamine depleted baseline state. These terms were confounded by medical history terms related to the underlying myelofibrosis.

**Time to Onset of WE**

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, see [Figure 2](#).

*Figure 2 Time to Onset of WE After the Start of fedratinib Treatment*



**Reviewer Comment:**

The TTO of WE among the adjudicated positive cases does not have a consistent temporal relationship to the start of fedratinib treatment. This feature of dispersed TTO is consistent with a complex

underlying mechanism. This observation does not support a simple binary causal phenomena where the offending agent, once introduced, causes a complete halt in core bioenergetic pathways and subsequent rapid development of WE. Rather, the observations support a multilayered process with dynamic interaction between layers and potential buffers in the interaction pathways. With this more complex model in mind, the dispersion of temporal relationship suggests fedratinib may introduce a partial interference or competitive block of thiamine function that could be, in part, dependent on underlying thiamine stores and dietary flux of thiamine.

### Nutritional Challenge

An objective marker of decrease in food intake is weight loss. Weight is captured from the ISS ADVS dataset to examine change from baseline weight in the time interval proximate to the diagnosis of WE. Weight loss entries will be considered related if they are entered within 21 days prior to the WE diagnosis start date or 21 days following the WE diagnosis date. This will capture weight that has been declining or is beginning to decline close to the identification of WE. The result of this approach reveals an entry for a negative percent change from baseline weight within a relevant timeframe for 4 of the 7 Core WE Cases. In one of the four cases the decline is a small 0.3 % from baseline, however this occurs on a downslope from a peak weight that occurred after baseline. The decline from this patient’s peak weight was 4.7 %. This may reflect a relevant deterioration in nutritional status. Alignment of percent weight change entries and WE diagnosis are presented in the Quantitative- Weight/ Nutritional Challenge/ MRI/ WE date/ Thiamine heading of [Appendix 2, Core Case Master Table](#).

### Baseline BMI, Weight Change, and Nutritional Status Parameters During fedratinib Treatment

To assess if a patient started fedratinib treatment in a nutritionally depleted state, a baseline BMI was calculated. Healthy BMI range is considered from 18.5 to 24.9. No baseline BMI was outside the healthy weight range. The minimum baseline BMI from among the 7 potential WE patients was 19.6. No patient was in an underweight range at baseline, [Table 2](#). None of the patients who are Core WE Cases appear to have started fedratinib treatment in a nutritionally depleted status.

*Table 2 Baseline BMI of 7 Core WE Cases*

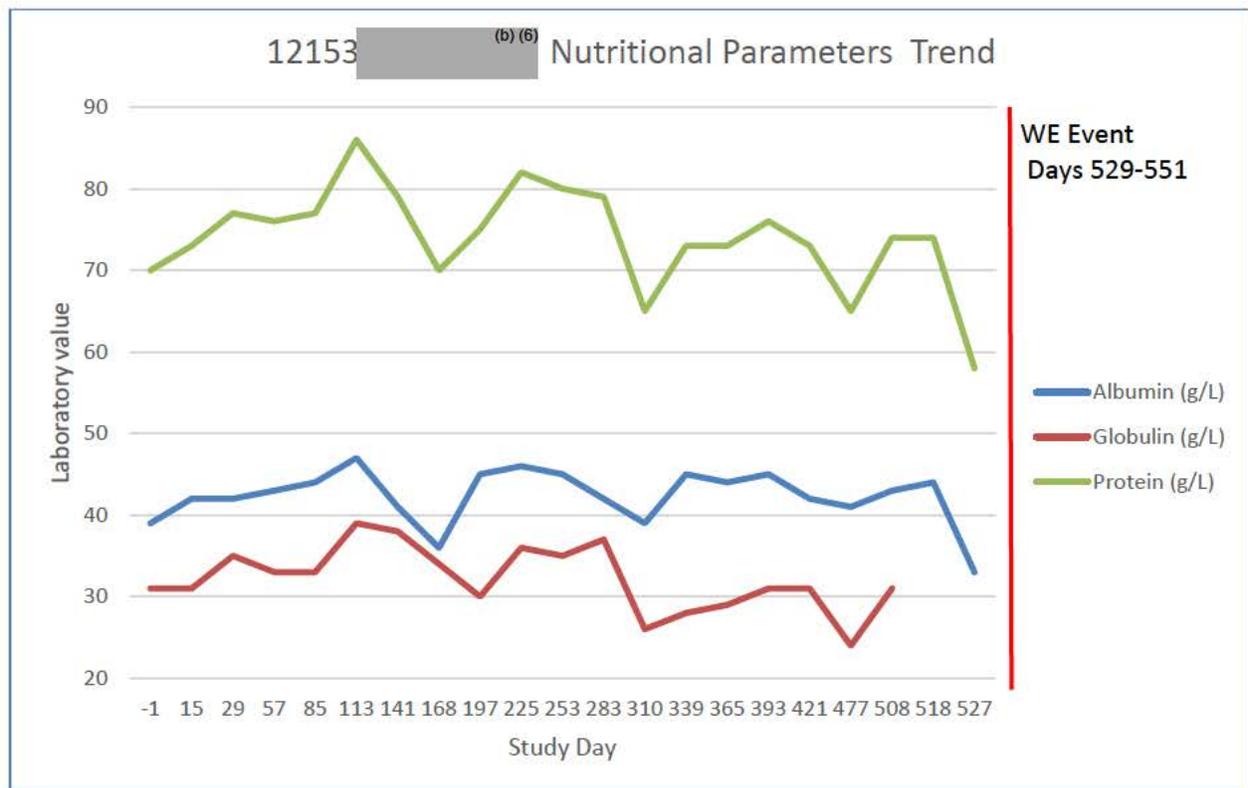
USUBJID	Baseline BMI
012153- (b) (6)	23.6
012153- (b) (6)	24.3
012153- (b) (6)	19.6
012153- (b) (6)	25.6
013519- (b) (6)	27.2
011936- (b) (6)	29.4
012042- (b) (6)	24.1

In addition to baseline BMI the patient weight by study day was examined for each Core WE case. This analysis reveals that patients 012153- (b) (6), 512153- (b) (6), 012153- (b) (6), 013519- (b) (6) and 012042- (b) (6) had a nutritional challenge present prior to the WE event, substantiated by a weight loss trend, see the graphic trends in [Appendix 3 Weights by Study Day, Core WE Cases](#). A possible nutritional challenge is identified in the trendline of patient 012153- (b) (6)

where there is a sustained weight gain from approximately study day 100 to 400. This is followed by a cluster of decreased weight values in the interval from day 400 to approximately study day 500. This shift in weight represents a negative change in nutritional status although it is uncertain if this of sufficient magnitude to account for the WE event. This situation, where a more modest, low magnitude nutritional challenge is identified, offers support for the possibility that fedratinib may cause an additional, independent but synergistic challenge, to the dynamic of thiamine economy. This hypothesis is considered in cases where nutritional challenge alone does not appear to account for the magnitude of depletion necessary for pathologic features of WE or peripheral neuropathy to emerge. Patient 012153- (b) (6) had an interval of weight loss and had just begun an upslope in weight trend when the WE event occurred. This is another event where there is a support for an independent contributory (synergistic) effect on thiamine depletion, pointing to a fedratinib contribution. In this case there is support for a nutritional challenge event; however, apparent recovery seen on an upslope in weight for about 3 months is seen, yet a WE event occurred. Patient 11936- (b) (6) had a WE event on a clear upslope of weight gain.

Serum albumin, globulin and protein are examined as (proxy) nutritional metrics across the timeline of fedratinib exposure for the core WE cases. Examination of nutritional parameter trend did not identify nutritional challenge in any case where weight loss was already supportive. Examination of the nutritional status trends reveals a notable decline only for patient 012153- (b) (6) who had a decline in serum albumin of 11g/L from day 518 to 527. This is informative because the same patient had only a modest decline from a peak body weight at the time of the WE event, see Figure 3 and Figure 5. This trend is consistent with a more substantive decline in nutritional status than is identified in the body weight trendline alone.

Figure 3 Patient 12153- (b) (6) Nutritional Metrics by Study Day



Reviewer Comment: when both the trend of body weight and the nutritional status metrics of albumin, globulin and serum protein are taken into consideration, 5 of the 7 Core WE Cases are associated with some evidence of nutritional challenge. From among the remaining cases, patient 12153- (b) (6) had a suspect nutritional challenge due to a weigh nadir 99 days prior to the WE event. However, the interval of increasing weigh, over the subsequent interval, greater than 3 months (following the nadir), should be adequate to repair nutritional deficit. Patient 11936- (b) (6) had a WE event on a sustained upslope of weight gain with no change in nutritional status metrics. These patients remain outliers where the relationship between the WE event, and nutritional challenge is least supported. This suggests a direct contribution from fedratinib.

### Nutritional Challenge Events

The ISS ADAE dataset is examined for nutritional challenge events and the alignment of these events with the occurrence of WE diagnosis. The relationship between the occurrence of nutritional challenge events and WE diagnosis is considered positive when they are entered within 30 days of the WE diagnosis day. Three patients from the Core WE Cases were seen to have temporal alignment of nausea and vomiting event and their diagnosis of WE. This alignment alone is not the sole determinant of nutritional challenge and does not exclude nutritional challenge as a medical issue for the remaining 4 patients. It is possible that not all challenge events were entered, and the absence of entries is not full assurance of sufficient nutritional maintenance. Change in appetite may cause decreased food intake but will only be captured if it rises to the threshold where the patient makes a report to the investigator.

Examination of the nutritional challenge preferred terms nausea and vomiting along with the CTCAE grade of the event is examined in [Table 3](#). A variable “Approximate Duration of Challenge prior to WE, is based on weight trend and/or nausea and vomiting events (days). In the table, 0 = none aligned with WE. This variable is created to assess the relationship of the duration of body weight trend and / or nutritional challenge events. There is alignment of N/V event seen for patient 012153- (b) (6) 012153- (b) (6) and 013519- (b) (6) see [Table 3](#) and full core case table in [Appendix 2, Core Case Master Table](#). When taking body weight trend into consideration along with N/V events, there is alignment of the WE event with nutritional challenge for patients 012153- (b) (6) and 012042- (b) (6) . No alignment is seen in either metric for patients 012153- (b) (6) and 011936- (b) (6) .

Table 3 Core WE Cases, Alignment of Nutritional Challenge Events with WE Event Date

	Nausea AESTDY	Vomiting AESTDY	Nausea Grade	Vomiting Grade	Weight % change from Baseline	WT Study day	Base BMI	Approximate Duration of Challenge prior to WE, based on weight trend and/or N/V events (days)	WE Event date	Wernicke Event Start day from AESTDY (this is the column heading)
012153- (b) (6)	1-44	1-44	2-3 not SAE	2-3 not SAE	-6.4, -7.9	29, 63	23.6	44		(b) (6)
012153- (b) (6)	169-196, 513-525	169-178, 513-525	2	2	+ 13.5 (change from peak day 339, - 3.4)	527	24.3	100		
012153- (b) (6)		1-18		3 SAE	-7.45	59	19.6	60		
012153- (b) (6)	174-176	174-176	1	1	-1.9, +1.56, +1.56	226, 273, 365	25.6	0		
012181- (b) (6) (hepatic encephalopathy)	2-14, 100-141, 185-201, 255-281	185-187	1-2	1	-1.8, -4.0	281, 304	26	N/A		
013519- (b) (6)	25-27	25-27, 65-71	1	1	-6.6	57	27.2	65		
011936- (b) (6)	15-28,	-1-28	1	1	+1.7, +4.4	253, 316	29.4	0		
012042- (b) (6)		391-410		3	-0.3 (change from peak day 169, - 4.7)	372	24.1	191		

MRI Findings (condensed version also included in Appendix 2, Core Case Master Table)

MRI images are presented in Attachment 9 of the Meeting Materials for the Type A meeting. This briefing package was submitted to IND 78286 on 3/17/17. These are small print images in the PDF document.

Patient 012153- (b) (6)

This patient had two MRI 's performed. The first was (b) (6) The FLAIR sequence reveals signal hyperintensity in the medial thalamus bilaterally, mamillary bodies, and periaqueductal gray matter. There is also some periventricular signal hyperintensity. The study is repeated on (b) (6) and reveals absence of the previously identified signal hyperintensity in the medial thalamus bilaterally, mamillary bodies, and periaqueductal gray matter. There is some periventricular signal hyperintensity remaining in the posterior lateral ventricles and deep occipital white matter. These findings are consistent with resolution of the WE lesions. The reviewer concludes the study of (b) (6) is positive for WE while the subsequent study of (b) (6) is negative.

Patient 012153- (b) (6)

An MRI is performed on (b) (6) this study reveals signal hyperintensities, on FLAIR sequence, in the mammillary bodies, periaqueductal gray matter and medial thalami. There was also abnormal signal in the putamen bilaterally that is of uncertain relationship to the diagnosis of WE. The reviewer concludes this study is positive for WE.

Patient 012153- (b) (6)

An MRI is performed on (b) (6) this study reveals signal hyperintensity, on FLAIR sequence, in the bilateral medial thalami, without signal changes in the periaqueductal gray matter or mammillary bodies. The reviewer concludes this study is possibly positive for WE.

Patient 012153- (b) (6)

An MRI was performed on (b) (6) (210 days following the WE event); there were no findings to suggest Wernicke's encephalopathy. The reviewer concludes this study is negative for WE.

Patient 012181- (b) (6)

An MRI was performed on (b) (6) there were no findings to suggest Wernicke's encephalopathy. The reviewer concludes this study is negative for WE.

Patient 013519- (b) (6)

An MRI was performed on (b) (6) and (b) (6) The 1<sup>st</sup> study, (b) (6) FLAIR image sequence had no findings of Wernicke's encephalopathy. There was a high signal lesion in the right anterior temporal lobe consistent with a history of past treatment of a brain metastatic lesion. The 2<sup>nd</sup> study on (b) (6) revealed signal hyperintensities in the medial thalamus bilaterally, mamillary bodies and periaqueductal gray matter on FLAIR sequence. These findings are consistent with development of WE over the 55-day interval from (b) (6) and (b) (6)

Patient 011936- (b) (6)

An MRI was performed on (b) (6) and (b) (6) The 1<sup>st</sup> study, (b) (6) revealed signal hyperintensity in the medial thalamus bilaterally, mamillary bodies and periaqueductal gray matter on FLAIR image sequence. The second study of (b) (6) revealed absence of the previously identified signal

hyperintensity in the medial thalamus bilaterally, mamillary bodies, and periaqueductal gray matter on FLAIR image sequence. The reviewer concludes the study of (b) (6) is positive for WE while the subsequent study of (b) (6) is negative for WE.

Patient 012042- (b) (6)

An MRI was performed on (b) (6) there were signal hyperintensities in the medial thalamus bilaterally, mamillary bodies and periaqueductal gray matter on FLAIR image sequence. These features are consistent with a diagnosis of WE. There were additional hyperintense lesions in the caudate nucleus and putamen bilaterally. The etiology of these lesions is uncertain, and it is not certain they are part of a thiamine deficiency state. The reviewer concludes the study is possibly positive for WE.

### Summary Review of Core WE Cases

An integrated assessment of the WE events is performed. The clinical and MRI features, alignment of nutritional challenge events with the WE start date, body weight trend, and the trend of nutritional status metrics are compiled to generate a conclusion whether or not the diagnosis is valid and the strength of the causal relationship between nutritional challenge, or markers of nutritional challenge to the WE diagnosis. Where evidence of nutritional challenge is weak or markedly out of alignment with the WE event date, an independent effect of fedratinib may be proposed. One potential WE case was adjudicated negative for a valid diagnosis of WE. This case, patient 012181- (b) (6) is best explained by hepatic encephalopathy. The remaining 7 cases are valid WE diagnoses. 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. This is most likely in patient 012153- (b) (6) where the basis for a nutritional challenge is speculative and patient 11936- (b) (6) where there is no objective support from the body weight trendline or nutritional status parameters. The summary assessment of all Core WE Cases is presented in [Table 4](#) with the complete table of variables of interest shown in [Appendix 2, Core Case Master Table](#).

Table 4 Core WE Cases, WE Diagnosis Summary Conclusion Table

USUBJID	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012181- (b) (6)	013519- (b) (6)	011936- (b) (6)	012042- (b) (6)
CONCLUSION, POSITIVE / NEGATIVE	POSITIVE, PLAUSIBLE NUTRITIONAL CHALLENGE	POSITIVE, POSSIBLE NUTRITIONAL CHALLENGE BUT DEVELOPMENT OF WE SUGGESTS POSSIBLE SYNERGY	POSITIVE, PLAUSIBLE CAUSE BY NUTRITIONAL CHALLENGE ALONE	POSITIVE, CLINICAL FEATURES HIGHLY SUPPORTIVE, THERE IS TENUOUS SUPPORT FOR A NUTRITIONAL CHALLENGE AS POSSIBLE CAUSE, THE WE EVENT OCCURED ON THE UPSLOPE TREND JUST AFTER WEIGHT NADIR. THIS SUPPORTS POSSIBLE SYNERGY WITH FEDRATINIB. MRI FOR DX DONE 210 DAYS AFTER WE EVENT WHILE THIAMINE WAS ADMINISTERED 218 DAYS AFTER THE WE EVENT	NEGATIVE, CLINICAL FEATURES VERY LOW SUPPORT- NARRATIVE "SLIGHHT FORGETFULNESS, HEPATIC DYSFUNCTION ONGOING, NUTRITIONAL CHALLENGE UNLIKELY, 100 DAYS AFTER WEIGHT NADIR WHILE WEIGHT ON UPSWING. ALTERNATE CONSIDERATION- HYPOTHETICAL ONLY, MRI ON DAY 296 MAY HAVE BEEN CONFOUNDED BY THIAMINE TREATMENT OR THE INTERVENTION WAS EARLY ENOUGH TO AVOID MORE THAN BRIEF CLINICAL SYMPTOMS AND ALSO AVOIDED STRUCTURAL BRAIN CHJANGE.	POSITIVE (fatal outcome). CLINICAL FEATURES STRONG SUPPORT. SEVERE NUTRITIONAL CHALLENGE. CONTINUOUS WEIGHT LOSS FROM START OF TREATMENT. DEVELOPED CLEAR MRI FEATURES OF WE OVER 55 DAYS. SEIZURE, COMA END EVENTS. SEVERE COURSE MAY INDICATE SYNERGY WITH NUTRITIONAL DEPLETION	POSITIVE, CLINICAL FEATURES STRONG SUPPORT. CONFOUNDED BY POSSIBLE STROKE, LAWNMOWER ACCIDENT AT 3 DAYS PRIOR TO (b) (6) HOSPITAL ADMISSION, HOWEVER MRI FINDING DFFINITE WE ON (b) (6). NO NUTRITIONAL CHALLENGE, EVENT FOLLOWING 179 DAYS OF INCREASING WEIGHT.. SUPPORT EFFECT OF FEDRATINIB EFFECT (WITH SPONTANEOUS RECOVERY- DIET. (PEAK WT APPROX DAY 380)	POSITIVE, MRI SUSPECT, CLINICAL FEATURES STRONG SUPPORT. NUTRITIONAL CHALLENGE SUSPECT, WEIGHT IN DOWNSLOPE, TEMPORALLY RELATED INTERVAL OF VOMITING GRADE 3. THIAMINE STARTED AFTER 2ND MRI AND NO CLINICAL DATA SUPPLIED UNTIL MARCH 2014 NOTING WE RESOLVED.

## Core WE Cases; Response to Thiamine

The ability to prevent or treat WE before permanent neural injury is a critical aspect that is necessary for the full consideration of the risk-benefit assessment of fedratinib. In three cases of a positive WE diagnosis, there is a clear temporal relationship between thiamine treatment and resolution of the WE event. This occurred in cases 012153- (b) (6) 012153- (b) (6) and 012153- (b) (6). The evidence for benefit of thiamine has strongest support in the profile of case 012153- (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, see [Appendix 2, Core Case Master Table](#).

In two cases (not part of the 3 reports noted in the previous paragraph), thiamine was administered after a retrospective diagnosis of WE. In case 012153- (b) (6) the report with the most tenuous support for nutritional challenge as a basis for WE, the thiamine was not administered until (b) (6) days after the diagnosis. There was a statement in the narrative that “the event of Wernicke’s encephalopathy was considered resolved with sequelae.” The second case with administration of thiamine after retrospective recognition of WE was patient 011936- (b) (6) who had a WE event day of 278 but thiamine was not administered until day 419. This patient is noted to have “stabilized and not recovered upon last contact”. In both cases that had such an extensive delay in thiamine administration, resolution of neurologic residua is not expected. In one report, patient 012042- (b) (6), there was a 36-day delay between diagnosis of WE and treatment with thiamine. In this case the patient is reported to have recovered. This appears to be a degree of spontaneous recovery, perhaps due to dietary thiamine, since a 36-day interval of critically low thiamine is not physiologically tolerable. Patient 013519- (b) (6) who had a fatal outcome following a nutritional challenge, did not have thiamine treatment before death.

In conclusion; there is a definitive positive response when thiamine is administered within 7 days of clinical onset based on the response of patients 012153- (b) (6) 012153- (b) (6) and 012153- (b) (6) see [Appendix 2, Core Case Master Table](#).

### VIII. WE-TERM CONTROLLED DATA

Study EFC12153 provides an interval, to treatment cycle 6, where there was approximately 168 days of placebo-controlled data. This interval is examined to assess if there is a differential frequency of WE-PN terms between the fedratinib treatment arms and placebo.<sup>1</sup> There were 24 entries captured by the WE-PN Query from 3 (3.2%), 8 (8.3%), and 8 (8.3%) patients from the PBO, 400mg and 500mg treatment arms respectively. The most frequently occurring terms were “neuropathy peripheral”, “hypoesthesia” and “tremor” occurring in the fedratinib treatment arms. There were 2 peripheral neuropathy terms and one encephalopathy term (dysphagia) in the PBO arm. In the 400mg treatment arm, there were 3 peripheral nerve term entries with 2 from hypoalgesia, and 1 each from neuralgia and polyneuropathy. There were terms from 4 patients in the WE (encephalopathy terms) term group including 2 entries for tremor, 1 from agitation, and 1 from disturbance of attention. In the 500mg arm, there were 4 entries from 5 patients from terms associated with peripheral neuropathy including “neuropathy peripheral”, “hypoesthesia”, “paraesthesia”, and “peripheral sensory neuropathy”. The remaining 5 preferred term entries in the 500mg arm were from the WE group of terms from 5 patients; these included 1 each for

<sup>1</sup> ECF12153 ADaM ADAE to cycle 6, TE, SF, no post crossover.

the term “tremor”, “dysphagia”, “encephalopathy”, “lethargy”, and “somnolence”. There was 1 SAE among all entries. This occurred with the term “encephalopathy” in the 500mg treatment arm, see [Table 5](#).

*Table 5 Study ECF12153 PBO Control Interval to End of Cycle 6.<sup>2</sup> WE-PN Terms by n Patients and Treatment Arm*

Preferred term	PBO		400mg		500mg	
	N unique patients	%	N unique patients	%	N unique patients	%
Dysphagia	1	1.05	0	0	1	1.03
Muscular weakness	1	1.05	0	0	0	0.00
Paraesthesia	1	1.05	0	0	1	1.03
Agitation	0	0	1	1.04	0	0.00
Disturbance in attention	0	0	1	1.04	0	0.00
Hypoaesthesia	0	0	2	2.08	1	1.03
Neuralgia	0	0	1	1.04	0	0.00
Polyneuropathy	0	0	1	1.04	0	0.00
Tremor	0	0	2	2.08	1	1.03
Encephalopathy	0	0	0	0	1	1.03
Lethargy	0	0	0	0	1	1.03
Neuropathy peripheral	0	0	0	0	2	2.06
Peripheral sensory neuropathy	0	0	0	0	1	1.03
Somnolence	0	0	0	0	1	1.03

There is a notably greater proportion of WE-PN terms in the fedratinib treatment arms although there is not a clear dose relationship; however, the fact that the 400 mg and 500 mg doses are similar may obscure any such relationship. It is unclear if the shift toward WE-PN terms in fedratinib treatment is a direct effect of fedratinib treatment or a secondary effect of gastrointestinal intolerance and nutritional challenge, and associated thiamine depletion. The same dataset is examined to determine if there is a disproportional frequency of these nutritional challenge terms in the fedratinib treatment arm. This analysis reveals a marked differentiation in frequency of the nutritional challenge terms between PBO and fedratinib treatment. Total nutritional challenge preferred term frequency was 24, 151, and 179 entries from the PBO, 400mg, and 500mg treatment arms respectively. The proportion of unique patients with nutritional challenge terms was 16.8%, 71%, and 72% from the PBO, 400mg, and 500mg treatment arm. The distribution for individual terms may be seen in [Table 6](#). Only one patient in the 500mg treatment arm, associated with the preferred term “vomiting”, had an SAE.

*Table 6 Study ECF12153 PBO Control Interval to End of Cycle 6. Nutritional challenge terms Nausea, Vomiting, Weight Decreased and Malnutrition by n Patients and Treatment Arm*

PT	PBO		400mg		500mg	
	n	%	n	%	n	%
Nausea	14	14.7	59	61.5	47	48.5
Vomiting	5	5.3	37	38.5	52	53.6
Weight decreased	3	3.2	4	4.2	9	9.3

<sup>2</sup> to cycle 6, TE, SF, no post crossover

	PBO		400mg		500mg	
PT	n	%	n	%	n	%
Malnutrition		0.0	1	1.0		0.0

Reviewer Comment: WE is caused by a deficiency of thiamine or, potentially, interference with thiamine function. Thiamine depletion may be caused by insufficient dietary intake. Reduced dietary intake may, in turn, be caused by the gastrointestinal intolerance induced by fedratinib. Finally, and a core consideration in the assessment of the relationship between fedratinib and WE, is whether the adverse effect of WE-PN is driven exclusively by nutritional challenge events that are associated with the preferred terms nausea, vomiting, and appetite decreased. The controlled dataset is examined to assess the difference in nutritional challenge entries between the placebo and fedratinib treatment arms. The above analyses reveal the predominance of WE-PN adverse effect terms. These are present with a higher frequency in the fedratinib treatment arms. In parallel with that disproportion is an even greater differential frequency of the terms nausea and vomiting in the fedratinib treatment arms. This association supports the hypothesis that the appearance of WE terms, if driven by thiamine depletion, is due to nutritional challenge of the gastrointestinal intolerance effects of fedratinib.

#### IX. WE-PN Terms in the Open Label ISS Dataset

The open label ISS ADaM ADAE dataset is examined. This dataset includes the open label data from studies ARD11936, ARD12042, ARD12181, ARD12888, EFC12153, INT12497, TED12037, TES13519 for the frequency of WE-PN terms and clusters of these terms within individual patients that potentially signals a case of WE.<sup>3</sup> The goal of this analysis is to identify patients with a cluster of WE-PN terms that may together indicate a case of WE. This analysis was divided into two parts. In the first part terms related only to WE (non-peripheral nerve AEs) were captured to allow an independent assessment of terms related primarily to central nervous system adverse effects. In the second part, the ISS ADAE dataset will be examined for the occurrence of all WE-PN terms that may be associated with a broader thiamine deficiency profile (WE & beriberi)

#### Analysis 1, WE Terms (encephalopathy related)

This analysis identified 18 patients with entries for 2 or more of the terms of interest, [Table 7](#). One patient had 4 associated preferred terms, these were lethargy, somnolence, memory impairment and Irritability. Two patients had entries for WE preferred terms. The first of these patients had entries for hallucination, delirium and amnesia while the second patient had entries for mental status changes, delirium and confusional state. The remaining 15 patients had entries for 2 preferred terms of interest. Because the goal of the analysis is to determine if a case of WE has been captured, it is necessary to obtain as much clinical information as possible. Those patients with a term entered as an SAE provide the opportunity to review a narrative report. There were 4 patients in this analysis that fulfilled this condition, see [Table 8](#). From among the 4 patients with an SAE entry 1 patient (012037-<sup>(b) (6)</sup>) had no narrative present. To assess the likelihood of WE in this patient, all AE terms entered for the patient are identified in addition to the study day of occurrence. This assessment revealed a very severe underlying illness and prolonged TTO for the AE of "mental status change". These features reduce the support for a WE event for patient 012037-<sup>(b) (6)</sup>. From among the remaining 3 patients, there were none with a

<sup>3</sup> ANLCAT = OL, SAFFL = Y, TR01AG2= Safety - Pool 2= 450 - < 550 mg, 300 - < 450 mg, >= 550 mg, <300mg. n = 6902

profile of clinical features consistent with WE. In patient 011936- (b) (6) the collection of encephalopathic terms was likely due to underlying dementia. In the second, patient 012181- (b) (6), the terms were due to an underlying infectious process that was causal for a delirium and in the third patient, 013519- (b) (6) the cluster of WE terms all occurred on day 5 of treatment and were likely due to severity of underlying illness.

Table 7 WE Terms Capture from the ISS OL Dataset.<sup>4</sup> Shaded Rows Represent a Preferred Term Entered as An SAE is Present.

USUBJID	Term 1	Term 2	Term 3	Term 4	Total terms	WE potential
011936 (b) (6)	Lethargy	Somnolence	Memory impairment	Irritability	4	
011936 (b) (6)	Hallucination	Delirium	Amnesia		3	no
012037	Mental status changes	Delirium	Confusional state		3	no
011936 (b) (6)	Memory impairment	Agitation			2	
011936 (b) (6)	Hallucination	Confusional state			2	
011936 (b) (6)	Somnolence	Encephalopathy			2	
012037	Dysphagia	Tremor			2	
012037	Tremor	Dysarthria			2	
012037	Gait disturbance	Tremor			2	
012037	Somnolence	Confusional state			2	
012037	Confusional state	Agitation			2	
012037	Tremor	Somnolence			2	
012042 (b) (6)	Memory impairment	Disturbance in attention			2	
012042 (b) (6)	Irritability	Dysphagia			2	
012042 (b) (6)	Tremor	Memory impairment			2	
012153 (b) (6)	Dysphagia	Memory impairment			2	
012181 (b) (6)	Confusional state	Cognitive disorder			2	no
013519 (b) (6)	Mental status changes	Lethargy			2	
013519 (b) (6)	Dysphagia	Altered state of consciousness			2	no

<sup>4</sup> ANLCAT = OL, SAFFL = Y, TR01AG2= Safety - Pool 2= 450 - < 550 mg, 300 - < 450 mg, >= 550 mg, <300mg. n = 6902

Table 8 Assessment of WE Diagnostic Potential for Patients in Table 7 with an SAE Term

USUBJID with SAE	comment
011936- (b) (6)	58 yo MRI marked ventricular enlargement, volume loss. Delirium and subsequent worsening associated with febrile event, hypotension. Mental status did not recover. Underlying dementia, possible NPH
012037- (b) (6)	no narrative present, 76 yo Male, the AE events were examined. Mental status change and delirium occurred on days 924 and 833 respectively. There are entries for lung infection on day 868 and "pneumonia fungal " on day 869. There were a total of 60 adverse event entries from 58 preferred terms over 924 days where 6 were SAEs and two of the SAEs were within 60 days of the mental status change. The severity of underlying and prolonged TTO for "mental status change" reduces the likelihood this is a WE event.
012181- (b) (6)	74 yo M, encephalopathic events 38 days on study day 533 days (at least 16 cycles) after final dose, grade 1, occurred with concurrent identification of abdominal abscesses. Events resolved after abscess drainage.
013519- (b) (6)	58yo F, mental status change reported pre-treatment. Events occurred on day 5 of study drug treatment. Patient had disease progression with fatal outcome on day 42. Delirium due to underlying illness

**Reviewer Comment:** Patients with 2 or more WE query term entries are captured. There was a total of 18 patients that fulfilled this criterion. Three patients had greater than 2 terms. Those with an SAE where a full narrative could be explored were assessed further. None of these, including two patients with three associated WE entries, had narrative clinical data that were consistent with a diagnosis of WE. In those patients where one of the WE-PN terms was entered as an SAE, there were plausible non-WE etiologies to explain the WE-PN terms in each case (n=4).

#### Analysis 2, WE-PN Terms (encephalopathy and peripheral nervous system terms)

Part 2 of the analysis of multiple term clusters is performed. In this second part, patients are captured from the ISS dataset<sup>5</sup> with 2 or more WE-PN terms (this method included the "peripheral neuropathy" SMQ). There were 30 patients identified with 2 or more WE-PN term entries. This method also captured all patients from analysis number 1.

The analysis revealed that one patient had 5 term entries and an additional 11 patients had three term entries. The remaining patients had 2 WE-PN term entries each. The gain of 12 patients in this analysis is due to the addition of peripheral-neuropathy-related preferred terms of interest. No additional SAEs were identified by addition of the peripheral-neuropathy terms. The 4 patients with an SAE identified in this analysis of WE-PN terms are duplicates to those identified in WE term query (without inclusion of the peripheral neuropathy SMQ). In order to evaluate the potential for a WE diagnosis among the remaining 26 patients (non-SAE narratives), the method is to examine the full array of AE entries for each patient ID using the ISS ADAE dataset (SAFFL = Y). Seventeen of the 26 patients are sampled and examined with the aforementioned method. A conclusion of WE or WE-like potential diagnosis is formulated. From among these 17 patients all but 2 had evidence of low WE potential diagnosis. One patient, 012037- (b) (6) had a value of "possible" entered. The possibility of WE was supported by nutritional challenge identified. There were multiple entries for event of nausea. The positive WE-PN events were not clustered in close temporal relationship on the timeline; rather, they were dispersed in time. This observation reduces the conclusion to "possible". A second patient, 011936- (b) (6) was designated as a "possible" thiamine deficiency syndrome, possibly dry beriberi due to the peripheral neuropathic entries. The possibility is supported by the occurrences of vomiting and asthenia which may

<sup>5</sup> ibid

be a backdrop for thiamine deficiency. The full compilation of adverse events and study day occurrence with resulting conclusion may be seen in [Table 9](#) and [Table 10](#).

WE-PN events occur in association with fedratinib treatment. These may be due to an alteration of thiamine economy. However, without objective measurement of thiamine levels, the diagnosis is speculative. Overall, where patients have WE-PN terms of increased frequency, the events do not tend to be entered in close temporal relationship, and frequently there are nearby entries on the study timeline for nutritional challenge events. This confounds judgment on the causal relationship between drug and the WE-PN adverse events. Therefore, the WE-PN events, overall, do not appear to be an independent, direct effect of the fedratinib. A synergy between nutritional challenge and fedratinib treatment, acting together on thiamine economy, cannot be excluded. This is a difficult signal to detect with clarity due to the background noise of common nutritional challenge (N/V- decreased appetite, nausea, vomiting, asthenia) as well as the severe underlying physiologic stress associated with the myelofibrosis disorders.

Table 9 Patients with 2 or more WE-PN Adverse Event Terms from ISS Dataset (SAFFL= Y). AE Terms and Conclusion on “WE Potential Diagnosis” (n=30)\*

USUBJID	term 1	term 2	term 3	term 4	term 5	total terms	WE / WE-like Potential diagnosis	
011936-	(b) (6)	Lethargy	Paraesthesia	Irritability	Memory impairment	Somnolence	5	low
011936-		Neuropathy peripheral	Paraesthesia	Confusional state			3	low
011936-		Hallucination	Amnesia	Delirium			3	
012037-		Confusional state	Delirium	Mental status changes			3	
012037-		Ataxia	Muscular weakness	Paraesthesia			3	low
012037-		Dysarthria	Facial paralysis	Tremor			3	low
012037-		Peripheral sensory neuropathy	Burning sensation	Cognitive disorder			3	low
012037-		Confusional state	Agitation	Neuropathy peripheral			3	possible
012037-		Tremor	Paraesthesia	Somnolence			3	low
012042-		Hypoaesthesia	Dysphagia	Irritability			3	low
012042-		Peripheral sensory neuropathy	Memory impairment	Tremor			3	low
012497-		Neuropathy peripheral	Peripheral motor neuropathy	Peripheral sensory neuropathy			3	low
011936-		Hypoaesthesia	Paraesthesia				2	low
011936-		Agitation	Memory impairment				2	low
011936-		Confusional state	Hallucination				2	low
011936-		Paraesthesia	Hypoaesthesia				2	WE-like, beriberi feature?
011936-		Memory impairment	Neuropathy peripheral				2	WE
011936-		Peripheral sensory neuropathy	Tremor				2	low
011936-		Encephalopathy	Somnolence				2	none
012037-		Dysphagia	Tremor				2	Not done
012037-		Gait disturbance	Tremor				2	Not done
012037-		Confusional state	Somnolence				2	Not done
012042-		Disturbance in attention	Memory impairment				2	Not done
012042-		Confusional state	Peripheral sensory neuropathy				2	Not done
012153-		Paraesthesia	Sensory disturbance				2	Not done

USUBJID		term 1	term 2	term 3	term 4	term 5	total terms	WE / WE-like Potential diagnosis
012153	(b) (6)	Dysphagia	Memory impairment				2	Not done
012153		Muscular weakness	Peripheral sensory neuropathy				2	Not done
012181		Cognitive disorder	Confusional state				2	Not done
013519		Lethargy	Mental status changes				2	Not done
013519		Altered state of consciousness	Dysphagia				2	Not done

\*shaded cells are an SAE

Table 10 Narrative Compilation of Adverse Events Along Study Timeline, Companion to Table 9.

USUBJID	Patient Profile
011936	(b) (6) 44 yo, 70 AE's from 48 PTs. The events of lethargy and paraesthesia occur early on the timeline at days 34 and 53 while memory impairment and irritability occurred at days 206 and 225, these latter 2 are grade 1 events. There are no entries for Ps that reflect depletion prior to the memory impairment event butt asthenia is entered at 3 months after memory impairment..
011936	64 yo M, with 41 AE entries from 24 preferred terms. The terms paraesthesia and neuropathy peripheral are entered as early as day 21. Paraesthesia ,neuropathy peripheral are again entered at days 113 and 170 respectively. Confusional state is not entered until day 589 concurrent with entries for pneumonia and sepsis. The confusional state is likely associated with infection while the neuropathic features are entered early in timeline, unlikely due to a thiamine depletion with chronicity.
011936	58 yo MRI marked ventricular enlargement, volume loss. Delirium and subsequent worsening associated with febrile event, hypotension. Mental status did not recover. Underlying dementia, possible NPH
012037	no narrative present, 76 yo Male, the AE events were examined. Mental status change and delirium occurred on days 924 and 833 respectively. There are entries for lung infection on day 868 and "pneumonia fungal " on day 869. There were a total of 60 adverse event entries from 58 preferred terms over 924 days where 6 were SAEs and two of the SAEs were within 60 days of the mental status change. The severity of underlying and prolonged TTO for "mental status change" reduces the likelihood this is a WE event.
012037	55 yo m, 47 AE entries from 35 preferred terms. This patient has no definite CNS / cognitive preferred term entry. Ataxia may be due to peripheral neuropathy. The first entries for Ataxia and paraesthesia occur at day 14. Ataxia reoccurs at day 203 and muscular weakness is entered at day 476. All events are grade 1 except the first Ataxia entry which is grade 2. The early entries for ataxia and paraesthesia are unlikely due to thiamine depletion by day 14 where peripheral neuropathic features are from chronic insufficiency.
012037	73 yo F with 26 AE entries from 23 preferred terms. The terms dysarthria , facial paralysis and tremor are all entered on study day 12. There are no concurrent CNS / cognitive dysfunction terms. Although captured by the encephalitis - peripheral neuropathy SMQ's they are non-specific. Pyrexia also occurs on day 12 and may represent an infection. This profile is not supportive of the cognitive or peripheral nervous system features of thiamine deficiency
012037	50 yo female, with 60 AE entries from 355 preferred terms. The AE burning sensation is entered at day 33, peripheral sensory neuropathy at day 57 and cognitive disorder at day 393. These are separated widely along the timeline. They are all grade 1 entries. diarrhea, nausea, decreased appetite and vomiting are entered early on the timeline at days 1 and 7 with later episodes of nausea and vomiting. The dispersion of events along the 1668 day exposure timeline do not point to a coherent underlying thiamine depletion physiology while the events of nausea and vomiting do support such a possibility.
012037	85 yo F with 76 AE entries from 40 preferred terms. There are 4 entries of confusional state at days 39, 244, 334, and 345 with an entry for agitation at day 96, Peripheral neuropathy is entered at day 338. There are multiple entries for gastrotoxic events of nausea, vomiting and diarrhoea in addition to multiple entries for signs of nutritional depletion that include decreased appetite, asthenia and dehydration. There are entries for Nausea and vomiting on study days 1 and 2 with diarrhoea at days 40 and 42. Dehydration, nausea, vomiting and diarrhoea are entered on day 87 , with vomiting and nausea as grade 2 events. Diarrhea and vomiting are entered on days 114 and

USUBJID	Patient Profile
	1244 as grade 1 events Decreased appetite appears again at day 226. Asthenia is first entered at day 334. Overall the recurrence of nutritional challenge terms with grade 1,2 and 3 events may result in thiamine depletion as a basis for the WE-PN terms.
012037-	(b) (6) 68 yo F with 90 AE entries from 56 preferred terms. Tremor occurs at days 22, 43 and 57. Paraesthesia and somnolence are entered at days 110 and 505. The dispersion along the timeline, and spectrum of terms are not supportive of thiamine deficiency features.
012042-	48 yo f with 46 AE entries from 29 preferred terms. The patient has an entry of hypoesthesia on study day 1 Irritability is entered on day 74 and dysphagia on day 411. This cluster of terms and associated timeline does not support a diagnosis of thiamine depletion effect.
012042-	59 yo m has 21 AE entries from 15 preferred terms. Memory impairment is entered on day 7 and tremor on day 15. There are two peripheral sensory neuropathy entries on days 253 and 672. Weight decrease is noted on day 561 while nausea and vomiting entries are present at days 141, 138. The memory impairment entry appears too early to be due to thiamine depletion while the peripheral neuropathy entries that occur are later in the timeline and following vomiting entries. Thiamine depletion on a chronic basis could be occurring and account for the peripheral neuropathy features. This isolated grade 1 memory impairment as a standalone event early in the timeline is unlikely a CNS effect of thiamine depletion or blockade.
012497-	51 yo m with 18 AE entries from 15 preferred terms. This patient has a short study timeline of 58 days. All AE terms of concern are peripheral neuropathy terms. These are entered at days 51 and 58. There is an entry for weight decreased on day 15, nausea on day 17 and weight decreased on day 58. The depletion terms raise the possibility of a thiamine depletion cause of peripheral neuropathic features. The neuropathic events are all grade 2 severity. Overall the data is too limited for conclusions of causality.
011936-	36 yo F with 38 AE entries from 27 preferred terms. There are entries of Paraesthesia and hypoesthesia on study days 123 and 170 respectively. There are entries of diarrhoea, dehydration, and vomiting on days 31, 58 and 120 respectively. The vomiting is a grade 3 toxicity entry. The preceding nutritional challenge events could contribute to thiamine deficiency. It is unclear why peripheral nervous system events would occur without some temporally related encephalopathy terms along the study timeline.
011936-	77 yo m with 55 AE entries from 28 preferred terms. Agitation is entered on day 138 and memory impairment on day 255. There are grade 1 events of nausea, vomiting and diarrhoea preceding the encephalopathy terms on days 56 and 86.
011936-	63 Yo m with 51 AE entries from 41 preferred terms. Confusion state occurred on study day 367 and hallucination on day 370. These events are preceded on the timeline by an entry fo leukocytosis Grade 4 , day 363, dyspnoea grade 3 day 363, hypoxia, grade 2 day 363. These background events suggest a significant infection and or respiratory compromise within a week of the mental status change events. The two WE term entries are confounded by indicators of concurrent medial illness.
011936-	55 yo m, with 48 AE entries from 30 preferred terms. The PN terms of interest occur at study day 32 , 255 and 668 entered as Paraesthesia, hypoesthesia and paraesthesia respectively. There are no WE terms. There are entries of Vomiting on study day 2 with an end date of 255 while additional entries for vomiting are present on study day 40 and 73. Asthenia is entered on study day 225. Peripheral edema is also entered on study day 32. The persistence and recurrence of vomiting entries as well as the entry of asthenia are a substrate for thiamine deficiency. The potential for a causal relationship between the peripheral neuropathic features and nutritional challenge is possible.
011936-	70 yo f with 33 entries from 18 preferred terms. Patient is one of the core WE cases
011936-	70 yo m with 28 AE entries from 23 preferred terms. The entries for tremor and peripheral sensory neuropathy occurred at study days 29 and 140 respectively. The events are both entered as CTCAE grade 1. The low grade and lack of temporal coupling reduces the likelihood that a unifying nervous system disease is present. There is evidence of persistent nutritional challenge as nausea from study day 15 to 56 and vomiting from study day 15 to 29. This may be a backdrop for thiamine depletion, however a causal relationship to the peripheral sensory neuropathy, as a possible dry beriberi sign is speculative.
011936-	40 yo f with 17 AE entries from 17 preferred terms. The entries for both somnolence and encephalopathy occur on day 85. There is a concurrent elevation of ALT to 43 x ULN and bilirubin to 6 x ULN both from normal baseline. There is an entry for hepatic failure also on day 85. These WE terms are due to hepatic failure
012037-	
012037-	
012037-	
012042-	
012042-	
012153-	
012153-	
012153-	
012181-	74 yo M, with 15 entries from 12 preferred terms. Evaluated fully in WE terms, had change in mental status due to abdominal abscess that resolved. The events occurred late on day 533 but were serious but graded at toxicity grade 1

USUBJID	Patient Profile
013519	(b) (6)
013519	58yo F, mental status change reported pre-treatment. Events occurred on day 5 of study drug treatment. Patient had disease progression with fatal outcome on day 42. Delirium due to underlying illness
*shaded cells are an SAE	

## Individual Frequency of WE (encephalopathy) and PN (peripheral nerve) Terms

Examination of the ISS ADAE dataset reveals there were 117 (18.5%) unique patients with WE-PN terms. When the terms are examined separately there was a higher frequency of PN terms than WE terms. There were 69 (10.9%) patients with PN terms and 60 (9.5%) patients with WE terms (including patients in contributing to both groups), [Table 11](#) . When the sets of WE and PN patients are examined separately, it is found that only 12 (1.9%) patients contribute adverse events to both the WE and PN adverse event datasets. This analysis reveals that the two sets of patients are mostly distinct where 48 (7.6%) patients have WE adverse event entries only and 57 (9.0%) patients have PN adverse events only, [Table 11](#).

*Table 11 ISS ADAE Dataset, Frequency of WE-PE Query terms Into Encephalopathy and Peripheral Nervous System Subsets.*

ISS ADSL Safety flag = 632	%	Denominator = 632
there were 117 unique patients with WE-PN terms	18.5	
<b>total pts with PN terms</b>	%	
69	10.9	
<b>Total pts with WE terms</b>		
60	9.5	
129	20.4	
<b>Patients with Entries in both WE and PN groups</b>		
12	1.9	
PN only		
57	9	
WE only		
48	7.6	
<b>Percent of patient contributing to Both PN &amp; WE (overlap n=12)</b>	10.3	Denominator = 117

Reviewer Comment: The separation of the subsets of patients who have WE and PN adverse entries suggests that these are distinct groups where the underlying driver of the adverse event may be a distinct rather than common disorder. Alternatively, if the underlying driver of the WE-PN constellation of AE's is thiamine deficiency, the separation of the two populations may be due to appearance at different stages of thiamine deficiency (either severity or duration of chronicity) and which separates the populations.

### Other Neurotoxicity

The consultation request poses the question of whether any data suggest an increased risk of other neurotoxicity with fedratinib. This question will be approached with an examination of the frequency of preferred terms contained in the "Nervous system disorders" SOC within the ISS ADAE dataset. This exam reveals a profile of preferred terms that is similar to the profile that is captured by the WE-PN composite query. These are terms consistent with CNS dysfunction as see in WE, including somnolence, memory impairment, amnesia, cognitive disorder, encephalopathy, and Wernicke's encephalopathy. In addition, there are terms associated with the MedDRA peripheral neuropathy SMQ, including paraesthesia, peripheral sensory neuropathy, hypoesthesia, and neuropathy peripheral. The terms from the peripheral neuropathy SMQ occur with a higher frequency than terms associated with CNS

dysfunction. The most frequent CNS dysfunction terms are lethargy and somnolence with a frequency of 1.3% for each. The least frequent peripheral neuropathy term is “neuropathy peripheral” with a frequency of 2.4%. The most common event from the “nervous system disorders” SOC are headache and dizziness with a frequency of 13.3 and 12.7 respectively. The distribution of nervous system disorder preferred terms is shown in [Table 12](#).

*Table 12 ISS ADAE<sup>6</sup>, Frequency and Proportion of TEAE*

<b>Preferred Term</b>	<b># patients</b>	<b>%</b>
Headache	84	13.3
Dizziness	80	12.7
Dysgeusia	27	4.3
Paraesthesia	20	3.2
Peripheral sensory neuropathy	20	3.2
Hypoaesthesia	15	2.4
Neuropathy peripheral	15	2.4
Tremor	15	2.4
Lethargy	8	1.3
Somnolence	8	1.3
Memory impairment	7	1.1
Sciatica	7	1.1
Wernicke's encephalopathy	6	0.9
Syncope	5	0.8
Amnesia	4	0.6
Hypogeusia	4	0.6
Sensory disturbance	4	0.6
Ataxia	3	0.5
Carpal tunnel syndrome	3	0.5
Cognitive disorder	3	0.5
Dizziness postural	3	0.5
Encephalopathy	3	0.5
Head discomfort	3	0.5
Migraine	3	0.5
Muscle contractions involuntary	3	0.5
Presyncope	3	0.5
Restless legs syndrome	3	0.5

A similar analysis of the ISS ADAE dataset is performed to capture any preferred terms from the “nervous system disorders” SODC that are entered as an SAE. This is done to assess the profile of terms associated with SAEs. This will provide an index of the severity of terms that are identified. There is a

<sup>6</sup> ISS ADAE dataset, SAFFL =Y, Denominator n=632, derived from ISS ADSL, SAFFL= Y

total of 33 SAEs from 30 (4.8%) patients in the ISS dataset. The most frequency SAE is Wernicke’s encephalopathy”. Six patients (all included in the core WE cases) experienced this SAE with a proportion of 0.95%. Headache occurred in three (0.47%) patients. There were several other terms associated with CNS dysfunction that had a maximum frequency of 0.32%. There were no peripheral neuropathy SMQ terms entered as an SAE. The distribution of SAE preferred terms is shown in [Table 13](#).

*Table 13 ISS ADAE,<sup>7</sup> Frequency and Proportion of TEAE*

Preferred Term	N Patients	% Patients
Wernicke's encephalopathy	6	0.95
Headache	3	0.47
Cerebrovascular accident	2	0.32
Dizziness	2	0.32
Encephalopathy	2	0.32
Haemorrhage intracranial	2	0.32
Syncope	2	0.32
Altered state of consciousness	1	0.16
Cerebral ischaemia	1	0.16
Cognitive disorder	1	0.16
Dementia Alzheimer's type	1	0.16
Embolic stroke	1	0.16
Epilepsy	1	0.16
Haemorrhagic stroke	1	0.16
Hydrocephalus	1	0.16
Hypoglycaemic coma	1	0.16
Migraine	1	0.16
Post herpetic neuralgia	1	0.16
Seizure	1	0.16
Somnolence	1	0.16
Transient ischaemic attack	1	0.16
Total	30	4.8

Reviewer Comment: Overall, the analysis of nervous system disorder preferred terms, both TEAE’s and SAE’s does not identify a neurotoxicity signal that is distinct from the encephalopathy and peripheral neuropathy signals already captured by the WE-PN query.

#### ISS ADAE Dataset; Response to Thiamine Treatment

A core mission of the consultation is to determine if the WE events are responsive to treatment. In the analysis of the core WE cases, it was possible, in three instances, to assess response to thiamine within a maximum of 8 days after initiation of thiamine treatment. In the ISS data, there is a subset of patients who continued fedratinib for an interval after thiamine treatment was started. This overlap is generally short because studies were discontinued shortly after thiamine was started. The strategy in this case was to examine the subset of patients in the ISS ADAE dataset where dates could be identified for

<sup>7</sup> Ibid

thiamine start date that preceded fedratinib end date. This interval was examined for the frequency of WE-PN terms.

There were 118 patients identified with fedratinib and thiamine treatment overlap of 1 day or greater. There were three patients with long overlap intervals without explanation for the extended thiamine treatment period. The reason may have been thiamine was an incidental concomitant medication, however in the calculation of the fedratinib exposure during this interval these patients are excluded. From among the remaining 115 patients the maximum exposure duration was 19 days with a mean and median of 4.2 and 4.0 days respectively.

From within this exposure interval for all patients with 1 day or greater of fedratinib – thiamine overlap, analysis of the ADAE dataset reveals 110 entries from 50 patients. From among these entries, there were 4 adverse events from 3 patients captured by the WE-PN query terms. One patient, 12181- (b) (6), was an original core WE case presented in [Appendix 2, Core Case Master Table](#). The second, patient, 012181- (b) (6) had two terms that were captured in the assessment of WE-PN terms analysis part 2 above and were secondary to systemic infection. The final, third patient, 012042- (b) (6), had peripheral neuropathy but was captured in the assessment of WE-PN terms analysis part 2 above and found to have low potential WE. There were two adverse event “peripheral sensory neuropathy” entries on study days 253 and 672. The study day 672 entry was captured in this fedratinib – thiamine overlap analysis. In the context of the chronic nutritional challenges and earlier entries for WE terms and a “peripheral sensory neuropathy” entry, it is possible this final neuropathy entry was due to a thiamine insufficiency syndrome; however, the patient was only on thiamine treatment for three days at the time of this final AE entry. The duration of treatment would be too short to expect resolution of the peripheral nerve disorder.

Reviewer Comment: In the short fedratinib – thiamine treatment overlap interval, there are 3 patients with WE-PN term entries. Two of the three entries were unrelated to possible WE diagnosis. In the third case where a thiamine deficiency may be considered, the treatment interval was too short for resolution of the adverse event. Although no WE-PN terms are found new to the interval without alternative explanation, the interval is too short to allow conclusions on the benefit of thiamine treatment.

#### X. Thiamine Depletion

Thiamine depletion with development of WE is often associated with alcohol abuse. However, the archetypical thiamine deficiency syndrome is beriberi, observed as a nutritional deficiency, especially in diets where the staple calorie source is polished white rice. In 1926, the anti-beriberi substance was crystalized and identified as “Vitamine” (currently as Vitamin B-1).<sup>8</sup> An understanding of a broader profile of thiamine depletion, such as is seen in beriberi, is informative to the setting of the medical condition of this consultation. Beriberi may be present chronically, with variable clinical features across individuals and variable expression of the deficiency signs and symptoms within an individual over time. Beriberi can occur after 3 months of a deficient dietary intake. Patients then develop symmetric motor or sensory peripheral neuropathy, loss of deep tendon reflexes, ataxia and vertigo, and horizontal nystagmus. The syndrome may include cardiac dysfunction with cardiac enlargement, tachycardia, high-output congestive heart failure, and peripheral edema. One author has called beriberi the “great imitator” due to the diversity of features that may present and the variation in severity of individual

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<sup>8</sup> Jansen BCT, Donath WF. On the isolation of the anti-beriberi vitamin. Proc K Acad Wet Amsterdam 1926;29:1390.

elements of the signs and symptoms. Physiologic stressors may also precipitate the expression of the thiamine deficiency syndrome.<sup>9</sup>

Recognition of thiamine deficiency may have become restricted to extreme states such as alcohol abuse since the era of food fortification. In recent decades, there is a recognition that thiamine deficiency should be considered in a variety of vulnerable populations including oncology patients, intensive care unit patients, hyperemesis gravidarum patients, post bariatric surgery patients, and hospitalized elderly patients.<sup>10, 11, 12, 13, 14</sup> In these populations, there is a dynamic between underlying thiamine reserves, input (variations / reliability of daily thiamine intake), and utilization (metabolic state, intrinsic and extrinsic physiologic stressors). When this dynamic causes a decline in availability that reaches a threshold that is below the patient's physiologic requirement, then manifestations of deficiency disease (WE, beriberi) will manifest. This manifestation will include the terms in the WE-PN preferred term query.

Reviewer Comment: Underlying disease, physiologic stressors such as infection, background total thiamine reserve, and deficient or interrupted dietary intake may interact and produce emergent signs and symptoms in the vulnerable population represented in the myelofibrosis – fedratinib treatment group that are in alignment with the broad features of thiamine deficiency syndrome. A key concept from examination of the medical literature on thiamine deficiency is that there is not a clear, binary expression of disease where a concise panel of pathognomonic features are either present or not present at a single point in time. Although overt WE could not be identified with certainty in the Part 1 and Part 2 examination of the ISS ADAE or the controlled ECF12153 dataset, the sporadic and irregular emergence of the WE-PN terms are consistent with the dynamic of thiamine deficiency.

## XI. Summary

The best sources of evidence for examination of the relationship between fedratinib treatment and the occurrence of WE and for examination of the role of nutritional challenge vs drug treatment as causal factors are the Core WE Cases. The examination of the occurrence of key preferred terms in the DB and ISS datasets for the assessment of thiamine deficiency disease or an additional neurotoxic effect, is limited to signal assessment and hypothesis generation.

Evaluation of the 7 Core WE Cases reveals a dominant but incomplete role of nutritional challenge in the emergence of WE. In 1 case the contribution of nutritional challenge appears incomplete (012153-<sup>(b) (6)</sup>

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<sup>9</sup> Lonsdale D., Marrs C. The History of Thiamine and Beriberi. In: Thiamine Deficiency Disease, Dysautonomia, and High Calorie Malnutrition. Academic Press Ltd-Elsevier Science Ltd, 24-28 Oval Road, London NW1 7dx, England. DOI: 10.1016/B978-0-12-810387-6.00001-0

<sup>10</sup> Sonnevile R, Verdonk F, Rauturier C, et al. Understanding brain dysfunction in sepsis. *Annals of Intensive Care* 2013;**3** doi: 10.1186/2110-5820-3-15[published Online First: Epub Date]].

<sup>11</sup> Nolan C, DeAngelis LM. The confused oncologic patient: a rational clinical approach. *Current Opinion in Neurology* 2016;**29**(6):789-96 doi: 10.1097/wco.0000000000000392[published Online First: Epub Date]].

<sup>12</sup> Stroh C, Meyer F, Manger T. Beriberi, a Severe Complication after Metabolic Surgery - Review of the Literature. *Obesity Facts* 2014;**7**(4):246-52 doi: 10.1159/000366012[published Online First: Epub Date]].

<sup>13</sup> Pepersack T, Garbusinski J, Robberecht J, Beyer I, Willems D, Fuss M. Clinical relevance of thiamine status amongst hospitalized elderly patients. *Gerontology* 1999;**45**(2):96-101 doi: 10.1159/000022070[published Online First: Epub Date]].

<sup>14</sup> Ahmad A. The various faces of Thiamine deficiency in a Skilled Nursing Facility (SNF). *Journal of the American Geriatrics Society* 2019;**67**:S20-S21

(b) (6), while in the second case (O11936-(b) (6)) there is no evidence in objective measures or nutritional challenge adverse effects of a nutritional challenge. In these latter 2 cases a direct or synergistic effect of fedratinib is plausible.

Evaluations of the distribution, severity, and alignment of WE-PN terms and of the nutritional challenge terms over the fedratinib study timeline were performed. These analyses reveal a frequency of terms that may be explained by waxing and waning thiamine deficiency disease due to a chronic and unstable dynamic of thiamine reserves as discussed in section X. However, the encephalopathy terms are not highly specific and may also be seen among many patient populations with severe medical illness independent of thiamine deficiency. Assessment of patients with 3 or more of these terms did not reveal any clear new WE case (previously undiagnosed).

Examination of the WE-PN terms did reveal a larger proportion of patients with peripheral neuropathy adverse event entries than encephalopathy adverse event entries. In addition, the two subsets were composed of different unique patients, with overlap of only 10% of patients. This suggests differing underlying drivers of the two adverse event subtypes. This may be explained by differing stages of thiamine deficiency. Alternatively, there may be an entirely different underlying pathology. Examination of the medical literature for adverse events seen in JAK inhibitors reveals that momelotinib (a JAK1 and JAK2 inhibitor) was found to be associated with a treatment-emergent peripheral neuropathy in 44% of patients.<sup>15</sup> This observation supports a hypothesis that peripheral neuropathy could be a class effect of JAK inhibitors. This also addresses one of the primary consult questions of whether there is evidence of additional neurotoxicity. Peripheral neuropathy adverse effect may be a neurotoxic effect distinct from thiamine deficiency.

Thiamine deficiency or interference with thiamine function is the primary underlying concern due to the cases of WE that emerged during fedratinib treatment. Interference with a thiamine transporter has been a concern in the nonclinical literature but the issue remains unresolved.<sup>16, 17</sup> A treatment intervention for this serious safety issue is a primary goal regardless of the underlying cause of the thiamine-related lesion. If fedratinib caused a complete and irreversible interference with thiamine function, a reasonable prediction would be that there should be a short, fixed time interval between initiation of treatment and development of WE. This scenario is not seen in the Core WE Cases. The 7 cases of WE have a broad dispersion of TTO for their WE adverse event (Figure 2). This observation offers some support to the hypothesis that potential fedratinib interference with thiamine function, or thiamine availability, is incomplete and is related to an interaction with the complex dynamic of thiamine economy of this vulnerable population. This is discussed above in Section X. In addition, in three of the Core WE Cases, there was a clear therapeutic response to thiamine treatment.

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<sup>15</sup> Abdelrahman RA, Begna KH, Al-Kali A, et al. Momelotinib treatment-emergent neuropathy: prevalence, risk factors and outcome in 100 patients with myelofibrosis. *British Journal of Haematology* 2015;**169**(1):77-80 doi: 10.1111/bjh.13262[published Online First: Epub Date].

<sup>16</sup> Zhang Q, Zhang Y, Diamond S, et al. The Janus Kinase 2 Inhibitor Fedratinib Inhibits Thiamine Uptake: A Putative Mechanism for the Onset of Wernicke's Encephalopathy. *Drug Metabolism and Disposition* 2014;**42**(10):1656-62 doi: 10.1124/dmd.114.058883[published Online First: Epub Date].

<sup>17</sup> Hood J, Hazell A. Fedratinib Does Not Inhibit Thiamine Uptake or Induce Experimental Wernicke's Encephalopathy in Nonclinical Studies. *Blood* 2017;**130**

- XII. Conclusion, Response to Consult Questions (outline items a,b)
- a. "DHP is requesting DNP review the cases and any other relevant information in the NDA submission to provide any additional input regarding the potential risk of WE that DNP may have and comment on whether the cases represent clear risk of WE or WE-like encephalopathy"

In our review of the Core WE Cases, we conclude that 7 of these 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 also of the broader spectrum of thiamine deficiency disorders; these include partial expressions of encephalopathy and peripheral nervous system dysfunction.

- b. "please comment on whether any data suggest an increased risk of neurotoxicity with fedratinib."

Review of the overall frequency, severity, dispersion over time, and distribution across patients of the WE-PN adverse events suggests that an independent peripheral nervous system toxicity may be present. These peripheral nervous system adverse effects, like the WE adverse event, may also be due to thiamine deficiency but the limitations of the data do not allow a certainty of distinction between these two possibilities.

- XIII. Comment and Recommendation
- a. Thiamine treatment is predicted to prevent the development of WE. Unless there is a risk of enhanced tumor proliferation, thiamine supplementation should be administered concurrently with fedratinib treatment, on a proactive basis. (b) (4)
  - b. Early recognition and rapid intervention are the most effective means to prevent sequelae of thiamine deficiency in general and WE specifically. We are in agreement with the goals of risk management to achieve these ends.
  - c. The peripheral nervous system adverse effect safety signal appears to be real, especially in light of the identification of this adverse effect in another JAK inhibitor. We recommend considering the addition of this risk to labeling.

### Appendix 1, Composite WE-PN Query Terms

Abnormal behaviour	Acute polyneuropathy	Anaesthetic complication
Acalculia	Acute psychosis	Angiopathic neuropathy
Acquired hepatocerebral degeneration	Affect lability	Anti-basal ganglia antibody positive
Acute disseminated encephalomyelitis	Agitation	Anti-ganglioside antibody positive
Acute encephalitis with refractory, repetitive partial seizures	Agitation neonatal	Anti-myelin-associated glycoprotein antibodies positive
Acute haemorrhagic leukoencephalitis	Agitation postoperative	Anti-myelin-associated glycoprotein associated polyneuropathy
Acute painful neuropathy of rapid glycaemic control	Agnosia	Anti-NMDA antibody positive
	Agraphia	
	Alexia	
	Altered state of consciousness	
	Amnesia	
	Amyotrophy	

Apathy	Convulsion in childhood	Encephalitis
Aphasia	Convulsion neonatal	Encephalitis allergic
Apraxia	Convulsions local	Encephalitis autoimmune
Areflexia	Coordination abnormal	Encephalitis brain stem
Asterixis	Cranial nerve paralysis	Encephalitis haemorrhagic
Ataxia	CSWS syndrome	Encephalitis post
Atonic seizures	Decreased nasolabial fold	immunisation
Autoimmune	Decreased vibratory sense	Encephalitis toxic
encephalopathy	Defiant behaviour	Encephalomyelitis
Autoimmune neuropathy	Delirium	Encephalopathy
Autonomic failure syndrome	Delirium febrile	Encephalopathy allergic
Autonomic neuropathy	Delirium tremens	Encephalopathy neonatal
Autonomic seizure	Delusion	Epilepsy with myoclonic-
Axonal neuropathy	Delusion of reference	atonic seizures
Bell's phenomenon	Delusion of replacement	Epileptic encephalopathy
Biopsy peripheral nerve	Delusional perception	Extensor plantar response
abnormal	Dementia	Extraocular muscle disorder
Bispectral index decreased	Dementia of the Alzheimer's	Eye movement disorder
Blindness cortical	type, with delirium	Facial nerve injury due to
Bradyphrenia	Demyelinating	birth trauma
Brow ptosis	polyneuropathy	Facial paralysis
Burning feet syndrome	Depressed level of	Facial paresis
Burning sensation	consciousness	Febrile convulsion
CAR T-cell-related	Derailment	Focal dyscognitive seizures
encephalopathy syndrome	Diabetic encephalopathy	Formication
Central nervous system	Diplopia	Gait apraxia
inflammation	Disinhibition	Gait disturbance
Cerebellar syndrome	Disorganised speech	Gaze palsy
Change in sustained	Disorientation	Generalised non-convulsive
attention	Distractibility	epilepsy
Chronic lymphocytic	Disturbance in attention	Generalised tonic-clonic
inflammation with pontine	Disturbance in social	seizure
perivascular enhancement	behaviour	Genital hypoaesthesia
responsive to steroids	Drug withdrawal convulsions	Glossopharyngeal nerve
Circadian rhythm sleep	Dysaesthesia	paralysis
disorder	Dysarthria	Guillain-Barre syndrome
Circumstantiality	Dyscalculia	Hallucination
Clonic convulsion	Dysgraphia	Hallucination, auditory
Clonus	Dyskinesia	Hallucination, gustatory
Cognitive disorder	Dyskinesia neonatal	Hallucination, olfactory
Coma	Dysmetria	Hallucination, synaesthetic
Coma neonatal	Dysphagia	Hallucination, tactile
Coma scale abnormal	Dyspraxia	Hallucination, visual
Confabulation	Dysstasia	Hallucinations, mixed
Confusion postoperative	Echolalia	Hemiapraxia
Confusional state	Electroencephalogram	Hemiparesis
Consciousness fluctuating	abnormal	Hepatic encephalopathy
Contrast encephalopathy	Electromyogram abnormal	

Hepatic encephalopathy	Loss of consciousness	Nystagmus
prophylaxis	Loss of proprioception	Obsessive rumination
Hereditary motor and	Memory impairment	Ocular dysmetria
sensory neuropathy	Mental disorder due to a	Oculofacial paralysis
Hostility	general medical condition	Oculogyric crisis
Hyperammonaemic crisis	Mental impairment	Ophthalmoplegia
Hyperammonaemic	Mental status changes	Organic brain syndrome
encephalopathy	Metabolic encephalopathy	Panencephalitis
Hyperreflexia	Miller Fisher syndrome	Paraesthesia
Hypersomnia	Minimal hepatic	Paraesthesia ear
Hypertensive	encephalopathy	Paralysis
encephalopathy	Mixed delusion	Paralysis recurrent laryngeal
Hypertonia	Mononeuritis	nerve
Hypoaesthesia	Mononeuropathy	Paraneoplastic
Hypoglossal nerve paralysis	Mononeuropathy multiplex	encephalomyelitis
Hypoglossal nerve paresis	Mood altered	Paranoia
Hypoglycaemic	Motor dysfunction	Paraparesis
encephalopathy	Multifocal motor neuropathy	Paresis
Hyponatraemic	Muscle atrophy	Paresis cranial nerve
encephalopathy	Muscular weakness	Partial seizures
Hyporeflexia	Musculoskeletal stiffness	Partial seizures with
Hyporesponsive to stimuli	Myelopathy	secondary generalisation
Hypotonia	Myoclonus	Peripheral motor neuropathy
Hypoxic-ischaemic	Nerve conduction studies	Peripheral nerve lesion
encephalopathy	abnormal	Peripheral nerve palsy
IIIrd nerve paralysis	Nerve degeneration	Peripheral nerve paresis
IIIrd nerve paresis	Neuralgia	Peripheral nervous system
Illogical thinking	Neuritis	function test abnormal
Illusion	Neurological examination	Peripheral sensorimotor
Incoherent	abnormal	neuropathy
Intensive care unit delirium	Neuromuscular pain	Peripheral sensory
Irritability	Neuromuscular toxicity	neuropathy
Irritability postvaccinal	Neuromyopathy	Peroneal nerve palsy
Ischaemic neuropathy	Neuronal neuropathy	Persecutory delusion
IVth nerve paralysis	Neuropathic muscular	Perseveration
IVth nerve paresis	atrophy	Personality change
Jealous delusion	Neuropathy peripheral	Personality change due to a
Joint position sense	Neuropathy vitamin B12	general medical condition
decreased	deficiency	Personality disorder
Judgement impaired	Neuropathy vitamin B6	Phrenic nerve paralysis
Kernicterus	deficiency	Pleocytosis
Lack of spontaneous speech	Neurotoxicity	Polyneuropathy
Lethargy	Non-24-hour sleep-wake	Polyneuropathy chronic
Leukoencephalomyelitis	disorder	Polyneuropathy idiopathic
Leukoencephalopathy	Noninfective encephalitis	progressive
Limbic encephalitis	Noninfective	Post cardiac arrest syndrome
Listless	encephalomyelitis	Posterior reversible
Loose associations	Notalgia paraesthetica	encephalopathy syndrome

Postoperative delirium  
Poverty of speech  
Presenile dementia  
Psychiatric decompensation  
Psychiatric symptom  
Psychomotor hyperactivity  
Psychotic behaviour  
Psychotic disorder  
Psychotic disorder due to a  
general medical condition  
Radiation neuropathy  
Rasmussen encephalitis  
Reflexes abnormal  
Restlessness  
Reye's syndrome  
Seizure  
Seizure anoxic  
Senile dementia  
Sensorimotor disorder  
Sensory disturbance  
Sensory loss  
Simple partial seizures  
Skin burning sensation  
Slow response to stimuli  
Sluggishness  
Small fibre neuropathy  
Social avoidant behaviour  
Somatic delusion  
Somatic hallucination  
Somnolence  
Somnolence neonatal  
Speech disorder  
Stupor  
Subacute myelo-  
opticoneuropathy  
Substance-induced psychotic  
disorder  
Suggestibility  
Suspiciousness  
Synkinesis  
Temperature perception test  
decreased  
Thinking abnormal  
Tick paralysis  
Tinel's sign  
Tongue movement  
disturbance  
Tongue paralysis

Tonic convulsion  
Toxic encephalopathy  
Toxic leukoencephalopathy  
Toxic neuropathy  
Transient psychosis  
Tremor  
Tremor neonatal  
Ulnar neuritis  
Unresponsive to stimuli  
Uraemic encephalopathy  
Vagus nerve paralysis  
Vascular dementia  
Vascular encephalopathy  
Vestibular nystagmus  
Visual field defect  
VIth nerve paralysis  
VIth nerve paresis  
Vocal cord paralysis  
Vulvovaginal hypoaesthesia  
XIth nerve paralysis

Appendix 2, Core Case Master Table

USUBJID / Demographic	012153- (b) (6)	012153 (b) (6)	012153- (b) (6)	012153- (b) (6)	012181- (b) (6)	013519- (b) (6)	011936 (b) (6)	012042- (b) (6)
Patient Order of Presentation in Sponsor Documents	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
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	500	500	500	500
Cycle of WE event	2	11	3	3	10	2	11	9
First Dose	(b) (6)							
Last dose	(b) (6)							
<b>Descriptive- PMH / Nutritional Challenge / Depletion terms / Key clinical Features</b>								
PMH	Angina Pectoris, Bronchitis, Coronary Arterial Stent Insertion, Depression, Gastritis Erosive, Gastroesophageal Reflux Disease, Hyperhidrosis, Hypertension, Polycythaemia Vera, Pyrexia, Weight decreased	Anaemia, Cardiac Failure Congestive, Cataract, Hyperhidrosis, Hypertension, Pyrexia, Weight Decreased	Diabetes Mellitus, Essential Hypertension, Hyperhidrosis, Mitral Valve Incompetence, Osteoporosis, Polycythaemia Vera, Pyrexia, Renal Failure Chronic, Weight Decreased	Dyspepsia, Hyperhidrosis, Hypertension, Pyrexia, Weight Decreased	Anaemia, Hyperhidrosis, Polycythaemia Vera, Pyrexia, Thrombocytopenia, Varices Oesophageal, Weight decreased	Abdominal Distension, Alcohol Use, Allergy To Plants, Appendicectomy, Aspiration Pleural Cavity, Diaphragmatic Rupture, Ear Discomfort, Electrocardiogram Q Wave Abnormal, Gastroesophageal Reflux Disease, House Dust Allergy, Hypertension, Mastication Disorder, Metastases To Central Nervous System, Pneumothorax, Polymyalgia	anemia, dizziness, chronic diarrhea, vomiting, weight loss, fatigue, renal failure and depression.	Aphthous Stomatitis, Drug Intolerance, Hypercholesterolaemia, Tonsillectomy

USUBJID / Demographic	012153 (b) (6)	012153 (b) (6)	012153 (b) (6)	012153 (b) (6)	012181 (b) (6)	013519 (b) (6)	011936 (b) (6)	012042 (b) (6)
						Rheumatica, Thyroidectomy, Uterine Leiomyoma, VIIth Nerve Paralysis		
<b>Nutritional Challenge factors (from sponsor)*</b>	From day 1 of Fedratinib cycle. Grade 2/3 nausea & vomiting for 2 months. Severe weight loss.	Nausea & vomiting. 4.9% weight loss. Hyponatremia	Chronic renal failure. 7.4% weight loss (when?). UTI,	Nausea & vomiting	GI hemorrhage from esophageal varices caused by splenic enlargement Hepatic encephalopathy diagnosis	Oro-facial cancer with CNS met. Difficulty eating. Gr3 anorexia. 6.6% body weight loss in preceding 3 weeks (preceding dates?). Wine 2X/day (last weight 10/1/13 VSDY 57, death (b) (6)	Gr. 2 cerebral ischemia. Anorexia. Chronic diarrhea. Grade 3 UTI. Recovery at 400 mg without dose interruption.	Pyrexia and vomiting.
<b>Other depletion terms on timeline (study day)</b>		Anemia, decreased appetite, fatigue, dyspnea, LV failure	Diarrhoea (days 1-18, grade 3, SAE)	Diarrhoea (170-183, 189-193), Anemia (198), Depression (86), tracheobronchitis (222-231)	Asthenia (187), Diarrhoea (2-14, 100-141), anemia (88), ascites (115), Weight decrease (173-201), GI Haemorrhage (72-80)	Bradycardia (baseline), Abdominal Pain (2-10, gr 2), Accidental OD (14), Fatigue (57), Decreased appetite (65), possible seizure (not PT) ((72), <b>FATAL</b>	Cerebral Ischemia (278-309), Memory impairment (316), Haemoglobin decreased (56, 113, 169), Peripheral neuropathy (169-197)m Oedema peripheral (337-365), Oral herpes (15-28), Urinary tract infection (278), Weight decreased (15-56)	Gastric disorder (15-113, 225-253), gastrointestinal disorder (391-400), Pyrexia (391)

USUBJID / Demographic	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012181- (b) (6)	013519- (b) (6)	011936- (b) (6)	012042- (b) (6)
<b>Key clinical features</b>	Upbeat nystagmus, axial ataxia, confusion, gait disorder	Mental status became worse?, drowsy, (Brain MRI revealed acute encephalopathy),	Decreased LOC, focal neurologic exam with right motor and sensory deficit. <b>ADAE:</b> "encephalopathy" entered day 79 Gr 3, (recovered), +SAE	5/9 dizziness and diplopia 5/20 , confusion, mental disorder, delirium, convulsions, ataxia, temporary cognitive deficit without memory loss. <b>ADAE:</b> Paraesthesia entered day 178, GR1, non SAE	forgetfulness, <b>ADAE:</b> "encephalopathy" entered on day 295, Gr 3, + SAE, noted as recovered. LAB VALUES: ALT & AST 4 entries with minimal elevation. Bilirubin: multiple entries > 2 x ULN. PT: normal range not provided, all values > 21 seconds which is higher than typical textbook range of 15 to 16 seconds	Nystagmus, confusion	Memory deficit, nystagmus, diplopia, Seizure? <b>ADAE:</b> memory impairment entered on day 316, Gr2, not SAE. Neuropathy peripheral entered on day 169, Gr1, not SAE.	Diplopia, episodic recent memory loss, disoriented to time, MMS 19, altered calculation, "difficulty performing everyday tasks"
<b>Possible alternate causes of clinical status</b>	Metabolic encephalopathy- dehydration, azotemia	Background medical status	Metabolic encephalopathy (azotemia), pneumonia – atelectasis,	Vestibular neuronitis, Seizure	Hepatic encephalopathy	Meningioencephalitis, viral, vascular. Epileptiform activity (MRI report of (b) (6) reveals "diffuse nonmetastatic and nonmeningial attachments"	subacute cortical infarct in the left parietal cortex	Early dementia, however no follow up neurologic exam or mental status are provided. No assessment on ability to perform daily tasks.
<b>Possible Thiamine depletion exacerbating factors (additional)</b>	Age, diuretic treatment	CHF, frailty	Age,		Hepatic insufficiency,	Background anorexia, occasional nausea and vomiting	Background chronic diarrhea, vomiting, weight loss	none
<b>Confounders of WE diagnosis</b>	<b>Confounded</b> , competing alternate Dx in geriatric patient,	<b>Confounded</b> by underlying chronic illness	<b>Confounded</b> by renal failure / insufficiency, focal neurologic findings, only decreased LOC as WE finding	<b>Confounded</b> by vestibular neuronitis, nutritional challenge of low grade vomiting	Hepatic encephalopathy	<b>Confounded</b> by possible seizure, pre-terminal medical state,	Confounded by cortical stroke	<b>Questionable</b> , no baseline mental status. Outside of mental status chg. Only nystagmus reported at secondary exam which may be physiologic.
<b>Strength of clinical features</b>	High	moderate	moderate	high	low	high	moderate	high

USUBJID / Demographic	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012181- (b) (6)	013519- (b) (6)	011936 (b) (6)	012042- (b) (6)
MRI (Images from Type A meeting package 3/14/17, Attachment # 9), DNP REVIEWER from	MRI performed on two dates are available. pathognomonic (b) (6) medial thalamic and mamillary body high signal on FLAIR image sequences. A FLAIR sequence on (b) (6) reveals resolution of these features while underlying subcortical white matter lesions are retained.	pathognomonic (b) (6) medial thalamic and mamillary body high signal on FLAIR image sequences. These features are consistent with WE. There is also some underlying periventricular white matter high signal lesion.	MRI study of (b) (6) reveals bilateral medial thalamic hyperintensity on FLAIR image. The quality is lower with less contrast, however the features are consistent with WE	MRI study of (b) (6) reveals a small amount of periventricular high signal but otherwise no high signal in the medial thalami, mamillary bodies or periaqueductal gray matter. There is encephalomalacia adjacent to the head of the right caudate nucleus consistent with an old infarct.	MRI on (b) (6) reveals no high signal lesion is present in the medial thalami, mamillary bodies, or periaqueductal gray matter.	MRI performed on two dates are available. The first on (b) (6) revealed a high signal lesion in the right anterior temporal lobe the radiologist indicates is consistent with a treated brain metastatic lesion. The second study on (b) (6) reveals pathognomonic features of WE with clear high signal lesion present in the medial thalamus bilaterally, periaqueductal gray and visible to a lesser extent in the mamillary bodies . Death day 72	An MRI study on (b) (6) FLAIR image reveals high signal lesions in the mamillary bodies, periaqueductal gray and bilateral medial thalami. A second MRI on (b) (6) reveals resolution of the high signal lesion in the mamillary bodies, periaqueductal gray and bilateral medial thalami.	An MRI performed on (b) (6) reveals high signal lesions on FLAIR weighted image in the periaqueductal gray and mamillary bodies. However, there is also uncharacteristic prominent high signal lesions in the head of the caudate nucleus and putamen bilaterally.
<b>Quantitative- Weight/ Nutritional Challenge/ MRI/ WE date/ Thiamine</b>								
N & V , GI - Nutritional approx. Challenge Date	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)
Nausea AESTDY	1-44	169-196, 513-525		174-176	2-14, 100-141, 185-201, 255-281	25-27	15-28,	
Vomiting AESTDY	1-44	169-178, 513-525	1-18	174-176	185-187	25-27, 65-71	-1-28	391-410
Nausea Grade	2-3 not SAE	2		1	1-2	1	1	
Vomiting Grade	2-3 not SAE	2	3 SAE	1	1	1	1	3
Weight % change from Baseline	-6.4, -7.9	+ 13.5 (change from peak day 339, -3.4)	-7.45	-1.9, +1.56, +1.56	-1.8, -4.0	-6.6	+1.7, +4.4	-0.3 (change from peak day 169, -4.7)
WT Study day	29, 63	527	59	226, 273, 365	281, 304	57	253, 316	372
Baseline BMI	23.6	24.3	19.6	25.6	26	27.2	29.4	24.1
Approximate Duration of Challenge prior to W, based on	44	100	60	0	N/A	65	0	191

USUBJID / Demographic	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012181- (b) (6)	013519- (b) (6)	011936- (b) (6)	012042- (b) (6)
weight trend and/or N/V events (days). 0 = none aligned with WE								
WE Event date	(b) (6)							
Wernicke Event Start day from AESTDY	44	529	79	240	295	65	278	360
WE Dates from AESTDY variable	44-112	529-551	79-95	240-535	295-304	65-73	278	360-373
MRI Date	(b) (6)							
MRI Study Day	50, 67	521	81	450	296	15, 70	279, 370	394
MRI Dx from Sponsor Neuroradiology table	5/5 Pathognomonic	3/5 Pathognomonic, 2/5 inconclusive	1/5 Pathognomonic, 2/5 not WE	1/5 Pathognomonic, 1/5 likely, 1/5 inconclusive, 2/5 not WE	5/5 not WE	3/5 Pathognomonic, 1/5 inconclusive, 1/5 not WE	4/5 Pathognomonic, 1/5 likely	3/5 Pathognomonic, 1 likely, 1 inconclusive
Thiamine Study Day Administered	51	525	81	458	292		419 (b) (6)	396
Thiamine administered	thiamine administered with benefit based on the timeline	Thiamine administered with benefit	Thiamine administered (benefit uncertain since level at EOS was normal)	thiamine administered	Thiamine administered	no thiamine administered	Thiamine administered, possible benefit (this was a retrospective case)	thiamine administered
Outcome	Resolved after thiamine treatment, partial resolution of MRI features	recovered 26 days after event	resolved	Prolonged recovery- recovery with sequela	full recovery (relation to thiamine treatment unclear)	fatal	stabilized and not recovered upon last contact	RECOVERED/RESOLVED, DOSE NOT CHANGED
<b>CONCLUSION DOMAINS</b>								
MRI: DNP reviewer conclusion	WE positive MRI 1, WE negative MRI 2	WE positive	WE possible	WE negative	WE negative	WE negative MRI 1, WE positive MRI 2	WE positive MRI 1, WE negative MRI 2	WE possible
Strength of clinical Features	High	moderate	moderate	high	low	high	moderate	high

USUBJID / Demographic	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012181- (b) (6)	013519- (b) (6)	011936- (b) (6)	012042- (b) (6)
WE INTEGRATED DIAGNOSIS, based on integration of clinical data and Neuroradiology conclusions	YES	YES	YES	YES	No	Yes	Yes	Yes
Final Conclusion of Nutritional Challenge Causality	yes	probable	yes	inconclusive	N/A	yes	No	Yes
Final Conclusion of Independent fedratinib causality	No	No	No	No	N/A	No	possible	No
Final Conclusion on Synergistic interaction of Nutritional Depletion and fedratinib treatment as Cause of WE (why)	least likely	Yes, (modest nutritional challenge with definite positive MRI)	least likely, (clear nutritional challenge, sustained weight loss prior to WE event)	Yes (event at weight nadir but duration of wt loss and poor alignment of nutritional challenge weaken support for nutritional challenge)	N/A	least likely (severe nutritional challenge from day 30 to event date, day 65,	Yes, there is no clear nutritional challenge with definite positive MRI 1.	least likely (WE event at weight downslope and related interval of Gr 3 N/V)
THIAMINE BENEFIT	POSITIVE	POSITIVE	POSITIVE	N/A	N/A	N/A	N/A	POSITIVE

USUBJID / Demographic	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012153- (b) (6)	012181- (b) (6)	013519- (b) (6)	011936- (b) (6)	012042- (b) (6)
CONCLUSION, POSITIVE / NEGATIVE	POSITIVE, PLAUSIBLE NUTRITIONAL CHALLENGE	POSITIVE, POSSIBLE NUTRITIONAL CHALLENGE BUT DEVELOPMENT OF WE SUGGESTS POSSIBLE SYNERGY	POSITIVE, PLAUSIBLE CAUSE BY NUTRITIONAL CHALLENGE ALONE	POSITIVE, CLINICAL FEATURES HIGHLY SUPPORTIVE, THERE IS TENUOUS SUPPORT FOR A NUTRITIONAL CHALLENGE AS POSSIBLE CAUSE, THE WE EVENT OCCURED ON THE UPSLOPE TREND JUST AFTER WEIGHT NADIR. THIS SUPPORTS POSSIBLE SYNERGY WITH FEDRATINIB. MRI FOR DX DONE 210 DAYS AFTER WE EVENT WHILE THIAMINE WAS ADMINISTERED 218 DAYS AFTER THE WE EVENT	NEGATIVE, CLINICAL FEATURES VERY LOW SUPPORT- NARRATIVE "SLIGHHT FORGETFULNESS.. HEPATIC DYSFUNCTION ONGOING, NUTRITIONAL CHALLENGE UNLIKELY, 100 DAYS AFTER WEIGHT NADIR WHILE WEIGHT ON UPSWING. ALTERNATE CONSIDERATION- HYPOTHETICAL ONLY, MRI ON DAY 296 MAY HAVE BEEN CONFOUNDED BY THIAMINE TREATMENT OR THE INTERVENTION WAS EARLY ENOUGH TO AVOID MORE THAN BRIEF CLINICAL SYMPTOMS AND ALSO AVOIDED STRUCTURAL BRAIN CHJANGE.	POSITIVE. CLINICAL FEATURES STRONG SUPPORT . SEVERE NUTRITIONAL CHALLENGE. CONTINUOUS WEIGHT LOSS FROM START OF TREATMENT. DEVELOPED CLEAR MRI FEATURES OF WE OVER 55 DAYS. SEIZURE, COMA END EVENTS. SEVERE COURSE MAY INDICATE SYNERGY WITH NUTRITIONAL DEPLETION	POSITIVE, CLINICAL FEATURES STRONG SUPPORT. CONFOUNDED BY POSSIBLE STROKE, LAWNMOWER ACCIDENT AT 3 DAYS PRIOR TO (b) (6) HOSPITAL ADMISSION, HOWEVER MRI FINDING DEFINITE WE ON (b) (6) NO NUTRITIONAL CHALLENGE , EVENT FOLLOWING 179 DAYS OF INCREASING WEIGHT. SUPPORT EFFECT OF FEDRATINIB EFFECT WITH SPONTANEOUS RECOVERY- DIET?. (PEAK WT APPROX DAY 380)	POSITIVE, MRI SUSPECT, CLINICAL FEATURES STRONG SUPPORT. NUTRITIONAL CHALLENGE SUSPECT, NUTRITIONAL STATUS METRICS STABLE BUT WEIGHT IN DOWNSLOPE, TEMPORALLY RELATED INTERVAL OF VOMITING GRADE 3. THIAMINE STARTED AFTER 2ND MRI AND NO CLINICAL DATA SUPPLIED UNTIL MARCH 2014 NOTING WE RESOLVED.

Appendix 3 Weights by Study Day, Core WE Cases

Figure 4 Patient 12153- (b) (6) Weight (Kg) by Study Day, WE day 44

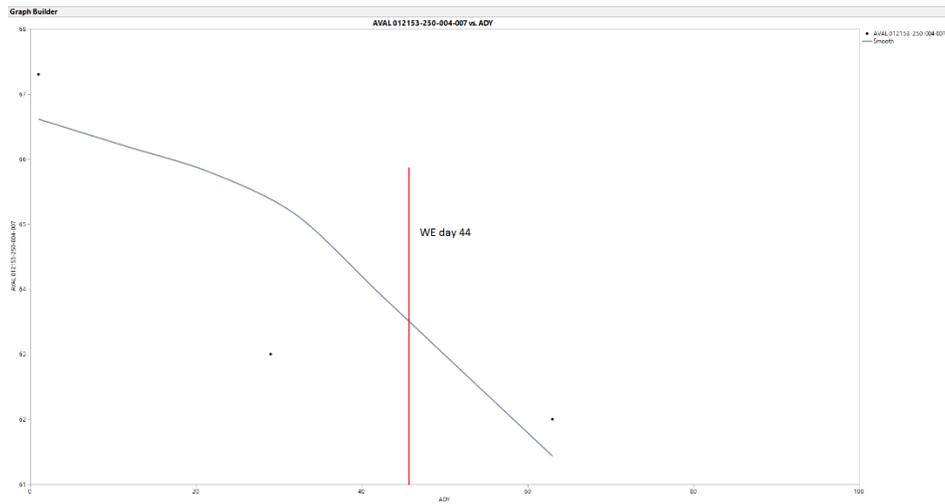


Figure 512153- (b) (6) Weight (Kg) by Study Day, WE day 529

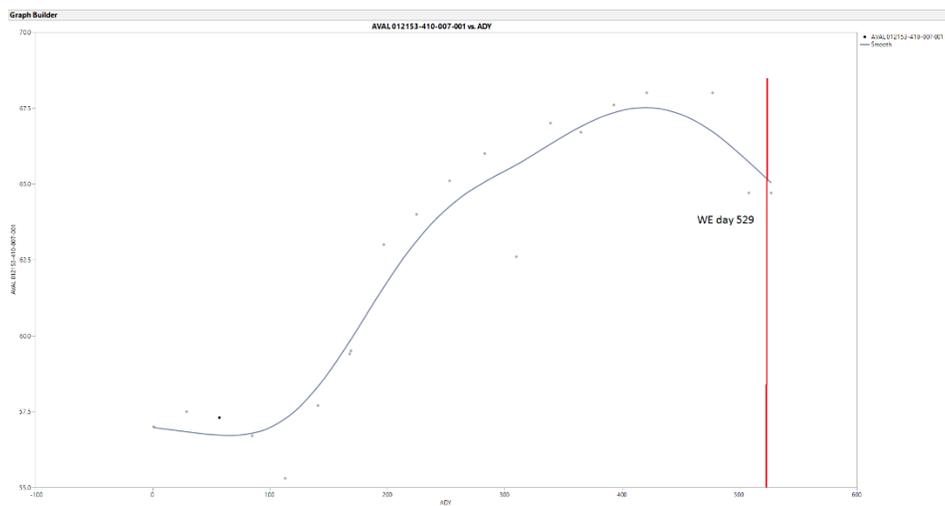


Figure 6 Patient 12153- (b) (6) Weight(Kg) by Study Day, WE day 79

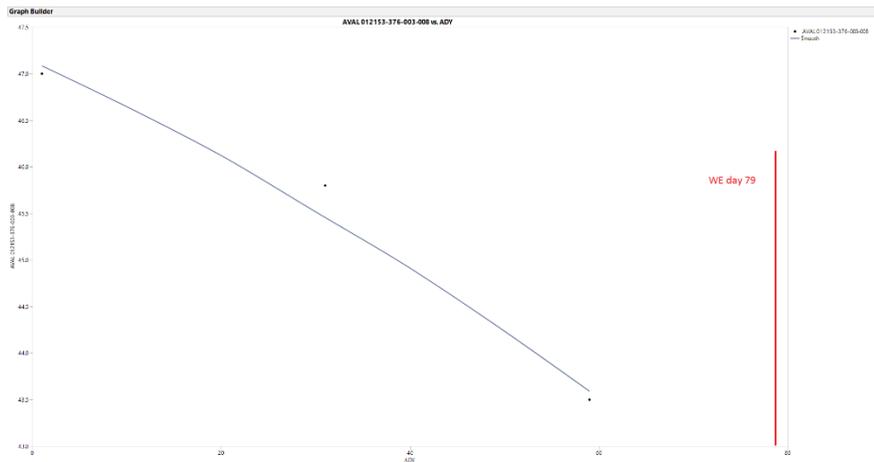


Figure 7 Patient 12153- (b) (6) Weight (Kg) by study Day, WE day 240

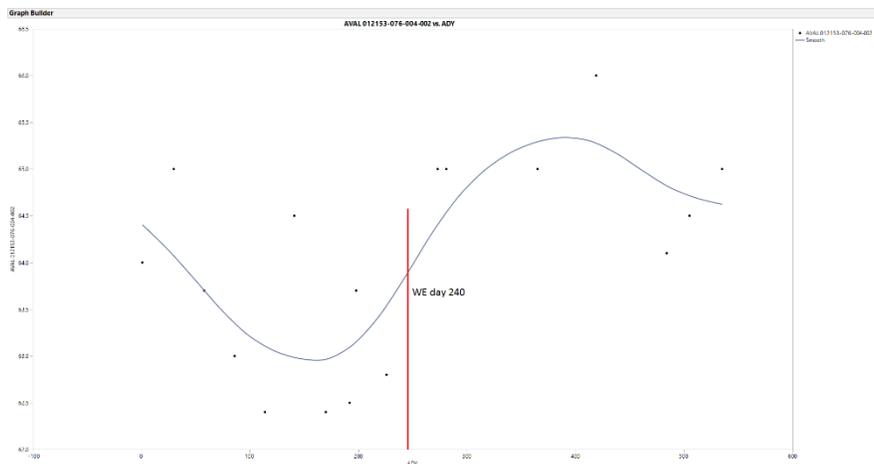


Figure 8 Patient 13519- (b) (6) Weight (Kg) by Study Day, WE day 65

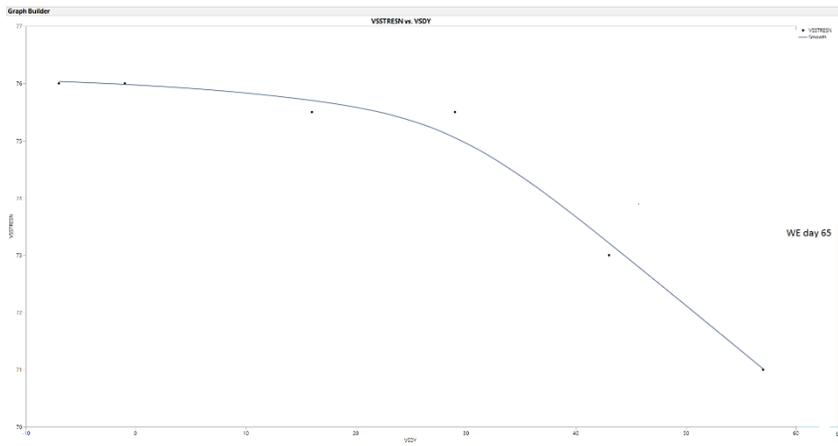


Figure 9 Patient 11936- (b) (6) Weight (Kg) by Study Day, WE day 278

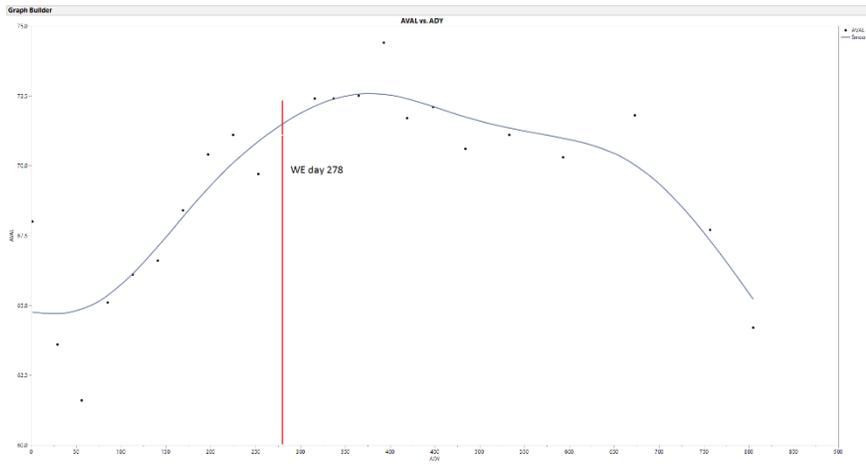
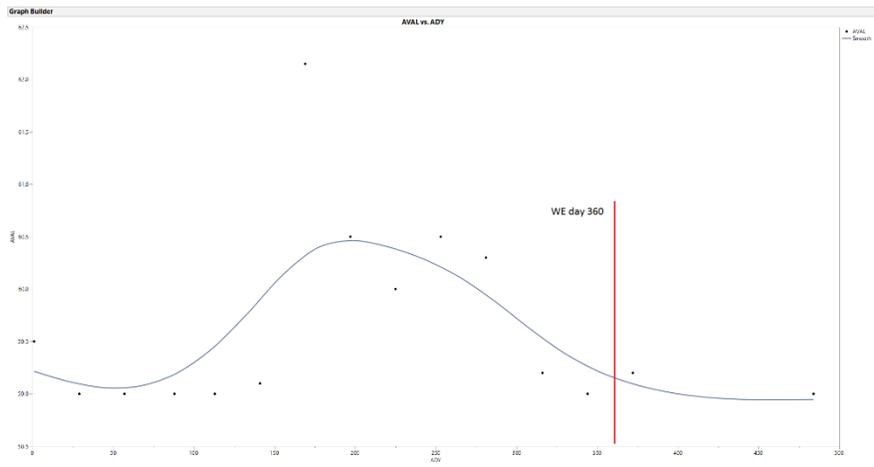


Figure 10 Patient 12042- (b) (6) Weight (kg) by Study Day, WE day 360



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/s/  
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STEVEN T DINSMORE  
05/03/2019 03:57:23 PM

PHILIP H SHERIDAN  
05/03/2019 05:10:13 PM

NICHOLAS A KOZAUER  
05/03/2019 05:23:26 PM

**Division of Hematology Products (DHP) Labeling Review**

<b>NDA Number</b>	212327
<b>Applicant</b>	Celgene
<b>Proprietary Name (nonproprietary name)</b>	INREBIC (fedratinib)
<b>Receipt Date</b>	01/03/2019
<b>PDUFA Goal Date (Internal Goal Date)</b>	September 3, 2019  (Target Date: August 16, 2019)
<b>Review Classification</b>	Priority
<b>Proposed Indication (or current indication if unchanged)</b>	INREBIC is indicated for the treatment of intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF [REDACTED] (b) (4))
<b>Dosing Regimen</b>	400 mg orally once daily
<b>From</b>	<b>Virginia Kwitkowski, MS, ACNP-BC</b>  <b>Associate Director for Labeling, DHP</b>

**Background of Application:**

In this review, I summarize the DHP labeling recommendations and edits in the Inrebic labeling. These edits are made to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Inrebic.

The following pages contain a summary of the labeling recommendations followed by the working version of the Inrebic labeling with my comments and suggested edits. Labeling meetings have not yet begun. Given that the scientific review of the labeling is ongoing, the labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the Inrebic labeling.

Summary of Labeling Recommendations: (see draft labeling below)

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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VIRGINIA E KWITKOWSKI  
05/02/2019 11:46:54 AM

## Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA # 212327
Submission Number	001
Submission Date	1/3/2019
Date Consult Received	2/20/2019
Clinical Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT reviews under IND 78286 dated [09/27/2012](#), [01/16/2013](#), [01/30/2013](#), [05/03/2013](#), and [06/04/2013](#) in DARRTS;
- Sponsor's [summary of clinical pharmacology](#) (Submission 0001);
- Proposed [label](#) (Submission 0001); and
- Study TES13159 [clinical study report](#) and [cardiac safety report](#) (Submission 0001).

### 1 SUMMARY

No large QTc prolongation effect (e.g. 20 ms) of fedratinib was detected in this QT assessment.

The effect of fedratinib was evaluated in Study TES 13519 at a daily dose of 500 mg. The data was evaluated using by-time central analysis as the primary analysis. The largest upper bound of the 2-sided 90% CI for the time-matched, mean difference from baseline (Treatment period: palonosetron + fedratinib 500 mg QD vs. Baseline period: palonosetron + placebo) was below 20 ms (Table 1). The findings of this analysis are further supported by the exposure-response analysis (section 4.5) and categorical analysis (section 4.4). No subject had QTcF >480 ms or  $\Delta$ QTcF >60 ms.

**Table 1: Largest Mean Increase in  $\Delta$ QTc by Time (FDA's PD Population)**

ECG parameter	Treatment	N	Time	Mean (ms)	90% CI (ms)
QTcF	Fedratinib 500 mg QD + Palonosetron 0.25 mg	31	4	4.3	(1.1, 7.5)

Study TES 13519 was conducted using the same formulation as that was used for Phase 3 study EFC12153, Phase 2 study ARD12888, and Phase 1 studies for drug-drug-interaction, organ impairment, and food effect. Fedratinib exposure in Study TES 13519 appears adequate to cover the therapeutic exposure at 400 mg QD in the patient populations (refer to Figure 35 in the sponsor's [summary of clinical pharmacology](#)).

#### 1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

#### 1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

## 2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 0001 from the QT-IRT. Our changes are highlighted ([addition](#), ~~deletion~~). This is a suggestion only and that we defer final labeling decisions to the Division.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

The potential for QTc prolongation with fedratinib was evaluated in <sup>(b) (4)</sup> 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. <sup>(b) (4)</sup>

*Reviewer's comment: The study does not include a proper placebo or positive control (refer to section 3.1). The data support the conclusion of a lack of large effect (i.e. 20 ms) and we do not draw any conclusions of a lack of an effect on QTc (see ICH E14 Q&A 6.1).*

## 3 SPONSOR'S SUBMISSION

### 3.1 OVERVIEW

Previously the QT-IRT reviewed and agreed with the QT assessment proposal (QT-IRT reviews under IND 78286 dated [01/16/2013](#), [01/30/2013](#), and [05/03/2013](#) in DARRTS). The therapeutic dose was changed from <sup>(b) (4)</sup> mg QD in the 05/03/2013 review to 400 mg QD based on current label.

Study TES13519 consisted of 2 consecutive segments (i.e. treatment period). Segment 1 was designed for QT assessment and Segment 2 was included for possibly extending treatment at the Investigator's discretion.

Segment 1 was a single sequence, crossover study in patients. In Segment 1, subjects received placebo on Day 1 and fedratinib 500 mg (5 × 100 mg capsules) QD for 14 days (Days 2 to 15). Subjects self-administered fedratinib (except on visit days). Subjects also received a single 0.25-mg intravenous dose of palonosetron 30 minutes prior to receiving placebo or fedratinib on Day 1, 14, and 15. At the discretion of the Investigator, subjects may also receive a single 1-mg oral dose of granisetron 1 hour prior to receiving fedratinib on Days 2 to 13.

Palonosetron has been tested in a TQT study and no clinically relevant effect was observed at the dose levels higher than what was included in Study TES 13519 (Palonosetron [injectable product label](#)). QT prolongation has been reported for intravenous granisetron use, however, cross-product comparison suggests a lack of clinically relevant effect with oral doses of 1 mg granisetron, because the mean C<sub>max,ss</sub> in cancer patients is expected to be lower than that evaluated in a TQT study with a subcutaneous formulation (Granisetron [tablet product label](#) and [subcutaneous product label](#)).

In Segment 1, continuous Holter ECG was collected on Day -1 (-25 to -1 hr prior to fedratinib dose), Day 1-2, and Day 15-16 at palonosetron predose (-0.5 hr), fedratinib predose (0 hr), 1, 2, 3, 4, 5, 6, 8, and 24 hr post fedratinib dose.

The sponsor used the average of all assessments during the drug-free day (Day -1) from 24 hours predose to 16 hours predose as the baseline, and considered Day 1 treatment (palonosetron+placebo) as the placebo control. The reviewers do not agree with this analysis plan. In a QT study with placebo control, the placebo control arm should be balanced in the overall study design. In this single sequence study, the placebo treatment is not balanced (i.e. palonosetron+placebo treatment is always on Day 1 and palonosetron+ fedratinib always on Day 15). Therefore, the reviewers used time-matched ECG data from Day 1 as the baseline.

In the original QT assessment proposal, the sponsor powered the study to exclude large mean effect based on by-timepoint analysis. In the current submission, the sponsor used concentration-QTc analysis as primary analysis and by-timepoint analysis as supportive analysis. The reviewers use concentration-QTc analysis as the supportive analysis for reasons described in Section 4.5.

## **3.2 SPONSOR'S RESULTS**

### **3.2.1 Central tendency analysis**

Fedratinib excluded the 20 ms threshold at the 500 mg QD dose. The sponsor's and reviewer's results are similar. Please see section 4.3 for additional details.

#### **3.2.1.1 Assay Sensitivity**

Not applicable. The goal is to exclude large effects.

##### **3.2.1.1.1 QT bias assessment**

Not applicable. The goal is to exclude large effects.

### **3.2.2 Categorical Analysis**

No subject had absolute QTcF>480 ms and no subject had  $\Delta$ QTcF>60 ms. Sponsor did not provide categorical tables for QTcF, HR, PR and QRS. Please see Section 4.4 for reviewer's results.

### **3.2.3 Safety Analysis**

At the time of database lock, a total of 31 subjects who received fedratinib had died, and of these, most (26 subjects) died of progressive disease. Deaths of the remaining 5 subjects were due to adverse events (3 subjects), other cancer (1 subject), or unknown causes (1 subject). Deaths due to AEs were Wernicke's encephalopathy (subject (b) (6)), hemoptysis (subject (b) (6)) and pneumonia aspiration (subject (b) (6)).

A total of 27 subjects (45.8%) treated with fedratinib experienced at least 1 SAE. The SAEs with the highest incidences were in the SOCs of gastrointestinal disorders and general disorders and administration site conditions, both 13.6%. Within these SOCs, only disease progression (5 subjects [8.5%]) and ascites (2 subjects [3.4%]) were reported

by more than 1 subject. Other SAEs reported by more than 1 subject were Escherichia bacteremia, anemia, pericardial effusion, and hemoptysis (2 subjects [3.4%] each). One subject each reported lipase increased and hyperlipasemia. Nonfatal, treatment-related SAEs were fungal esophagitis, vomiting, fatigue, decreased appetite, epilepsy, muscular weakness, diarrhea, gastric perforation, altered state of consciousness, dizziness, anemia, respiratory failure, lipase increased, and hyperlipasemia.

Ten subjects (16.9%) had a TEAE during fedratinib treatment which led to treatment discontinuation. The only events experienced by more than 1 subject were nausea and vomiting (each n = 2 [3.4%]). The remaining events experienced by 1 subject each were: soft tissue infection, decreased appetite, WE, hemoptysis, pneumonia aspiration, diarrhea, gastric perforation, renal failure chronic, fatigue, and GGT increased.

**Reviewer's comments:** No clinically significant cardiac events associated with QTc prolongation were detected in this study.

### **3.2.4 Exposure-Response Analysis**

The sponsor used Day -1 data as the baseline,  $\Delta$ QTcF as the dependent variable, treatment (placebo vs. fedratinib), time since last dose, centered baseline, and fedratinib concentration as the covariates, and subject as a random effect on the slope and intercept. The predicted  $\Delta\Delta$ QTcF interval at geometric mean peak fedratinib concentration (i.e. 3614.6 ng/mL) is 0.56 (-1.80, 2.93) ms.

The reviewer used Day 1 data as the time-matched baseline. The conclusion (i.e. a lack of large mean effect) of the reviewer's analysis is supported by the sponsor's results. Please see section 4.5 for additional details.

## **4 REVIEWERS' ASSESSMENT**

### **4.1 EVALUATION OF THE QT/RR CORRECTION METHOD**

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e.  $|\text{mean}| < 10$  bpm) were observed (see Sections 4.3.2 and 4.5).

### **4.2 ECG ASSESSMENTS**

#### **4.2.1 Overall**

Overall ECG acquisition and interpretation in this study appears acceptable.

#### **4.2.2 QT bias assessment**

Not applicable.

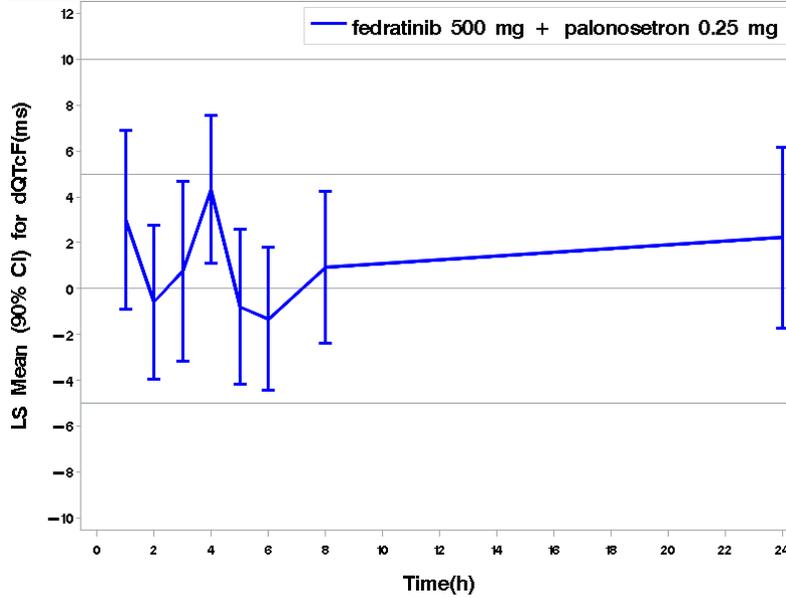
### **4.3 CENTRAL TENDENCY ANALYSIS**

#### **4.3.1 QTc**

The PD population was used for by time central tendency analysis. For QTcF data analysis we focus on fedratinib (500 mg QD) administered as 14-day repeated dose

(Figure 1). The largest upper bound of the 2-sided 90% CI for the mean difference (treatment - baseline) in QTcF is 7.5 ms at 4 hours post-dose.

**Figure 1: Mean and 90% CI of  $\Delta$ QTcF Time Course for Fedratinib 500 mg QD + Palonosetron 0.25 mg**



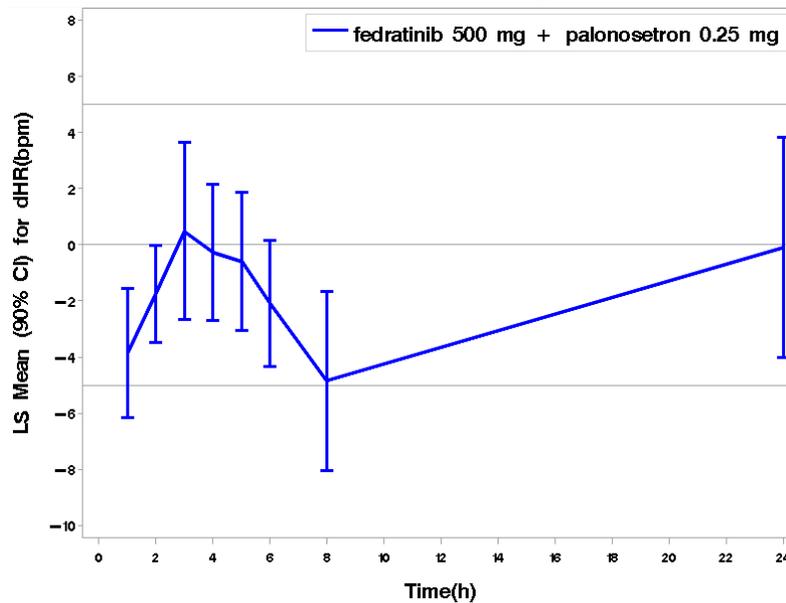
#### 4.3.1.1 Assay sensitivity

Not applicable.

#### 4.3.2 HR

The same data and descriptive analysis were performed based on  $\Delta$ HR (Figure 2).

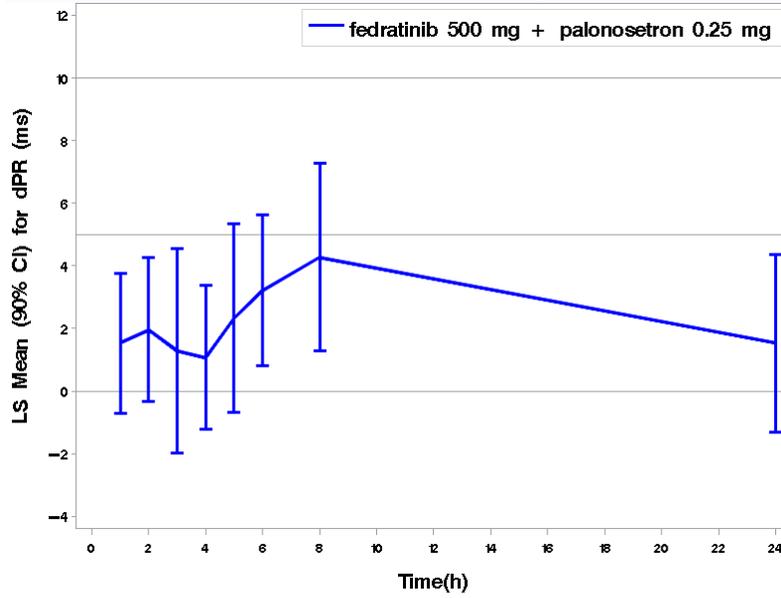
**Figure 2: Mean and 90% CI of  $\Delta$ HR Time Course for Fedratinib 500 mg QD + Palonosetron 0.25 mg**



### 4.3.3 PR

The same descriptive analysis was performed based on  $\Delta$ PR interval (Figure 3).

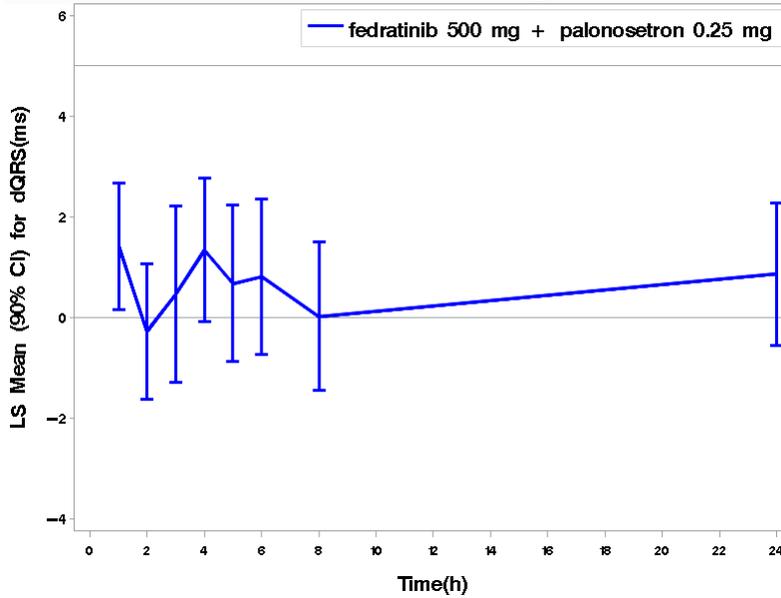
**Figure 3: Mean and 90% CI of  $\Delta$ PR Time Course for Fedratinib 500 mg QD + Palonosetron 0.25 mg**



### 4.3.4 QRS

The same descriptive analysis was performed based on  $\Delta$ QRS interval (Figure 4).

**Figure 4: Mean and 90% CI of  $\Delta$ QRS Time Course for Fedratinib 500 mg QD + Palonosetron 0.25 mg**



## 4.4 CATEGORICAL ANALYSIS

### 4.4.1 QTc

Table 2 lists the number of subjects and the number of observations whose QTcF values are  $\leq 450$  ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 2: Categorical Analysis for QTcF**

Treatment Group	Total (N)		Value $\leq 450$ ms		450 ms < Value $\leq 480$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fedratinib 500 mg + Palonosetron 0.25 mg	43	344	38 (88.4%)	328 (95.3%)	5 (11.6%)	16 (4.7%)

Table 3 lists the categorical analysis results for  $\Delta$ QTcF. No subject's  $\Delta$ QTcF was above 60 ms.

**Table 3: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total (N)		Value $\leq 30$ ms		30 ms < Value $\leq 60$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fedratinib 500 mg + Palonosetron 0.25 mg	43	343	42 (97.7%)	342 (99.7%)	1 (2.3%)	1 (0.3%)

### 4.4.2 PR

The outlier analysis results for PR are presented in Table 4. Two subjects experienced PR  $>220$  ms in fedratinib group; however, both subjects had PR  $>200$  ms at baseline.

**Table 4: Categorical Analysis for PR**

Treatment Group	Total (N)		Value $\leq 200$ ms		200 ms < Value $\leq 220$ ms		Value $> 220$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fedratinib 500 mg + Palonosetron 0.25 mg	43	344	39 (90.7%)	313 (91.0%)	2 (4.7%)	21 (6.1%)	2 (4.7%)	10 (2.9%)

### 4.4.3 QRS

The outlier analysis results for QRS are presented in Table 5. Three subjects experienced on-treatment QRS  $>110$  ms; however, all three subjects had QRS  $>110$  ms at baseline.

**Table 5: Categorical Analysis for QRS**

Treatment Group	Total (N)		Value $\leq 100$ ms		100 ms < Value $\leq 110$ ms		Value $> 110$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fedratinib 500 mg + Palonosetron 0.25 mg	43	344	34 (79.1%)	292 (84.9%)	6 (14.0%)	35 (10.2%)	3 (7.0%)	17 (4.9%)

### 4.4.4 HR

The outlier analysis results for HR are presented in Table 6. Five subjects experienced HR  $>100$  bpm with HR baseline  $>100$  bpm.

**Table 6: Categorical Analysis for HR**

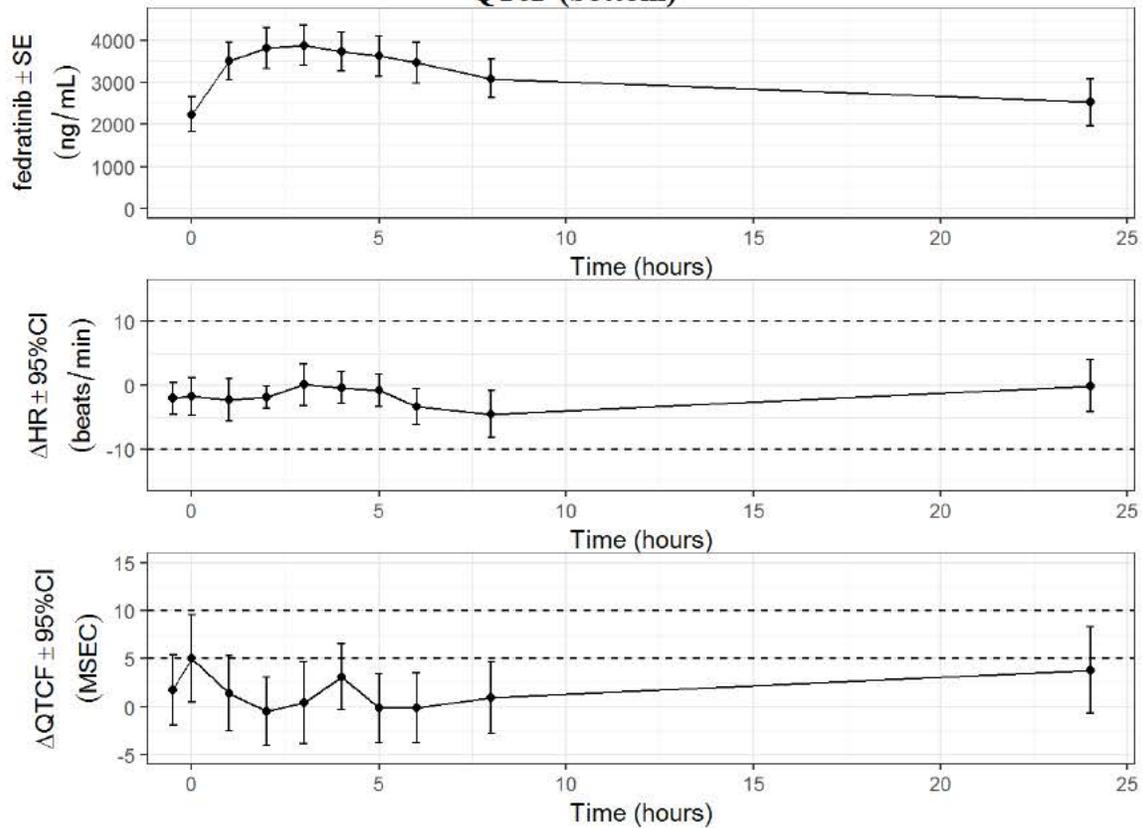
Treatment Group	Total (N)		Value ≤ 100 bpm		Value > 100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fedratinib 500 mg + Palonosetron 0.25 mg	43	344	38 (88.4%)	317 (92.2%)	5 (11.6%)	27 (7.8%)

#### 4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between fedratinib concentration and  $\Delta$ QTcF calculated from the difference between Day 15 measurements and the time-matched baseline on Day 1.

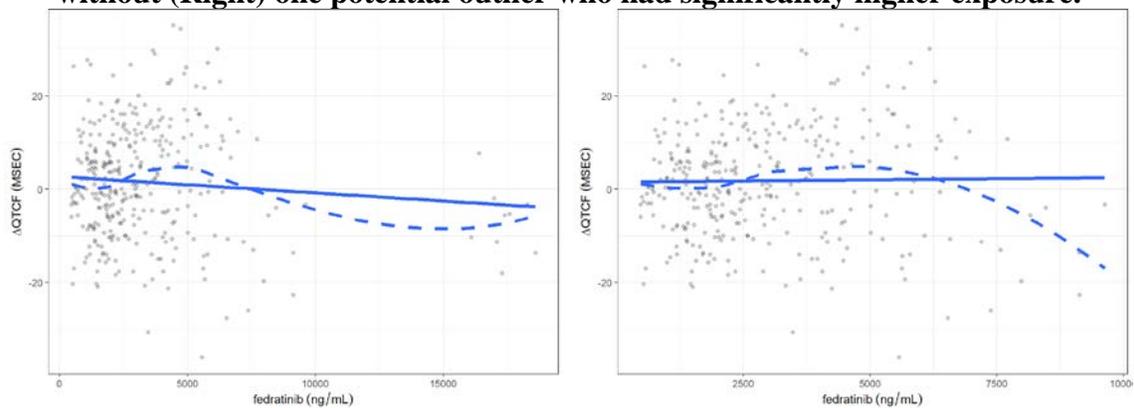
Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and  $\Delta$ QTcF and 3) presence of non-linear relationship. An evaluation of the time-course of drug concentration and changes in  $\Delta$ HR and  $\Delta$ QTcF is shown in Figure 5, which shows an absence of significant changes in HR. Other than the observations at 4 hour postdose, there appeared to be a trend of smaller extent of  $\Delta$ QTcF increase with higher fedratinib concentration. The plot does not suggest significant delayed effect between PK and  $\Delta$ QTcF profiles.

**Figure 5: Time course of drug concentration (top), heart rate (middle) and QTcF (bottom)**

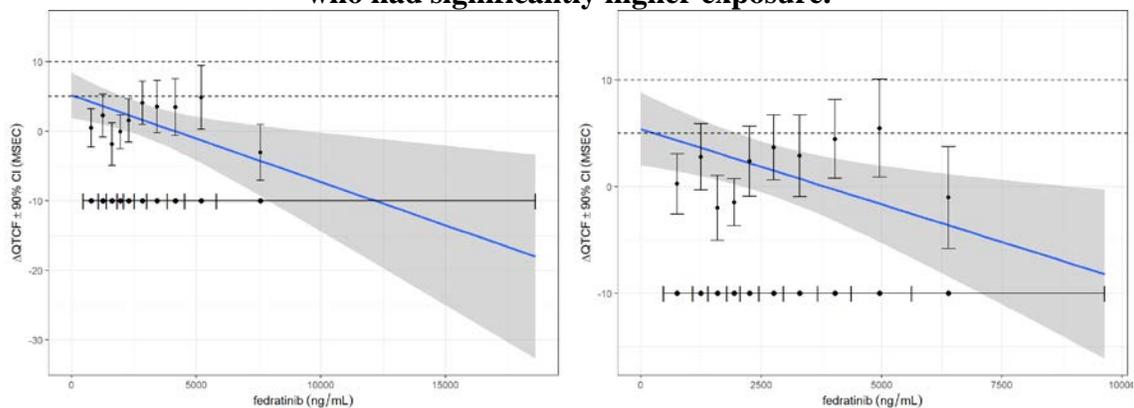


After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and  $\Delta\text{QTcF}$  was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between drug concentration and  $\Delta\text{QTcF}$ . One subject contributed to all the concentration measurements that were  $>15000$  ng/mL while concentrations measurements in the other patients were all below 10000 ng/mL. Even though the observations at the high concentration range deviate from linearity, there are no signs of nonlinear relationship that suggests a saturable exposure-response model. Therefore, a linear model (i.e.  $\Delta\text{QTcF} \sim 1 + \text{conc.} + \text{centered baseline} + (\text{conc.} \mid \text{usubjid})$ ) was applied to the dataset with or without the potential outlier who had significantly higher exposure than the other patients. The models predicted a lack of large mean effect at the geometric mean of the maximum steady state exposure at the 500 mg QD dose (i.e. 3423 ng/mL or 3274 ng/mL, with or without the potential outlier). The goodness-of-fit plot is shown in Figure 7.

**Figure 6: Assessment of linearity of concentration-QTc relationship with (Left) or without (Right) one potential outlier who had significantly higher exposure.**



**Figure 7. Goodness-of-fit plot with (Left) or without (Right) one potential outlier who had significantly higher exposure.**



The concentration-QTc analysis is based on the assumption that there is no pharmacodynamic interaction between palonosetron, granisetron, and fedratinib; there are no single-agent data to verify this assumption. In addition, the single-dose level design and PK sampling at steady state is not ideal for providing a wide exposure margin. While the standard residual vs. concentration plot and qq plot do not show significant deviation from normality, the goodness-of-fit plot suggests an underestimate of exposure-response

relationship (i.e. the slope) in fedratinib exposures less than 5000 ng/mL. However, this should not impact the final conclusion on a lack of large mean effect in the range of therapeutic exposure. No further evaluation on concentration-QTc analysis was pursued.

#### **4.5.1 Assay sensitivity**

Not applicable.

#### **4.6 SAFETY ASSESSMENTS**

No additional safety analyses were conducted.

#### **4.7 OTHER ECG INTERVALS**

No clinically significant changes in PR or QRS were observed.

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NAN ZHENG  
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MOH JEE NG  
04/25/2019 09:10:57 AM

DALONG HUANG  
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MOHAMMAD A RAHMAN  
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MICHAEL Y LI  
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LARS JOHANNESSEN  
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CHRISTINE E GARNETT  
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