

**NIHR Innovation Observatory
Evidence Briefing: June 2018**

Fedratinib for myelofibrosis

NIHRIO (HSRIC) ID: 23927

NICE ID: 9909

LAY SUMMARY

Myelofibrosis is a cancer of the bone marrow in which the marrow is replaced by scar tissue. The early stages of myelofibrosis may be asymptomatic in some people while others may have severe symptoms from the onset. As the bone marrow becomes more scarred, it is less able to produce blood cells leading to enlargement of spleen and liver. Enlargement of spleen may cause abdominal pain, shortness of breath, early satiety and faecal incontinence, along with progressive anaemia. Other symptoms include incurable itch, general malaise, weight loss, night sweats, low grade fever, anaemia, fatigue, and pallor. Many people with myelofibrosis have mutations in a gene known as JAK2 gene.

Fedratinib is in development for the treatment of disease-related splenomegaly (enlarged spleen) or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, including patients who have been previously exposed with ruxolitinib. Fedratinib is an inhibitor of JAK2 with potential to kill cancer cells. Fedratinib is given by mouth as capsule. If licensed fedratinib will offer an additional option for the treatment for patients with myelofibrosis.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, including patients who have been previously exposed with ruxolitinib.

TECHNOLOGY

DESCRIPTION

Fedratinib (SAR302503) is an orally bioavailable, small-molecule, adenosine triphosphate (ATP)-competitive inhibitor of Janus-associated kinase 2 (JAK2) with potential antineoplastic activity. Fedratinib competes with JAK2 as well as the mutated form AK2V617F for ATP binding, which may result in inhibition of JAK2 activation, inhibition of the JAK-signal transducers and activators of transcription (STAT) signalling pathway, and the induction of tumour cell apoptosis.¹

In the phase II trial, NCT01523171 patients were given fedratinib 400mg capsules, and in the phase III trial, NCT01437787, patients were given fedratinib 400mg or 500mg capsules, once daily for 28 days.^{2,3}

Fedratinib does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Currently, ruxolitinib is the only drug approved by the EMA for the treatment of myelofibrosis.⁴ Compared with ruxolitinib, fedratinib is a more specific inhibitor of JAK2 (vs other JAK family kinases) and appears to have activity against a broader family of kinases and kinase mutants.⁵ If licensed fedratinib will offer an additional treatment option for myelofibrosis in the first-line setting, and additionally may provide an option for patients who have been previously exposed to ruxolitinib.

DEVELOPER

Celgene Ltd.

PATIENT GROUP

BACKGROUND

Myelofibrosis (MF) is a cancer of the bone marrow in which the marrow is replaced by fibrous tissue. Myelofibrosis can be considered primary (also known as chronic idiopathic myelofibrosis), or secondary to either polycythaemia vera (PV) a disorder in which the bone marrow makes too many red blood cells, or essential thrombocythaemia (ET) disorder in which the bone marrow makes too many platelets.⁶ Collectively, these conditions are considered myeloproliferative neoplasms (MPN) and are relatively uncommon.⁷

The early stages of MF can be variable; some people remain symptomatic while others can experience severe symptoms from the onset. As the bone marrow becomes more fibrotic, its ability to produce blood cells becomes impaired. To compensate for this, the spleen and liver become enlarged as a response to an increased effort to produce more blood cells. This is known as splenomegaly which

may result in abdominal pain, dyspnoea, early satiety and faecal incontinence, along with progressive anaemia. Splenomegaly can also lead to problems with blood circulation in the liver and spleen. Other symptoms include incurable itch, general malaise, weight loss, night sweats, low grade fever, anaemia, fatigue, and pallor.⁶

Many people with MF have mutations in a gene known as JAK2 gene. JAK signalling controls cytokines and growth factors that are important for blood cell production and immune function. Regardless of mutational status, loss of regulation of the JAK signalling pathway is thought to be the underlying mechanism of the disease in myelofibrosis.⁶

Research shows that about 50-60% of people with MF have a mutation or alteration in a protein called JAK2. A further 30% of patients have mutations in a gene called calreticulin referred to as CALR and between 5-10% of patients have mutations in the platelet hormone receptor/thrombopoietin receptor called MPL.⁸

CLINICAL NEED and BURDEN OF DISEASE

NICE indicates that MF has an estimated annual incidence of 0.75 per 100,000. The median survival is 5 years from onset, but variation is wide; some patients have a rapidly progressing disorder with short survival. The peak incidence of primary myelofibrosis is between 50 and 70 years of age.⁹

In 2016, there were 2,226 newly registered patients of other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue (ICD-10 code: D47) in England.¹⁰

In England, in 2016-17 there were 109 admissions leading to 286 finished consultant episode bed days due to other specified neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue (ICD-10 code: D47.7).¹¹

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pacritinib for treating myelofibrosis (GID-TA10133). Expected publication date: TBC.
- NICE technology appraisal. Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (TA386). March 2016.

NHS ENGLAND and POLICY GUIDANCE

No relevant guidelines identified.

OTHER GUIDANCE

London Cancer Alliance. LCA Haemato-Oncology Clinical Guidelines: Acute Leukaemias and Myeloid Neoplasms: Part 4: Myeloproliferative Neoplasms. 2015.⁷

Reilly JT, et al. Use of JAK inhibitors in the management of myelofibrosis: a revision of the British Committee for Standards in Haematology Guidelines for Investigation and Management of Myelofibrosis 2012. Br J Haematol 2014;167:418-420

CURRENT TREATMENT OPTIONS

Allogeneic stem cell transplant is the only potentially curative treatment for myelofibrosis, however, it is only suitable for people who are fit enough to undergo treatment. Other treatment options aim to relieve symptoms and improve quality of life. These include hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion.⁶

NICE guidelines recommend ruxolitinib as an option for treating disease-related splenomegaly or symptoms in adults with primary myelofibrosis post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, only in people with intermediate-2 or high-risk disease.¹²

There are no approved treatments options post ruxolitinib. Therefore, the treatment pathway for patients post-ruxolitinib is unclear.^a

EFFICACY and SAFETY

Trial	JAKARTA, NCT01437787 , EFC12153, EudraCT 2011-001897-25; fedratinib vs placebo; phase III
Sponsor	Sanofi
Status	Completed
Source of Information	Trial registry; ³ publication ¹³
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, crossover assignment, double-blind, placebo-controlled
Participants	n=289; aged 18 years and older; intermediate or high-risk primary myelofibrosis (MF), post-polycythaemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis
Schedule	Randomised to receive: ^a 400mg capsules once daily for 28 days. Treatment was for as long as patients benefited from treatment, until progression of disease or until patients experienced unacceptable levels of toxicity. or 500mg capsules once daily for 28 days. Treatment was for as long as patients benefited from treatment, until progression of disease or until patients experienced unacceptable levels of toxicity. or

^a Information provided by company

	Placebo capsules once daily for 28 days
Follow-up	Active treatment for as long as patients benefited from treatment, until progression of disease or until patients experienced unacceptable levels of toxicity. Follow-up duration was until death. ^a
Primary Outcomes	Response Rate (RR), defined as the proportion of patients who have a $\geq 35\%$ reduction in volume of spleen size from baseline to week 24 (at the end of cycle 6), and confirmed 4 weeks thereafter [Time frame: 6 months]
Secondary Outcomes	<ul style="list-style-type: none"> • Symptom response rate (SRR): Proportion of patients with $\geq 50\%$ reduction from baseline to the end of cycle 6 in the total symptom score. [Time frame: 6 months] • Overall survival of either 400 mg/day or 500 mg/day of investigational medicinal product (IMP) as compared to placebo. [Time frame: approximately 5 years] • Progression free survival of either 400 mg/day or 500 mg/day of IMP as compared to placebo. [Time frame: approximately 5 years] • Proportion of patients who have $\geq 25\%$ reduction in volume of spleen size at end of cycle 6, and confirmed 4 weeks thereafter. [Time frame: 6 months] • Duration of spleen response, measured by MRI (or CT scan in patients with contraindications for MRI). [Time frame: 2 years] • Safety as assessed by clinical and laboratory events graded by the NCI CTCAE v4.03. [Time frame: approximately 5 years] <p>Exploratory endpoints:^a</p> <ul style="list-style-type: none"> • Rates of CR (complete remission), PR (partial remission), CI (clinical improvement), SD (stable disease), PD (progressive disease), and relapse as measured by the modified IWG-MRT response criteria. • To evaluate the effect of IMP on the JAK2 allele burden. • To evaluate the effect of IMP on bone marrow with regard to cytogenetics, cellularity, blast count, and presence or absence of reticulin fibrosis. • Change on health-related QOL and utility using the EQ-5DTM questionnaire. • Change from baseline in each of the individual symptoms of the MPN-SAF (complete MPN-SAF assessment). This assessment will be conducted at the screening visit and at Day 1 of Cycle 7
Key Results	A total of 289 patients were randomized: median age 65 years; 59% male; 63% primary MF; 48% high-risk MF; 67% JAK2V617F positive; 16% platelet count $< 100 \times 10^9/L$; median baseline spleen volume 2559 mL (range 316–8244). ^a Median (range) exposures for placebo, 400 mg and 500 mg groups were 24 (2–34), 30 (1–55) and 28 (1–60) weeks, respectively. Spleen RRs at week 24 (placebo 1%; 400 mg 47%; 500 mg 49%), and confirmed at week 28 (placebo 1%; 400 mg 36%; 500 mg 40%), were significantly ($p < 0.0001$) higher in both fedratinib groups compared with placebo. Nineteen patients had a spleen response at week 24 not confirmed 4 weeks later (spleen reduction 25–35% [n=10]; image not available/evaluable [n=8]; image taken outside time window [n=1]). Spleen RRs by baseline platelet level at week 24 were as follows – platelets ≥ 100 (400mgs 49%; 500mgs 51%; placebo 1%) & platelets < 100

	(400mgs 36%; 500mgs 40%; placebo 0%). Patients treated with fedratinib had significantly ($p < 0.0001$) greater improvements in MF symptoms compared with placebo. ¹³
Adverse effects (AEs)	The most common all grade non-hematologic treatment-emergent adverse event (TEAE) was diarrhoea (16%, 66% and 56% of patients in the placebo, 400 mg and 500 mg groups, respectively). Grade 3/4 diarrhoea was reported in 5% of patients in both the 400 mg and 500 mg dose groups. The most common hematologic TEAE was anaemia (any grade 91%, 99% and 98%; Grade 3/4 25%, 43% and 60% in the placebo, 400 mg and 500 mg groups, respectively). Rates of Grade 3/4 thrombocytopenia were 9% (placebo), 17% (400 mg), and 27% (500 mg). Incidences of Grade 3/4 liver function tests (placebo/400 mg/500 mg) were: bilirubin, 2%/2%/1%; ALT, 0%/3%/3%; and AST, 1%/2%/2%. Overall treatment discontinuation rates up to 24 weeks of treatment were placebo (8%), 400mgs (14%) and 500mgs (25%). Twenty-four patients died during the study (10, 4 and 10 in the placebo, 400 mg and 500 mg groups, respectively); the most common causes of death: disease progression (placebo [n=5]; 400 mg [n=2]; 500 mg [n=4]) and adverse events (placebo [n=4]; 400 mg [n=1]; 500 mg [n=4]). ¹³
Expected reporting date	-

Trial	JAKARTA2, NCT01523171 , ARD12181, EudraCT 2011-005226-21; fedratinib (single experimental arm); phase II
Sponsor	Sanofi
Status	Completed (study terminated early due to clinical hold. The clinical hold has since been lifted, but there are no plans to resume the study) ^a
Source of Information	Trial registry; 2 publication ¹⁴
Location	EU (incl UK), USA and/or Canada
Design	Single group assignment, uncontrolled, open label
Participants	n=97; aged 18 years and older; intermediate or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis; previously received ruxolitinib treatment
Schedule	Patients were given 400mg capsules once daily for 28 days for and a flexible dosing regimen was utilised to optimise efficacy, up to 600 mg daily. The treatment was for as long as patients benefited from treatment, until progression of disease or until patients experienced unacceptable levels of toxicity. ^a
Follow-up	Active treatment : for as long as patients benefited from treatment, until progression of disease or until patients experienced unacceptable levels of toxicity. Follow-up was intended until death. ^a
Primary Outcomes	Response rate (RR), defined as the proportion of subjects who have a $\geq 35\%$ reduction from baseline in volume of spleen at the end of cycle 6 as measured by magnetic resonance imaging (MRI) (or CT scan in subjects with contraindications for MRI) [Time frame: 6 months]

Secondary Outcomes	<ul style="list-style-type: none"> • Symptom response rate (SRR): Proportion of subjects with a $\geq 50\%$ reduction from baseline to the end of cycle 6 in the total symptom score using the modified MFSAF [Time frame: 6 months] • Duration of spleen response, measured by MRI (or CT scan in subjects with contraindications for MRI) [Time frame: 6 months] • Proportion of subjects with a $\geq 50\%$ reduction in length of spleen by palpation from baseline at the end of cycle 6 [Time frame: 6 months] • Response rate by cycle 6: Response Rate by Cycle 6 is defined as the proportion of subjects who have a $\geq 35\%$ reduction from baseline in volume of spleen at any time up to Cycle 6 as measured by MRI (or CT scan in subjects with contraindications for MRI). • The effect of SAR302503 on the JAK2V617F allele burden [Time frame: 2 years] <p>Exploratory endpoints:^a</p> <ul style="list-style-type: none"> • Overall survival • Bone marrow assessments: Bone marrow analyses, including cytogenetics, cellularity, blast count, and the degree of reticulin fibrosis will be performed for every subject at screening, optional at Day 1 of Cycle 4, at end of Cycle 6, at the end of every 6 cycles thereafter for two years, and at EOT. • JAK-STAT and other pathway signalling (Optional) • Tumour-specific mutation analysis
Key Results	<p>This phase 2 study met its primary endpoint, suggesting that patients with ruxolitinib-resistant or ruxolitinib-intolerant myelofibrosis might achieve significant clinical benefit with fedratinib. The study was terminated early due to a safety concern, but after additional data was analysed and assessed by the FDA the clinical hold on the development of fedratinib was lifted.¹⁴</p>
Adverse effects (AEs)	<p>Common grade 3–4 adverse events included anaemia (37 [38%] of 97 patients) and thrombocytopenia (21 [22%] of 97), with 18 (19%) patients discontinuing due to adverse events. Seven (7%) patients died during the study, but none of the deaths was drug related.¹⁴</p>
Expected reporting date	<p>-</p>

ESTIMATED COST and IMPACT

COST

The cost of fedratinib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

Reduced mortality/increased length of survival

Reduced symptoms or disability

Other

No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

Increased use of existing services

Decreased use of existing services

Re-organisation of existing services

Need for new services

Other

None identified

IMPACT ON COSTS and OTHER RESOURCE USE

Increased drug treatment costs

Reduced drug treatment costs

Other increase in costs

Other reduction in costs

Other

None identified

OTHER ISSUES

Clinical uncertainty or other research question identified

None identified

REFERENCES

¹ PubChem. *Fedratinib*. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Tg-101348#section=Top> [Accessed on 6 June 2018]

² ClinicalTrials.gov. *Phase II, Open Label, Single Arm Study of SAR302503 In Myelofibrosis Patients Previously Treated With Ruxolitinib (JAKARTA2)*. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT01523171> [Accessed on 6 June 2018]

³ ClinicalTrials.gov. *Phase III Study of SAR302503 in Intermediate-2 and High Risk Patients With Myelofibrosis (JAKARTA)*. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT01437787> [Accessed on 7 June 2018]

⁴ Electronic Medicines Compendium. *Jakavi*. Available from: <https://www.medicines.org.uk/emc/product/7786/smpc> [Accessed on 6 June 2018]

⁵ Pardanani A, Harrison C and Cortes JE. Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis, A Randomized Clinical Trial. *JAMA Oncol*. 2015;1(5):643–651. Available from: <http://doi:10.1001/jamaoncol.2015.1590>

⁶ National Institute for Health and Care Excellence. *Pacritinib for treating myelofibrosis*. Available from: <https://www.nice.org.uk/guidance/gid-ta10133/documents/draft-scope-post-referral> [Accessed on 6 June 2018]

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- ⁷ London Cancer Alliance. *LCA Haemato-Oncology Clinical Guidelines: Acute Leukaemias and Myeloid Neoplasms: Part 4: Myeloproliferative Neoplasms*. Available from: <http://www.londoncanceralliance.nhs.uk/media/110759/lca-myeloproliferative-neoplasms-clinical-guidelines-april-2015.pdf> [Accessed on 6 June 2018]
- ⁸ MPN Voice. *Myelofibrosis (MF)*. Available from: <http://www.mpnvoice.org.uk/about-mpns/questions-about-mpns/myelofibrosis.aspx> [Accessed on 6 June 2018]
- ⁹ National Institute for Health and Care Excellence. *Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis – final scope*. Available from: <https://www.nice.org.uk/guidance/ta386/documents/myelofibrosis-splenomegaly-symptoms-ruxolitinib-review-ta289-id831-final-scope2> [Accessed 25 June 2018]
- ¹⁰ Office for National Statistics. *Cancer Registration Statistics, England, 2016*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/dataset/cancerregistrationstatisticscancerregistrationstatisticsengland> [Accessed on 6 June 2018]
- ¹¹ Office for National Statistics. Hospital Episode Statistics. *Primary diagnosis: 34 character 2016-17*. Available from: <https://www.ons.gov.uk/> [Accessed on 7 June 2018]
- ¹² National Institute for Health and Care Excellence. *Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis*. Available from: <https://www.nice.org.uk/guidance/ta386/resources/ruxolitinib-for-treating-diseaserelated-splenomegaly-or-symptoms-in-adults-with-myelofibrosis-pdf-82602853065925> [Accessed on 6 June 2018]
- ¹³ Pardanani A, Harrison CN, Cortes JE, Cervantes F, Mesa RA et al. Results Of a Randomized, Double-Blind, Placebo-Controlled Phase III Study (JAKARTA) Of The JAK2-Selective Inhibitor Fedratinib (SAR302503) In Patients With Myelofibrosis (MF). *Blood*. 2013; 122(21): 393. Available from: <https://doi.org/10.1001/jamaoncol.2015.1590>
- ¹⁴ Harrison CN, Schaap N, Vannucchi AM, Kiladjian J, Tiu Rv et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. *The Lancet Haematology*. 2017; 4(7): e317-324. Available from: [https://doi.org/10.1016/S2352-3026\(17\)30088-1](https://doi.org/10.1016/S2352-3026(17)30088-1)