Health Technology Briefing
May 2022

Momelotinib for the treatment of symptomatic and anaemic myelofibrosis

Company/Developer	Sierra Oncology Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28643	NICE ID: 10513	UKPS ID: Not Availbale

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Momelotinib is currently in clinical development for the treatment of symptomatic myelofibrosis with anaemia. Myelofibrosis is a rare blood cancer, where the bone marrow is too active so scar tissue builds up inside the bone marrow and blood cells cannot develop properly. The reduction in blood cells can result in anaemia, amongst other symptoms such as tiredness, shortness of breath and easily bleeding and bruising. Treatment of myelofibrosis includes therapy with a class of medicines called JAK inhibitors, but approximately half of myelofibrosis patients eligible for JAK inhibitor therapy are moderately to severely anaemic. Currently approved JAK inhibitors only address symptoms and reduce bone marrow activity, which can lead to worsening anaemia, resulting in dose reductions that potentially reduce treatment effect.

Momelotinib is a potent inhibitor of JAK1, JAK2 and, uniquely amongst the JAK-inhibitor class, Activin A receptor, type I (ACVR1). Due to this unique profile, it is the first JAK inhibitor to demonstrate positive data for all key hallmarks of the disease, which include symptoms, anaemia, and enlargement of the spleen. It will be self-administered as once daily oral tablets. If approved, momelotinib would add an alternative treatment pathway for myelofibrosis patients for whom other therapy is insufficient or for those with anaemia.

Proposed Indication

Treatment of disease-related splenomegaly or symptoms in anaemic adult patients with high risk, intermediate-2, or intermediate-1 risk primary myelofibrosis (PMF), post-polycythaemia vera (PV) myelofibrosis, or post-essential thrombocythemia (ET) myelofibrosis who are Janus kinase inhibitor (JAKi) naive or have been treated with a JAK-inhibitor.[1,a]

Technology

Description

Momelotinib (MMB, GS-0387, CYT387) is a potent inhibitor of Janus kinase1 (JAK1), Janus kinase2 (JAK2) and, uniquely amongst the JAK-inhibitor class, Activin A receptor, type I (ACVR1).[1,2] This unique profile results in demonstrable clinical activity against each of the three hallmark features of myelofibrosis (MF) – anaemia, constitutional symptoms and splenomegaly – across the continuum of intermediate/high risk patients including JAKi-naïve and previously JAKi-treated subjects. Momelotinib's anaemia benefit is primarily achieved through direct inhibition of ACVR1 leading to a decrease in circulating hepcidin. Hepcidin is often markedly elevated in MF and contributes to an iron restricted anaemia. By lowering hepcidin, a corresponding increase in serum iron occurs with consequent clinically relevant increases in haemoglobin and red blood cells due to increased iron availability for erythropoiesis. Momelotinib has also been shown to stabilise, and in some cases ameliorate, thrombocytopenia.[2]

Momelotinib is in clinical development for the treatment of disease-related splenomegaly or symptoms in anaemic adult patients with myelofibrosis, who are JAK-inhibitor naïve or were previously treated with a JAKi therapy.[1,a] In the phase III clinical trials (NCT01969838 SIMPLIFY-1, NCT02101268 SIMPLIFY-2 and NCT04173494 MOMENTUM), 200mg momelotinib was self-administered orally as tablet once daily.[1,3-6]

Key Innovation

The first approved JAKi, ruxolitinib, demonstrated a rapid and durable improvement of symptoms and splenomegaly accompanied with better overall survival in MF patients. However, ruxolitinib-related adverse effects and resistance are limitations, so there is an urgent need to develop new JAK inhibitors to retain the efficacy of ruxolitinib and avoid its deficiency.[7] Approximately half of myelofibrosis patients are moderately to severely anaemic when eligible for JAK inhibitor treatment.

Furthermore, currently approved JAK inhibitors only address symptoms and splenomegaly and are myelosuppressive. This can lead to worsening anaemia, resulting in dose reductions that potentially reduce treatment effect.

Momelotinib is the first and only JAK inhibitor to demonstrate positive data for all key hallmarks of the disease—symptoms, splenic response and anaemia.[8] If approved, momelotinib will provide an alternative treatment option for symptomatic myelofibrosis with anaemia.

Regulatory & Development Status

Momelotinib currently does not currently have a Marketing Authorisation in the EU/UK for any indication.

Momelotinib was granted FDA fast track designation for the treatment of for the treatment of patients with intermediate/high-risk MF who have previously received a JAK inhibitor in June 2019.[9]

[a]Information provided by Sierra Oncology Inc.

Patient Group

Disease Area and Clinical Need

Myelofibrosis (MF) is a rare blood cancer that results from dysregulated JAK-STAT signalling and is characterised by constitutional symptoms, splenomegaly (enlarged spleen) and progressive anaemia.[8] In MF, the bone marrow is too active so scar tissue builds up inside the bone marrow and blood cells cannot develop properly. Primary MF is when people who have no history of problems with their bone marrow get MF. Secondary myelofibrosis is where the condition develops in people who have other bone marrow disorders such as polycythaemia vera or essential thrombocythemia. As the number of new blood cells fall in the bone marrow, the liver and spleen try to make more blood cells, but they are not as good at making them as the bone marrow, leading to fewer red blood cells, resulting in anaemia. Research suggests that exposure to the chemical benzene may increase the risk of developing myeloproliferative neoplasms. More than 55% with myelofibrosis have a change in a gene a called JAK2, which makes a protein that controls how many blood cells the stem cells make. Up to 35% have a change in the CALR gene. When the JAK2 or CALR gene becomes mutated the bone marrow may not function correctly. This means scar tissue can build up in the bone marrow. Other symptoms of MF can include tiredness, shortness of breath, easily bruising and bleeding, gout and bone pain.[10]

The number of people diagnosed each year with MF is estimated to be 2 to 3 cases per 100,000 and it is equally common in men and women. It primarily affects middle-aged and elderly people and is hardly ever diagnosed in children.[11] The average age at diagnosis is 65 years.[10] The specific population likely to be eligible to receive momelotinib could not be estimated from available published sources.

Recommended 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.[12]

The National Institute for Health and Care Excellence (NICE) recommends ruxolitinib as an option for treating disease-related splenomegaly or symptoms in adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythemia myelofibrosis, only in people with intermediate-2 or high risk disease.[12,13]

NICE also recommends fedratinib for use within the Cancer Drugs Fund as an option for treating disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis in adults. It is recommended only if they have previously had ruxolitinib and the conditions in the managed access agreement for fedratinib are followed.[14]

Clinical Trial Information

Trial	**MOMENTUM, NCT04173494, EudraCT 2019-000583-18;** A Randomized, Double-blind, Phase 3 Study to Evaluate the Activity of Momelotinib Versus Danazol in Symptomatic, Anaemic Subjects With PMF, or Post-PV/ET MF Who Were Previously Treated With JAK Inhibitor Therapy **Phase III:** Active, not recruiting

	Location(s): 13 countries in EU, US, Australia, Canada, Asia, and UK **Study completion date:** December 2021
Trial Design	Randomised, parallel assignment, quadruple-masked, double-blind
Population	N = 195 (actual); high risk, intermediate-2, or intermediate-1 risk PMF, PV myelofibrosis, or post-ET myelofibrosis who were previously treated with an approved JAKi therapy; aged 18 years and older.
Intervention(s)	Momelotinib oral tablets
Comparator(s)	Danazol oral capsules
Outcome(s)	• Total Symptom Score (TSS) response rate at Week 24 measured using the Myelofibrosis Symptom Assessment Form v4.0 [Time Frame: Week 24 landmark] defined as the proportion of patients with a ≥50% reduction in mean MFSAF TSS over the 28 days immediately before the end of week 24 compared with baseline See trial record for full list of other outcomes.
Results (efficacy)	195 patients (momelotinib n = 130; danazol n = 65):[15,16] • Primary Endpoint of Total Symptom Score (TSS) of >50% reduction from baseline: 24.6% in the momelotinib arm vs. 9.2% in the control arm (p=0.0095) • Secondary Endpoint of Transfusion Independence (TI): 30.8% in the momelotinib arm vs. 20% in the control arm (one-sided p=0.0064; non-inferiority) • Secondary Endpoint of Splenic Response Rate (SRR) ≥35%: 23.1% in the momelotinib arm vs. 3.1% in the control arm (p=0.0006)
Results (safety)	The rate of Grade 3 or worse adverse events in the randomized treatment period was 54% in the momelotinib arm and 65% in the control arm. Serious treatment emergent adverse events were 35% in the momelotinib arm and 40% in the control arm.[15] Favourable trend for overall survival observed at Week 24 HR 0.506 and p value = 0.072, favouring momelotinib.[17]

Trial	**SIMPLIFY-2, NCT02101268, EudraCT 2013-005007-13**; A Phase 3, Randomized Study To Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects With Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis Who Were Treated With Ruxolitinib **Phase III:** Completed **Location(s):** 4 countries in EU, UK, US, Canada and Israel. **Study completion date:** April 2019
Trial Design	Randomised, open-label, parallel assignment

Population	N=156 (actual); high-risk or intermediate-2 risk PMF, Post-PV/-ET MF or intermediate-1 risk with symptomatic splenomegaly and/or hepatomegaly; aged 18 years and older.
Intervention(s)	Momelotinib oral tablets
Comparator(s)	Best Available Treatment (BAT)
Outcome(s)	Primary - Splenic response rate at Week 24 [proportion of participants achieving a ≥ 35% reduction in spleen volume at Week 24 from baseline] See trial record for full list of other outcomes.
Results (efficacy)	Seven (7%) of 104 patients in the momelotinib group and three (6%) of 52 in the BAT group had a reduction in the spleen volume by at least 35% compared with baseline (proportion difference [Cochran–Mantel–Haenszel method], 0·01; 95% CI −0·09 to 0·10), p=0·90).[5]

Results (safety)

Treatment Emergent Adverse Events Occurring in ≥10% of Either Treatment Arm NOTE. Data presented as No. (%).[5]

	Double-blind phase	
Treatment-Emergent Adverse Event	Momelotinib	BAT
Diarrhoea	34 (32.7%)	8 (15.4%)
Cough	18 (17.3%)	6 (11.5%)
Pyrexia	15 (14.4%)	4 (7.7%)
Anaemia	16 (15.4%)	10 (19.2%)
Asthenia	20 (19.2%)	11 (21.2%)
Thrombocytopoenia	18 (17.3%)	6 (11.5%)
Nausea	20 (19.2%)	5 (9.6%)
Fatigue	16 (15.4%)	10 (19.2%)
Abdominal pain	16 (15.4%)	8 (15.4%)
Oedema peripheral	11 (10.6%)	6 (11.5%)
Dizziness	16 (15.4%)	4 (7.7%)
Headache	16 (15.4%)	3 (5.8%)
Dyspnoea	13 (12.5%)	7 (13.5%)
Urinary tract infection	11 (10.6%)	4 (7.7%)
Pruritus	13 (12.5%)	4 (7.7%)

Trial	**SIMPLIFY-1, NCT01969838, EudraCT 2013-002707-33**; A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib vs. Ruxolitinib in Subjects With Primary Myelofibrosis (PMF) or Post-Polycythemia Vera or Post-Essential Thrombocythemia Myelofibrosis (Post-PV/ET MF) **Phase III:** Completed **Location(s):** 13 countries in EU, US, Australia, Canada, Asia, and UK **Study completion date:** May 2019
Trial Design	Randomised, parallel assignment, quadruple-masked, double-blind

<table>
<tr><td>Population</td><td>N=432 (actual); high-risk or intermediate-2 risk PMF, Post-PV/-ET MF or intermediate-1 risk with symptomatic splenomegaly, hepatomegaly, anaemia (haemoglobin < 10.0 g/dL), and/or unresponsiveness to available therapy; aged 18 years and older</td></tr>
<tr><td>Intervention(s)</td><td>Momelotinib oral tablets</td></tr>
<tr><td>Comparator(s)</td><td>Ruxolitinib oral tablets</td></tr>
<tr><td>Outcome(s)</td><td>Primary - Splenic response rate at Week 24 [proportion of participants achieving a ≥ 35% reduction in spleen volume at Week 24 from baseline]

See trial record for full list of other outcomes.</td></tr>
<tr><td>Results (efficacy)</td><td>Spleen volume was reduced ≥35% from baseline in 26.5% (57 of 215) of patients who received momelotinib and 29.0% (63 of 217) of patients who received ruxolitinib, with a noninferiority proportion difference of 0.09 (95% CI, 0.02 to 0.16). Because the lower bound of the two-sided 95% CI was > 0, momelotinib met the primary end point of noninferiority to ruxolitinib (P = .011).[6]</td></tr>
<tr><td>Results (safety)</td><td>Treatment Emergent Adverse Events Occurring in ≥10% of Either Treatment Arm NOTE. Data presented as No. (%).[6]
<table>
<tr><td></td><td colspan="2">Double-blind phase</td></tr>
<tr><td>Treatment-Emergent Adverse Event</td><td>Momelotinib</td><td>Ruxolitinib</td></tr>
<tr><td>Thrombocytopenia</td><td>40 (18.7)</td><td>63 (29.2)</td></tr>
<tr><td>Diarrhoea</td><td>38 (17.8)</td><td>43 (19.9)</td></tr>
<tr><td>Headache</td><td>37 (17.3)</td><td>43 (19.9)</td></tr>
<tr><td>Dizziness</td><td>34 (15.9)</td><td>25 (11.6)</td></tr>
<tr><td>Nausea</td><td>34 (15.9)</td><td>8 (3.7)</td></tr>
<tr><td>Fatigue</td><td>31 (14.5)</td><td>26 (12.0)</td></tr>
<tr><td>Anaemia</td><td>29 (13.6)</td><td>82 (38.0)</td></tr>
<tr><td>Abdominal pain</td><td>22 (10.3)</td><td>24 (11.1)</td></tr>
</table></td></tr>
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<table>
<tr><td>Trial</td><td>NCT03441113, EudraCT 2017-004350-42; Extended Access of Momelotinib for Subjects with PMF or Post-PV / -ET MF
Phase III: Active
Location(s): 11 countries in EU, US, Australia, Canada, Asia ans UK
Primary completion date: December 2026</td></tr>
<tr><td>Trial Design</td><td>Non-randomised, parallel assignment, open label</td></tr>
<tr><td>Population</td><td>N=400 (estimated); enrolled in trial NCT01969838, NCT02101268, NCT04173494 and NCT02124746; aged 18 years and older.</td></tr>
<tr><td>Intervention(s)</td><td>Momelotinib oral tablets,</td></tr>
<tr><td>Comparator(s)</td><td>-</td></tr>
<tr><td>Outcome(s)</td><td>Number of Participants Who Had Access to, and Received the Intervention [Time Frame: Participants will be assessed every 12 weeks until discontinuation.</td></tr>
</table>

	Participation in this extended access study has been an average of approximately 8 months.]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of momelotinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (TA756). December 2021.
- NICE technology appraisal. Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (TA386). March 2016.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Pan-London Blood Cancer. Pan-London Haemato-Oncology Clinical Guidelines. January 2020.[18]
- European Society for Medical Oncology. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2015.[19]
- British Society for Haematology. 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. June 2014.[20]
- International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN). Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. August 2013.[21]
- British Society for Haematology. Guideline for the diagnosis and management of myelofibrosis. June 2012.[22]

Additional Information

Sierra Oncology Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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