Momelotinib (Omjjara®) for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis (PMF), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis

General information

Drug description [1]

The active substance of Omjjara® is momelotinib, an antineoplastic protein kinase inhibitor. Its antineoplastic activity is linked to the selective inhibition of the Janus Associated Kinases (JAKs) involved in the signalling mediation of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Indication [1]

Momelotinib (Omjjara®) is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have PMF, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are JAK inhibitor naïve or have been treated with ruxolitinib.

Incidence [2]

PMF is a rare disease, the incidence rate is 0.5-1.5/100,000 persons per year.
The median age at diagnosis is 65 years; men are more often affected than women.

Current treatment [2]

For the treatment of anaemia in patients with PMF, Onkopedia recommends the following:

- For the treatment of anaemia requiring therapy, in particular with additional autoimmune haemolysis (low haptoglobin and potential positive Coombs test), corticosteroids can be used.
- Starting with an initial dose of 0.5 mg/kg prednisolone for three weeks, the dose should be reduced subsequently and a long-term therapy using low doses (below the Cushing threshold) can be administered as appropriate.
- About one third of patients respond to this therapy; however, most of them respond transiently.
- It should be ensured that anaemia is not caused by hypoferremia.
- Administration of erythropoietin at an initial dose of 3 x 10,000 I.U. per week leads to a response in about 50% of patients; response can take up to 3 months. Complete remissions can be achieved in about 20-25% of cases. Serum erythropoietin < 125 U/l is required to achieve a beneficial response. With pegylated long-term compounds, similar response rates can be achieved. However, it should be considered that splenomegaly can be increased in the course of erythropoietin therapy by stimulation of extramedullary haematopoiesis.
- Currently, due to lacking efficacy and safety data, there is no recommendation for the combination therapy of erythropoietin and ruxotinib.

For the treatment of splenomegaly in patients with PFM, Onkopedia recommends:

- Currently, due to efficacy and approval status, JAK2 inhibitors (ruxolitinib, fedratinib) are used for the therapy of splenomegaly.
- Only in case of patients who do not response or who have undesirable side effects, radiation of the spleen or splenectomy can be discussed.

For the treatment of disease-related symptoms or splenomegaly in patients with post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, Onkopedia recommends:

- In patients with intermediate 2- or high-risk disease, eligibility for allogeneic SCT should be tested.
- In patients with low risk- or intermediate 1-risk, therapy options are:
  - Ruxolitinib or fedratinib
  - Therapy focussed on problems: erythropoietin, erythrocyte transfusion, hydroxyurea, (peg-)interferon, steroids, androgens or imides.
  - Participation in clinical trials.

Regulatory status

EMA [1]	FDA [3]
Approval status for this indication: On 9 November 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for **Omjjara®** The full indication is:	**Approval status for this indication**: not approved On 15 September 2023, the FDA approved momelotinib (**Ojjaara®**) for the treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis or secondary

❖ Omjjara® is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are JAK inhibitor naïve or have been treated with ruxolitinib. Omjjara will be available as 100 mg, 150 mg and 200 mg film-coated tablets. **Other indications**: none ✓ **Orphan status**	myelofibrosis (post polycythaemia vera and post-essential thrombocythemia), in adults with anaemia. **Other indications**: none

Manufacturer

Omjjara® is manufactured by GlaxoSmithKline.

Costs

Currently, there is no cost information available.

Study characteristics [4-6]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
MOMENTUM NCT04173494	195 (2:1)	momelotinib (200 mg orally once per day) + danazol placebo	danazol (300 mg orally twice per day) + momelotinib placebo	Myelofibrosis Symptom Assessment Form (MFSAF) TSS response rate at week 24	-	international, double-blind, randomised, controlled, phase 3 study	JAK	Sierra Oncology	MOMENTUM trial [6]

Inclusion criteria[1]	Exclusion criteria	Patient characteristics at baseline (I vs. C, n=130 vs. n=65)
❖ ≥ 18 years with confirmed diagnosis of PMF in accordance with the WHO 2016 criteria, or post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis in accordance with the IWG-MRT criteria ❖ Symptomatic, defined as a MFSAF TSS of ≥10 units assessed by a single MFSAF v4.0 assessment during screening prior to Day BL1. ❖ Anaemic, defined as any of the following: • For any subject having received a transfusion within 28 days prior to the first day of Baseline assessments (BL1), with pre-transfusion Hgb < 10 g/dL or • For subjects without ongoing JAK inhibitor therapy at screening; Hgb < 10 g/dL during the Baseline Period (Days BL1 to Day BL7), or	❖ Use of the following treatments within the time periods noted: • Momelotinib at any time. • Approved JAK inhibitor therapy within 1 week prior to Day BL1. • Active anti-MF therapy as defined in Study Protocol within 1 week prior to Day BL1. • Supportive care including steroids for non-MF indications may be used as defined Study Protocol. • Potent cytochrome P450 3A4 (CYP3A4) inducers within 1 week prior to randomization. • Investigational agent within 4 weeks prior to Randomization Erythropoiesis stimulating agent within 4 weeks prior to randomization. • Danazol within 3 months prior to randomization. • Splenic irradiation within 3 months prior to randomization.	❖ Median age: 71 years (range, 65–75) vs. 72 years (range, 67–78) ❖ Male sex: 61% vs. 68% ❖ Mean BMI (kg/m^2): 25.2 vs. 25.7 ❖ Race • White: 82% vs. 77% • Asian: 9% vs. 9% • Black: 2% vs. 3% • Hispanic: 4% vs. 9% ❖ Myelofibrosis subtype • Primary: 60% vs. 71% • After polycythaemia vera: 21% vs. 17% • After essential thrombocythaemia: 19% vs. 12% ❖ DIPSS risk category

[1] For detailed in- and exclusion criteria, please see study protocol.

- For subjects receiving ongoing JAK inhibitor therapy at screening; Hgb < 10 g/dL during screening, prior to the last day of Baseline assessments (Day BL7).

❖ Previously treated, with an approved JAK inhibitor for PMF or post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis for ≥ 90 days, or ≥ 28 days if JAK inhibitor therapy is complicated by red blood cell transfusion requirement of ≥ 4 units in 8 weeks, or Grade 3/4 AEs of thrombocytopenia, anaemia, or haematoma
- Subjects who discontinued JAK inhibitor therapy prior to Screening require no additional non-treatment interval.
- For subjects with ongoing JAK inhibitor therapy at Screening, JAK inhibitor therapy must be tapered over a period of at least 1 week. Subjects receiving a low dose of JAK inhibitor, may have a reduced taper period, or no taper, with the sponsor's approval. A non-treatment interval begins ≥ 7 days prior to Day BL1.

❖ Baseline splenomegaly, defined as having a palpable spleen at ≥ 5 cm, below the LCM, or with volume ≥ 450 cm3 on imaging, assessed during screening at any point prior to randomization.

❖ High risk, intermediate-2, or intermediate-1 risk as defined by DIPSS, or DIPSS-plus.

❖ No allogeneic stem cell transplant planned.

❖ Acceptable laboratory assessments:
- ANC ≥ 0.75 × 10^9/L
- PLT ≥ 25 × 10^9/L
- Peripheral blast count < 10%
- AST/SGOT and ALT/SGPT ≤ 3 × ULN
- Calculated creatinine clearance ≥ 30 mL/min
- Direct bilirubin ≤ 2.0 × ULN

❖ ECOG performance status of 0, 1, or 2.

❖ Life expectancy >24 weeks.

❖ Able to understand and willing to sign the informed consent form.

❖ Willing and able to complete PRO assessments using an ePRO device according to protocol.

- Current treatment with simvastatin, atorvastatin, lovastatin or rosuvastatin.

❖ History of prostate cancer, with the exception of localized prostate cancer that has been treated surgically or by radiotherapy with curative intent and presumed cured.

❖ Prostate specific antigen > 4 ng/mL.

❖ Unsuitable for spleen volume measurements due to prior splenectomy or unwilling or unable to undergo an MRI or CT scan for spleen volume measurement per protocol requirements in Study Protocol.

❖ Any of the following:
- Uncontrolled intercurrent illness.
- Significant active or chronic bleeding event ≥ Grade 2 per CTCAE v5.0, within 4 weeks prior to randomization.
- Unstable angina pectoris within 6 months prior to randomization.
- Symptomatic congestive heart failure within 6 months prior to randomization.
- Uncontrolled cardiac arrhythmia within 6 months prior to randomization.
- QTcF interval > 500 msec, unless attributed to bundle branch block.
- Current progressive thrombosis despite treatment.
- History of porphyria.
- Child-Pugh score ≥ 10.
- Psychiatric illness, social situation, or any other condition that would limit compliance with trial requirements or may interfere with the interpretation of study results, as judged by investigator or sponsor.
- Inability or unwillingness to comply with the protocol restrictions on MF therapy and other medications prior to and during study treatment.

❖ Subjects with a prior or concurrent malignancy, whose natural history or treatment has a significant potential to interfere with the safety or efficacy assessment of the investigational regimen.

❖ Known clinically significant anaemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary haemolytic anaemia, or gastrointestinal bleeding, or thalassemia.

❖ Known positive status for HIV.

❖ Chronic active or acute viral hepatitis A, B, or C infection, or hepatitis B or C carrier.

- Intermediate-1: 5% vs. 5%
- Intermediate-2: 55% vs. 62%
- High: 38% vs. 29%
- Missing: 1% vs. 5%

❖ JAK2 Val617Phe mutation
- Positive: 75% vs. 78%
- Negative: 22% vs. 18%
- Unknown or missing: 4% vs. 3%

❖ ECOG performance status
- 0: 12% vs. 23%
- 1: 64% vs. 52%
- 2: 24% vs. 25%

❖ Mean previous JAK inhibitor duration: 138.5 weeks vs. 124.8 weeks

❖ TSS
- Mean: 28.0 vs. 25.7
- Median: 26.4 vs. 23.6
- ≥22: 59% vs. 60%

❖ Haemoglobin
- Mean (g/dL): 8.1 vs. 7.9
- Median (g/dL): 8.0 vs. 8.0
- ≥8 g/dL: 52% vs. 51%
- Transfusion independent: 13% vs. 15%
- Transfusion dependent: 48% vs. 52%

❖ Red blood cell units transfused ≤8 weeks before randomisation
- 0: 22% vs. 20%
- 1–4: 45% vs. 42%
- ≥5: 34% vs. 38%

❖ Central spleen volume (cm^3)
- Mean: 2367 vs. 2288
- Median: 2112 vs. 2059
- Palpable spleen length below the left costal margin ≥12 cm: 42% vs. 43%

❖ Platelet count (× 10^9 cells per L)
- Mean: 151.7 vs. 130.7
- Median: 97 vs. 94

❖ Neutrophil count (× 10^9 cells per L)
- Mean: 8.6 vs. 6.9

❖ WOCBP, men with partners of childbearing potential, and subjects with pregnant or lactating partners must agree to follow the contraceptive requirements of the clinical trial protocol, effective from the first administration of momelotinib, throughout the trial and for 6 months after the last dose of momelotinib.	❖ Unresolved non-hematologic toxicities from prior therapies that are > Grade 1 per CTCAE v5.0. ❖ Presence of peripheral neuropathy ≥ Grade 2 per CTCAE v5.0. ❖ Women who are already pregnant or lactating. ❖ Known intolerance or hypersensitivity to momelotinib or danazol, their metabolites, or formulation excipients. ❖ Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.	• Median: 4.7 vs. 3.6 ❖ Peripheral blasts (%) • Mean: 2.1 vs. 1.9 • Median: 1 vs. 1

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Database cutoff date 3 December 2021:</u> **Patients reporting a 50% or more reduction in MFSAF TSS from baseline at week 24**: 25% vs. 9%; proportion difference 16% (95% CI 6–26, p=0.0095) **Transfusion independence at week 24 was achieved by 30% vs. 20%;** non-inferiority difference of 14% (95% CI 2–25; one-sided p=0.0116) **Splenic response rate (≥25% reduction):** 39% vs. 6%; two-sided p<0.0001 (superior) **Absolute TSS change from baseline**: −11.5 vs. −3.9; two-sided p=0.0014 (superior) **Splenic response rate (≥35% reduction):** 22% vs. 3%; two-sided p=0.0011 (superior) **Rate of zero transfusions to week 24**: 35% vs. 17%; two-sided p=0.0012 (superior) **HR for OS:** 0.73 (95% CI, 0.38–1.41; p=0.35) **HR for leukaemia-free survival**: 0.65 (95% CI, 0.35–1.21; p=0.17) **Median follow-up time for OS:** 275 days (95% CI, 238–314; range 41–476) **Median Follow-up time for leukaemia-free survival:** 281 days (95% CI 238–316; range 41–476) **Additional pre-planned and exploratory post-hoc analyses in thrombocytopenic groups in patients with baseline platelet counts of < 100 × 10^9 cells per L:** • Week 24 TSS rates: 29% vs. 15% • Transfusion independence rates (27% vs. 21%) • Splenic response rates based on 35% reduction or more (20% vs. 6%) **Additional pre-planned and exploratory post-hoc analyses in thrombocytopenic groups in patients with baseline platelet counts of < 50 × 10^9 cells per L:** • Week 24 TSS rates: 22% vs. 8% • Splenic response rates based on 35% reduction or more: 22% vs. 0 • Transfusion independence rates: 17%vs. 15% • Week 24 event-free rates for OS: 94% vs. 62%	**Anaemia grade ≥3:** 75% vs. 61% **Thrombocytopenia grade ≥3:** 28% vs. 26% **Serious infections:** 15% vs. 17% **Peripheral neuropathy grade ≤2:** 4% vs. 2% **increased alanine aminotransferase:** 7% vs. 8% **Increased aspartate aminotransferase:** 5% vs. 5% **AEs leading to study drug discontinuation:** 18% vs. 23% **Deaths as of the data cutoff date:** 21% vs. 19% **Fatal AEs[2]:** 12% vs. 17% **Safety profile in patients with platelet counts < 50 × 10^9 cells per L:** • **Thrombocytopenia grade ≥3:** 44% vs. 15% • **Haemorrhage grade ≥3:** 6% vs. 0

ESMO-MCBS for Haematological Malignancies version 1.0 [7]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS for Haematological Malignancies was not applicable because the primary endpoint "MFSAF-TSS response rate at week 24" could not be assessed.											

Risk of bias (RCT) [8]

[2] Infections and infestations were the most commonly reported fatal events with momelotinib (6%) and anaemia was the most reported fatal event with danazol (5%).

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	yes[3] unclear risk	yes low risk	yes[4] high risk	High risk

Ongoing trials

NCT number/trial name	Description	Estimated study completion date
Currently, no ongoing phase 2 or phase 3 trials were identified via ClinicalTrials.gov.		

Available assessments

- In May 2020, NIHR published a Health Technology Briefing "Momelotinib for the treatment of symptomatic and anaemic myelofibrosis" [9].
- No further assessments were identified via NICE, CADTH, G-BA and ICER.

Other aspects and conclusions

- In November 2023, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Omjjara®, indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are JAK inhibitor naïve or have been treated with ruxolitinib. This indication is **not approved by the FDA**. However, in September 2023, the FDA approved momelotinib (Ojjaara®) for the treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis or secondary myelofibrosis (post polycythaemia vera and post-essential thrombocythemia), in adults with anaemia.
- **MOMENTUM (NCT04173494)** is an international, **double-blind, randomised, controlled, phase 3 study**, aiming to **confirm** the differentiated clinical benefits of momelotinib vs. the active comparator danazol in JAK-inhibitor-exposed, symptomatic patients with anaemia and intermediate-risk or high-risk myelofibrosis. Eligible patients were ≥18 years with primary myelofibrosis or post-polycythaemia vera or post-essential thrombocythaemia myelofibrosis who were previously treated with an approved JAK inhibitor for 90 days or more or 28 days or more if therapy was complicated by four units or more of red blood cells transfused in 8 weeks, or grade 3 or 4 AEs of thrombocytopenia, anaemia, or haematoma; were symptomatic, defined as a TSS of 10 or more assessed by a single MFSAF at screening; were anaemic; had platelets of more than 25×10^9 cells per L without requirement for platelet transfusion; had baseline splenomegaly; were high risk, intermediate-2 risk, or intermediate-1 risk and had an ECOG PS of 0-2. There was a wide range of exclusion criteria, including momelotinib at any time, approved JAK inhibitor therapy within 1 week prior to Day BL1, active anti-MF therapy as defined in Study Protocol within 1 week prior to Day BL1 and supportive care including steroids for non-MF indications may be used as defined Study Protocol.
- The **primary endpoint was the MFSAF-TSS response rate at week 24**; a **significantly** greater proportion of patients in the momelotinib group reported a 50% or more reduction in TSS than in the danazol group (25% vs. 9%); proportion difference 16% (95% CI 6–26), p=0.0095.
- The **ESMO-MCBS for Haematological Malignancies was not applicable** because the primary endpoint "MFSAF-TSS response rate at week 24" could not be assessed.
- Although the trial was conducted in a randomised, double-blind design, the **risk of bias was considered high** due to the involvement of the sponsor throughout the trial (design, conduct, data collection and analysis).
- Currently, there are **no ongoing** phase 2 and phase 3 **trials**.
- Despite the clinically significant improvements in myelofibrosis-associated symptoms, anaemia measures, and spleen response, and the favourable safety results, there are some **limitations**. Due to the **planned crossover at week 24** for the danazol group, patient follow-up is ongoing and **long-term survival analyses are not possible**. Although the trial was conducted in a double-blinded design, according to the authors, patients and investigators might have tried to **predict their treatment assignment** based on previous JAK inhibitor experience. Furthermore, results showed a higher rate of transfusion independence at week 24 in momelotinib-randomised splenic responders which is **confounded** by the fact that proportionally more splenic responders were available for assessment at week 24, as patients who discontinued early were considered non-responders.

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[3] According to the authors, patients and investigators might have tried to predict their treatment assignment based on previous JAK inhibitor experience.

[4] The funder of the study had a role in study design, study administration, and study conduct. Study data were collected by site staff and study investigators, followed by verification and analysis by the study sponsor.

Abbreviations: AE=adverse event, AJ=adjustment, ANC = absolute neutrophil count, ALT/SGPT = alanine aminotransferase/ serum glutamic-pyruvic transaminase, AST/SGOT = aspartate aminotransferase/ glutamic-oxaloacetic transaminase, BL=baseline, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CT=computed tomography, CTCAE=Common Terminology Criteria for Adverse Events, DIPSS=Dynamic International Prognostic Scoring System, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, Hgb=haemoglobin, HIV=Human Immunodeficiency Virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, I.U.=International Unit, IWG-MRT=International Working Group-Myeloproliferative Neoplasms Research and Treatment, JAK=Janus kinase, MFSAF=Myelofibrosis Symptom Assessment Form, LMC=left costal margin, MG=median gain, MRI=magnetic resonance imaging, n=number of patients, NICE=National Institute for Health Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PLT = platelet count , PM=preliminary grade, PMF=primary myelofibrosis, PRO=patient-reported outcome, QoL=quality of life, SAE=serious adverse event, SCT=stem cell transplantation, ST=standard treatment, TSS=total symptom score, ULN=upper limit of normal, WHO=World Health Organization, WOCBP=woman of childbearing potential

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