NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Imetelstat for treating relapsed or refractory intermediate-2 or high-risk myelofibrosis after janus kinase inhibitor treatment

Company/Developer	Geron Corporation

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 10242	NICE ID: 8376	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Imetelstat is in clinical development for the treatment of intermediate-2 or high-risk myelofibrosis (MF) in patients who are relapsed (the disease has come back) or refractory (the disease has stopped responding to a treatment) to Janus-Kinase (JAK) inhibitor treatment. MF is a rare blood cancer that causes scarring of the bone marrow which makes it more difficult to produce blood cells. As MF progresses, symptoms might include tiredness, shortness of breath, pain and discomfort in the abdomen, bone pain, and very itchy skin. The exact cause of MF is not known. JAK inhibition is used as a first line treatment for intermediate to high-risk MF. However, it is not uncommon for patients to lose response to JAK inhibition over time. Survival following discontinuation are poor, and there is currently no standard treatment approach for patients who are relapsed/refractory to JAK inhibitors. There is therefore an unmet need for additional treatment options for this population.

Imetelstat is an inhibitor of an enzyme called telomerase which is active in tumour cells. Imetelstat works by selectively killing cells in the bone marrow which are the source of disease in blood cancers such as MF. Imetelstat is administered intravenously (into the vein). If licenced, imetelstat will provide an additional treatment option for intermediate-2 or high-risk MF in patients who are relapsed/refractory to JAK inhibitor treatment.

Proposed Indication

Imetelstat for the treatment of intermediate-2 or high-risk myelofibrosis (MF) in patients who are relapsed/refractory to Janus Kinase (JAK) inhibitor treatment.[1]

Technology

Description

Imetelstat (GRN163L, JNJ-63935937) works by blocking the activity of an enzyme called telomerase. Telomerase is involved in regulating cell growth and division. In cells dividing rapidly such as cancer cells, telomerase is very active, which enables cells to divide without control. By blocking the activity of telomerase, this medicine is expected to stop the uncontrolled division of abnormal immature blood cells, therefore slowing the progression of MF.[2]

Imetelstat is in clinical development for the treatment of intermediate-2 or high-risk MF in patients who are relapsed/refractory to JAK-inhibitor treatment. In the phase III trial (NCT04576156), imetelstat sodium is administered at 9.4 mg/kg intravenous (IV) every 21 days (±3 days).[1]

Key Innovation

Approximately 60% of patients with MF are categorised as intermediate-2 or high-risk disease, thereby comprising a large population with symptomatic disease, poor survival, and an overall high unmet medical need.[3] In the setting of relapsed/refractory disease, prognosis has been characteristically poor. JAK inhibition with approved drugs has become the first line treatment for symptomatic or intermediate to high-risk MF. However, in treatment with some drugs after three years of therapy, approximately half of all patients with MF will likely have stopped treatment.[4] Poor outcomes have been documented after JAK inhibitor discontinuation, including poor overall survival after ruxolitinib in the range of 11 to 16 months.[5] Currently, there is no standard treatment approach for patients who are relapsed/refractory to JAK inhibitors.[3] There is therefore an unmet need for the treatment of relapsed/refractory MF.[6]

If licenced, imetelstat will provide an additional treatment option for intermediate-2 or high-risk MF in patients who are relapsed/refractory to JAK inhibitor treatment.

Regulatory & Development Status

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

Imetelstat is also in phase III/II clinical development for:[7]

- Myelodysplastic syndrome
- Acute myeloid leukemia

Imetelstat has the following regulatory designations/awards:

- An orphan drug in the EU in 2015 for the treatment of MF.[2,8]
- A Fast Track designation by the US FDA for the treatment of adult patients with intermediate-2 or high-risk MF whose disease has relapsed after or is refractory to JAK inhibitor treatment, or relapsed/refractory MF in September 2019. The Fast Track designation includes patients with primary MF and MF developed after essential thrombocythemia or polycythemia vera.[9]

Patient Group

Disease Area and Clinical Need

MF is a rare blood cancer. It causes scarring of the bone marrow which makes it more difficult to produce blood cells. It is one of a group of conditions called myeloproliferative neoplasms or myeloproliferative disorders.[10] MF can affect people of any age, but it usually affects people older than 50 years.[11] MF usually develops slowly and doesn't cause symptoms at first. As the condition progresses it causes symptoms. These might include tiredness and shortness of breath due to low numbers of red blood cells, pain and discomfort in the abdomen due to enlarged liver and spleen, bone pain, bleeding and bruising easily, fever, night sweats and very itchy skin (pruritus).[12] MF can happen on its own (primary MF) or it can develop from another bone marrow disorder (secondary MF).[11] The exact cause of MF is not known but it occurs when bone marrow stem cells develop mutations in their DNA.[11,12] MF is divided into different risk groups which can describe how quickly or slowly MF may develop, and the risk of it developing into leukaemia: low risk, intermediate-1, intermediate-2, and high.[13,14] Relapsed disease means a cancer has come back. Refractory disease means a cancer has stopped responding to a treatment.[15]

The number of people diagnosed each year with MF will be two to three cases per 100,000 and it is equally common in men and women.[16] The average age at diagnosis is 65 years.[12] In England (2022-23), there were 497 finished consultant episodes (FCEs) and 464 admissions for other specified diseases of blood and blood-forming organs (ICD-10 code D75.8), which resulted in 397 day cases and 292 FCE bed days.[17] Patients in the low- and intermediate-1 risk categories have a median overall survival (OS) exceeding 14 years, whereas patients with intermediate-2 or high-risk MF have median OS of only 4 and 1.5 years, respectively.[3]

Recommended Treatment Options

NICE recommends the following treatment options for MF after JAK inhibitor treatment:[18,19]

- Fedratinib for disease-related splenomegaly or symptoms of primary MF, post-polycythaemia vera MF or post-essential thrombocythaemia MF in adults, only if they have previously had ruxolitinib
- Momelotinib for MF-related splenomegaly or symptoms in adults with moderate to severe anaemia who have not had a JAK inhibitor or have had ruxolitinib, only if they have intermediate-2 or high-risk myelofibrosis

Clinical Trial Information

Trial	NCT04576156, EudraCT 2020-003288-24; A Randomized Open-Label, Phase 3 Study to Evaluate Imetelstat (GRN163L) Versus Best Available Therapy (BAT) in Patients With Intermediate-2 or High-risk Myelofibrosis (MF) Relapsed / Refractory (R/R) to Janus Kinase (JAK) Inhibitor **Phase III** – Recruiting **Location(s):** Eleven EU countries, UK, USA and other countries **Primary completion date (estimated):** April 2026
Trial Design	Randomised, parallel assignment, open label
Population	N=320 (estimated); aged 18 years and older; diagnosis of primary myelofibrosis according to the revised World Health Organisation (WHO) criteria or post-essential thrombocythemia-MF or post-polycythemia vera-MF according to the

	International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria.
Intervention(s)	Imetelstat sodium 9.4 mg/kg (IV)
Comparator(s)	Best available therapy (non-JAK-inhibitor treatment, which may include but is not limited to hydroxyurea, thalidomide or an analog of thalidomide, interferon, danazol, hypomethylating agents, chemotherapy or radiotherapy)
Outcome(s)	Primary outcome: overall survival [Time frame: baseline (day 1) until end of study (approximately 3 years)] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT02426086; EudraCT 2015-000946-41; A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects With Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor **Phase II –** Completed **Location(s):** Five EU countries, UK, USA, Canada and other countries **Actual study completion date :** February 2020
Trial Design	Randomised, parallel assignment, single masking (participant)
Population	N=107 (actual); aged 18 years and older; diagnosis of primary myelofibrosis (PMF) according to the revised WHO criteria or thrombocythemia-myelofibrosis (PET-MF) or post-polycythemia vera-myelofibrosis (PPV-MF) according to the IWG-MRT criteria.
Intervention(s)	**Arm A:** imetelstat sodium 4.7 mg/kg (IV) **Arm B:** imetelstat sodium 9.4 mg/kg (IV)
Comparator(s)	No comparator
Outcome(s)	Primary outcomes: • Percentage of participants with spleen response [Time frame: week 24] • Percentage of participants with symptom response [Time frame: week 24] See trial record for full list of other outcomes.
Results (efficacy)	Study enrolment was closed early, and patients treated with 4.7 mg/kg were permitted to continue treatment with 9.4 mg/kg. At week 24, spleen and symptom response rates were 10.2% and 32.2% in the 9.4 mg/kg arm and 0% and 6.3% in the 4.7 mg/kg arm. Treatment with imetelstat 9.4 mg/kg led to a median OS of 29.9 months and bone marrow fibrosis improvement in 40.5% and variant allele frequency reduction of driver mutations in 42.1% of evaluable patients. Fibrosis improvement and variant allele frequency reduction correlated

	with OS. Target inhibition was demonstrated by reduction of telomerase activity and human telomerase reverse transcriptase level and correlated with spleen response, symptom response, and OS.[20]
Results (safety)	The most frequently reported treatment-emergent adverse events (TEAEs) included thrombocytopenia, anaemia, neutropenia, nausea, and diarrhoea. Fifty-two patients (88.1%) in the 9.5 mg/kg arm and 39 patients in the 4.7 mg/kg arm experienced grade ≥ 3 TEAE(s). The most common grade 3 or 4 TEAEs were haematologic and included anaemia, thrombocytopenia, and neutropenia. The majority of grade 3 or 4 cytopenias were manageable and reversible within 4 weeks.[20]

Clinical Trial Information	
Trial	NCT01731951; A Pilot Open-Label Study of the Efficacy and Safety of Imetelstat (GRN163L) in Myelofibrosis and Other Myeloid Malignancies **Phase II –** Completed **Location(s):** USA **Actual study completion date:** May 2018
Trial Design	Randomised, parallel assignment, open label
Population	N=80 (actual); aged 18 years and older; diagnosis of one of the following: primary MF per the revised WHO criteria, post-polycythemia vera/essential thrombocythemia myelofibrosis (Post-ET/PV MF) per the IWG-MRT criteria, or high-risk or Intermediate-2 risk MF (as defined by the Dynamic International Prognostic Scoring System).
Intervention(s)	Imetelstat 7.4-9.4 mg/kg (IV)
Comparator(s)	No comparator
Outcome(s)	Primary outcomes: • MF participants: percentage of participants with overall response (OR) – (clinical improvement [CI] or partial remission [PR] or complete remission [CR]) per International Working Group - Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria [Time frame: up to first 9 cycles of treatment (each cycle was 21 days for arms A and B and 28 days for arms E and F)] • Blastic MF/AML participants: percentage of participants with overall response [Time frame: up to first 9 cycles of treatment (each cycle was 28 days for arm D)] • MDS participants: percentage of participants with OR (hematologic improvement [HI] or PR or CR) per IWG criteria [Time frame: up to first 9 cycles of treatment (each cycle was 28 days for arm G)] See trial record for full list of other outcomes.
Results (efficacy)	There were 7 (21.2%) complete (CR; n=4) or partial (PR; n=3) remissions, occurring at a median of 5 cycles of treatment (range 1-9). All 4 CR patients experienced reversal of BM fibrosis and 3 of them a complete molecular response. Six of the

	7 CR/PR patients remain in remission (median 9.9 months, range 4.8-14.7). Other responses included anaemia response in 4 (31%) of 13 transfusion-dependent patients, >50% reduction in palpable spleen size in 9 (39%) of 23 evaluable patients, ≥50% reduction in leukocyte count in 8 (80%) of 10 patients with marked leukocytosis (WBC >25 x 10(9)/L), resolution of leukoerythroblastosis in the majority of patients, and normalisation of platelet count in 9 (75%) of 12 patients with thrombocytosis.[21]
Results (safety)	Treatment-related grade 4 neutropenia was seen in 6 (18%) patients and grade 4 thrombocytopenia in 7 (21%). Grade 3 anaemia was seen in 9 (27%) patients. Two patients experienced grade 4+ non-haematologic AE: grade 5 intracranial haemorrhage (related), grade 5 upper gastrointestinal haemorrhage (not related); other grade 3+ non-haematologic AEs were seen in only one patient.[21]

Estimated Cost

The cost of imetelstat is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (TA11370). Expected date of issue October 2024.
- NICE technology appraisal. Momelotinib for treating myelofibrosis-related splenomegaly or symptoms (TA957). March 2024.
- NICE technology appraisal. Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (TA756). December 2021.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- British Society for Haematology. The management of myelofibrosis: A British Society for Haematology Guideline. 2023.[22]
- RM Partners West London Cancer Alliance. Pan-London Haemato-Oncology Clinical Guidelines. 2020.[23]

Additional Information

Geron Corporation did not update 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.

A MAA for imetelstat is currently under review by the EMA for the treatment of transfusion-dependent anaemia in patients with lower risk myelodysplastic syndromes.[24]

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