Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING SEPTEMBER 2018

Luspatercept for myelodysplastic syndromes (MDS) associated anaemia

NIHRIO ID	8558	**NICE ID**	9513
Developer/Company	Celgene Ltd & Acceleron Pharma Inc	**UKPS ID**	642753

Licencing and market availability plans	Currently in phase III clinical trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Luspatercept is an erythroid (red blood cell) maturation agent administered by subcutaneous injection and is in clinical development for the treatment of adult patients who have serious blood disorders such as anaemia associated with myelodysplastic syndromes (MDS). MDS are a group of disorders in which red blood cells, white blood cells, and platelets produced by the bone marrow (the spongy tissue inside the large bones) do not grow and mature normally. MDS are long-term debilitating and life-threatening diseases. They can lead to severe anaemia, infections or bleeding, and can result in leukaemia (cancer of the white blood cells). MDS patients currently have few approved therapeutic options and may require repeated blood transfusions.

Luspatercept is a recombinant engineered protein designed to enhance the maturation of red blood cells produced in the bone marrow. This leads to the production of healthy red blood cells and increased haemoglobin levels, improving symptoms in patients with anaemia. Luspatercept is a novel approach for treating anaemia associated with MDS, with potential to improve many patients' lives by reducing or eliminating the need for frequent and lifelong blood transfusions.

PROPOSED INDICATION

Treatment of adult patients with very low, low and intermediate risk myelodysplastic syndromes (MDS) associated anaemia and who are ring sideroblast positive (RS+) and require red blood cell (RBC) transfusions and have received or are not eligible for erythropoiesis-stimulating agent (ESA) therapy[a]

TECHNOLOGY

DESCRIPTION

Luspatercept (ACE-536) is a soluble, recombinant fusion protein composed of a modified form of the extracellular domain of human activin receptor type IIb (ActRIIb) and linked to the human IgG1 Fc domain, with red blood cell stimulating activity. Upon subcutaneous administration, luspatercept inhibits several ligands in the transforming growth factor (TGF)-beta superfamily. This prevents activation of a variety of TGF-beta superfamily members involved in late stage erythropoiesis and results in an increased differentiation and proliferation of erythroid progenitors.[1]

In the phase III clinical trial (MEDALIST; NCT02631070) of patients with anaemia due to very low, low, or intermediate risk myelodysplastic syndromes (MDS), luspatercept is administered by subcutaneous injection at a starting dose of 1.0mg/kg every 3 weeks. The primary endpoint is Red Blood Cell Transfusion Independent (RBC-TI) ≥8 weeks during weeks 1-24.[2,3]

INNOVATION AND/OR ADVANTAGES

MDS patients currently have few approved therapeutic options. Erythropoiesis-stimulating agents (ESAs) work on early stage of erythroid progenitor cells and, although often prescribed in MDS, have limited effect. In many patients with lower-risk MDS, anaemia will eventually become resistant to ESAs and will require repeated RBC transfusions. Long-term RBC transfusion dependence has several detrimental clinical effects including iron overload, and a negative impact on patients' quality of life (QoL).

Luspatercept works by targeting specific TGF-beta proteins involved in late-stage RBC maturation, stimulating RBC production and thereby preventing anaemia. This mechanism of action has the potential to be transformative for patients with serious RBC disorders by significantly reducing or eliminating the need for frequent and lifelong blood transfusions.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

- Luspatercept is in phase III development for beta-thalassemia and phase II development for myelofibrosis.[4]
- Luspatercept was designated an orphan drug in the EU in 2014, and the USA in 2013, for MDS.[5,6]

[a] Information provided by Celgene Ltd

PATIENT GROUP

DISEASE BACKGROUND

Myelodysplastic syndromes (MDS) comprise a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells, white blood cells and platelets may all be affected by MDS.[7] Anaemia occurs when there is reduced number of red blood cells or haemoglobin, an iron rich protein which carries oxygen throughout the body. This can make the patient feel very tired, look pale, be short of breath, feel cold or get chest pains. They may also have infections, bleeding or bruising if the white blood cells and/or platelets are affected.[8]

MDS affect patients' QoL due to debilitating symptoms such as fatigue and dyspnoea. Treating patients with symptoms of MDS may require intravenous drug infusions and blood transfusions and some may develop complications such as severe infections which can involve hospitalisation and eventual iron overload. MDS are caused by a cumulative acquisition of genetic errors in the bone marrow and common abnormalities include chromosomal deletions in 5q, 7, 20q, Y and trisomy 8. Other risk factors include previous cancer therapy (including radiotherapy) and environmental toxins. MDS are associated with an increased risk of transformation to acute myeloid leukaemia (AML). AML is a fast-developing type of blood cancer that affects the blood and bone marrow, with poor prognosis if left untreated. Approximately 30% of patients with MDS will progress to AML.[7]

MDS are subdivided using the Revised International Prognostic Scoring System (IPSS-R), International Prognostic Scoring System (IPSS), French-American-British (FAB) and World Health Organisation (WHO) classification systems. Based on the proportion of leukaemic cells (or 'blasts'), bone marrow cytogenetic findings, and the presence of cytopenia(s), the IPSS-R classifies outcome as very low-risk, low-risk, intermediate-risk, high-risk or very high-risk. Low risk and intermediate-1 risk MDS together form approximately 70% of all MDS.[7,9,]

CLINICAL NEED AND BURDEN OF DISEASE

The incidence of MDS in the EU has been approximated at 4 per 100, 000 (reaching 40–50/100 000 in patients aged ≥70 years).[14] This is consistent with figures for the UK, also quoted as 4 per 100,000 with an incidence of >30 per 100,000 aged ≥70 years.[9]

The 5-year survival rate for MDS within the EU has previously been estimated at 31%.[10]

According to HES data for England, there were 57,366 hospital admissions with a primary diagnosis of MDS (ICD-10 code D46) in which 2,863 were related to refractory anaemia with ringed sideroblasts.[11]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

The mainstay of treatment for MDS is best supportive care (transfusions, iron chelation therapy, growth factors, antibiotics, antivirals and/or antifungals, and nutrition support)[b] to control the symptoms of bone marrow failure. Low-dose standard chemotherapy or immunosuppressive therapies are used for some patients. For people with low risk MDS, often a preferred approach is

[b] Information provided by Celgene Ltd

one of no active treatment or 'watchful waiting' and for some people, stem cell transplantation is a potentially curative treatment option. Many patients become RBC transfusion dependent, particularly those with low or intermediate-1 risk MDS. A major goal of treatment is then to achieve transfusion independence and a number of treatments can be used to reduce or eliminate the transfusion need for MDS patients.[7,12]

Red cell transfusion is given primarily to correct symptomatic anaemia, thereby improving QoL. The threshold haemoglobin concentration for transfusion will vary from patient to patient due to co-morbidities such as chronic pulmonary disease and heart failure, therefore it is generally accepted that there is not an international defined haemoglobin value below which transfusion therapy is needed. Chronic red cell transfusion will lead to complications including iron overload and the development of red cell alloantibodies. Consideration should be given to extended red cell phenotyping in patients who are regularly transfused, and cytomegalovirus testing is recommended for patients who are eligible for a stem cell transplant.[9,13]

CURRENT TREATMENT OPTIONS

- RBC transfusions are a treatment option for MDS patients with anaemia. Long-term RBC transfusions have several detrimental clinical effects including iron overload, and a negative impact on patients' QoL. Iron chelation may be required in patients receiving frequent transfusion to avoid iron-related cardiac, hepatic and endocrine toxicities. Chronic anaemia requiring frequent RBC transfusion can lead to increased morbidity as a result of cardiac failure, falls, fatigue, and lower QoL.[14,15,16]
- ESAs, i.e., recombinant erythropoietin (EPO) or darbepoetin (DAR), remain the first choice treatment of anaemia in most lower risk MDS without del(5q). Eepoetin alfa (Eprex) is approved for use in the EU for the treatment of symptomatic anaemia (haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL). Response to EPO is limited and resistance or failure to respond remains a challenge in patients who became resistant or who do not respond to EPOs. Patients will then return to treatment with RBC transfusions.[14,16]
- Lenalidomide is recommended as an option by NICE, within its marketing authorisation, for treating transfusion-dependent anaemia caused by low- or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.[7]

PLACE OF TECHNOLOGY

If licensed, luspatercept may offer a novel treatment option for adult patients with very low, low and intermediate risk MDS associated anaemia and who are RS+ and require RBC transfusions and have received or are not eligible for ESA therapy.[b]

CLINICAL TRIAL INFORMATION

Trial	MEDALIST, NCT02631070, ACE-536-MDS-001; luspatercept vs placebo; phase III
Sponsor	Celgene Ltd
Status	Complete but unpublished

Source of Information	Abstract[3], trial registry[2], manufacturer[17,c]
Location	11 EU countries (incl UK), USA, Canada and Turkey
Design	Randomised, placebo-controlled, parallel assignment
Participants	n=229; ≥ 18 years of age; MDS; very low, low, or intermediate risk disease with ring sideroblasts requiring RBC transfusions
Schedule	Randomised 2:1 to luspatercept 1.0 mg/kg starting dose or placebo SC every 3 wks ≥ 24 wks (day 1 of every 21 day cycle). No crossover was permitted after randomisation.
Follow-up	Patients with evidence of clinical benefit and no progression to IPSS-R high/very high-risk MDS or AML at wk 25 enter a double-blind extension phase until loss of clinical benefit, unacceptable toxicity, disease progression, withdrawal of consent or other discontinuation criteria. Post-treatment long-term follow-up is ≥ 2 years.
Primary Outcomes	• Red Blood Cell Transfusion Independence (RBC-TI) ≥ 8 weeks
Secondary Outcomes	• RBC-TI ≥ 12 weeks [Time frame: Up to approximately 48 weeks] • RBC-TI ≥ 8 weeks [Time frame: Up to approximately 48 weeks] • Reduction in RBC units transfused over 16 weeks [Time frame: Up to approximately 48 weeks] • Proportion of subjects achieving modified hematologic improvement - erythroid (mHI-E) per International Working Group (IWG) over any consecutive 56 days [Time frame: Up to approximately 48 weeks] • Mean haemoglobin increase ≥ 1.0 g/dL [Time frame: Up to approximately 48 weeks] • Duration of RBC-TI [Time frame: Up to approximately 3.5 years] • Change in EORTC QLQ-C30 score [Time frame: Up to approximately 3.5 years] • Hematologic improvement - neutrophils (HI-N) per IWG [Time frame: Up to approximately 48 weeks] • Mean decrease in serum ferritin [Time frame: Up to approximately 48 weeks] • Mean decrease in iron chelation therapy (ICT) use [Time frame: Up to approximately 48 weeks] • Time to RBC-TI [Time frame: Up to approximately 48 weeks] • Number of subjects progressing to AML [Time frame: Up to approximately 3 years] • Progression to AML AML [Time frame: Up to approximately 3 years] • Overall survival [Time frame: Up to approximately 3.5 years] • Adverse events [Time frame: Up to approximately 3.5 years] • Anti-drug antibodies [Time frame: Up to approximately 3.5 years] • Pharmacokinetics – AUC [Time frame: Up to approximately 1 year] • Pharmacokinetics – Cmax [Time frame: Up to approximately 1 year] • Hematologic improvement- platelets (HI-P) per IWG [Time frame: Up to approximately 48 weeks] • A population PK model and exposure-response relationship [Time frame: Up to approximately 3 years]
Key Results	Luspatercept achieved a highly statistically significant improvement in the primary endpoint of RBC transfusion independence of at least 8 consecutive weeks during the first 24 weeks compared to placebo. In addition, luspatercept

[c] Information provided by Celgene Ltd

	also met the key secondary endpoint of demonstrating a highly statistically significant improvement in RBC transfusion independence of at least 12 consecutive weeks during the first 24 weeks. Modified IWG mHI-E, a meaningful secondary endpoint, was also achieved.
Adverse effects (AEs)	Adverse events observed in the study were generally consistent with previously published data. Data from MEDALIST will be submitted to a future medical meeting in 2018.
Expected reporting date	Primary completion date reported as Nov 2017. Estimated study completion date of Nov 2020.

ESTIMATED COST

The cost of luspatercept is not yet known.

ADDITIONAL INFORMATION

Celgene Ltd

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality (TA322). September 2014
- NICE technology appraisal. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218). March 2011
- NICE guideline. Haematological cancers: Improving outcomes (NG47). May 2016

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified

OTHER GUIDANCE

- London Cancer. Guidelines for the Diagnosis and Management of Adult Myelodysplastic Syndromes. 2015[9]
- European Society for Medical Oncology. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2014[14]
- British Journal of Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. 2014[18]

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