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HEALTH TECHNOLOGY BRIEFING
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Luspatercept for the treatment of adults with non-transfusion dependent beta (β)-thalassaemia

NIHRIO ID	26959	**NICE ID**	10389
Developer/Company	Celgene Ltd	**UKPS ID**	655745

Licensing and market availability plans	Currently in phase II clinical trials

SUMMARY

Luspatercept is under clinical development for the treatment of adult patients with beta-thalassaemia who don't regularly require blood transfusion. Thalassaemia is a commonly inherited blood disorder resulting from an abnormality in one of the genes that affects the production of haemoglobin, a protein in red blood cells that carries oxygen throughout the body . Beta-thalassaemia is a subtype caused by a specific gene mutation. People with thalassaemia produce either little or no normal haemoglobin. Current treatment options for beta-thalassaemia are limited to blood transfusions with its associated risks and complications.

Luspatercept, administered via subcutaneous injection, is a recombinant engineered protein designed to attach to certain proteins that slow down the maturation of red blood cells. This leads to the production of healthy red blood cells and increased haemoglobin levels, leading to improved symptoms in patients with beta-thalassaemia intermedia and major. Luspatercept is a novel approach for treating anaemia, with potential to improve many patients' lives by reducing or eliminating the need for frequent and lifelong blood transfusions.

PROPOSED INDICATION

Treatment of anaemia in adults with non-transfusion dependent beta (β)- thalassaemia.[a]

TECHNOLOGY

DESCRIPTION

Luspatercept (Reblozyl, ACE-536) is an activin receptor Type IIB fusion protein. The therapy is designed to promote production of healthy red blood cells. In patients with beta-thalassaemia, the bone marrow has too many precursor red blood cells that fail to develop into mature red blood cells. Luspatercept has been designed to attach to certain proteins in the body which slows down (or inhibits) the maturation of red blood cells. By attaching to these 'inhibitory' proteins, luspatercept is expected to trap the proteins so they cannot exert their normal effect on the red blood cells in part to restore a more normal equilibrium and increase production of red blood cells. This is expected to improve the symptoms of patients with beta thalassemia intermedia and major. Early studies have shown that luspatercept may improve anaemia.[1,2]

Luspatercept is current in phase II development for the treatment of of anaemia in adults with non-transfusion dependent beta (β)- thalassaemia. In a phase II clinical trial (BEYOND; NCT03342404), participants receive 1mg/kg of luspatercept subcutaneously every 21 days and dose can be escalated up to 1.25mg/kg.[3]

INNOVATION AND/OR ADVANTAGES

Luspatercept has the potential to provide benefit in a variety of conditions in which ineffective erythropoiesis contributes significantly to anaemia and overall disease morbidity, including beta-thalassaemia. In beta-thalassaemia, luspatercept is a novel approach for treating anaemia. Current treatment options for beta-thalassaemia are limited to blood transfusions and iron chelating agents which remain the mainstay of treatment. However, these treatments may lead to complications such as viral infections, iron overload and other complications.[1,2]

In a phase II trial, luspatercept improved haemoglobin levels, decreasing the need for blood transfusions in both dependent and non-dependent beta-thalassaemia.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Luspatercept currently has Marketing Authorisation in the EU/UK for the treatment of transfusion dependent beta-thalassemia in adults and myelodysplastic syndromes.[5]

The most common side effects of luspatercept in patients with beta thalassaemia (which may affect more than 15 in 100 people) were headache, bone and joint pain.[5]

Luspatercept is in phase III development for myelodysplastic syndromes, erythrocyte transfusion, primary myelofibrosis and post-polycythemia.[6] Luspatercept is in phase II development for primary myelobifrosis and anaemia.[6]

[a] Information provided by Celgene on UK PharmaScan

- Luspatercept was granted EU orphan drug status by the EMA in August 2014 for the treatment of beta thalassaemia intermedia and major.[1]
- Luspatercept was granted fast track designation by the US FDA for the treatment of patients with transfusion dependent and non-transfusion dependent beta-thalassaemia in May 2015.[7]

PATIENT GROUP

DISEASE BACKGROUND

Thalassaemia is an inherited blood disorder that reduces the production of functional haemoglobin (the protein in red blood cells that carries oxygen). This causes a shortage of normal functioning red blood cells and low levels of oxygen in the bloodstream. There are two main types of thalassaemia: alpha thalassaemia and beta thalassaemia, which affect a different part of the haemoglobin molecule. Haemoglobin is made up of two different components (subunits): alpha globin and beta globin.[8] Beta-thalassaemia is caused by mutations in the HBB gene, which provides instructions for making beta globin, and is typically inherited in an autosomal recessive manner. This means that people with thalassemia major or thalassemia intermedia have a mutation in both of their copies of the HBB gene. People who have only one HBB gene mutation (carriers) typically are said to have thalassemia minor (or trait) and usually do not have symptoms, but may have some symptoms of anaemia.[9]

Beta-thalassaemia comprises a number of different phenotypes with varying severity, including:[9]

- Transfusion-dependent thalassaemia: Includes patients with beta-thalassaemia major or severe forms of beta-thalassaemia intermedia which require regular red blood cell transfusions
- Non-transfusion dependent thalassaemia: Includes patients with mild-to-moderate beta-thalassaemia intermedia who may require infrequent transfusions to manage the disease and its complications
- Beta-thalassaemia trait (minor): heterozygous patients with mild, usually asymptomatic anaemia that generally does not require treatment (excluded from the luspatercept target patient population).

The signs and symptoms of thalassemia vary depending on the severity of the condition. People affected by milder forms of thalassemia can develop mild anaemia or may have no signs or symptoms of the condition at all. Intermediate forms of thalassemia can cause mild to moderate anaemia and iron overload, which may be associated with other health problems, including: slowed growth, delayed puberty, bone problems and/or an enlarged spleen. In addition to the signs and symptoms seen in intermediate thalassemia, people with severe forms of thalassemia may also experience severe anaemia, iron overload, poor appetite, paleness, dark urine, yellow discoloration of skin (jaundice), and enlarged liver or heart.[8]

The long-term prognosis for people with thalassaemia depends on the type and severity of the condition. For example, severe thalassaemia can cause early death due to heart failure or liver complications, while less severe forms of thalassaemia often do not shorten lifespan. Improved treatment options have resulted in increased survival and better quality of life for people affected by moderate to severe thalassaemia.[8]

CLINICAL NEED AND BURDEN OF DISEASE

According to the report performed by the Orphanet Report Series in June 2019, the prevalence estimated worldwide for beta-thalassaemia was 1.0 per 100,000 people.[10] Applying this estimate to the 2019 mid-year population estimates for England, this would equate to approximately 563 cases of beta-thalassaemia.[11]

The National Haemoglobinopathy Registry reports 1,380 people diagnosed with beta-thalassaemia in the UK as of June 2019. Among them, 246 have beta-thalassaemia intermedia.[12]

In England in 2018-2019 there were 13,841 hospital admissions, 13,891 finished consultant episodes and 1,470 bed days for a primary diagnosis of beta-thalassemia (ICD-10 code D56.1).[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

People with thalassaemia major or other serious types require specialist care throughout their lives. Currently, the main treatments for beta thalassaemia are:[2]

• Blood transfusions – regular blood transfusions, typically every 2- 5 weeks are given to treat and prevent anaemia. Those with non-transfusion dependent beta-thalassaemia have them less frequently
• Chelation therapy – treatment with medications to remove the excess iron from the body that builds up as a result of the disease and the regular blood transfusions. Some people experience a build-up of iron even without transfusions and need treatment for this.

The only possible cure for thalassaemia is a stem cell or bone marrow transplant, however, this is not done very often because of the significant risks involved.[2]

CURRENT TREATMENT OPTIONS

To remove excess iron from the body, chelating agents are used.There are 3 chelating agents currently available:[2]

- desferrioxamine (DFO) – given as an infusion, where a pump slowly feeds the liquid medicine through a needle into your skin over 8 to 12 hours; this is done 5 or 6 times a week
- deferiprone (DFP) – taken as a tablet or liquid 3 times a day; it's sometimes used alongside DFO to reduce the number of infusions you need
- deferasirox (DFX) – taken once a day as a tablet that you dissolve in a drink

PLACE OF TECHNOLOGY

If licensed, luspatercept may offer a treatment option for anaemia in adults with non-transfusion dependent beta-thalassaemia

CLINICAL TRIAL INFORMATION

Trial	**BEYOND;** NCT03342404, EudraCT Number 2015-003225-33; A Phase 2, Double-Blind, Placebo Controlled Multicenter Study to Determine the Efficacy and Safety of Luspatercept (ACE-536) in Adults With Non-Transfusion Dependent Beta (B)-Thalassemia **Trial phase** – Phase II, ongoing **Location(s): EU (incl UK), USA and other countries** **Primary completion date:** September 14 2020
Trial design	Randomised, parallel assignment, quadruple-blinded, multicentre, placebo-controlled study
Population	N=145; 18 years and older; Subject must have documented diagnosis of β-thalassemia or hemoglobin E/ β-thalassemia; Subject must be non-transfusion dependent, defined as 0 to 5 units of red blood cells (RBCs) received during the 24-week period prior to randomization.
Intervention(s)	Luspatercept at 1mg/kg subcutaneously once every 21 days, dose can be esculated up to 1.25mg/kg
Comparator(s)	Placebo of normal saline solution subcutaneously once every 21 days
Outcome(s)	Proportion of subjects who have an increase from baseline ≥1.0 g/dl in mean of hemoglobin values over a continuous 12-week interval Week 13 to Week 24 in the absence of transfusions [Time Frame: Up to approximately week 24] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of luspatercept is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Chronic iron overload (in people with thalassaemia) - desferrioxamine, deferiprone and deferasirox (ID350). Expected date of issue to be confirmed.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England Clinical Commissioning Policy: Management of Fetal Anaemia Secondary to Red Cell Alloimmunisation (fetal transfusion). E12/P/. January 2015.
- NHS England. 2013/14 NHS Standard Contract for Specialised Services for Haemoglobinopathy care (all ages). B08/S/a.

OTHER GUIDANCE

- UK Thalassemia Society. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. 2016.[14]

ADDITIONAL INFORMATION

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