Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING
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Luspatercept for adult patients with beta-thalassemia who require red blood cell transfusions

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Developer/Company	Celgene Ltd	**UKPS ID**	642727

Licencing and market availability plans	Currently in phase III clinical trials

SUMMARY

Luspatercept is a subcutaneous injection medicine under clinical development for the treatment of adult patients with beta-thalassemia who 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. Beta-thalassemia is a subtype caused by a specific gene mutation. People with thalassaemia produce either little or no normal haemoglobin which can make them very anaemic (tired, short of breath and pale). Beta-thalassaemia major is the most severe type of beta-thalassaemia with patients requiring regular blood transfusions for survival. Patients with beta-thalassemia intermedia also need transfusions at different times of their lives. Current treatment options for beta-thalassemia are limited to blood transfusions with its associated risks and complications.

Luspatercept 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-thalassemia 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

For treatment of regularly transfused Beta-thalassemia (regularly transfused defined as 6 – 20 units of RBCs within 24 weeks)

TECHNOLOGY

DESCRIPTION

Luspatercept (ACE-536) is a first-in-class activin receptor Type IIB fusion protein. The therapy is designed to promote production of healthy red blood cells. In patients with beta-thalassemia, 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' (TGF-beta family) proteins, luspatercept is expected to trap the proteins so they cannot exert their abnormal 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, an aspect of beta-thalassemia that is not targeted by currently authorised treatments.[1,2]

In the current phase III randomised, double-blind, placebo-controlled clinical trial (BELIEVE; NCT02604433), subjects receive luspatercept at a starting dose of 1 mg/kg, subcutaneously once every 21 days with best supportive care. Duration of treatment is not reported.[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-thalassemia. In beta-thalassemia, 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. Current treatment options for beta-thalassemia 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. Results from the phase II clinical trial demonstrated a 50% reduction in transfusion burden in any 12 weeks of treatment, compared to the 12 weeks prior to treatment.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

- 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 designated US orphan drug status by the FDA in November 2013 for the treatment of beta thalassaemia.[5]
- 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.[6]

Luspatercept is in phase III development for anaemia due to very low, low, or intermediate risk myelodysplastic syndromes.[7]

Luspatercept is in phase II development for the following indications:[7]

- Myelofibrosis patients with anaemia (both transfusion dependent and non-transfusion dependent)
- Non-transfusion dependent beta-thalassemia
- Anaemia in patients with lower risk myelodysplastic syndromes

PATIENT GROUP

DISEASE BACKGROUND

Thalassemia 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 thalassemia: alpha thalassemia and beta thalassemia, which affect a different part of the haemoglobin molecule. Haemoglobin is made up of two different components (subunits): alpha globin and beta globin. Alpha thalassemia is caused by mutations (gene deletion in chromosome 16) in the *HBA1* and/or *HBA2* genes, which provide instructions for making alpha globin, whilst beta-thalassemia is caused by mutations in the *HBB* gene, which provides instructions for making beta globin. Each person has two copies of each of these genes, one inherited from the mother and one from the father. Loss (deletion) of some or all of the *HBA1* and/or *HBA2* genes results in a shortage of alpha globin, leading to alpha thalassemia and mutations in the *HBB* gene leads to reduced levels of beta globin, causing beta-thalassemia.[8]

Beta-thalassemia comprises a number of different phenotypes with varying severity, including:

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

The main management methods include blood transfusions, chelation therapy, and engaging in a healthy lifestyle, including eating a healthy diet, doing regular exercise and not smoking or drinking excessive amounts of alcohol to stay as healthy as possible. The only possible cure for thalassemia is a stem cell or bone marrow transplant, but this is not done very often because of the availability of appropriate donors and the significant risks associated with the transplant procedures.[2]

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 thalassemia depends on the type and severity of the condition. For example, severe thalassemia can cause early death due to heart failure or liver complications, while less severe forms of thalassemia 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 thalassemia.[8]

CLINICAL NEED AND BURDEN OF DISEASE

It has been estimated that about 1.5% of the global population (80 to 90 million people) are carriers of beta-thalassemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world.[9]

The estimated annual incidence of individuals with beta-thalassemia major and minor is 1 per 10,000 people in the European Union, the equivalent to 51,000 people.[1] The prevalence of this form of thalassemia is not known (data source published in 2010).[10]

According to Thalassemia International Federation, only about 200,000 patients with thalassemia major are alive and registered as receiving regular treatment around the world.[9]

All types of thalassemia can be fatal in some cases, particularly when there are multiple gene mutations that affect the production of the globin chains. In 2013, 25,000 deaths were attributable to thalassemia.[10]

In 2016-17 in the UK there were 13,577 hospital admissions, 13,621 finished consultant episodes and 1,960 bed days for a primary diagnosis of beta-thalassemia (ICD-10 code D56.1).[11]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Infants with beta-thalassaemia should be monitored carefully for clinical signs indicative of the need for transfusion. Transfusion should be started promptly when there is clinical evidence of severe anaemia, failure to thrive and/or thalassaemic bone deformity. A protocol for iron chelation therapy in children and adults should be shared between the specialist haemoglobinopathy centre and local hospital teams within the clinical network, and reviewed at regular intervals. This should be based on current published evidence, expert opinion, and national specialist commissioning guidance.[12]

CURRENT TREATMENT OPTIONS

People with thalassemia major or other serious types require specialist care throughout their lives.

Currently, the main treatments for beta thalassemia are:

- Blood transfusions – regular blood transfusions, typically every 2- 5 weeks are given to treat and prevent anaemia.

- 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 thalassemia is a stem cell or bone marrow transplant, however, this is not done very often because of the significant risks involved.[2]

PLACE OF TECHNOLOGY

If licensed, luspatercept may offer a treatment option for patients with beta-thalassemia who require red blood cell transfusions, which could reduce or eliminate the need for frequent and lifelong blood transfusions.

CLINICAL TRIAL INFORMATION

Trial	BELIEVE, NCT02604433, ACE-536-B-THAL-001, EudraCT-2015-003224-31, 2015-003224-31, IRAS 193141, UKCTG-34874; luspatercept plus best supportive care versus placebo plus best supportive care; phase III.
Sponsor	Celgene
Status	Ongoing.
Source of Information	Trial registry.[3]
Location	5 EU countries (including the UK), USA, Canada and other countries.
Design	Randomised, double blind, placebo-controlled.
Participants	n=336; aged 18 years and older; documented diagnosis of β-thalassemia or haemoglobin E/β-thalassemia (β-thalassemia with mutation and/or multiplication of alpha globin is allowed); regularly transfused, defined as: 6-20 red blood cell (RBC) units in the 24 weeks prior to randomization and no transfusion-free period for ≥ 35 days during that period.
Schedule	Participants are randomly assigned in a 2:1 ratio to one of 2 treatment arms: • Experimental arm – subjects receive luspatercept at a starting dose of 1 mg/kg, subcutaneous(ly) (SC) once every 21 days along with best supportive care. • Placebo arm – subjects receive normal saline solution subcutaneous(ly) (SC) once every 21 days along with best supportive care.
Follow-up	Follow up of outcome measures for up to 3 years post last dose.
Primary Outcomes	Proportion of subjects with haematological improvement from week 13 to week 24 compared to 12-week prior to randomisation [time frame: up to approximately week 24]: Haematological improvement is defined as ≥ 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units from week 13 to week 24 compared to the 12-week. Reported as the number

	of RBC units transfused from week 13 to week 24, and in the 12 weeks prior to randomisation.
Secondary Outcomes	• Proportion of subjects with haematological improvement from week 37 to week 48 compared to the 12-week interval prior to randomisation [time frame: up to approximately 48 weeks] • Proportion of subjects with a ≥50% reduction in red blood cell transfusion burden from week 37 to week 48 [time frame: up to approximately 48 weeks] • Proportion of subjects with a ≥50% reduction in red blood cell (RBC) transfusion burden from week 13 to week 24 [time frame: up to approximately 24 weeks] • Mean change from baseline in transfusion burden (RBC units) from week 13 to week 24 [time frame: Up to approximately 24 weeks] • Mean change from baseline in liver iron concentration (LIC, mg/g dw) by magnetic resonance imaging (MRI) [time frame: up to approximately 48 weeks] • Mean change from baseline in mean daily dose of iron chelation therapy (ICT) [time frame: up to approximately 48 weeks] • Mean change from baseline in serum ferritin [time frame: up to approximately 48 weeks] • Mean change from baseline in total hip and lumbar spine bone mineral density (BMD)by Dual energy x-ray absorptiometry (DXA) [time frame: Up to approximately 48 weeks] • Mean change from baseline in myocardial iron by magnetic resonance imaging (MRI) [time frame: up to approximately 48 weeks] • TranQOL quality of life tool administered within 4 weeks prior to Dose 1 Day 1, and weeks 12, 24, 36 and 48, then every 12 weeks during long term period [Time Frame: Up to last QoL measurement visit] • SF-36 Quality of Life tool administered within 4 weeks prior to dose 1 day 1, and weeks 12, 24, 36 and 48, then every 12 weeks during long term treatment period [time frame: up to last QoL measurement visit] • The effect of luspatercept on healthcare resource utilization (hospitalizations) versus placebo [Time Frame: Until end of study] • Proportion of subjects who are transfusion independent for ≥8 weeks during treatment [time frame: up to approximately 48 weeks] • Proportion of subjects who are transfusion independent for ≥8 weeks during treatment [time frame: up to approximately 48 weeks] • Duration of reduction in transfusion burden [time frame: Up to approximately 48 weeks] • Duration of transfusion independence [time frame: up to approximately 48 weeks]

	• Time to erythroid response [time frame: up to approximately 48 weeks] • Post-baseline transfusion events frequency versus placebo [time frame: up to approximately 48 weeks] • Pharmacokinetic - AUC [time frame: up to 9 weeks post last dose] • Pharmacokinetic - Cmax [time frame: up to 9 weeks post last dose] Adverse events (Aes) [time frame: up to 9 weeks post last dose. Only related Aes from week 9 until end of study]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date recorded as 24 Nov 2017. Estimated study completion date recorded as 7 June 2025.

ESTIMATED COST

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance proposed. LentiGlobin for treating beta-thalassaemia major (ID968). Expected date of issue to be confirmed.
- 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

- Public Health England. NHS Sickle Cell and Thalassaemia Screening Programme Standards, Third Edition. 2017.[13]

- UK Thalassemia Society. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. 2016.[12]

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