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Crizanlizumab (formerly SelG1) for sickle cell disease

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LAY SUMMARY

Sickle cell disease (SCD) describes a group of inherited diseases. People with SCD have abnormal haemoglobin, a protein found in red blood cells that carry oxygen throughout the body. This abnormal haemoglobin is called haemoglobin S or sickle haemoglobin. Red blood cells that contain normal haemoglobin are disc shaped. This shape allows the cells to be flexible so that they can move through large and small blood vessels to deliver oxygen. Sickle-shaped cells are not flexible and can stick to vessel walls, causing a blockage that slows or stops the flow of blood which cause painful crises (sickle cell crises). When this happens, oxygen can't reach nearby tissues and organs and can lead to serious conditions that can have a significant impact on a person's life. SCD can sometimes lead to problems such as strokes, serious infections and lung problems, which can occasionally be fatal.

Crizanlizumab is a medicine under development for the preventative treatment of SCD painful crisis. Circulating platelets (type of cells in the blood that has a role in blood clotting and stopping of bleeding) in SCD patients express higher levels of P-selectin, a protein that drives the blockage of blood vessels. Crizanlizumab acts by blocking P-selectin and thus can prevent blockage in small blood vessels and maintain blood flow. Therefore, if licensed, crizanlizumab will offer a new treatment option for patients with sickle cell-related pain crises.

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TARGET GROUP

Sickle-cell disease (SCD) (for the prevention of sickle-cell crises) – in addition to or without concomitant hydroxyurea

TECHNOLOGY

DESCRIPTION

Crizanlizumab (SEG101, formerly SelG1) is a humanised anti-P-selectin monoclonal antibody that binds a molecule called P-selectin on the surface of endothelial cells and platelets in the blood vessels, causing a blockade of P-selectin. P-selectin drives the vaso-occlusive process. Vaso-occlusive crises occur episodically when sickle-shaped red blood cells block blood flow through blood vessels.[1] Circulating platelets in SCD patients are chronically activated and express higher levels of P-selectin,[2] which plays a critical role in the initial adhesion and migration of platelets and leukocytes to areas of injury and inflammation. P-selectin also plays a prominent role in haemostasis and thrombosis.[3] Therefore, the therapeutic blockade of P-selectin can prevent painful vaso-occlusion in small blood vessels and maintain blood flow.[1]

In the phase II clinical trial (SUSTAIN; NCT01895361), crizanlizumab was given intravenously at either low-dose (2.5 mg per kilogram of body weight) or high-dose (5.0 mg per kilogram) 14 days after an initial dose and then every four weeks over a period of 50 weeks and at week 52.[4,5]

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

INNOVATION and/or ADVANTAGES

Crizanlizumab is a potential new disease-modifying, preventive treatment option for patients with sickle cell pain crises; the first in nearly 20 years within Europe. Findings from the phase II clinical trial (NCT01895361) showed that crizanlizumab reduced the annual rate of sickle cell-related pain crises (SCPC) by 45.3% with high-dose crizanlizumab compared to placebo in patients with or without hydroxyurea therapy.[1,4] Therefore, if licensed, crizanlizumab will offer a new treatment option for patients with sickle cell-related pain crises.

DEVELOPER

Novartis Pharmaceuticals UK Ltd

AVAILABILITY, LAUNCH or MARKETING

Humanised monoclonal antibody against P-selectin was designated an orphan drug in the EU for the treatment of sickle cell disease in August 2012.[6]

PATIENT GROUP

BACKGROUND

The term sickle cell disease (SCD) describes a group of inherited red blood cell disorders. People with SCD have abnormal haemoglobin, called haemoglobin S or sickle haemoglobin, in their red blood cells. This disease is passed by genes from parents to their children; therefore it is an inherited disease. Patients with SCD inherit an abnormal haemoglobin gene (genetic mutation) from each parent. This results in the formation of abnormal haemoglobin. Haemoglobin is a protein in red blood cells that carries oxygen throughout the body. The abnormal haemoglobin in patients with SCD is known as

sickle haemoglobin (HbS). At least one of those two inherited abnormal genes causes a person's body to make HbS. When a person has two HbS genes (Hb SS) the disease is called sickle cell anaemia (which is the most common and the most severe form of SCD). There are two other common forms of SCD: haemoglobin SC disease and haemoglobin Sβ thalassaemia.[7]

Red blood cells that contain normal haemoglobin are disc shaped (like a doughnut without a hole). This shape allows the cells to be flexible so that they can move through large and small blood vessels to deliver oxygen. HbS is not like normal haemoglobin. It can form stiff rods within the red blood cells, changing it into a crescent or sickle shape. Sickle-shaped cells are not flexible and can stick to vessel walls, causing a blockage that slows or stops the flow of blood. When this happens, oxygen cannot reach nearby tissues. This can cause attacks of sudden, severe pain, called pain crises. These pain attacks can occur without warning, and a person often needs to go to the hospital for effective treatment.[7]

People born with sickle cell disease sometimes experience problems from early childhood, although most children have few symptoms and lead normal lives most of the time. The main symptoms of SCD are: pain crises (also called sickle cell crises), an increased risk of serious infections, and anaemia. Some people also experience other problems such as delayed growth, strokes and lung problems.[8]

Generally, the life expectancy for a person with SCD tends to be shorter than normal, but this can vary depending on the exact type of SCD they have, how it is treated, and the problems they experience. Currently, people with sickle cell anaemia (the most severe form of SCD) typically live until 40-60 years of age. Milder types of SCD may have no impact on life expectancy.[8]

CLINICAL NEED and BURDEN OF DISEASE

SCD is estimated to affect 1 in every 2,000 live births in England, and it is now the most common genetic condition at birth. It is estimated that about 350 babies are born each year in England with SCD and a further 9,500 babies are found to be carriers of the disease. It is estimated that there are more than 12,500 people with SCD in England, and about 240,000 carriers.[9]

In England in 2016 to 2017, there were 24,586 admissions for sickle cell disorder (ICD-10: D57), 12,279 day cases, 44,865 bed days, and 29,031 finished consultant episodes (FCE). For sickle-cell anaemia with crisis (ICD-10: D57.0), there were 11,713 admissions, 710 day cases, 15,951 FCE resulting in 40,478 bed days.[10]

A study on trends in hospital admissions for SCD in England, 2001/02 to 2009/10 showed that the overall admission rate per 100,000 population has risen from 21.2 per 100,000 in 2001/02 to 33.5 per 100,000 in 2009/10. This rise in admission rates has occurred in every age and sex group with the exception of women aged 30–39 years, whose admission rate per 100,000 population declined from 52.4 to 45.3 over the time period.[11]

The long-term effects of SCD often begin to emerge during the teenage years and this may be a time of increased episodes of sickle cell crisis, especially in young men. This evidently can have a major impact on education, career, future employment prospects, and social relationships. With improvements in health and social status, especially access to health care, the life span of those with SCD has improved tremendously and many are living for 50 or 60 years, especially in the UK.[12]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Clinical guideline. Sickle cell disease: managing acute painful episodes in hospital (CG143). June 2012.
- NICE Quality standard. Sickle cell disease (QS58). April 2014.
- NICE Medical technologies guidance. Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease (MTG28). March 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2016/17 NHS public health functions agreement: Service specification No. 18 NHS sickle cell and thalassaemia screening programme.
- NHS England. Revised Specialised Commissioning CQUINs 2017-18 / 2018-19. September 2016.
- NHS England. Improving Value for Patients from Specialised Care CQUIN Schemes for Prescribed Specialised Services for April 2016 to March 2017. Volume II - The Schemes. March 2016.
- NHS England. 2013/14 NHS standard contract for specialised services for haemoglobinopathy care (all ages). B08/S/a
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OTHER GUIDANCE

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- US Department of Health & Human Services: NIH National Heart, Lung, and Blood Institute. Managing acute complications of sickle cell disease. In: Evidence-based management of sickle cell disease. 2014.[19]

CURRENT TREATMENT OPTIONS

Stem cell or bone marrow transplants are the only cure for SCD, but they are not done very often because of the significant risks involved. The main risk is graft versus host disease, which is a life-threatening problem where the transplanted cells start to attack the other cells in the body. Stem cell transplants are generally only considered in children with SCD who have severe symptoms that have

not responded to other treatments, when the long-term benefits of a transplant are thought to outweigh the possible risks.[20]

The main treatments of SCD involve the prevention and treatment of painful episodes (sickle cell crisis). To reduce the chance of sickle cell crisis, the patient may need to avoid dehydration by drinking plenty of fluids, stop getting cold by wearing appropriate clothing, and to avoid sudden changes in temperature. For the treatment of sickle cell crisis, over the counter pain killers can be used to relieve the pain, also drinking plenty of fluids and using warm towels or heat pads on the affected part of the body.

Hydroxycarbamide (hydroxyurea) may be recommended if the patient continues to experience pain episodes. Hydroxycarbamide is a medication that is usually taken orally. It can lower the amount of other blood cells, such as white blood cells and platelets (clotting cells), so regular blood tests will usually be recommended to monitor patient's health.[20]

Treatment of anaemia caused by SCD may require dietary supplements such as folic acid especially for children with restricted diet, such as vegetarian or vegan diet. Anaemia caused by SCD is not the same as the more common iron deficiency anaemia. Patients should not take iron supplements to treat it without seeking medical advice as they could be dangerous. If anaemia is particularly severe or persistent, treatment with blood transfusions or hydroxycarbamide may be necessary.[20] NICE recommends the use of Spectra Optia for automated red blood cell exchange in patients with SCD who need regular transfusion.[21]

EFFICACY and SAFETY	
Trial	**SUSTAIN, NCT01895361, SelG1-00005; crizanlizumab 2.5 mg/kg vs crizanlizumab 5.0 mg/kg vs placebo; phase II**
Sponsor	Reprixys Pharmaceutical Corporation.
Status	Completed
Source of Information	Trial registry,[4] publication[5]
Location	Brazil, Jamaica, USA
Design	Multicentre, randomized, placebo-controlled, double-blind
Participants	n=198; aged 16-65 years; males and females; SCD (HbSS, HbSC, HbSβ^o-thalassemia, or HbSβ^+-thalassemia); if receiving hydroxyurea or erythropoietin, treatment must have been prescribed for at least 6 months, with the dose stable for at least 3 months; between 2 and 10 sickle cell-related pain crises in the past 12 months.
Schedule	Patients were randomised in a 1:1:1 ratio, by an interactive Web- or voice-response system to receive low-dose crizanlizumab (2.5 mg per kilogram of body weight), high-dose crizanlizumab (5.0 mg per kilogram), or placebo. Patients received two doses of crizanlizumab or placebo 2 weeks apart (loading doses) and then received a dose every 4 weeks (maintenance dosing) through week 50 for a total of 14 doses administered. Each dose was administered intravenously over a period of 30 minutes.
Follow-up	Active treatment for 52 weeks, follow-up one year.
Primary Outcomes	Rate of sickle cell-related pain crises [Time Frame: One year]
Secondary Outcomes	Time Frame: One year • Annual rate of days hospitalized • Time to first sickle cell-related pain crisis • Time to second sickle cell-related pain crisis • the annual rate of uncomplicated crises (defined as crises other than the acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism), • the annual rate of the acute chest syndrome • Brief Pain Inventory questionnaire.[5]
Key Results	The median rate of crises per year was 1.63 with high-dose crizanlizumab versus 2.98 with placebo (indicating a 45.3% lower rate with high-dose crizanlizumab, P=0.01). The median time to the first crisis was significantly longer with high-dose crizanlizumab than with placebo (4.07 vs. 1.38 months, P=0.001), as was the median time to the second crisis (10.32 vs. 5.09 months, P=0.02). The median rate of uncomplicated crises per year was 1.08 with high-dose crizanlizumab, as compared with 2.91 with placebo (indicating a 62.9% lower rate with high-dose crizanlizumab, P=0.02).[5]
Adverse effects (AEs)	Adverse events that occurred in 10% or more of the patients in either active treatment group and at a frequency that was at least twice as high as that in the placebo group were arthralgia, diarrhoea, pruritus, vomiting, and chest pain.[5]
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of crizanlizumab is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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