Health Technology Briefing
April 2022

Crizanlizumab for the prevention of recurrent vaso-occlusive crises in children with sickle cell disease

Company/Developer	Novartis Pharmaceuticals UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28955	NICE ID: 10766	UKPS ID: 664770

Licensing and Market Availability Plans

Currently in phase III/II clinical trials

Summary

Crizanlizumab has been developed for the prevention of recurrent vaso-occlusive crises in sickle cell disease (SCD). SCD is an inherited condition that causes red blood cells to become rigid and misshapen, often in a sickle shape. As these cells cannot move freely, this can cause blockages known as vaso-occlusion which leads to insufficient oxygen being delivered to tissues and organs, causing ischaemic injuries and excruciating pain. The frequency, severity and duration of these crises varies. There are very few NICE recommended treatment options for SCD and there are none for the paediatric population. This, therefore, is an area of significant unmet need.

Crizanlizumab contains a type of protein, which has been designed to recognise and attach to a protein called 'P-selectin' that is present on the surface of the cells lining the blood vessels. By attaching to P-selectin, crizanlizumab is expected to prevent the deposit of sickle and inflammatory cells in blood vessels, thereby allowing a better blood flow and improving the symptoms of the disease. If licenced, crizanlizumab, administered intravenously, will provide a preventative treatment for vaso-occlusive crises in SCD in paediatric patients.

Proposed Indication

Prevention of recurrent vaso-occlusive crises (VOCs) in patients with sickle cell disease (SCD).[1,2]

Technology

Description

Crizanlizumab (Adakveo, SelG1, SEG101) is a selective IgG2 kappa humanised monoclonal antibody (mAb) that binds to P-selectin with high affinity and blocks the interaction with its ligands, including P-selectin glycoprotein ligand 1. Crizanlizumab can also dissociate preformed P-selectin/PSGL-1 complex. P-selectin is an adhesion molecule expressed on activated endothelial cells and platelets. It plays an essential role in the initial recruitment of leukocytes and the aggregation of platelets to the site of vascular injury during inflammation. In the chronic pro-inflammatory state associated with SCD, P-selectin is over-expressed and circulating blood cells and the endothelium are activated and become hyper adhesive. P-selectin-mediated multi-cellular adhesion is a key factor in the pathogenesis of vaso-occlusion and VOC. Elevated levels of P-selectin are found in patients with SCD. Binding P-selectin on the surface of the activated endothelium and platelets has been shown to effectively block interactions between endothelial cells, platelets, red blood cells and leukocytes, thereby preventing vaso-occlusion.[3]

In a phase II clinical trial (NCT03474965), 5mg/kg crizanlizumab is administered by intravenous injection (IV) on day one of week 1 and 3 in a 4-week cycle then every 4 weeks.[1,a]

Key Innovation

There is an unmet need for effective treatments for people with SCD. They also face health inequalities because the condition is not well understood, results in disability, and is more common in people of African or African-Caribbean family origin, who tend to have poorer health outcomes than other ethnicities. Crizanlizumab, therefore, aims to reduce these inequalities and meet the unmet need.[4] While there is a NICE recommendation for the 16 years and above population, there is no recommendation for younger children.

If licenced, crizanlizumab would offer a therapy for the prevention of recurrent vaso-occlusive crises (VOCs) in SCD patients.

Regulatory & Development Status

Crizanlizumab has a conditional Marketing Authorisation in the EU/UK for the prevention of recurrent vaso-occlusive crises (VOCs) in SCD patients aged 16 years and older.[3]

Crizanlizumab is currently in phase III/II trials for other SCD populations.[5]

Crizanlizumab received the following awards/designations: [6,7]

- Orphan Drug Designation from the EMA for the treatment of SCD in August 2012
- Orphan Drug Designation from the US FDA for the treatment of SCD in July 2008

Patient Group

Disease Area and Clinical Need

[a] Information provided by Novartis Pharmaceuticals UK Ltd

Sickle cell disease (SCD) is an inherited chronic haemolytic anaemia that results from a single amino acid substitution in the β-globin chain, producing the abnormal haemoglobin-S (HbS).[8] The condition causes red blood cells to become rigid and misshapen, to resemble a crescent (or sickle). Sickle-shaped red blood cells do not flow easily through the blood vessels and can cause blockages (vaso-occlusion) in different parts of the body. Episodes of vaso-occlusion are known as vaso-occlusive crises. These lead to insufficient oxygen being delivered to tissues and organs, causing ischaemic injuries and excruciating pain. The frequency, severity and duration of these crises vary. Painful (known as pain crises) or damaging blockages, for example to the lung (known as acute chest syndrome) or brain (leading to a stroke), are called acute sickle cell crises. Other complications of vaso-occlusive crises include blindness because of damage to the retina, skin ulcers if small blood vessels are blocked, and increased risk of infection if there is sustained damage to the spleen. Other sickle cell crises are a result of severe anaemia. These include splenic sequestration (the spleen gets enlarged because sickle red blood cells get trapped in the spleen), aplastic crisis (the bone marrow suddenly stops producing red blood cells because of a virus), and haemolytic crisis (increased rate of red blood cell destruction).[9] SCD is found at a low frequency in all populations, the highest prevalence occurring in people of African and African-Caribbean origin. Cases also occur in families originating from the Middle East, India and the eastern Mediterranean, with increasing numbers of cases in mixed-race families.[10]

SCD is one of the commonest serious genetic conditions in England, affecting approximately 1 in 2,436 live births. The birth prevalence in some urban areas may be as high as 1 in 300.[10] A recent analysis of multiple databases concluded there are 14,000 people with a diagnosis of SCD living in the UK equivalent to 1 in 4,600.[11] In 2020-21 in the UK there were 9,646 hospital admissions with a primary diagnosis of sickle-cell disorders with crisis (ICD-10 code D57.0), 13,129 finished consultant episodes (FCE) and 31,148 FCE bed days.[12]

Recommended Treatment Options

There are currently no NICE recommended treatment options for the paediatric SCD population. Established clinical management includes hydroxycarbamide, blood transfusions and allogeneic stem cell transplants.[10]

Clinical Trial Information

Trial	**SOLACE-KIDS;** NCT03474965, 2017-001747-12; A Phase 2,Multicenter,Open-Label Study to Assess Appropriate Dosing and to Evaluate Safety of Crizanlizumab With or Without Hydroxyurea/Hydroxycarbamide in Sequential Descending Age Groups of Paediatric Sickle Cell Disease Patients With Vaso-Occlusive Crisis **Phase II –** Suspended **Location(s):** USA, 5 EU countries, UK, Canada and other countries **Primary Completion Date:** June 2023
Trial Design	Single group assignment, open label
Population	N=100; aged 6 months to 17 years old; confirmed diagnosis of SCD; experienced at least 1 VOC within the preceding 12 months prior to screening
Intervention(s)	Crizanlizumab administered IV on week 1 day 1, week 3 day 1 and day 1 of every 4-week cycle
Comparator(s)	No comparator

Outcome(s)	• Pharmacokinetics (PK) (AUCd15) after 1st dose [Time frame: Day 15] • Pharmacodynamics (PD) (AUCd15) after 1st dose [Time frame: Day 15] • PK (AUCtau) after multiple dose [Time frame: Week 15] • PD (AUCtau) after multiple dose [Time frame: Week 15] • PK (Cmax) after 1st dose and multiple dose [Time frame: Week 1 and week 15] • PK pre-dose concentrations [Time frame: Week 1 to week 19] • Frequency of any adverse events (AEs) as a measure of safety and tolerability [Time frame: 6 months, 2 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**STAND; NCT03814746, 2017-001746-10;** A Phase III, Multicenter, Randomized, Double-blind Study to Assess Efficacy and Safety of Two Doses of Crizanlizumab Versus Placebo, With or Without Hydroxyurea/ Hydroxycarbamide Therapy, in Adolescent and Adult Sickle Cell Disease Patients With Vaso-Occlusive Crises **Phase III –** active, not recruiting **Location(s):** UK, 8 EU countries, US, Canada and other countries **Primary Completion Date:** May 2022
Trial Design	Parallel assignment, quadruple blinded, placebo controlled
Population	N=240; aged 12 years and older; Confirmed diagnosis of SCD; Experienced at least 2 VOCs
Intervention(s)	• 5mg/kg crizanlizumab IV • 7.5mg/kg crizanlizumab IV
Comparator(s)	Matched placebo
Outcome(s)	Rate of VOC events leading to healthcare visit [Time frame: 1 year] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Crizanlizumab is already marketed in the UK for the treatment of SCD in adults; a 10mg/ml vial costs £1038.00.[13]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Voxelotor for treating sickle cell disease. (GID-TA10505). Expected publication date to be confirmed.
- NICE technology appraisal. Crizanlizumab for preventing sickle cell crises in sickle cell disease. (TA743). November 2021.
- NICE clinical guideline. Sickle cell disease: managing acute painful episodes in hospital. (CG143). June 2012.
- NICE quality standard. Sickle cell disease. (QS58). April 2014.

NHS England (Policy/Commissioning) Guidance

- NHS England. Allogeneic haematopoietic stem cell transplantation for adults with sickle cell disease. 190138P. December 2019.
- NHS England. Commissioning Medicines for Children in Specialised Services. 170001/P. March 2017.
- NHS England. 2013/14 NHS standard contract for specialised services for haemoglobinopathy care (all ages). B08/S/a.

Other Guidance

- National Haemoglinopathy Panel. Crizanlizumab National Guideline. 2022.[14]
- Sickle Cell Society. Sickle Cell Disease in Childhood: Standards and Recommendations for Clinical Care. 2019.[10]

Additional Information

References

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