Health Technology Briefing
April 2024

Alpha-1 antitrypsin for treating high risk, acute graft versus host disease in people aged ≥ 12 years

Company/Developer	CSL Behring UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28719	NICE ID: Not available	UKPS ID: 660545

Licensing and Market Availability Plans

Phase III clinical trial ongoing.

Summary

Alpha-1 antitrypsin is currently in development for the treatment of high risk, acute graft versus host disease (aGvHD) in people aged ≥ 12 years following an allogeneic haematopoietic stem cell transplant (HSCT) for any indication. A stem cell transplant replaces damaged blood cells with healthy ones from another person (a donor). GvHD is a frequent complication of allogenic stem cell transplantation and involves a reaction between the donor cells and the recipient's native tissues, leading to injury of the recipient's tissues. GvHD occurs in acute and chronic form. aGVHD usually manifests within 100 days following HSCT whereas chronic GVHD generally manifests later (>100 days). Systemic corticosteroids are used as a first-line treatment for aGvHD, however, roughly half of patients become refractory to this treatment, meaning that the disease progresses or there is no response after treatment. As the number of patients undergoing allogenic HSCT increases, developing safe and effective treatments for aGvHD is increasingly important, especially for those whose disease becomes refractory to systemic steroid therapy.

Alpha-1 antitrypsin can prevent lethal aGVHD by mechanisms that include reduction of proinflammatory cytokines, increases in T regulatory cells, and decreases in T effector cells, which are proteins of the immune system. Alpha-1 antitrypsin is administered intravenously and if licensed, will offer an additional treatment option for people ≥ 12 years of age with high risk aGvHD following HSCT for any indication.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

For the treatment of high risk acute graft versus host disease (aGvHD) in subjects ≥ 12 years of age following allogeneic haematopoietic stem cell transplant (HSCT) for any indication.[1]

Technology

Description

Alpha-1 antitrypsin (AAT, alpha-1 proteinase inhibitor, Respreeza, Zemaira) is a 52-kDa circulating protease inhibitor produced by the liver that inactivates several serine proteases from neutrophils and macrophages and protects tissues from proteolytic degradation.[2,3] More recently appreciated immune regulatory roles for alpha-1 antitrypsin, independent of protease inhibition, include induction of interleukin 10 (IL-10), suppression of plasma proinflammatory cytokines, and in vivo induction of tolerance during experimental islet cell transplantation. Alpha-1 antitrypsin can prevent lethal aGvHD by mechanisms that include reduction of proinflammatory cytokines, increases in T regulatory cells, and decreases in T effector cells.[4]

Alpha-1 antitrypsin is currently in development for the treatment of high risk aGvHD in subjects ≥ 12 years of age following allogeneic HSCT for any indication. In the phase III clinical trial (BMT CTN 1705, NCT04167514), alpha-1 antitrypsin is administered intravenously.[1]

Key Innovation

HSCT remains the only curative treatment in a number of paediatric haematological pathologies despite acute and long-term toxicities.[5] Even with routine prophylaxis, clinically significant aGvHD requiring systemic corticosteroids occurs in ~40% of patients undergoing human leukocyte antigen (HLA)-matched allogeneic HSCT. Roughly half of the patients requiring high-dose corticosteroids will not respond, a condition termed steroid-refractory (sometimes also called steroid-resistant) aGvHD (SR-aGvHD), which is associated with poor overall survival. Although several immunosuppressive therapies have been attempted in SR-aGvHD, no consensus on treatment exists, given the marginal response rates and increased risk of infection. As the number of patients undergoing allogenic HSCT increases, developing safe and effective treatments for aGvHD is increasingly important, especially for those whose disease becomes refractory to systemic steroid therapy.[6]

Alpha-1 antitrypsin can prevent lethal aGVHD by mechanisms that include reduction of proinflammatory cytokines, increases in T regulatory cells, and decreases in T effector cells.[4] If licensed, alpha-1 antitrypsin will offer an additional treatment option for people ≥ 12 years of age with high risk aGvHD following HSCT for any indication.

Regulatory & Development Status

Human alpha-1 antitrypsin (solution) currently has Marketing Authorisation in the EU/UK to slow the progression of emphysema in patients with severe alpha$_1$-proteinase inhibitor deficiency.[7]

Alpha-1 antitrypsin is in phase II clinical development for eosinophilic esophagitis.[8]

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Patient Group

Disease Area and Clinical Need

GvHD is a complication of allogeneic HSCT and is a major cause of post-transplant mortality and morbidity. It is caused by immune incompatibility between the graft (donor) and recipient tissues. The graft cells recognise the recipient tissues as foreign and mount an immune response against them. There are two types of GvHD: aGvHD and chronic GvHD (cGvHD). aGvHD generally starts within 100 days of transplant and is graded in severity from I (mild) through II (moderate), III (severe) to IV (very severe) according to the modified Seattle Glucksberg criteria. The grades correlate to survival prognosis with 5-year survival of 25% for grade III and 5% for grade IV disease.[9] It is well established that patients with severe (clinical grade III–IV) aGvHD are less responsive to steroid treatment leading to poor survival and high transplant-related mortality (TRM).[10] aGvHD occurs primarily in the skin, gastrointestinal tract, and liver and can occur in allogenic HSCT recipients despite prophylaxis. Patients usually present with a maculopapular rash, nausea, vomiting, profuse watery diarrhoea, abdominal cramping, and hyperbilirubinemia with jaundice.[6] As aGvHD is a result of an alloimmune effect the major risk for occurrence is the presence of HLA disparity and increasing degrees of HLA-mismatching increase the probability of more severe disease. Other important and consistent risk factors include older patient age, the use of female donors for male recipients, prior alloimmunization of the donor, and the nature of GvHD prophylaxis.[11]

Depending on a number of patient- and transplant-related variables, the incidence of aGvHD ranges from 10% to 80% with symptoms usually developing 2–3 weeks post-transplant.[12] The rate of aGvHD amongst paediatric allograft recipients shows similar incidence compared to adults, and the British Society for Blood and Marrow Transplantation (BSBMT) UK Outcomes Register (2007-2012 cohort) identifies 697 patients with all grades of aGvHD, whilst the incidence of the most severe Grade III-IV categories is 134 patients.[9] In England 2022-23, there were 3,840 finished consultant episodes (FCE) and 3,670 admissions for bone-marrow transplant rejection (ICD-10 code T86.0) which resulted in 6,634 FCE bed days and 2,811 day cases.[13]

Recommended Treatment Options

There is no treatment option recommended by NICE for aGvHD. Current prophylaxis options for aGvHD are ciclosporin, methotrexate, mycophenolate mofetil and antithymocytic globulin.[14] Systemic corticosteroids are a first-line therapy for grade II-IV GvHD.[15] Extracorporeal photopheresis is recommended by NHS England for GvHD following HSCT.[9]

Clinical Trial Information

Trial	**BMT CTN 1705;** NCT04167514; A Randomized, Double-Blind, Placebo-Controlled Multicenter Phase III Trial of Alpha 1 - Antitrypsin (AAT) Combined with Corticosteroids vs Corticosteroids Alone for the Treatment of High Risk Acute Graft-versus-Host Disease (GVHD) Following Allogeneic Hematopoietic Stem Cell Transplant **Phase III** – Ongoing **Location:** USA **Primary completion date:** May 2024
Trial Design	Randomized, double-blind, placebo-controlled

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Population	N=136; subjects with aGvHD after allogeneic HSCT for any indication; ≥ 12 years of age.
Intervention(s)	Alpha-1 antitrypsin for intravenous administration
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Percent of participants with complete or partial response to aGVHD treatment. [Time Frame: 28 days post-randomization] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of alpha-1 antitrypsin for the treatment of aGvHD is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance awaiting development. Inolimomab (Leukotac) for acute graft versus host disease (aGvHD) after Allo-HSCT (GID-TA10823). Expected date of issue to be confirmed.
- NICE technology appraisal guidance awaiting development. Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (GID-TA11512). Expected date of issue to be confirmed.
- NICE technology appraisal guidance awaiting development. Ruxolitinib for treating acute graft-versus-host disease after allogeneic stem cell transplant in people 28 days to 17 years (GID-TA11494). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Abatacept for preventing moderate to severe acute graft-versus-host disease after haematopoietic stem cell transplant in people 6 years and over (GID-TA10996). Expected date of issue to be confirmed.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages). B04/P/a. July 2021
- NHS England. Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation). 16069/P. March 2017

Other Guidance

- Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, Bonifazi F et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. February 2020.[16]

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Additional Information

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