NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
December 2023

Ruxolitinib for treating chronic graft versus host disease after allogeneic stem cell transplant in paediatric patients

Company/Developer	Novartis Pharmaceuticals UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27728	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II clinical development.

Summary

Ruxolitinib is in clinical development for the treatment of chronic graft versus host disease (cGvHD), after allogeneic stem cell transplant (AlloSCT) in children. AlloSCT is a type of haematopoietic cell transplant (HCT), in which stem cells from a healthy donor are transplanted to the patient to replace stem cells that were destroyed during chemotherapy treatment. Chronic graft versus host disease (cGvHD), is a frequent complication of AlloSCT, where the donor's T-cells (white blood cells) fight the patient's organs and tissue, reducing their ability to carry out their normal function. This occurs 100 days after AlloSCT. The most frequently affected areas are the skin, mouth, lungs, and eyes. Treatment for cGvHD can be very complex and requires a combination of therapies. Corticosteroids remain the first-line treatment for chronic GvHD.

Ruxolitinib works by blocking the action of enzymes known as Janus kinases (JAKs), which are involved in the production and growth of blood cells and immune function. By blocking JAKs, ruxolitinib reduces the abnormal production of blood cells, thereby reducing the symptoms of the disease. Ruxolitinib is administered as oral tablets and if licenced, will offer an additional treatment option for children with cGvHD after AlloSCT.

Proposed Indication

Treatment of paediatric patients with moderate and severe chronic graft vs. host disease after allogeneic stem cell transplant.[1]

Technology

Description

Ruxolitinib (Jakavi) is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC50 values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. JAK-STAT signalling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GvHD pathogenesis.[2]

Ruxolitinib is currently in clinical development for the treatment of moderate and severe cGvHD in paediatric patients. In the phase II trial, (NCT03774082), participants received 5mg ruxolitinib tablet or ruxolitinib oral paediatric formulation (dosage based on age group) twice a day.[1]

Key Innovation

cGvHD is one of the major causes of late mortality after AlloSCT. Moderate and severe cGvHD is associated with poor health-related quality of life and substantial disease burden.[3] This is particularly important and functionally relevant in paediatric patients who have a longer life expectancy than adults. There is currently a huge unmet need, especially in paediatric patients aged under 12 years, in therapy for cGvHD, because there are few publications that address the challenges of therapy for cGvHD in this age group[4,5]

Ruxolitinib is a selective inhibitor of JAK1/2 enzymes.[2] Ruxolitinib was well tolerated in a cohort of 20 children and young adults, of which 16 children had cGvHD, comprising both moderate and severe cGvHD. Ruxolitinib showed promising responses for cGvHD as salvage and second-line therapy, reducing the need for prolonged or intensive steroid exposure with its side effects.[6] If licensed, ruxolitinib will offer an additional treatment option for children with cGvHD after AlloSCT.

Regulatory & Development Status

Ruxolitinib oral tablet currently has Marketing Authorisation in the EU/UK for the treatment of:[7]

- adolescents and adults with aGvHD and cGvHD who have an inadequate response to corticosteroids.
- adults with myelofibrosis
- adults with polycythaemia vera

Ruxolitinib is currently in phase II and III clinical trials for paediatric patients in:[8]

- prevention of severe acute GvHD
- high risk acute GvHD
- GvHD prophylaxis in aplastic anaemia patients
- early lung dysfunction after haematopoietic stem cell transplant
- primary haemophagocytic lymphohistiocytosis
- acute lymphoblastic leukaemia
- hair regrowth in patients with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)-associated alopecia areata
- macrophage activation syndrome
- hypereosinophilic syndrome

Patient Group

Disease area and clinical need

cGvHD is a common, potentially life-threatening, long-term debilitating complication of AlloSCT.[9] GvHD happens when the T cells in the donated stem cells or bone marrow attack the host's body cells. This is because the donated cells (the graft) see the host cells as foreign and attack them.[10] GvHD is a syndrome of variable clinical features resembling autoimmune and other immunologic disorders.[4] Historically, any manifestation of GvHD that was present (or continued) at 100 days after HCT or thereafter was arbitrarily defined as cGvHD. According to the National Institute of Health (NIH) consensus, cGvHD diagnosis requires the presence of at least 1 diagnostic clinical sign of cGvHD or the presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant tests, scoring of organ manifestation and exclusion of other possible diagnosis. The proposed global assessment of severity (mild, moderate, or severe) is derived by combining organ- and site-specific scores.[11] The diagnostic criteria for cGvHD were developed primarily from adult data, and it remains unknown whether the NIH-Consensus can be easily applied to children given the potential difficulties with assessment in paediatrics. In children, the most common organs involved with diagnostic or distinctive manifestations of cGvHD are the mouth, skin, eyes, and lungs.[5] The likelihood of developing cGvHD depends on the source of the Haemopoietic Stem Cell grafts, being highest if the graft is from peripheral blood stem cells, especially if Human Leukocyte Antigen-mismatched, and lowest from umbilical cord blood. Risk factors for the development of cGvHD include aGvHD, donor age, alloimmunised female donor to male recipient, graft source, use of total body irradiation, HLA-mismatch, and T-cell repleted grafts.[4] The symptoms depend on which parts of the body are affected, it may include dry eyes, sensitivity to bright light or vision changes, dry mouth, ulcers, fatigue, muscle weakness, joint pain/stiffness, skin rashes, shortness of breath and weight loss.[12]

The incidence of cGvHD is lower in paediatric patients than in adults. cGvHD affects between 6 and 33% of the paediatric patients, depending upon graft source.[5,13] According to the British Society of Bone and Marrow Transplantation and Cellular Therapy (BSBMTCT) Outcomes Register, a total of 296 AlloSCT were performed in paediatric patients in the UK (2021).[14] There are more allografts performed (70%) than autografts in paediatrics. The incidence of cGvHD is 20-30%. The 5-year overall survival has improved significantly from 63% to 75% in paediatric allografts.[15]

Recommended Treatment Options
NICE does not currently recommend any treatment options for the treatment of cGvHD in paediatric patients.

Clinical Trial Information

Trial	**REACH5; NCT03774082, EudraCT2018-003296-35;** A phase II open-label, single-arm, multi-centre study of ruxolitinib added to corticosteroids in paediatric subjects with moderate and severe chronic graft vs. host disease after allogeneic stem cell transplantation **Phase II-** Active, not recruiting **Location(s)-** 4 EU countries, Canada and others **Study completion date-** October 2024
Trial Design	Open-label, single-group assignment
Population	N=46 (actual), children (28 days- <18 yrs.) with treatment naïve or steroid-refractory moderate to severe chronic graft vs. host disease after allogeneic stem cell transplantation
Intervention(s)	5mg ruxolitinib tablet or ruxolitinib oral paediatric formulation twice a day
Comparator(s)	None
Outcome(s)	Primary outcome measures; Overall response rate (ORR) [Time Frame: Cycle 7 Day 1(C7D1) (Day 168)] ORR is defined as the proportion of subjects demonstrating a complete response (CR) or partial response (PR) without requiring additional systemic therapies for an earlier progression, mixed response or non-response. The response is assessed per NIH consensus criteria (Lee et al 2015) and response scoring will be relative to the organ stage at the start of the study treatment. See trial records for full list of other outcomes
Results (efficacy)	Among all points (pts) the ORR at C7D1 was 40% (18/45; 90% confidence interval [CI] 27.7, 53.3) and the Best overall response (BOR) rate up to C7D1 was 82.2% (37/45; 90% CI 70.2, 90.8) ORR at C7D1 in treatment-Naïve and Steroid Refractory pts were 41.2% and 39.3%, respectively. Of pts receiving corticosteroids (CS) at baseline (40/45; 88.9%), 42.5% (17/40) stopped or completely tapered CS and 75.0% (30/40) had a ≥50% reduction from baseline at least once by C7D1. Among all pts, the CS-free ORR at data cut-off was 37.8% (17/45; 90% CI 25.7, 51.1).[16]
Results (safety)	The median duration of ruxolitinib (RUX) exposure was 55.1 weeks (range 2.1–112.1). In total, 97.8% (44/45) of pts had an adverse event (AE) (any grade) and 64.4% had a ≥3 grade AE. Most frequently reported AEs were anaemia (22.2% any grade; 20.0% ≥3 grade), COVID-19 (17.8% any grade; 4.4% ≥3 grade) and decreased neutrophil count (17.8% any grade; 17.8% ≥3 grade). Overall, 73.3% (33/45) of pts had an infection. Viral infections occurred in 40.0% (18/45) of pts, including 17.8% (8/45) SARS-CoV-2 infections; bacterial and fungal infections occurred in 2.2% and 11.1%

	of pts, respectively. Overall, 10 (22.2%) pts died during the study. Three (6.7%) pts died whilst receiving RUX or within 30 days of the last study dose; causes of death were aspergillus pneumonia, septic shock and acute respiratory distress syndrome (1 pt each).[16]

Estimated Cost

Ruxolitinib is already marketed in the UK; a pack of 56 × 5mg costs £1,428, a pack of 56 x 10mg costs £2,856, a pack of 56 x 15mg costs £2,856 and a pack of 56 x 20mg costs £2,856.[17]

Relevant Guidance

NICE Guidance

No relevant guidance was identified.

NHS England (Policy/Commissioning) Guidance

NHS England. Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation. 16069/P. March 2017.

Other Guidance

- Oxford University Hospitals. Diagnosis and management of cutaneous graft versus host disease 2022.[18]
- National Comprehensive Cancer Network guidelines for patients- Graft-Versus-Host Disease.2021.[19]
- University of Wisconsin Hospitals and Clinical Authority guideline. Chronic Graft-Versus-Host Disease: Diagnosis and Treatment - Adult/Paediatric - Inpatient/Ambulatory.2019.[20]

Additional Information

Novartis Pharmaceuticals UK Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.