NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
November 2023

Ruxolitinib for grades II-IV treatment-naïve or steroid-refractory acute graft versus host disease

Company/Developer	Novartis Pharmaceuticals UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 25409	NICE TSID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Phase I/II clinical trial completed

Summary

Ruxolitinib is in clinical development for the treatment of patients aged 28 days to 17 years with a clinically confirmed diagnosis of grades II-IV treatment-naïve or steroid-refractory acute graft versus host disease (aGvHD) and who have undergone allogeneic stem cell transplantation (alloSCT) from any donor source using bone marrow, peripheral blood stem cells, or cord blood. Graft versus host disease (GvHD) is a frequent complication of bone marrow or stem cell transplantation using tissue from another person. This is called an allogeneic transplant and is used to treat carefully selected patients with a range of blood problems and other illnesses that affect the immune system. It involves replacing diseased or damaged cells with healthy cells from another person (a donor). There are two types of GvHD: acute (aGvHD) and chronic (cGvHD). aGvHD generally starts within 100 days of transplant. A stage II-IV refractory aGvHD is a moderate to very severe aGvHD that is resistant to treatment. The symptoms of aGvHD can include diarrhoea, shortness of breath, an itchy rash, joint pain, dry flaky skin, jaundice, and dry mouth. Risk factors associated with aGvHD include donor/recipient age and sex, donor parity (the number of childbirths of a donor), and total body irradiation (radiotherapy to the whole body).

Ruxolitinib is an oral drug that falls under the class of drugs known as Janus kinase (JAK) inhibitors. JAKs are involved in the development and activation of blood cells that play a role in graft-versus-host disease. By blocking JAKs, ruxolitinib reduces the production of blood cells, thereby reducing the symptoms of the disease. If licensed, ruxolitinib may provide a new treatment option for children aged 28 days to 17 years with grade II-IV treatment-naïve or steroid-refractory aGvHD.

Proposed Indication

Treatment of children aged 28 days to 17 years with grade II-IV treatment-naïve or steroid-refractory acute graft versus host disease (aGvHD).[1]

Technology

Description

Ruxolitinib (Jakavi) is a selective inhibitor of the Janus associated kinases (JAKs) JAK1 and JAK2. These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.[2] The JAK and signal transducers and activators of transcription (JAK-STAT) signalling pathways play an important role in immune-cell activation and tissue inflammation during aGVHD.[3,4]

Ruxolitinib is currently in development for the treatment of patients aged 28 days to 17 years with a clinically confirmed diagnosis of grades II-IV aGvHD, and who have undergone allogeneic stem cell transplantation from any donor source (matched unrelated donor, sibling, haplo-identical) using bone marrow, peripheral blood stem cells, or cord blood. In phase I/II clinical trial (NCT03491215), participants received a 5mg oral dose of ruxolitinib or an oral paediatric formulation and dosage based on age group.[1]

Key Innovation

Haematopoietic stem cell transplantation (HSCT) remains the only curative treatment in a number of paediatric haematological pathologies despite acute and long-term toxicities.[5] Acute graft-vs-host disease (aGvHD) is a major complication of allogeneic stem cell transplantation.[6] Corticosteroids are the first-line treatment for GvHD, but the response rate is approximately 50%, and a significant number of patients experience steroid-refractory GvHD.[3] There is currently no standardised second-line strategy for steroid-resistant aGvHD.[5] Ruxolitinib is currently indicated for the second-line treatment of patients with aGvHD aged 12 years and above.[2] If licensed, ruxolitinib may provide a new treatment option for children aged 28 days to 17 years with grade II-IV treatment-naïve or steroid-refractory aGvHD.

Regulatory & Development Status

Ruxolitinib currently has Marketing Authorisation in the EU/UK for [2]:

- the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythemia myelofibrosis
- the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea
- the treatment of patients aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids
- the treatment of patients aged 12 years and older with chronic graft versus host disease who have inadequate response to corticosteroids

Ruxolitinib is also in phase II/III development for over 200 indications including:[7]

- atopic dermatitis
- advanced cutaneous squamous cell carcinoma
- haematologic malignancy
- bronchiolitis obliterans syndrome
- hand eczema
- prurigo nodularis

- T-cell large granular lymphocyte leukaemia
- myelofibrosis
- polycythemia vera
- lichen sclerosus
- cutaneous lichen planus
- viltiligo

Patient Group

Disease Area and Clinical Need

GvHD is a complication of allogeneic haematopoietic stem cell transplantation (Allo-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.[8] There are two types of GvHD: acute (aGvHD) and chronic (cGvHD). aGvHD generally starts within 100 days of transplant. aGvHD is graded in severity from I (mild) through II (moderate), III (severe) to IV (very severe) according to the modified Seattle Glucksberg criteria. The grade correlates to survival prognosis with 5-year survival of 25% for grade III and 5% for grade IV disease.[8] The symptoms of aGvHD can include diarrhoea, shortness of breath, an itchy rash, joint pain, dry flaky skin, jaundice, and dry mouth.[9] Numerous risk factors associated with the occurrence of aGvHD have been described, such as human leukocyte antigen (HLA) disparity, donor/recipient age and sex, donor parity, total body irradiation (TBI), and conditioning regimen intensity.[10]

The incidence of aGvHD varies widely and can be as high as 20–80%.[10] The rate of aGvHD amongst paediatric allograft recipients shows similar incidence compared to adults, and the British Society for Blood and Marrow Transplantation (BSBMT) 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.[8] In England (2022-23) there were 282 finished consultant episodes (FCEs) and 258 admissions for other specified disorders involving the immune mechanism, not elsewhere classified (ICD-10 code D89.8), which resulted in 184 day cases and 681 FCE bed days.[11] Grade correlates to survival prognosis with 5-year survival of 25% for grade III and 5% for grade IV disease.[8]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatment options for aGvHD. Current prophylaxis options for aGvHD are ciclosporin, MTX, alemtuzumab, mycophenolate mofetil and antithymocytic globulin but there are currently no approved therapies.[12] Extracorporeal photopheresis is recommended by NHS England for GvHD following HSCT.[8]

Clinical Trial Information

TriaII	NCT03491215, EudraCT 2018-000422-55; A Phase I/II Open-label, Single-arm, Multi-center Study of Ruxolitinib Added to Corticosteroids in Pediatric Patients With Grade II-IV Acute Graft vs. Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation. **Phase I/II** - Completed **Location(s):** Five EU countries, Canada, Japan and South Korea **Study Completion Date:** February 2023
Trial Design	Interventional, open-label, single group assignment

Population	N=45 (actual); patients aged ≥28 days to <18 years with a clinically confirmed diagnosis of grades II-IV aGvHD within 48 hours prior to study treatment start, and who have undergone alloSCT from any donor source (matched unrelated donor, sibling, haplo-identical) using bone marrow, peripheral blood stem cells, or cord blood.
Intervention(s)	Ruxolitinib 5mg twice daily
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: - Phase I: Measurement of pharmacokinetic (PK) parameter, AUC, in aGvHD and SR-aGvHD patients [Time Frame: 28 days] - Phase I: Measurement of PK parameter, Cmax, in aGvHD and SR-aGvHD patients [Time Frame: 28 days] - Phase I: Measurement of PK parameter, T1/2, in aGvHD and SR-aGvHD patients [Time Frame: 28 days] - Phase I: Measurement of PK parameter, Ctrough, in aGvHD and SR-aGvHD patients [Time Frame: 28 days] - Phase I: Age-based determination of recommended phase 2 dose (RP2D) for each of the groups 2-4 [Time Frame: 28 days] - Phase II: Overall response rate (ORR) [Time Frame: 28 days] See trial record for a full list of other outcomes
Results (efficacy)	The ORR in all pts was 84.4% (38/45) at day 28, with a durable ORR at day 56 of 66.7% (30/45; Table 2). ORR at day 28 and durable ORR at day 56 among treatment-naïve pts were 69.2% (9/13) and 61.5% (8/13), respectively; and among SR pts, 90.6% (29/32) and 68.8% (22/32), respectively.[6]
Results (safety)	The most frequently reported AEs were in line with those previously observed in RUX clinical trials.[6]

Estimated Cost

Ruxolitinib is already marketed in the UK. A pack of 56 x 5mg tablets costs £1,428, while a pack of 56 x 10mg, 56 x 15mg or 56 x 20mg tablets cost £2,856.[13]

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.

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[14]
- Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P et al. Diagnosis and management of acute graft-versus-host disease. April 2012[15]

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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