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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Ruxolitinib for acute graft versus host disease (aGvHD)

NIHRIO ID	12967	**NICE ID**	10195
Developer/Company	Novartis Pharmaceuticals UK Ltd	**UKPS ID**	644002

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Ruxolitinib is in clinical development for acute graft versus host disease (aGvHD). After a donor stem cell transplant, the donor's stem cells (the graft) may sometimes react against the host's own cells. This is called GVHD. aGVHD is most likely to happen in the first three months after transplant. The symptoms depend on which parts of the body are affected. It often causes an itchy skin rash. If the bowel, the stomach or the liver are affected, the patient may have sickness and diarrhoea. aGVHD is graded by how severe it is. It goes from grade 1, which is mild, to grade 4 which is very severe. Current standard treatment includes the use of steroids but this is often associated with significant side effects. Steroid resistance in GvHD may also develop which is difficult to treat and associated with a high mortality.

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 diseases. Ruxolitinib is administered as oral tablets and if licenced, will offer a treatment option for patients with steroid-refractory aGvHD after allogeneic hematopoietic stem cell transplantation.

PROPOSED INDICATION

Treatment of adults and adolescents ≥ 12 years with steroid-refractory acute graft versus host disease (aGvHD) after allogeneic hematopoietic stem cell transplantation.[1,2,a]

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. Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC_{50} ranging from 80-320 nM.[3]

Ruxolitinib is currently in clinical development for the treatment of steroid-refractory aGvHD. In the phase III clinical trial (NCT02913261, REACH2), participants received either ruxolitinib 10 mg orally twice daily (BID) or best available therapy (BAT). There is no maximum duration for study treatment reported on the trial registry.[2]

INNOVATION AND/OR ADVANTAGES

The standard first line therapy of acute and chronic GvHD is the administration of steroids in conjunction with calcineurin inhibitors. However, prolonged and/or intensive steroid exposure is associated with a variety of side effects such as increased infection rates, myelopathy, and atrophy of the skin. Beyond the first line therapy, there is no standard defined so far. Steroid resistant acute GvHD is difficult to treat and associated with a high mortality. Common drugs and measures used in this situation have moderate success rates.[4]

Ruxolitinib is an inhibitor of Janus kinases 1/2 that has shown to reduce the proliferation of t-effector cells and suppression of proinflammatory cytokine production showing their positive effects in experimental murine GvHD.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, ruxolitinib is licensed in the EU/UK for the treatment of:[3]

- disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.
- adults with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

The most frequently reported adverse drug reactions were thrombocytopenia, anaemia, neutropenia, urinary tract infections, bleeding, bruising, weight gain, dizziness, headache, raised aspartate aminotransferase, raised alanine aminotransferase, and hypercholesterolaemia, hypertriglyceridemia, and high blood pressure.[3,5]

[a] Information provided by Novartis Oncology on the UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Graft versus host disease (GvHD) is a possible complication of a bone marrow or stem cell transplant from another person. GvHD means the graft reacts against the host. The graft is the donated marrow or stem cells. The host is the person receiving the transplant. GvHD happens because the transplant affects the immune system. The donor's bone marrow or stem cells will contain some T cells. T cells are a type of white blood cell that helps fight infections. T cells attack and destroy cells they see as foreign, and potentially harmful such as viruses. Normally T cells do not attack its own body cells, because they recognise proteins on the cells called HLA (human leukocyte antigens).[6]

After a transplant, the bone marrow starts making new blood cells from the donor stem cells. These new blood cells have the donor's HLA pattern. They recognise the HLA pattern on the body cells as different (foreign) and may begin to attack some of them. The GvHD may affect different areas of the body. Most commonly it affects the skin, digestive system (including the bowel and stomach) or the liver.[6]

The GvHD can be classified acute and chronic, depends on when it starts after the transplant.

Acute GvHD (aGvHD), generally starts within 100 days of transplant but it can sometimes happen after this time. It usually happens about 2 to 3 weeks after the transplant when the new bone marrow begins to make blood cells. It can be mild or severe, and often starts with a rash on the palms of hands, the soles of feet, the ears, and the face. The rash may be itchy or painful. It may also affect the mouth, the gut (digestive system) and the liver. This can cause diarrhoea, sickness, loss of appetite, and yellowing of the skin (jaundice).[6]

There are 4 grades which range from grade 1 to grade 4 and it depends on: the number of organs affected (skin, bowel, or liver) - GvHD can affect any or all of these 3 organs and how bad the GvHD is. Grade 1 is mild GvHD. It means up to a quarter (25%) of the skin is affected. Grade 2 is moderate GvHD. It means up to half of the skin (25 to 50%) is affected. There are mild changes in liver or may have some mild diarrhoea or feel sick. Grade 3 is severe GvHD. It means more than half of the skin (over 50%) is affected. It may look as though it's severe sunburn. The liver is affected and the person may have stomach cramps and diarrhoea. Grade 4 is very severe GvHD. The skin has blistered and may have broken down in places. The skin may be yellow (jaundiced) because the liver is not working properly. There may be severe diarrhoea.[7]

Chronic GvHD (cGvHD) starts more than 100 days after the transplant. A person is more likely to get cGvHD when aGvHD has developed previously but it can happen even without having had aGvHD. cGvHD can be mild or severe, and for some people can go on for several months or even years. It may affect the skin, the gut, the liver, the mouth, the eyes, the lungs, the vagina, and the joints.[6]

CLINICAL NEED AND BURDEN OF DISEASE

The British Society for Blood and Marrow Transplantation (BSBMT) outcomes register (2007-2012) identifies the rate of aGVHD (all grades) for adults allograft recipients ranges from 31-50% depending on stem cell source (2,180 patients, 2007-2012 cohort). The incidence of the most severe Grade 3-4 categories of aGvHD requiring a second or subsequent lines of therapy is below 10% (364 patients, 2007-2012 cohort).[8]

The rate of aGvHD amongst paediatric and adults allograft recipients was similar, the BSBMT Outcomes Register identified 697 patients with all grades of aGvHD between 2007-2012, whilst the number of patients in grade 3-4 categories was 134 patients.[8]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The goal of any treatment is the effective control of GvHD whilst minimising the risk of toxicity and relapse. In many cases, patients are treated prophylactically where high probability of GvHD is present. Combination therapies are often required.[8] Treatment for GvHD depends on a number of factors and these include what type of GvHD the patient have and where patient have it.[9]

General treatment is based on drugs that reduce the body's immune response and reduce the number of T cells. The most common treatment is corticosteroids (usually prednisolone). Sometimes steroids and ciclosporin do not control GvHD. In this case, other treatments, which may include: infliximab, etanercept, sirolimus, mycophenolate mofetil, and a type of light therapy called extracorporeal photopheresis (ECP).[7]

There are some things that can be done to help keep the skin more comfortable. These include: wear cotton clothes, trying not to get too hot or too cold, using unperfumed soaps, using warm, not hot, water for washing, letting the skin dry in the air, or gently patting it dry, keeping the skin well moisturised with unperfumed creams or lotions, and covering up the skin in the sun.[7]

GvHD of the gut might cause sickness or diarrhoea and the symptoms might be controlled using: fluids by drip into a vein, to prevent and treat dehydration, painkillers if the patient has any abdominal cramps, anti-sickness drugs if the patient feels sick, drugs to control the diarrhoea, and feeding through a tube into the stomach or directly into the bloodstream, if the patient cannot eat and is losing weight.[7]

To control the symptoms of acute liver GvHD, the patient might have: drugs to relieve itchy, jaundiced skin; blood transfusions if the patient has a low red blood cell count (anaemia), or a low platelet count; and painkillers.[7]

CURRENT TREATMENT OPTIONS

For patients with aGvHD:[8]
Topical therapies (including hydrocortisone, eumovate, betnovate and dermovate) and optimisation of calcineurin inhibitors (tacrolimus or cyclosporine) and/or mycophenolate mofetil are the preferred approaches in the management of grade I disease.

Where patients present with grade II-IV GvHD, systemic corticosteroids (methylprednisolone) are indicated first-line. Dosage varies depending on severity, with 1mg/kg/day indicated for patients with grade II and 2mg/kg/day indicated for patients with grades III-IV disease.

Where patients present with acute intestinal GvHD and are at risk of developing adverse effects or becoming corticosteroid dependent, non-absorbable steroids (budesonide or beclomethasone) are indicated to reduce dose of systemic steroids. Combination therapy is common in steroid refractory patients, with the following treatments indicated: mammalian target of rapamycin inhibitors (sirolimus) and/or mycophenolate mofetil.

Where patients fail to show complete response (i.e. steroid-refractory aGvHD), have developed significant adverse effects to first-line treatments or are steroid dependent, Extracorporeal photopheresis (ECP) should be offered.

PLACE OF TECHNOLOGY

If licensed, ruxolitinib will offer a treatment option for patients with steroid-refractory aGvHD after allogeneic hematopoietic stem cell transplantation, who currently have limited options.

CLINICAL TRIAL INFORMATION

Trial	REACH2, NCT02913261, CINC424C2301; aged ≥12 years; ruxolitinib vs best available therapy (BAT); phase III
Sponsor	Novartis Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[2]
Location	EU countries (including the UK), Canada and other countries
Design	Randomised, active-controlled, open-label; parallel assignment
Participants	N=310; aged 12 years and older; have undergone Allogeneic Stem Cell Transplantation (alloSCT) from any donor source (matched unrelated donor, sibling, haploidentical) using bone marrow, peripheral blood stem cells, or cord blood; clinically diagnosed Grades II to IV acute GvHD as per standard criteria occurring after alloSCT requiring systemic immune suppressive therapy; and confirmed diagnosis of steroid refractory aGvHD defined as patients administered high-dose systemic corticosteroids (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]), given alone or combined with calcineurin inhibitors (CNI); requirement for an increase in the corticosteroid dose to methylprednisolone ≥2 mg/kg/day (or equivalent prednisone dose ≥2.5 mg/kg/day) or failure to taper the methylprednisolone dose to <0.5 mg/kg/day (or equivalent prednisone dose <0.6 mg/kg/day) for a minimum 7 days.
Schedule	Participants were randomised to one of the treatment arms: - Ruxolitinib tablet at a dose of 10 mg orally twice day (BID). - BAT as selected by the investigator.
Follow-up	Up to 24 months
Primary Outcomes	Overall Response Rate (ORR) [Time frame: 28 days]
Secondary Outcomes	• Durable ORR[Time frame: day 56] • ORR [Time frame: day 14] • Duration of response (DOR) [Time frame: up to 24 months] • Cumulative steroid dose [Time frame: 56 days] • Overall Survival (OS) [Time frame: up to 24 months] • Event-free survival [Time frame: up to 24 months] • Failure-Free survival (FFS) [Time frame: up to 24 months] • Non Relapse Mortality (NRM) [Time frame: up to 24 months] • Malignancy Relapse/Progression (MR) [Time frame: up to 24 months] • Incidence of chronic GvHD [Time frame: up to 24 months]

	• Pharmacokinetic (PK) parameter: Plasma concentration at peak (CMax) after single dose and at steady state of ruxolitinib in corticosteroid refractory acute GvHD patients [Time frame: 168 days] • Exposure-efficacy relationship of ruxolitinib in corticosteroid refractory aGvHD [Time frame: 168 days] • Patient Reported Outcomes (PROs): Functional Assesment of Cancer Therapy-Bone Marrow Transplantation (FACT-BMT) [Time frame: baseline, up to 30 day follow-up visit] • Patient Reported Outcomes (PROs): EuroQol-5D-5L change [Time frame: baseline, up to 30 day follow-up visit] • Pharmacokinetic (PK) parameter: Area Under the Curve (AUC) after single dose and at steady state of ruxolitinib in corticosteroid refractory acute GvHD patients [Time frame: 168 days] • Pharmacokinetic (PK) parameter: total body clearance of ruxolitinib from the plasma after single dose and at steady state of ruxolitinib in corticosteroid refractory acute GvHD patients [Time frame: 168 days] • Pharmacokinetic (PK) parameter: apparent volume of distribution during terminal phase after single dose and at steady state of ruxolitinib in corticosteroid refractory acute GvHD patients [Time frame: 168 days] • Best Overall Response (BOR) [Time frame: up to day 28] • Pharmacokinetic (PK) parameter: Ctough [Time frame: 168 days]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date was June 2019.

Trial	REACH-1, NCT02953678, INCB 18424-271; aged ≥12 years old; Ruxolitinib in combination with corticosteroids (prednisone or methylprednisolone); phase II
Sponsor	Incyte Corporation
Status	Ongoing and published
Source of Information	Trial registry,[1] Publication[10]
Location	USA
Design	Single group assignment, open-label study
Participants	N=71, aged ≥ 12 years older; have undergone first allo-HSCT from any donor source using bone marrow, peripheral blood stem cells, or cord blood for hematologic malignancies; clinically suspected Grades II to IV aGVHD as per MAGIC guidelines, occurring after allo-HSCT with any conditioning regimen and any anti-GVHD prophylactic program; and steroid-refractory acute GVHD.
Schedule	Participants began oral administration of ruxolitinib at 5 mg BID; if stable after the first 3 days of treatment, the dose could be increased to 10 mg BID. Either oral prednisone or IV methylprednisolone may be used to begin corticosteroid treatment at the investigator's discretion.
Follow-up	Up to 180 days
Primary Outcomes	ORR at day 28 [Time frame: from baseline to day 28]
Secondary Outcomes	• Six-month Duration of Response (DOR) [Time frame: from baseline to day 180]

	• ORR [Time frame: from baseline to days 14, 56, and 100] • Three-month DOR [Time frame: from baseline to 84 days] • NRM [Time frame: from baseline to months 6, 9, 12, and 24] • Relapse Rate [Time frame: from baseline to day 84] • Relapse-related mortality rate [Time frame: from baseline to day 84] • FFS [Time frame: from baseline to day 84] • OS [Time frame: from baseline to day 84] • Incidence and Severity of Adverse Events [Time frame: from consent to 30-35 days after end of treatment, up to 24 months]
Key Results	At Day 28, ORR was 54.9% (CR, 26.8%). Responses were observed irrespective of aGVHD grade and SR criteria. Best ORR at any time during treatment was 73.2% (CR, 56.3%). Median (range) time to response was 7 (6-49) days. Median DOR with minimum 6 months follow-up was 345 days for both day 28 responders and for patients who had a best overall response at any time during treatment. Four patients (5.6%) had malignancy relapse. Non relapse mortality at 6 months was 44.4%. Median overall survival had not been reached for day 28 responders.
Adverse effects (AEs)	The most frequently reported hematologic treatment-emergent adverse events (TEAEs) were anaemia (64.8%), thrombocytopenia (62.0%), and neutropenia (47.9%). Cytomegalovirus infection (12.7%), sepsis (12.7%), and bacteraemia (9.9%) were the most frequently reported infections. Fatal ruxolitinib-related TEAEs were sepsis and pulmonary haemorrhage (1 patient each) and were attributed to both ruxolitinib and corticosteroid.
Expected reporting date	Study completion date is June 2020.

ESTIMATED COST

Ruxolitinib is already marketed in the UK. The NHS indicative price for ruxolitinib is:[11]

- A pack of 56 x 5 mg tablets costs £1428.00
- A pack of 56 x 10, 15 and 20 mg tablets costs £2856.00

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- Oxford University Hospitals. Diagnosis and management of acute graft versus host disease. 2018.[12]
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ADDITIONAL INFORMATION

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