NIHR | Innovation Observatory

# HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

# Belumosudil for graft versus host disease

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| **NIHRIO ID** | 13112 | **NICE ID** | 10694 |
| **Developer/Company** | Kadmon International LTD | **UKPS ID** | N/A |

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| **Licensing and market availability plans** | Currently in phase II clinical trials |

## SUMMARY


Belumosudil is in clinical development for the treatment of chronic graft-versus-host disease (cGVHD). cGVHD is an immune-mediated, inflammatory disease with potential fibrotic manifestations in which immune cells from the graft attack the recipient cells after a haemopoietic stem cell transplantation (HSCT). cGVHD is characterised by inflammation and fibrotic processes which can lead to chronic disability when affecting multiple organs including joints or extensive areas of the skin. cGvHD is associated with poor quality of life and significant morbidity and mortality. Many sufferers require several lines of treatment consisting primarily of immunosuppressants, and due to intolerable side effects and low efficacy, additional therapies are required to manage this unmet need.

Belumosudil is a selective inhibitor of a signalling pathway that controls inflammatory responses, thereby reducing inflammation. By affecting several other regulatory pathways, belumosudil can also reduce the formation of fibrosis. By reducing the two main characteristics of cGVHD, belumosudil, administered orally, has the potential to offer an additional third-line or greater treatment for patients with cGvHD who have received at least two prior lines of systemic therapy.


## PROPOSED INDICATION

Treatment of adult and paediatric patients over the age of 12 with cGvHD after failure of at least two prior lines of systemic therapy.[1,2]

# TECHNOLOGY

## DESCRIPTION

Belumosudil (REZUROCK™, KD025) is an oral selective rho-associated coiled-coil containing protein kinase-2 (ROCK2) inhibitor with 100-fold selectivity for ROCK2 over ROCK1. ROCK2 inhibition acts on both the dysregulated adaptive immune system and the fibrosis that occurs due to aberrant tissue repair. Specifically, ROCK2 inhibition leads to the downregulation of signal transducer and activator of transcription 3 (STAT3) phosphorylation and the consequent decreased expression of type 17 helper T (Th17) cell–specific transcription factors. Moreover, selective ROCK2 inhibition restores immune homeostasis by shifting the Th17/regulatory T (Treg) cell balance via a signal transducer and activator of transcription 5 (STAT5)-dependent mechanism. ROCK signalling plays a central role in multiple fibrotic pathways. ROCK2 activation by profibrotic mediators, such as lysophosphatidic acid and TGF-β, results in polymerisation of G-actin to F-actin. This frees myocardin-related transcription factors and leads to the activation of profibrotic gene expression. This promotes the differentiation of fibroblasts into myofibroblasts and increases the production of collagen, both of which are key features of fibrotic diseases.[3-6]

In phase II clinical trials (NCT03640481, NCT02841995), belumosudil 200mg is given orally once or twice daily.[1,2]

## INNOVATION AND/OR ADVANTAGES

Current treatment options for cGvHD after first-line therapy have many intolerable side effects leading to a need for further safe and effective treatments.[7,8] In phase II trials, belumosudil has been shown to be well tolerated with limited serious adverse side effects and targets both fibrosis and inflammation. In these trials, high overall response rates (ORRs) were seen in all patient subgroups, regardless of length of time from diagnosis to treatment, including those with severe cGVHD, involvement of ≥4 organs and a refractory response to prior lines of therapy.[9,10]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Belumosudil does not currently have Marketing Authorisation in the EU/UK for any indication.

Belumosudil is currently in phase II clinical trials for systemic sclerosis. [11]

# PATIENT GROUP

## DISEASE BACKGROUND

Graft-versus-Host Disease (GVHD) is a frequent complication of allogeneic haematopoietic stem cell transplantation (AlloHSCT) and can be serious and life threatening. 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: acute and chronic. Both can present with mild to severe symptoms, however, cGVHD usually presents with a wider range of inflammatory and fibrotic manifestations and can affect almost any organ. Typical symptoms may include skin thickening

and severe rash/erythema, nail loss, dry mouth and oral lesions, dry eyes, sore muscles and joints, raised liver enzymes, and later manifestations such as scarring of lung tissue with reduced lung function.[12]

cGVHD is staged as either limited or extensive and can be graded further by severity (mild, moderate, or severe). Extensive cGVHD causes a great degree of morbidity with loss of health and an increased risk of infection. It can be life limiting.[12]

Risk factors associated with cGVHD are hemopoietic cell transplantation (HCT) with human leukocyte antigen (HLA)-matched unrelated donors, HCT with HLA-mismatched related donors, HCT with HLA-mismatched unrelated donors, all compared with HCT with HLA-matched related donors, the use of a female donor for a male recipient, grafting with mobilised blood cells, and older donor and recipient age.[13]

## CLINICAL NEED AND BURDEN OF DISEASE

The rate of cGVHD in adult allograft recipients ranges from 30-40% and is 5-6% for extensive cGVHD who require second or subsequent lines of therapy.[12]

In 2019, the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) reported a total of all peripheral stem cell transplants (SCTs) in UK and Republic of Ireland to be 1,400.[14] The hospital episode statistics (HES) for procedures or interventions for England in 2019-2020, recorded a total of 1,130 finished consultant episodes for allogeneic peripheral blood stem cell transplant (OPCS4 X33.6). [15] Using the NHS figures, around 339-452 patients will suffer from cGVHD and around 57-68 could benefit from treatment with belumosudil.[12]

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

A multi-disciplinary team is called with the accountable transplant physician, nurse and consultant in whichever organ is principally involved to discuss treatment options available. 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.[12]

Corticosteroids are used as first-line treatments, with an initial starting dose of 1mg/kg prednisolone. Where patients are at risk of developing adverse effects or becoming corticosteroid dependent, calcineurin inhibitors (tacrolimus or cyclosporine) are used to reduce dose of systemic steroids.[16]

## CURRENT TREATMENT OPTIONS

According to NHS England, the following treatment options are recommended for cGVHD that has been previously treated with at least 2 therapies:[12]

- Mycophenolate mofetil
- Methotrexate
- Pulsed corticosteroids

## PLACE OF TECHNOLOGY

If licensed, belumosudil will offer an additional treatment option for patients over 12 years old with cGVHD after failure of at least two prior lines of systemic therapy.

## CLINICAL TRIAL INFORMATION

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| **Trial** | **ROCKstar;** NCT03640481**;** A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects With Chronic Graft Versus Host Disease (cGVHD) After At Least 2 Prior Lines of Systemic Therapy<br>**Phase II** - Recruiting<br>**Location(s):** US<br>**Primary completion date:** July 2022 |
| **Trial design** | Randomised, parallel assignment, open-label |
| **Population** | N=166 (estimated); 12 years and older; subjects who have had allogeneic haematopoietic cell transplant (HCT); previously received at least 2 and not more than 5 lines of systemic therapy for cGVHD |
| **Intervention(s)** | • Arm A: belumosudil 200 mg once daily (QD), orally<br>• Arm B: belumosudil 200 mg twice daily (BID), orally |
| **Comparator(s)** | No comparator |
| **Outcome(s)** | Overall Response Rate (ORR) [Time frame: 6 months]<br><br>See trial record for full list of other outcomes |
| **Results (efficacy)** | • The best ORR (95% CI) of belumosudil 200 mg QD and 200 mg BID was 74% (62%-84%) and 77% (65%-87%), respectively, with high response rates observed in all subgroups.<br>• All affected organs demonstrated complete responses.<br>• The median duration of response (DOR) was 54 weeks; 44% of subjects have remained on therapy for ≥1 year. Symptom reduction with belumosudil 200 mg QD and 200 mg BID was reported in 59% and 62% of subjects, respectively.[9] |
| **Results (safety)** | • Adverse events (AEs) were consistent with those expected in patients with cGVHD receiving corticosteroids and other immunosuppressants. Sixteen subjects (12%) discontinued belumosudil due to possible drug-related AEs.[9] |

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| **Trial** | NCT02841995**;** A Phase 2a, Dose-Escalation, Open-Label Study to Evaluate the Safety, Tolerability, and Activity of KD025 in Subjects With Chronic Graft Versus Host Disease<br>**Phase II** – Active, not recruiting<br>**Location(s):** US<br>**Primary completion date: December** August 2021 |
| **Trial design** | Randomised, parallel assignment, open-label |
| **Population** | N=54; 18 years and older; subjects who have had allogeneic hematopoietic cell transplant (HCT) |
| **Intervention(s)** | • Belumosudil 200 mg once daily (QD), orally<br>• Belumosudil 200 mg twice daily (BID), orally |

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| | • Belumosudil 400mg once daily, orally |
| **Comparator(s)** | No comparator |
| **Outcome(s)** | • Overall response criteria [Time frame: Response assessment is measured at day 1 of every cycle starting at cycle 2 (ex: cycle 2 day1, cycle 3 day1, cycle 4 day1, etc.). Cycle length is 28 days.]<br>• Number of Subjects Experiencing Adverse Events as a Measure of Safety and Tolerability [Time frame: From patient consent to 28 days post last belumosudil dose.] |
| **Results (efficacy)** | • The ORR (95% CI) with belumosudil 200 mg once daily, 200 mg twice daily, and 400 mg once daily was 65% (38% to 86%), 69% (41% to 89%), and 62% (38% to 82%), respectively.<br>• Responses were clinically meaningful, with a median duration of response of 35 weeks, and were associated with quality-of-life improvements and corticosteroid (CS) dose reductions.<br>• CS treatment was discontinued in 19% of patients.<br>• The failure-free survival rate was 76% (62% to 85%) and 47% (33% to 60%) at 6 and 12 months, respectively.<br>• The 2-year overall survival rate was 82% (69% to 90%).[10] |
| **Results (safety)** | • Belumosudil was well-tolerated, with low rates of cytopenia.<br>• There were no unexpected adverse events and no apparent increased risk of infection, including cytomegalovirus infection and reactivation.[10] |

# ESTIMATED COST

The cost of belumosudil outside the U.S. is not yet available.

# 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

- British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation (BCSH/BSBMT). Diagnosis and management of chronic graft versus-host disease. 2012.[16]

## ADDITIONAL INFORMATION

Kadmon International 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.

## REFERENCES


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