SMC2583

belumosudil film-coated tablet (Rezurock®)

Sanofi

09 June 2023

The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: treatment of patients aged 12 years and older with chronic graft-versus-host disease (chronic GvHD) who have received at least two prior lines of systemic therapy.

Key points:

- Chronic GvHD is a severely debilitating condition affecting multiple organs that is associated with pain, and difficulties with mobility, sight, eating, self-care and activities of daily living. There are limited effective treatment options.
- In pooled data from two open-label, phase II studies belumosudil was associated with clinically relevant overall response rate, 73%, in patients with chronic GvHD who had received two prior lines of therapy.
- The efficacy and safety of belumosudil relative to relevant comparators is unknown.
- As belumosudil is administered orally at home, it may have advantages compared with alternative treatments administered in hospital or specialist centres. Improvements in quality of life from baseline, assessed using the 7-day Lee Symptom Scale summary score, were identified in some patients treated with belumosudil.
- The company presented a three state partitioned survival model to estimate the economic outcomes of belumosudil relative to a basket comparator the company believed representative of Scottish practice. Some of the modelling assumptions were conservative, however uncertainty on the long term health benefits had the potential to reduce the modelled cost-effectiveness of belumosudil.
- The costs of belumosudil relative to the expected health outcomes are high, and there were outstanding uncertainties in the economic case, some of which may contribute to worse results than predicted in the base case.

Chair
Scottish Medicines Consortium

SMC ultra-orphan designation

Belumosudil has been validated as meeting SMC ultra-orphan criteria:

- The prevalence of chronic GvHD is estimated to be ≤1 in 50,000 (or around 100 people in Scotland).
- Belumosudil has Great Britain (GB) orphan designation for the treatment of GvHD and this was maintained at the time of Marketing Authorisation.
- Chronic GvHD is severely debilitating due to a range of substantial symptoms that can affect multiple-organs, leading to ongoing, pain, discomfort and difficulties with mobility, sight, eating, self-care and activities of daily living.
- Chronic GvHD requires highly specialised management in teams responsible for patients who have undergone allogeneic haematopoietic stem cell transplant (alloHSCT), which is a complex procedure carried out in highly specialised Bone Marrow Transplant (BMT) units.

1. Clinical context

1.1. Background

Belumosudil is an inhibitor of Rho-associated, coiled-coil containing protein kinase-2 (ROCK2). It alters immune cell function and fibrotic pathways and has shown activity in vivo in models of disease including chronic GvHD. It is the first ROCK2 inhibitor licensed for treatment of chronic GvHD and is administered as an oral tablet, at a dose of 200mg once daily (or twice daily for those taking strong CYP3A inducers or proton pump inhibitors).[1]

1.2. Nature of condition

In an alloHSCT, the patient (host) receives donor stem cells (graft) from another person. GvHD develops if graft white blood cells involved in immune responses (T-cells and B-cells) attack the host patient's own cells. This may be acute, with inflammatory skin, gastrointestinal and liver symptoms or chronic, with inflammation and fibrosis affecting a single organ or presenting as a systemic, multi-organ condition with a wide range of symptoms that vary in severity. These can involve the skin, nails, hair, mouth, eyes, gastro-intestinal tract, lungs, musculoskeletal system, liver, genitalia, kidneys, heart and nerves. Chronic GvHD is a major complication of alloHSCT and a leading cause of non-relapse death.[2-4]

Prior to developing GvHD, patients have already endured a difficult treatment journey for a significant, life-threatening illness that necessitated an alloHSCT. They may be suffering physically and mentally from the effects of prior treatment. In this context, GvHD has a profound psychological impact and, depending on the range of symptoms, it can substantially reduce quality of life. Patients may experience pain and discomfort and have difficulties with mobility, sight, eating and activities of daily living. Their symptoms can prevent participation in work, caring responsibilities, education and socialising. They may require assistance with self-care and accessing healthcare for their ongoing medical needs. Changes in their family's ability to work may lead to financial difficulties and worries. Family carers of patients with GvHD suffer from anxiety and depression at higher rates than the general population.[5]

There is no established therapeutic pathway for chronic GvHD and many treatments are used off-label. An advisory board of Scottish clinical experts convened by the company stated that initial treatment is corticosteroid with or without a calcineurin inhibitor (ciclosporin or tacrolimus). Sirolimus is given to those who fail to respond. The next stage includes organ-specific treatments for mild to moderate disease: rituximab for joints, mycophenolate mofetil for skin, gastro-intestinal specific medicines (for example etanercept, vedolizumab); and, for patients with severe disease, extra corporeal photopheresis (ECP) and/or ruxolitinib. In the absence of a submission, SMC issued advice (SMC2498) in June 2022 that ruxolitinib is not recommended for use for chronic GvHD in NHS Scotland. However, a clinical expert consulted by the company advised that BMT units access this via Individual Patient Treatment Request (IPTR). In Scotland, ECP is available at two centres and is usually carried out over two consecutive days every two weeks. Scottish clinical experts, consulted by the company, advised that ruxolitinib is used for patients who do not live close to centres offering ECP and for patients with more debilitating disease. The combination of ECP plus ruxolitinib is used for patients who are deteriorating rapidly.[6, 7] In the submission, the company identified the comparators as ECP, ruxolitinib, rituximab, imatinib, sirolimus and mycophenolate mofetil. Clinical experts consulted by SMC considered that belumosudil fills an unmet need in patients with chronic GvHD who have received at least two prior lines of systemic therapy as there are limited effective treatment options.

2. Impact of new technology

Comparative efficacy

Two uncontrolled, phase II studies provide evidence for belumosudil in the treatment of chronic GvHD: ROCKStar and a dose-finding study (KD025-208). These are detailed in Table 2.1.

Table 2.1 Overview of relevant study/studies

Criteria	ROCKStar (KD025-213)	KD025-208
Study design	Open-label, phase II study	Open-label phase II dose-finding study
Eligible patients	Age ≥12 years; 2 to 5 prior LOT for chronic GvHD post-alloHSCT; persistent chronic GvHD symptoms; Karnofsky or Lansky performance score ≥60; stable corticosteroids ≥2 weeks.	Age ≥18 years; 1 to 3 prior LOT for chronic GvHD post-alloHSCT; persistent chronic GvHD symptoms; Karnofsky Performance score >40; stable corticosteroids.
Treatments	Belumosudil 200mg once or twice daily till PD or toxicity. Other GvHD treatments continued.	Belumosudil 200mg once or twice daily or 400mg once daily till PD or toxicity. Other GvHD treatments continued.
Randomisation	Stratified by prior ibrutinib and severe disease (yes or no). Equally assigned.	Patients were not randomised; they were assigned to sequential cohorts.
Primary outcome	ORR assessed by investigator.	ORR assessed by investigator.
Secondary outcomes	DOR, FFS, OS, LSS	DOR, FFS, OS, LSS
Statistical analysis	Secondary not control for multiplicity.	Secondary not control for multiplicity.

alloHSCT = allogeneic haematopoietic stem cell transplant; DOR = duration of response; FFS = failure-free survival, defined as defined time from start of belumosudil to new chronic GvHD therapy, relapse, or non-relapse mortality; GvHD = graft versus host disease; LOT = lines of therapy; LSS Lee Symptom Score; ORR = overall response rate,

defined as complete response or partial response on 2014 National Institutes of Health (NIH) Consensus Criteria; OS = overall survival; PD = progressive disease.

The primary analysis of ROCKStar was after at least 6 months follow-up.[8, 9] Analysis of this study and KD025-208 after 24-months' follow-up supported the economic analyses and results for the licensed dose (200mg once daily) at this cut-off are detailed in Table 2.2, including the subgroup relevant to the licensed indication: patients with ≥2 prior lines of therapy.[10-14]

Table 2.2: Results for belumosudil 200mg daily in KD025-213 and KD025-208 at 24 months.[10-14]

	KD025-213 (ROCKStar)	KD025-208 (Dose-finding)	KD025-213 and KD025-208
Population	All mITT	All mITT	≥2 prior LOT
	n = 66	n = 17	n = 81
Overall response rate (ORR)	49 (74%)	11 (65%)	59 (73%)
Complete response	4 (6.1%)	0	*
Partial response	45 (68%)	11 (65%)	*
Median duration of response (DOR), weeks			
Until deterioration from best response	22.1	*	*
Until lack of response	96	*	*
Failure free survival (FFS)			
Events	39	*	*
KM estimated median, months	13.4	15.2	13.7
KM estimated 24-month FFS	40%	*	39%
Overall survival (OS)			
Deaths	12	3	*
KM estimated 24-month OS	84%	*	84%
7-point reduction in Lee Symptom Score (LSS)	41 (62%)	9 (53%)	*
Concomitant Medicines			
Corticosteroid dose reduction	64% (42/66)	76% (13/17)	68% (55/81)
Corticosteroid discontinuation	29% (19/66)	24% (4/17)	28% (23/81)
Calcineurin inhibitor dose reduction	46% (11/24)	*	NR
Calcineurin inhibitor discontinuation	21% (5/24)	*	NR

FFS = failure free survival, defined as the time from start of belumosudil to addition of a new chronic GvHD therapy, relapse, or non-relapse mortality; FU = follow-up; KM = Kaplan-Meier; LOT = lines of therapy, mITT = modified intent-to-treat, defined as all patients who received at least one dose of study drug; NR = not reported; ORR = overall response rate; OS = overall survival. *the company considered these results confidential.

The economic model is informed by a naive indirect comparison of pooled data for belumosudil from KD025-213 (ROCKStar) and KD025-208 studies in subgroup with ≥2 prior systemic lines of therapy and a basket of best available therapies, with data from the open-label phase III study, REACH-3.[9, 11, 13, 15] This is detailed in Table 2.3.

Table 2.3: Summary of indirect treatment comparison[9, 11, 13, 15]

Criteria	Overview
Design	Naïve indirect comparison
Population	Treatment-experienced patients with chronic GvHD post-alloHSCT
Comparators	Best available therapies (physicians choice of second-line therapy in REACH-3)
Studies included	Belumosudil: KD025-213 plus KD025-208 in patients with ≥2 prior LOT Best available therapies: REACH-3

Outcomes	Failure-free survival, overall survival, overall response rate, time to response, duration of response, time to treatment discontinuation, adverse events grade ≥3
Results	A quality adjusted life year gain with belumosudil versus best available therapies.

alloHSCT = allogeneic haematopoietic stem cell transplant; ; GvHD = graft-versus-host disease; LOT = line of therapy.

*Other data were also assessed but remain confidential.**

Comparative safety

Pooled data from KD025-213 and KD025-208 at two years follow-up in patients who received belumosudil 200mg daily indicate that adverse events were reported by 99% (82/83) and were treatment-related in 72%. The incidence of adverse events of at least grade 3 severity was 63% (treatment-related 18%) and of serious adverse events was 43% (treatment-related 7.2%). Four patients (4.8%) had adverse events with a fatal outcome and one of these was considered by the investigator (but not the company) to be possibly treatment-related. Cytopenias were reported by 18% of patients and infections or infestations by 66% of patients and were of at least grade 3 severity in 22%. Other common adverse events included fatigue (45%), diarrhoea (40%), nausea (35%), dyspnoea (30%), cough (26%), peripheral oedema (26%), headache (25%), vomiting (25%), hypertension, arthralgia, decreased appetite, pyrexia, abdominal pain, hyperglycaemia and muscle spasm (17%). [14, 16]

*Other data were also assessed but remain confidential.**

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- In a pooled analysis of patients who had received at least two prior lines of therapy, the addition of belumosudil to standard of care was associated with a substantial ORR of 73%, with two-year failure-free survival and overall survival rates of 39% and 84%. During treatment with belumosudil, 68% of patients were able to reduce their dose of corticosteroid and 28% discontinued this. These were considered clinically relevant in a regulatory review.[14]
- Belumosudil is the first ROCK2 inhibitor licensed in GB for treatment of chronic GvHD.[1]
- Clinical experts consulted by SMC considered that belumosudil is a therapeutic advancement due to the lack of current treatment options that can be used after initial treatment with corticosteroid, calcineurin inhibitor and sirolimus. They note that belumosudil is likely to replace ruxolitinib in this setting.

Key uncertainties:

- Data supporting the licensed indication in patients who have received at least two prior lines of therapy were from post-hoc subgroup analysis of pooled data from two phase II studies. In both studies a new line of therapy was defined as initiation of at least one new systemic therapy for chronic GvHD. Where it was the intention to initiate more than one medicine at the same time, start dates could not be more than four weeks apart.[8, 12] In practice, there is no standard treatment pathway.[6, 7] This creates challenges in identifying the patient population defined by prior line of therapy and the relevant comparators.
- Within the belumosudil 200mg once daily group in KD205-213 (ROCKStar), patients continued concomitant immunosuppressive treatments, including corticosteroid (99%); calcineurin inhibitor (36%); sirolimus (26%); ECP (26%); and mycophenolate mofetil (17%).[9] However, the submission notes that belumosudil is intended for use as a monotherapy in the treatment of chronic GvHD.
- The naïve indirect comparison of belumosudil versus best available therapy was limited by differences across the populations, particularly in prior line of therapy, with the belumosudil patients having ≥2 prior lines of therapy and best available therapy patients having only one prior line of therapy (that is, third-line or later versus second-line). A greater proportion of belumosudil patients had severe GvHD (70% versus 54%). There was heterogeneity across the groups in subsequent therapies, with 37% of patients in the REACH-3 control arm crossing over to ruxolitinib. There was variation in assessment of some outcomes, with best ORR at any time for belumosudil compared with ORR at 24 weeks in the best available therapy group. There was heterogeneity in duration of follow-up with this being greater for belumosudil. Some data (10%) for belumosudil were from the 200mg twice daily groups of the phase II studies, where patients were not receiving the concomitant proton pump inhibitor or CYP3A inducers required for this dose. Medicines in the control group of REACH-3 may not be representative of Scottish practice or the basket of best available therapies in the economic model.[9, 11, 13, 15] In addition, weaknesses characteristic of all naïve indirect comparisons limit the analyses. Despite the naïve indirect comparison, the comparative efficacy of belumosudil versus relevant comparator is uncertain.
- The open-label, uncontrolled design of the studies limits the assessment of subjective outcomes, such as quality-of-life and safety.

*Other data were also assessed but remain confidential.**

3. Impact beyond direct health benefits and on specialist services

In addition to its clinical effects, belumosudil may benefit the patient and service through its once daily oral dosing regimen that is taken at home. This provides advantages in accessing treatment particularly compared with one of the alternate treatment options, ECP, which requires clinic visits, specialised equipment and specially trained staff that are available at only two centres in Scotland.[6] For patients and their carers who live a significant distance from the specialist centres, the benefits of belumosudil as an alternative to ECP would be greater. Benefits would also be obtained compared with other alternate treatment options that are administered parenterally and/or have more monitoring requirements. The clinical benefits in controlling the disease and once daily dosing regimen may help patients and their carers return to their usual daily activities, including work, family responsibilities and social activities. This is likely to have a positive psychological benefit for the patient and their family/carers and may help them financially.

The introduction of belumosudil is not expected to have significant service implications. No additional impact is expected on NHS staffing, infrastructure or training requirements. If ECP was replaced by belumosudil, this may free-up capacity at specialist centres. [6, 7]

4. Patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a joint patient group submission from Anthony Nolan and Leukaemia Care. Both organisations are registered charities.
- Anthony Nolan has received 6% pharmaceutical company funding in the past two years, with none from the submitting company. Leukaemia Care has received 27% pharmaceutical company funding in the past two years, with none from the submitting company.
- Chronic GvHD onset varies significantly from one patient to another, both in terms of timing and severity, with multiple treatments having to be administered. The impact on quality of life can be significant, affecting people's eyesight, lung capacity, dietary needs, personal relationships, and capacity to work and have a social life. Managing the inflammatory symptoms can take months or several years, with long-term side effects potentially leading to life-long disabilities.

- It is not uncommon for some patients to be referred for 4th, 5th, or 6th line therapies; an effective 3rd line therapy would be beneficial to the patient and cost-effective in the long term. Patients described the need to take multiple drugs for managing their chronic GvHD over a prolonged period as well as the need to go into and remain in hospital for emergencies, usually within the first two years post-transplant.
- Patients that are due to receive a third line therapy are likely to be battling multiple, significant side effects of their GvHD, such as severe inflammation of their eyes and skin. As such, a quick and effective third line therapy is needed to reduce the most significant side effects and control the impact and severity of GvHD. As some patients currently continue to be referred onwards to 4th and 5th line therapies, belumosudil holds the potential of resolving or managing a patient's advanced chronic GvHD without further interventions.
- Patients favour a treatment that can be administered orally; as such there is the potential for both quality of life and cost-saving benefits of belumosudil over other treatments.

5. Value for money

5.1. Economic case

The details of the economic case are summarised in Table 5.1.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	40 years
Population	Patients aged 12 years and older with chronic GvHD who have received at least two prior LOT.
Comparators	Belumosudil was compared against a basket comparator comprising ECP (52%), mycophenolate mofetil (18%), imatinib (4%), sirolimus (4%) and ruxolitinib (20%). The company labelled the comparator ruxolitinib plus best available therapy.
Model description	The company used a three state partitioned survival model, with a four week cycle length. The three states were failure-free, failure and dead. The failure-free and failure states were subsequently broken down into sub-states capturing response and treatment status, which impacted upon cost and health outcome accumulation.
Clinical data	Clinical data on belumosudil came from the two phase II studies, ROCKstar and KD025-208.[10-14] For the analysis, the 200mg once daily belumosudil patients were pooled together across the two studies, as were the 200mg twice daily patients. These data were weighted under the assumption that 10% of patients would receive twice daily dosing, matching the proportion expected to receive proton pump inhibitors or strong CYP3A inducers. The remaining 90% of belumosudil patients were assumed to receive once daily dosing. The data from ROCKstar and KD025-208 studies were used to inform the clinical outcomes of response rates, failure free survival (FFS) and overall survival.

	Data from the REACH-3 study were used to populate inputs for the comparator arm.[15] The ruxolitinib data from REACH-3 were used to inform response rates, FFS and overall survival for ruxolitinib patients. The investigators' choice arm was used as a proxy for best available therapy and informed response rates, FFS and overall survival outcomes for best available therapy patients. The company weighted the data under the assumption that 20% of patients received ruxolitinib and 80% best available therapy. The possibility of an indirect or mixed treatment comparison was assessed, but no network could be established, and so a naïve comparison was used to gauge the scale of the treatment effect.
Extrapolation	Data were extrapolated beyond the observation periods of the studies using survival modelling. Within the belumosudil arm jointly fitted models were applied across the two dosing groups. Similarly, joint models were used to extrapolate within the ruxolitinib plus best available therapy group. The generalised gamma model was used to extrapolate all FFS curves. The exponential model was used to extrapolate all overall survival curves. Time to response curves and duration of response curves were used to predict whether a patient would be in response (either partial or complete) or in lack of response. Finally, the disaggregation between partial and complete response, and treatment status in the failure state was based on rates observed in the studies.
Quality of life	Health state utility values for the failure-free state were estimated from Patient-Reported Outcomes Measurement Information System Global Health (PROMIS-GH) scores collected as part of the ROCKstar study. PROMIS-GH scores were mapped to EQ-5D-3L values using the algorithm developed by Thompson et al. (2017).[17] The utility value for patients in the failure sub-states were estimated from the literature.[18-22]
Costs and resource use	Medicine costs included in the analysis were acquisition costs, administration costs and adverse event costs. The model included costs for one subsequent line of therapy. Wider health costs covered disease management and were estimated from analysis of the Hospital Episode Statistics database and a previous health technology assessment (HTA) submission.[19]
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. The results presented do not take account of the PAS for ruxolitinib. SMC is unable to present the results provided by the company which used an estimate of the PAS price for ruxolitinib due to commercial confidentiality and competition law issues.

5.2. Results

The base case analysis, inclusive of the PAS discount on belumosudil but not on ruxolitinib, suggested that belumosudil would lead to higher costs and higher health outcomes than the basket comparator. The main driver of cost differences was the acquisition cost of belumosudil. The main source of differences in quality adjusted life years was greater occupancy of the failure-free state for belumosudil patients. The resulting incremental cost effectiveness ration (ICER) was estimated at £83,163.

*Other data were also assessed but remain confidential.**

5.3. Sensitivity analyses

The company provided a wide variety of sensitivity and scenario analyses. One way sensitivity analysis suggested that the largest drivers of change in the economic results were the parameters within the survival equations for time to treatment discontinuation, FFS and overall survival.

A selection of scenarios exploring areas of uncertainty are presented in the table below. These include the PAS discounts on belumosudil, but not that on ruxolitinib.

Table 5.3 Scenario analysis (PAS discount on belumosudil only)

#	Scenario description	Base case description	ICER	% change from base case
1	Time horizon: 50yrs	Time horizon: 40yrs	£83,133	0.00%
2	Time horizon: 30yrs		£84,645	1.8%
3	0% of patients receiving twice daily belumosudil	10% of patients receiving twice daily belumosudil	£78,948	-5.1%
4	30% of patients receiving twice daily belumosudil		£91,262	9.7%
5	0% patients on ruxolitinib in comparator arm	20% patients on ruxolitinib in comparator arm	£82,729	-0.5%
6	50% patients on ruxolitinib in comparator arm		£83,815	0.8%
7	100% patients on ruxolitinib in comparator arm		£84,837	2.0%
8	FFS for all treatments: Joint Fit - Gamma	FFS for all treatments: Joint Fit – Generalised gamma	£93,657	12.6%
9	OS for all treatments: Joint Fit – Log-normal	OS for all treatments: Joint Fit - Exponential	£140,736	69.2%
10	OS for all treatments: Joint Fit – Log-logistic		£125,485	50.9%
11	Maximum treatment duration for belumosudil,	Maximum treatment duration for belumosudil,	£64,332	-22.6%

	ruxolitinib, mycophenolate mofetil, imatinib, and sirolimus is 3 years	ruxolitinib, mycophenolate mofetil, imatinib, and sirolimus is lifetime (i.e. fully dependent upon TTD modelling)		
12	Maximum treatment duration for belumosudil, ruxolitinib, mycophenolate mofetil, imatinib, and sirolimus is 5 years		£71,518	-14.0%

Abbreviations: *ICER = incremental cost-effectiveness ratio, FFS=failure free survival, OS = overall survival*

5.4. Key strengths:

The key strengths of the analysis were identified as:

- There is some uncertainty on what treatments would be displaced by belumosudil, however, clinicians consulted by SMC indicated it may be used in place of ruxolitinib. Reassuringly, altering the proportions of patients receiving ruxolitinib within the basket comparator had a very modest impact upon the economic results (see scenarios 6 and 7 in Table 5.3)
- There is some uncertainty on whether the basket (ruxolitinib plus best available therapy) comparator used in the economics is reflective of Scottish practice, and what treatment would be displaced by belumosudil. However, clinicians consulted by SMC indicated that ruxolitinib may be most likely to be replaced, and reassuringly, alternative proportions of patients receiving that treatment had a very modest impact upon the economic results (scenarios 6 and 7)
- In several areas the modelling appeared to be conservative. These areas included assuming a constant cost for patients in the failure-free state, despite clinical feedback received by the company suggesting costs may decline significantly when a proportion of patients can be categorized as in remission. This could be as high as 40% of patients in the failure-free state at 5 years. Similarly, the modelling approach to treatment duration may overestimate the time a patient received treatment in both arms relative to clinical expectations the company received, which stated patients are unlikely to receive treatment beyond 3 to 5 years. This overestimation inflated costs more steeply in the belumosudil arm, increasing the ICER (see scenarios 11 and 12).

5.5. Key uncertainties:

The key uncertainties of the analysis were identified as:

- The fact that belumosudil was not used as a monotherapy within the clinical studies introduces generalisability issues, which led to uncertainty in the economic analysis.

- There are no head-to-head data comparing belumosudil and a relevant comparator. Instead the analysis relied on a naïve comparison, with significant heterogeneity between the included studies. While the company speculated some differences would have made the analysis conservative that remained highly uncertain.
- There was disagreement among clinical experts consulted by SMC on the proportion of patients in Scotland eligible to receive twice daily dosing of belumosudil. The modelled proportion aligned with patients receiving proton pump inhibitors and CY3PA inducers. In the base case this was assumed 10%, but some experts believed it could be as high as 30%, which would increase the ICER (see scenario 4).
- The company used survival modelling to extrapolate observed data out across the 40 year time horizon of the model. In some instances the observed study data were relatively immature and scenario analysis indicated that alternative assumptions could lead to significant upward increases in the ICER (see scenarios 8, 9 and 10).

*Other data were also assessed but remain confidential.**

6. Costs to NHS and Personal Social Services

The submitting company estimated there would be 12 patients eligible for treatment with belumosudil in each year. The estimated uptake rate was 100% in both year 1 and year 5, resulting in 12 patients receiving treatment each year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

7. Guidelines and protocols

The British Committee for Standards in Haematology (BCSH) and the British Society for Blood and Marrow Transplantation (BSBMT) published diagnosis and management of chronic graft-versus-host disease was published in 2012.[2] See here.

8. Additional information

8.1. Product availability date

27 March 2023

8.2. Summary of product characteristics

See SPC for further information including dosing and safety. Belumosudil film-coated tablet (Rezurock®) SPC.[1]

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Belumosudil	200mg orally once daily (or twice daily if used with proton pump inhibitor or CYP3A inducer)	81,390 to 162,781

Doses are for general comparison and do not imply therapeutic equivalence. Costs from new product assessment form (NPAF). Costs do not take any patient access schemes into consideration.

References

1. Aventis Pharma Ltd. Belumosudil film-coated tablet (Rezurock®) Summary of Product Characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 17 March 2023. .
2. Dignan FL, Amrolia P, Clark A, et al. Diagnosis and management of chronic graft-versus-host disease. Br J Haematol 2012; 158(1): 46-61.
3. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biology Blood Marrow Transplant 2015; 21(3): 389-401.e1.
4. Mawardi H, Hashmi SK, Elad S, et al. Chronic graft-versus-host disease: Current management paradigm and future perspectives. Oral Dis 2019; 25(4):931-48.
5. Sanofi. Patient Interviews Transcript, 2022. Data-on-file.
6. Sanofi. Belumosudil in chronic GVHD - Advisory board in preparation for the Scottish Medicines Consortium (SMC) submission - Meeting Report November 2022. Data-on-file. .
7. Sanofi. Scottish Clinician Interview, 2022. Data-on-file.
8. Kadmon Pharmaceuticals. Clinical study report for KD025-213 (ROCKStar), Primary Analysis: Data through data cut-off date of 19 February 2020. Data-on-file, 16 July 2020.
9. Cutler C, Lee SJ, Arai S, et al. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. Blood 2021; 138(22): 2278-89.
10. Kadmon Pharmaceuticals. Clinical study report for KD025-213 (ROCKStar), Additional Analysis: Data through data cut-off date of 19 August 2021. Data-on-file.
11. Kadmon Pharmaceuticals. Additional analysis: pooled data with multiple lines of therapy. Data-on-file
12. Kadmon Pharmaceuticals. Clinical study report for KD025-208, 7 July 2020. Data-on-file.
13. Jagasia M, Lazaryan A, Bachier CR, et al. ROCK2 inhibition with belumosudil (KD025) for the treatment of chronic graft-versus-host disease. J Clin Oncol 2021; 39(17): 1888-98.
14. US Food and Drug Administration (FDA). Belmodusil Multidisciplinary Review. www.fda.gov.
15. Zeiser R, Polverelli N, Ram R, al. Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. N Engl J Med 2021; 385(3): 228-38.
16. Kadmon Pharmaceuticals. Integrated Safety Summary. Data-on-file.
17. Thompson NR, Lapin BR, Katzan IL. Mapping PROMIS Global Health Items to EuroQol (EQ-5D) Utility Scores Using Linear and Equipercentile Equating. Pharmacoeconomics. 2017;35(11):1167-76. Epub 2017/07/16. 10.1007/s40273-017-0541-1
18. Crespo C, Pérez-Simón JA, Rodríguez JM, Sierra J, Brosa M. Development of a population-based cost-effectiveness model of chronic graft-versus-host disease in Spain. Clin Ther. 2012;34(8):1774-87. Epub 2012/07/28. 10.1016/j.clinthera.2012.06.029
19. National Institute for Health and Care Excellence. Single Technology Appraisal. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]. Committee Papers. TA642.
20. National Institute for Health and Care Excellence. Single Technology Appraisal. Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]. Committee Papers. TA813.
21. Aristides M, Barlev A, Barber B, Gijsen M, Quinn C. Population preference values for health states in relapsed or refractory B-precursor acute lymphoblastic leukemia in the United Kingdom. Health and quality of life outcomes. 2015;13(1):1-7.

22. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A*, et al.* Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health and quality of life outcomes. 2010;8(1):1-9.

This assessment is based on data submitted by the applicant company up to and including 12 May 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.