**National Institute for Health and Care Excellence**

**Single Technology Appraisal**

# Belumosudil for treating chronic graft versus host disease after 2 or more therapies [ID4021]
# Response to stakeholder organisation comments on the draft remit and draft scope

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

## Comment 1: the draft remit and proposed process

| Section | Stakeholder | Comments [sic] | Action |
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| Appropriateness of an evaluation and proposed evaluation route | Sanofi | Chronic graft-versus-host disease (cGVHD) is caused by allogeneic haematopoetic stem cell transplantation (AlloHSCT) in patients already suffering with haematologic malignancies and is the major cause of post-transplant morbidity. There are only two licensed treatments for cGVHD, ciclosporin (a broad-spectrum immunosuppressant) and ruxolitinib (a more recently licensed JAK inhibitor) in Great Britain. Neither are recommended by NICE and no NICE appraisals are currently ongoing or planned for these or other treatments. Ruxolitinib is no longer available under any access scheme in England.<br><br>Recently belumosudil was validated as an ultra-orphan (UO) medicine (IND 3612) by the SMC and on this basis Scottish patients will have access to the medicine in Q2 2023, well ahead of English patients. Given the high unmet need, early access in Scotland and the very positive but limited data from the current evidence base which is reliant on uncontrolled Phase IIa/b studies, we | Thank you for your comment. The routing of this topic was discussed in the topic selection oversight panel meeting and it was considered that this topic would be routed as a single technology appraisal. Please see the final HST checklist for details. |

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| | | believe that belumosudil should be considered as a candidate for a pilot in a Rapid Entry to Managed Access (REMA) scheme. This should be followed by NICE assessment mirroring the process to be followed in Scotland after a period of company-sponsored data collection as an alternative to moving straight to HTA now. We would welcome the opportunity to discuss this further with NICE / NHSE.<br><br>Regardless of the timing of the assessment (REMA vs. standard HTA) the route proposed in the draft remit is not appropriate. Belumosudil should be evaluated through the Highly Specialised Technology (HST) appraisal route and sufficiently meets all the necessary routing criteria.<br><br>Routing Criteria 1. The condition is very rare defined by 1:50,000 in England:<br>Belumosudil is designated an orphan medicine by the MHRA [1] and will be assessed as an ultra-orphan medicine by the SMC. Overall, the prevalence of cGVHD is expected to be less than 1,100 patients in England (see Table 1). It is important to note that the licensed indication is much narrower than the overall prevalence of the disease.<br><br>Table 1. Estimated incidence of cGVHD<br>Proportion Number Reference<br>AlloHSCTs in the UK and Republic of Ireland (2020) - 1,476 BSBMTCT 2020 [2]<br>Proportion of UK and Republic of Ireland AlloHSCTs conducted in England 90.8% - 6,973 adult AlloHSCTs conducted in the UK and | |

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| | | Republic of Ireland between 2009-2014; 90.8% (6,332 / 6,973) took place in England [3]<br><br>Number of AlloHSCTs in England (per year) - 1,340 Calculation (90.8% * 1,476)<br><br>Estimated incidence of cGVHD in England (per year) 30% of AlloHSCTs 402 BSBMTCT 2015 [3]. Calculation (30% * 1,340)<br><br>Based on the incidence rates above, it is reasonable to assume that the prevalence of cGVHD is less than the cut-off HST prevalence of 1,100 patients in England for two reasons:<br><br>1) cGVHD is the leading cause of non-relapse mortality after AlloHSCT [4,5]. Non-relapse mortality at one year is 19% among patients receiving AlloHSCT in the UK and Republic of Ireland (regardless of presence of GVHD) [3]. Overall survival from onset of cGVHD has been reported to be 66-94% at one year, and 53-71% at four years [6].<br><br>2) Some of the patients diagnosed with cGVHD present with mild disease which may resolve with topical or limited systemic treatment [7,8].<br><br>The number of patients eligible for belumosudil within the licence indication would be significantly smaller than the total cGVHD population.<br><br>Routing Criteria 2. Normally, no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications | |

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| | | Belumosudil is licensed for the treatment of patients after two prior lines of systemic therapy. This patient pool is considerably lower than the overall prevalence of cGVHD and is expected to be more in line with the number of disabling extensive cases in the UK (see Table 2).<br><br>Table 2. Estimated eligible cGVHD population<br>Proportion Number Reference<br>Number of AlloHSCT in England (per year) - 1,340 See Table 1<br>Proportion of disabling extensive cGVHD in all cases 5% - BSBMTCT 2015 [3]<br>Number of disabling extensive cGVHD cases in England (per year) - 67 Calculation (5% * 1,340)<br><br>This number is in line with the number of patients expected to be eligible for belumosudil under the licensed indication quoted in the NIHR Health Technology Briefing from September 2021 (57 to 68 patients) [9].<br><br>Routing criteria 3: The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life<br>cGVHD affects patients who have already undergone intensive clinical interventions and have often had to deal with the trauma of being diagnosed with a life-threatening condition, such as leukaemia. Many patients with cGVHD experience significant depression or anxiety symptoms [10,11]. | |

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| | | cGVHD can cause severe disabilities such as joint contractures (deformities caused by joint tightening), loss of sight, and end-stage lung disease which can severely limit activities of daily living. The immune system can be suppressed, leading to recurrent or life-threatening infections, which can limit patients' ability to go out in public or perform normal tasks [11].<br><br>Some studies have shown that patients with cGVHD are less likely to return to work within a two-year period following AlloHSCT than those without cGVHD [12,13].<br><br>GVHD is a leading cause of death and morbidity in patients who undergo AlloHSCT, often as a result of organ failure or infection [14,15]. In the UK, between 2009-2014, GVHD was the cause of 27% of non-relapse deaths in patients who received AlloHSCT [3].<br><br>Routing criteria 4: There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.<br>There are no NICE approved therapies for cGVHD and ciclosporin is the only licensed medicine which is also reimbursed.<br><br>Due to the complex, heterogenous nature of cGVHD, many patients require multiple lines of therapy to control the disease. These patients can experience multiple treatment failures, leaving clinicians with no definitive therapy options in later stages. | |

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| | | Some fibrotic manifestations, such as lung and joint cGVHD, are particularly challenging to treat [16]. Belumosudil has demonstrated positive efficacy in organs which are known to be more challenging to treat, which may offer additional benefit to patients [17].<br><br>References:<br>1. MHRA Orphan Register (2022). Available: https://www.gov.uk/government/publications/orphan-registered-medicinal-products/orphan-register#rezurock. Accessed: 09/2022.<br>2. British Society of Blood and Marrow Transplantation and Cellular Therapies (BSBMTCT). Annual Activity Report 2020. Available: https://bsbmtct.org/activity/2020/ . Accessed: 09/2022.<br>3. British Society of Blood and Marrow Transplantation and Cellular Therapies (BSBMTCT) (2015). 8th Report to Specialist Commissioners Report 2020. Available: https://www.uhs.nhs.uk/Media/SUHTExtranet/<br>WessexBloodAndMarrowTransplantationService/BSBMT-8th-Report-To-Commissioners.pdf. Accessed: 09/2022.<br>4. Arora M, Cutler C, Jagasia M, et al. Late acute and chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2016. pp. 22(3):449-455.<br>5. Wingard J, Maihail N, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. J Clin Oncol. 2011. pp. 29(16):2230-223. | |

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| | | 6. Csanadi M, Agh T, Tordai A, et al. A systematic literature review of incidence, mortality, and relapse of patients diagnosed with chronic graft versus host disease. Expert review of hematology. 2019. 12(5): 311-323.<br><br>7. Filipovich A, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood & Marrow Transpl. 2005. 11(12): 945-956.<br><br>8. Wolff D, Gerbitz A, Ayuk F, et al. Consensus Conference on Clinical Practice in Chronic Graft-versus-Host Disease (GVHD): First-Line and Topical Treatment of Chronic GVHD. Biol Blood & Marrow Transpl. 2010. 16(12): 1611-1628.<br><br>9. NIHR Health Observatory (2021). Belumosudil for graft-versus-host disease. Available: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/13112-Belumosudil-for-Graft-Versus-Host-Disease-v1.0-SEPT2021-NON-CONF-.pdf. Accessed: 09/2022.<br><br>10. El-Jawahri A, Pidala J, Khera N, et al. Impact of psychological distress on quality of life, functional status, and survival in patients with chronic graft-versus-host disease. Transplantation and cellular therapy. 2018. 24(11): 2285-2292.<br><br>11. Pidala J, Kurland B, Xiaoyu C, et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. Blood. 2011. 117(17):4651-4657.<br><br>12. Wong F, Francisco L, Togowa K, et al. Longterm recovery after hematopoietic cell transplantation: predictors of quality-of-life concerns. Blood. 2010. 115(12):2508-2518. | |

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| | | 13. Worel N, Biener D, Kalhs P, et al. Long-term outcome and quality of life of patients who are alive and in complete remission more than two years after allogeneic and syngeneic stem cell transplantation. Nature. 2002. 30:619-626.<br>14. DeFilipp Z, Alousi A, Pidala J, et al. Nonrelapse mortality among patients diagnosed with chronic GVHD: an updated analysis from the Chronic GVHD Consortium. Blood advances. 2021. 5(20): 4278-4284.<br>15. Styczynski J, Tridello G, Koster L, et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. Bone Marrow Transplant. 2020. 55(1): 126-136.<br>16. Mawardi H, Hashmi S, Elad S, et al. Chronic graft-versus-host disease: Current management paradigm and future perspectives. Oral diseases. 2019. 25(4):931-948.<br>17. Cutler C, Lee S, 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): 2278-2289. | |
| | Anthony Nolan | Belumosudil (Rezurock) is a selective ROCK2 inhibitor for the treatment of chronic graft-versus-host disease (cGVHD) in in adult and pediatric patients aged ≥ 12 years after the failure of at least two prior lines of systemic therapy.<br><br>It would be appropriate to evalutate this technology using the routine NICE appraisial methods for medicines. | Thank you for your comment. |

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| | | It is suggested that this technology has the potential to offer clinical benefit in efficacy and tolerance in managing Chronic Graft vs Host Disease (cGvHD) following an allogenic Hematopoietic stem-cell transplantation (HSCT).<br><br>There remains a significant unmet need in effectively treating chronic GVHD. Existing treatments and regimens vary in effifacy, resulting in clinicians resorting to multiple lines of therapy for some patients.<br><br>Approxiamtely 50%–60% of patients with cGvHD will require a second-line treatment within 2 years, but at the moment there is no consensus on the optimal choice of agents for second or further lines of therapy[1].<br><br>[1] - Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, et al. Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant* (2011) 17:1–17. doi: 10.1016/j.bbmt.2010.05.011 | |
| | Kings College Hospital London | The evaluation route proposed is satisfactory.<br>Steroid refractory chronic graft-versus-host disease (cGVHD) is currently an unmet need for patients treated with allogeneic haematopoietic stem cell transplant.<br>Even if there is a progressive improvement in the knowledge of its pathogenesis, there is still a lack of standard of care in treatment of these patients. Also, the drugs that are currently approved in the third line settings have a broad-spectrum mechanism of action where multiple cellular pathways are involved. | Thank you for your comment. |

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| | | Modern medications that are becoming available in the cGVHD treatment landscape are targeted against cellular key points that sustain the abnormal alloreaction.<br><br>Therefore, an appropriated evaluation (as the current one) of proposed medications is needed to ensure a safe and effective treatment to the patients. | |
| Wording | Sanofi | The wording in the remit largely reflects the decision problem associated with belumosudil. However, it is important to note that the licence for belumosudil positions the medicine after two systemic therapies:<br><br>Belumosudil is indicated for the treatment of patients aged 12 years and older with cGVHD who have received at least two prior lines of systemic therapy [1].<br><br>In this context prior topical treatments are not prior lines of therapy. A line of systemic therapy may also refer to a combination of treatments (e.g. corticosteroids and calcineurin inhibitors [CNIs]) prescribed at the same time. Further discussion of this important point is provided below in the comparators section.<br><br>We suggest the following small change to the wording of the remit:<br><br>To appraise the clinical and cost effectiveness of belumosudil within its marketing authorisation for treating chronic graft versus host disease after two or more systemic therapies. | Thank you for your comment. The wording has been updated in the final scope. |

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| | | References:<br>1. MHRA. Belumosudil Summary of Product Characteristics (2022). Available: https://mhraproducts4853.blob.core.windows.net/docs/f2dd1f798bdb88b97ad6b7f77040faaa081faba7. Accessed: 09/2022. | |
| | Anthony Nolan | The wording of the remit is relfective of the parameters and design set out in the ROCKstar Study[2].<br><br>The study's cohorts includes subjects with cGVHD who had received 2 to 5 prior lines of therapy.<br><br>[2] - Cutler C, Lee SJ, Arai S, Rotta M, Zoghi B, Lazaryan A, Ramakrishnan A, DeFilipp Z, Salhotra A, Chai-Ho W, Mehta R, Wang T, Arora M, Pusic I, Saad A, Shah NN, Abhyankar S, Bachier C, Galvin J, Im A, Langston A, Liesveld J, Juckett M, Logan A, Schachter L, Alavi A, Howard D, Waksal HW, Ryan J, Eiznhamer D, Aggarwal SK, Ieyoub J, Schueller O, Green L, Yang Z, Krenz H, Jagasia M, Blazar BR, Pavletic S. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. Blood. 2021 Dec 2;138(22):2278-2289. doi: 10.1182/blood.2021012021. Erratum in: Blood. 2022 Mar 17;139(11):1772. PMID: 34265047; PMCID: PMC8641099. | Thank you for your comment. |

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| | Kings College Hospital London | Anticipating median duration to response of 5 weeks (based on published ROCKSTAR study data) with nearly 90% of responses occurring within 6 months of treatment.<br>A potential anticipated savings will depend on alternative treatment options available. Most notable comparison is with use of ECP. In Brazil, a 6-month estimate of direct costs of ECP to treat an adult patient with chronic GVHD is US$ 50,000 vs. US $67,200 for ibrutinib (420mg QD) and US$ 35,000 for ruxolitinib (10 mg BID) (Fatobene et al 2022). Another excellent cost-effectiveness analysis was published in 2018 (Yalniz et al 2018) from patients treated in US for cGVHD using currently available therapies including ECP, ruxolitinib and ibrutinib (Belumosudil data not available), highlighting significant cost burden with these therapeutic options to achieve CR.<br>A US study looked at budget impact model of Belumosudil for cGVHD treatment (Bachier et al2022) with a 5 year-time horizon. Based on belumosudil utilization increasing to 55% in 3 L and 4 L + by 2026, cost savings of ~5.5% and 6.7% ($128.8 and $4.9 Mil USD) were observed from national and payer perspectives, respectively. Cost savings in 2026 were derived from fewer AEs<br>($108.4 and $3.9 Mil USD, for national and payer perspectives; e.g. neutropenia, and<br>thrombocytopenia) and reduced HCRU ($65.1 and $2.3 Mil USD, for national and payer perspectives; e.g. emergency room visits, ICU stays, etc.). In addition, it is anticipated that with an excellent side effect profile and appropriate use at the right<br>point in clinical pathway, belumosudil may reduce indirect costs of hospitalisation days, blood tests/transfusion needs for myelosuppression concerns with other treatment options, need for central venous devices for ECP or management of infection related complications related to other immunosuppressive treatments, leading to significant overall cost savings as | Thank you for your comment. |

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| | | well as improvement in patient reported QoL. There is no published data currently available to confirm these indirect costs savings. | |
| Timing Issues | Sanofi | cGVHD is an immune-mediated inflammatory and fibrotic multisystem disease brought about by the prior treatment of patients already suffering with haematologic malignancies. It is the major cause of post-transplant morbidity. As such it can significantly compromise the clinical and quality of life benefits offered by AlloHSCT [1-3].<br><br>Ciclosporin and ruxolitinib are the only licensed treatments for cGVHD in the UK. However, ruxolitinib is not routinely commissioned for new patients with cGVHD. Evidence for other treatments for steroid-refractory cGVHD consists mainly of case series and small, non-controlled clinical studies [4].<br><br>Therefore, an urgent unmet need exists for effective new treatment options with a favourable safety profile in the management of cGVHD.<br><br>Belumosudil has been recognised by the regulators as an innovative medicine. It received an innovation passport from the MHRA (April 2021) and FDA Orphan Drug Designation (October 2017). In addition, the FDA granted priority review and breakthrough therapy designation in October 2018. It was approved under Project Orbis procedure in Australia, Canada, and Great Britain and received orphan status from the MHRA at the point of licensure. The SMC have approved belumosudil for their ultra-orphan (UO) pathway.<br><br>Great Britain could be the first region outside of the US with widespread access and the opportunity to generate early real-world data. Requirements | Thank you for your comment. The timing of this appraisal will follow our single technology appraisals process, for further details see the methods guide section 5.2 |

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| | | to secure EU marketing authorisation are currently being explored with the EMA.<br><br>Following UO designation belumosudil will launch in Scotland in ~Q2 2023, well ahead of England. Consequently, we are very keen to explore the potential for belumosudil to be a pilot for a Rapid Entry to Managed Access (REMA) scheme in England and would welcome discussion with NICE / NHSE about how this might be achieved.<br><br>References:<br><br>1. MacDonald K, Hill G, Blazar B, et al. Chronic graft-versus-host disease: biological insights from preclinical and clinical studies. Blood. 2017.129(1):13-21.<br><br>2. Jagasia M, Greinix H, 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 of blood and marrow transplantation: Journal of the American Society for Blood and Marrow Transplantation. 2015. 21(3):389-401.<br><br>3. Styczyński J, Tridello G, Koster L, et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. Bone Marrow Transplant. 2020. 55(1):126-36.<br><br>4. Dignan F, Amrolia P, Clark A. Diagnosis and management of chronic graft-versus-host disease. British Journal of Haematology. 2012. 158:46–61. | |

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| | Anthony Nolan | Management protocols used around the world have largely stayed unchanged for decades.<br><br>Chronic GvHD is identified as a patient experiencing severe complications of allogeneic hematopoietic stem cell transplantation that affects various organs leading to a reduced quality of life. It is regarded as chronic once symptoms persisst after Day 100 following an allogenic infusion.<br><br>First line treatments typically include topical therapies, systemic corticosteroids or calcineurin inhibitors.<br><br>Second line or subsequent therapy is guided by grade and clinical presentation of GvHD and treatments of clinical interest include other immunosuppressant therapies such as imatinib and sirolimus, newer biological therapies such as rituximab and infliximab and ECP, and cell therapy such as mesenchymal stem cells.<br><br>Unfortunately, steroid response decreases with increasing disease severity, with many patients will become refractory to steroid treatment, in turn leading to an increase in non-relapse mortality4.<br><br>Considering the wide range of second-line and subsequent lines of therapies are recommended for GvHD treatment, clinical evidence remains stubbornly disappointing.<br><br>Therefore, a significant clinical unmet need does exist for cGvHD treatments that carry high rate of efficacy, support increased patient tolerance and help | Thank you for your comment. The timing of this appraisal will follow our single technology appraisals process, for further details see the methods guide section 5.2 |

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| | | to improve patient's overall quality-of-life as they recover in their transplant journey.<br><br>3 - NHS England (2017) Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation. 16069/P. Accessed May 2022.<br><br>4 - Hooker DS, Grabe-Heyne K, Henne C, Bader P, Toumi M, Furniss SJ. Improved Therapeutic Approaches are Needed to Manage Graft-versus-Host Disease. Clin Drug Investig. 2021 Nov;41(11):929-939. doi: 10.1007/s40261-021-01087-6. Epub 2021 Oct 16. PMID: 34657244; PMCID: PMC8556206. | |
| | Kings College Hospital London | Patients affected with steroid refractory cGVHD that fail third line of treatment have no effective and safe treatment options available. Also, the third line of treatment is protean at different transplant centres across England because it relies on personal experience with some medications.<br>These elements contribute to the social and economic burden of cGVHD patients.<br>The patients experience a negative quality of life characterized by active GVHD, onset of side effects from the medications administered for the treatment of this complication. Also, this translated in frequent admissions or attendance to the haematology day unit to treat either side effect from the administered medications or opportunistic infection (i.e. fungal infection) as consequence of immune suppressive therapy.<br>Moderate to severe steroid refractory GVHD of lung, liver, gastrointestinal tract and mouth are associated with an increased mortality of patients in | Thank you for your comment. The timing of this appraisal will follow our single technology appraisals process, for further details see the methods guide section 5.2 |

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| | | remission from their original indication to transplant (Inamoto Y, et al. - haematologica \| 2014; 99(10)).<br>Based on what written above, the evaluation of belumosudil can be considered a matter of urgency. | |
| Additional comments on the draft remit | Sanofi | None | No action required. |
| | Anthony Nolan | None | No action required. |
| | Kings College Hospital London | None | No action required. |

**Comment 2: the draft scope**

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| Background information | Sanofi | 1. It is important to consider the heterogeneous, complex nature of cGVHD throughout this appraisal process. The pathophysiology of cGVHD involves both inflammatory and fibrotic pathways with varying clinical impact. Individual patients can present with differing multi-organ manifestations of varying severities. Selective ROCK2 inhibition has been shown to impact fibrotic manifestations which are difficult to manage and the impact on inflammatory pathways (Th17 / Treg) of belumosudil is expected to impact the disease without significant immunosuppression (which is an issue with many of the treatments currently used) [1].<br>2. The reference used to estimate the epidemiology of cGVHD is 10 years old. To ensure factual accuracy, NICE may wish to consider | Thank you for your comments.<br>1. The background information is intended a brief summary of the disease area.<br>2. The final scope was updated to reflect the |

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| | | using a more recent proprietary report available through the BSBMTCT [2].<br>3. Whilst the description of lines of treatment in this section is reflective of the NHS England clinical commissioning policy [3], it may be clearer to consultees to describe the positioning in terms of "prior systemic therapies". For example, use of ECP following systemic corticosteroids and sirolimus would by definition be a third line systemic therapy, rather than a second line treatment option. This nomenclature may avoid confusion when considering the licensed indication of belumosudil, which is after "at least two prior lines of systemic therapy", rather than it being a "third line treatment option". This important point is explained in more detail below, under "Comparators".<br>4. Belumosudil is currently licensed for use in Great Britain but not the UK (i.e. the current MHRA marketing authorisation does not apply to Northern Ireland). The text should be updated to say Great Britain instead of UK.<br><br>**References:**<br>1. Zanin-Zhorov A, Blazar B. ROCK2, a critical regulator of immune modulation and fibrosis has emerged as a therapeutic target in chronic graft-versus-host disease. *Clin Immunol*. 2021. 230:108823.<br>2. British Society of Blood and Marrow Transplantation and Cellular Therapies (BSBMTCT) (2015). 8th Report to Specialist Commissioners Report 2020. Available: https://www.uhs.nhs.uk/Media/SUHTExtranet/WessexBloodAndMarrowTransplantationService/BSBMT-8th-Report-To-Commissioners.pdf. Accessed: 09/2022.<br>3. NHS England. (2017). Clinical commissioning policy: Treatments for GVHD following haematopoetic stem cell transplantation. Available: | most recent BSBMTCT report.<br><br>3. After consideration at a scoping workshop the definition of treatment lines in the final scope has been amended.<br><br>4. The final scope has been amended to reflect this point. |

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| | | https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf Accessed: 09/2022. | |
| | Anthony Nolan | The background text would benefit from including the following additonal points:<br><br>- Key to successful collaborative management includes early recognition in making the diagnosis of chronic GVHD, comprehensive evaluation at the onset and periodically during the course of the disease. This can support improved patient outcomes and overall quality-of-life[5].<br><br>- Manifestations typically appear within the first year after HCT, most often when doses of immunosuppressive medications are weaned. The disease can begin as early as 2 months and as late as 7 years after HCT, although onset at >1 year from HCT occurs in <10% of cases[6].<br><br>- References to the BSBMTCT register should be reviewed and updated. The 13th outcomes report is now available, covering patient cohorts between 2016-2020 inclusive.<br><br>- In the context of cost effectiveness, it should be noted that GvHD also has a significant impact on healthcare resources, with patients experiencing more and longer hospitalisations and incurring greater healthcare costs. | Thank you for your comment. The background is intended to be a brief summary only.<br><br>The final scope has been amended to refer to the 13th BSBMTCT report and to note that manifestations usually appear within 1 year of HCT. |

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| | | - A description of the aims involved in 'effective management of cGvHD would be helpful - to balance the need for immunosuppression in order to control the GvHD, whilst maintaining a degree of immunocompetence against infection.<br><br>[5] - Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. Blood. 2015 Jan 22;125(4):606-15. doi: 10.1182/blood-2014-08-551994. Epub 2014 Nov 14. PMID: 25398933; PMCID: PMC4304105.<br><br>[6] - Flowers ME, Inamoto Y, Carpenter PA, Lee SJ, Kiem HP, Petersdorf EW, Pereira SE, Nash RA, Mielcarek M, Fero ML, Warren EH, Sanders JE, Storb RF, Appelbaum FR, Storer BE, Martin PJ. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood. 2011 Mar 17;117(11):3214-9. doi: 10.1182/blood-2010-08-302109. Epub 2011 Jan 24. PMID: 21263156; PMCID: PMC3062319. | |
| | Kings College Hospital London | The background of the draft scope is adeguate even if there is no mention of overlapping graft versus host disease.<br>This entity is characterised by the onset of features of chronic GVHD before day 100 or the onset of acute manifestation of GVHD after day 100.<br>The former is not a such rare entity as it is described to happen in patients underwent to reduced intensity conditioning (RIC), that are the majority of conditioning regimen administered to adults in England.<br>The latter is less frequent, and it is quite commonly diagnosed following the administration of donor lymphocyte infusion (DLI). | Thank you for your comment. We have updated the references to reflect the latest BSBMTCT report. The final scope has been amended to reflect this. |

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| | | Also, it is worth to highlight that the rate of cGvHD in adult allograft recipients ranges from 30-40% (1,970 patients, 2016-2020 adult cohort) and is 11% for extensive cGvHD (651 patients, 2016-2020 BSBMTCT adult cohort), who will require second or subsequent lines of therapy.<br>In the 2016-2020 BSBMTCT paediatric patient cohort, the overall rate of cGVHD was 24% at 5 years with 208 patients suffering from cGvHD, while 62 (4.1%) patients have extensive cGvHD, who will require subsequent therapy | |
| Population | Sanofi | The definition of the population should mandate the use of 'systemic' therapies in line with the licence [1] – see comments on the draft remit above.<br>We suggest the following change to the wording:<br><br>People aged 12 and over with chronic graft versus host disease after 2 or more **systemic** therapies.<br><br>**References:**<br>1. MHRA. Belumosudil Summary of Product Characteristics (2022). Available: https://mhraproducts4853.blob.core.windows.net/docs/f2dd1f798bdb88b97ad6b7f77040faaa081faba7. Accessed: 09/2022. | Thank you for your comment. The population in the final scope has been amended in line with the suggestion made and to reflect lines of therapy as suggested previously. |
| | Anthony Nolan | The defiined populations is in line with the parameters of the ROCKstar study.<br><br>Use for under 12s should be explored if it deemed to be of clinical benefit, and the safe administration of oral medicine, at the correct dosage can be agreed. | Thank you for your comment. NICE can only appraise within the marketing authorisation of a treatment which |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | | would exclude under 12s from consideration. |
| | Kings College Hospital London | Yes | No action required |
| Subgroups | Sanofi | Due to the consistent clinical efficacy across multiple subgroups studied, we do not think that other sub-groups should be considered separately. This includes the subgroup suggested in the draft scope: *'Number and type of previous treatments'.*<br><br>A Forest plot providing an analysis of best overall response rate (ORR) in a range of subgroups is available in the PhII publication of the belumosudil ROCKstar study. Subgroups were assigned according to severity, duration of disease, number of organs at baseline, and prior systemic therapy. Best ORR was 76% for the total modified intention to treat (mITT) population, with high ORRs (61-85%) observed in all subgroups analysed. Efficacy of belumosudil was maintained irrespective of prior treatment [1].<br><br>Section 5.2 of the SmPC states that:<br>*'No clinically relevant differences in belumosudil pharmacokinetics were observed with regard to age, race, sex, weight or renal impairment (mild or moderate; severe renal impairment has not been studied)'* [2]<br><br>Based on the pharmacokinetics and clinical trial outcomes evidence we do not think that other sub-groups should be considered separately. | Thank you for your comment. We heard at the workshop that it could be useful to explore the two subgroups based on site and previous treatments .The committee will decide on the relevance of any subgroups and may want to explore subgroups in which cost-effectiveness may differ. |

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| | | **References:**<br>1. Cutler C, Lee S, 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): 2278-2289.<br>2. MHRA. Belumosudil Summary of Product Characteristics (2022). Available: https://mhraproducts4853.blob.core.windows.net/docs/f2dd1f798bdb88b97ad6b7f77040faaa081faba7. Accessed: 09/2022. | |
| | Anthony Nolan | Within the draft scope, potential sub-groups are defined as “Number and type of previous treatments”.<br><br>It is unclear how the inclusion of this group affects the introduction of this technology within existing management protocols for cGvHD.<br><br>Also, is the intention that there are certain first and second line treatments which will make the use of Belumosudil prohibitive as third line therapy?<br><br>Clariification as to the intent of this statement would be welcomed. | Thank you for your comment. We heard at the workshop that it could be useful to explore the two subgroups based on site and previous treatments .The committee will decide on the relevance of any subgroups and my want to explore subgroups in which cost-effectiveness may differ. |
| | Kings College Hospital London | Yes, and this is consequence of the potential protean organ involvement from cGVHD. | Thank you for your comment. We heard at the workshop that it could be useful to |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | There is a body of evidence that shows that patients affected joint, oral, ocular, upper GI and pulmonary have a high overall response to belumosudil (range from 57 to 87% of patients).<br>Also, a recent analysis of patients affected with bronchiolitis obliterans (a very difficult form of chronic GVHD of the lung) showed that belumosudil has a huge therapeutic benefit in these patients.<br>**Based on these considerations, and also considered the study of Inamoto Y, et al, there should be a special focus on patients affected with pulmonary, oral, ocular, upper GI and joint cGVHD.** | explore the two subgroups based on site and previous treatments .The committee will decide on the relevance of any subgroups and my want to explore subgroups in which cost-effectiveness may differ. |
| Comparators | Sanofi | Not all the relevant comparators reflecting the licence for belumosudil after two prior lines of systemic therapy have been included in the scope.<br><br>When defining the comparator set it is critical to understand the nuances of the real-world treatment pathway for cGVHD and to appreciate that prior lines of therapy and numbers of prior treatments are not synonymous. Lines can be both individual treatments and combinations. For this reason, whilst important to establish the list of commissioned medicines, we do not believe that the definition of 'lines' within the NHS commissioning policy [1] should be the rigid basis for the choice of comparators in this appraisal.<br><br>The licensed indication for belumosudil is:<br>"*Patients aged 12 years and older with cGVHD who have received at least two prior lines of systemic therapy*" [2] | Thank you for your comment. After consideration at the scoping workshop the treatment pathway and comparators in the final scope have been updated. The appraisal committee will discuss the current treatment pathway during the development of this appraisal. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | The definition of a line of therapy within the clinical trial and consequently informing this licence positioning was based on National Institutes of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in cGVHD:<br>*"First-line treatment is defined as the beginning of systemic*<br>*treatment for chronic GVHD, typically with NIH global level 2 severity… Subsequent lines of treatment are most clearly defined by the introduction of any systemic agent not previously used in the regimen for first-line treatment"* [3].<br><br>This differs from the wording in the NHS England clinical commissioning policy for GVHD, which describes "lines of therapy" as groups of treatment options (either individual treatments or combinations with no consideration of the timing of initiation) which can be used in succession **before moving** to the next line of therapy [1].<br><br>In the belumosudil trial program patients were categorised by the number of prior systemic treatments AND the timing of the initiation of these therapies. First line treatment could be systemic steroids AND, for example, a CNI initiated within 4 weeks of each other but if the CNI therapy was added in after 4 weeks it was considered second line according to the NIH definition.<br><br>The commissioning policy also states that "third line treatments" - mycophenolate mofetil, methotrexate, and pulsed corticosteroids - should only be used after two different "second line" options. This is clearly a non-sequitur since under this definition all third line options must be considered at | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | least fourth line or later, if the timing of initiation for 'first-line' therapies is taken into account [1].<br><br>For example, based on clinical guidelines, a patient with cGVHD may receive corticosteroids, the subsequent addition of a CNI, followed by sirolimus, ECP, and then imatinib. According to the commissioning policy, imatinib would be described as a second line treatment, despite the four systemic therapies being used prior to it.<br><br>By categorising belumosudil as a third line treatment option, according to the rigid definitions contained within the commissioning policy, the medicine could be relegated to use after five prior systemic therapies (i.e. corticosteroids, CNIs, sirolimus, and two second line treatment options) in clinical practice. The high unmet need and lack of compelling evidence for many of the unlicensed therapies that would be used ahead of belumosudil in this scenario were discussed above. It is not appropriate to inadvertently enforce this many step-through treatments onto the highly burdened cGVHD patient population eligible for belumosudil by limiting the comparator set with this appraisal. This is neither aligned to the clinical evidence base nor the licensed indication for belumosudil.<br><br>There is substantial heterogeneity in patients with cGVHD, with each patient potentially presenting with their own unique combination of up to nine organs involved, with potentially three levels of severity. As such, clinical practice is highly variable according to the major disease manifestation, and treatment may not strictly follow the commissioning policy treatment pathway [4]. | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | A collection of best available therapies should realistically be drawn from all the agents listed after first line in the NHSE policy. Consequently, Best Available Therapy (BAT) – as a mixture of the following therapies is the most appropriate comparator:<br>ECP, Sirolimus, Pentostatin, Rituximab, Imatinib, Mycophenolate mofetil, Methotrexate, and pulsed corticosteroids.<br><br>It is important to note that BAT has been recognised as an appropriate comparator in this population by the regulatory authorities.<br><br>We would particularly like to emphasise that ECP is a critical comparator to be included in this basket of best available therapies. Whilst some of the other treatments listed above are not widely prescribed, ECP is often used in clinical practice in England. It can be implemented anywhere in the treatment algorithm we have described above but particularly after steroids followed by CNI or other 'first line' treatment option, making it the third systemic therapy.<br><br>**References:**<br>1. NHS England. (2017). Clinical commissioning policy: Treatments for GVHD following haematopoetic stem cell transplantation. Available: https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf. Accessed: 09/2022.<br>2. MHRA. Belumosudil Summary of Product Characteristics (2022). Available: https://mhraproducts4853.blob.core.windows.net/docs/f2dd1f798bdb88b97ad6b7f77040faaa081faba7. Accessed: 09/2022.<br>3. Martin P, Lee S, Przepiorka D, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. The 2014 Clinical Trial Design | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | Working Group Report. *Biol Blood Marrow Transplant*. 2015. 21(8):1343-1359.<br>4. Sanofi (2022). Belumosudil Advisory Board. (Data on file: MAT-XU-2201910 v1.0). | |
| | Anthony Nolan | As per British Committee for Standards in Haematology (BCSH) and the British Society for Bone Marrow Transplantation (BSBMT) guidelines for the 'Diagnosis and management of chronic graft-versus-host disease'[7].<br><br>- ECP, imatinib and rituximab may be considered as third line treatment options in chronic GvHD involving other organs (2C)<br><br>It shpuld also be noted that the FDA has approved Ruxolitinib for he treatment of chronic graft-versus-host disease (cGVHD) after the failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older[8].<br><br>The REACH-3 Study involved two arms, with a total of 329 patients – receiving either ruxolitinib 10 mg twice daily (n = 165) or best available therapy (BAT) (n = 164). The overall response rate through Cycle 7 Day 1 was 70% (95% CI, 63-77) in the ruxolitinib arm, and 57% (95% CI, 49-65) in the BAT arm.<br><br>The mean duration of response for Belumosudil registered 54 weeks; 44% of subjects have remained on therapy for >1 year. Compared to Ruxolitinib with 100 weeks before either death or a new therapy was registered.<br><br>Whilst not currently licensed for this indication in the UK, it should be | Thank you for your comment. It was discussed at a scoping workshop and the comparators in the final scope have been amended. The appraisal committee will discuss the current treatment pathway during the development of this appraisal. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | considered as a known comparator in published pharmacology and wider global chronic GvHD management.<br><br>[7] - Dignan, F.L., Amrolia, P., Clark, A., Cornish, J., Jackson, G., Mahendra, P., Scarisbrick, J.J., Taylor, P.C., Shaw, B.E., Potter, M.N. and (2012), Diagnosis and management of chronic graft-versus-host disease. Br J Haematol, 158: 46-61. https://doi.org/10.1111/j.1365-2141.2012.09128.x<br><br>[8] - Robert Q Le, Xin Wang, Hongfei Zhang, Hongshan Li, Donna Przepiorka, Jonathon Vallejo, Ruby Leong, Lian Ma, Kirsten B Goldberg, Richard Pazdur, Marc R Theoret, Angelo De Claro, FDA Approval Summary: Ruxolitinib for Treatment of Chronic Graft-Versus-Host Disease after Failure of One or Two Lines of Systemic Therapy, The Oncologist, Volume 27, Issue 6, June 2022, Pages 493–500, https://doi.org/10.1093/oncolo/oyac042 | |
| | Kings College Hospital London | Inhibition of the Rho-associated coiled-coil kinase 2 (ROCK2) has been shown to inhibit STAT3 signaling, thereby downregulating pro-inflammatory Th17 cells and stimulating expansion of regulatory T cells, that improves tolerance. An additional function of the ROCK family is the regulation of profibrotic pathways, and ROCK inhibitors have been shown to prevent collagen formation and fibrosis. For these reasons, ROCK2 is an attractive target in the treatment of chronic graft-versus-host disease (cGvHD) reducing inflammation and. Belumosudil is the first and only approved therapy inhibiting Rho-associated coiled-coil kinase 2 (ROCK2).<br>Based on these premises, there is no real comparator to this treatment, which has a unique mechanism of action.<br>The current comparators (mycophenolate, methotrexate, pulsed steroids, pentostatin, imatinib and rituximab) are the ones currently approved but they have a completely different mechanism of action and also of toxicities. | Thank you for your comment. It was discussed at a scoping workshop and the comparators in the final scope have been amended. The appraisal committee will discuss the current treatment pathway during the development of this appraisal. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | It is important to highlight that there is no standard 2nd line therapy in cGVHD. The current 2nd or 3rd line treatment options have limited efficacy and do not necessary fit in the algorithm in real world practice for steroid refractory cGVHD. The choice of treatment for steroid refractory cGVHD is largely patient-specific and based on several factors, including clinical experience and published evidence, risk profile, disease history, comorbidities, individual tolerance to medication, and access to ongoing clinical trials.<br>The ECP is missing from the comparator list, and this treatment strategy is very often administered beyond second line. | |
| Outcomes | Sanofi | Yes, the outcomes listed are appropriate. In addition to complete response and overall response, response to treatment should also include failure-free survival (FFS, defined as the absence of cGVHD treatment change, non-relapse mortality, and recurrent malignancy). FFS is a valuable, objective measure which correlates with overall improvement [1-2]. Capturing the absence of treatment change as well as clinical benefit makes FFS a useful measure which may more accurately reflect real world practice. FFS was used as a secondary endpoint in the Phase II clinical trials for belumosudil [3].<br><br>**References:**<br>1. Martin P, Lee S, Przepiorka D, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. The 2014 Clinical Trial Design Working Group Report. *Biol Blood Marrow Transplant*. 2015. 21(8):1343-1359.<br>2. Jacobsohn D. FFS: an end(point) to our problems in chronic GVHD trials? *Blood*. 2014;124(8):1216-1217. | Thank you for your comment. Failure free survival has been included in the final scope. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | 3. Cutler C, Lee S, 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): 2278-2289. | |
| | Anthony Nolan | The outcome measures listed in the draft scope are considered appropriate to capturing key benefits and contrainidications of this technology. | Thank you for your comment |
| | Kings College Hospital London | The most important measure is overall response rates, which is clinically meaningful correlating with patient reported outcomes using standard tools (Multiple tools are used to measure quality-of-life (QoL) in patients with cGVHD, including the Patient-Reported Outcomes Measurement Information System (PROMIS)-Global Health (GH), the PROMIS 29, the Short Form (SF)-36, and the Lee Symptom Scale (Lee et al. 2018).<br>Another outcome that must be considered is the Failure Free survival demonstrating durability of treatment responses and surrogate marker for consequent reduction in morbidity<br><br>Also, it is fundamental to consider the improvement in overall survival over 5 years<br><br>Lastly, the Cost-effectiveness with improvement in quality-adjusted life years (QALYs). | Thank you for your comment. The list of outcomes was updated after discussion at a scoping workshop, please see the final scope. |
| Equality | Sanofi | Currently, only 72% of patients from White, Caucasian, backgrounds can find the best possible stem cell tissue match from a stranger. This drops, significantly, to 37% for patients from a minority ethnic background [1]. Mismatched, unrelated donors are consistently reported as a risk factor for cGVHD, which is an iatrogenic complication resulting from AlloHSCT [2,3]. | Thank you for your comment. The equality issues have been included in the final scope and will be |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | Therefore, it is plausible that cGVHD is more likely to occur in people from a minority ethnic background.<br><br>The draft remit and scope do not discriminate against these groups. However, it is worth noting that the current lack of licensed, reimbursed, effective treatments with a favourable safety profile may disadvantage these populations.<br><br>Skin manifestations are some of the most common and major complications of cGVHD, and dermatological assessment is therefore required for disease diagnosis and severity grading. It has been suggested that current validated physician- and patient-reported outcomes measures may not adequately capture the subtle changes in patients with non-white skin [4]. Clinicians we have spoken to have noted that this could potentially lead to errors or delays in diagnosis for such patients.<br><br>Geographical access to ECP services and specialist blood and marrow transplant clinics can be a barrier to people in lower socio-economic groups who are unable to take time off work or afford to travel to appointments. Access to ECP can be particularly challenging given the need for two 1–2-hour procedures on consecutive days every fortnight or every month. Having the option of an oral treatment alternative could be particularly beneficial in these groups. This has also been noted by clinicians we have spoken to.<br><br>Therefore, a NICE recommendation in this therapy area could have a positive impact on people protected by the equality legislation. | considered by the committee throughout the process of this appraisal. |

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| | | **References:**<br>1. Anthony Nolan. Facts and Stats. Available: https://www.anthonynolan.org/front/facts-and-stats Accessed: 09/2022.<br>2. Flowers M, Inamoto Y, Carpenter P, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood*. 2011. 117(11):3214-3219.<br>3. Anasetti C. Use of alternative donors for allogeneic stem cell transplantation. *Hematology Am Soc Hematol Educ Program.* 2015. (1): 220–224.<br>4. Smith Z, Rosenstein R, Banerjee S, et al. Quality of life in patients with skin of color and chronic graft-vs-host disease. *JAMA Dermatol*. 2020;156(5):589-590. | |
| | Anthony Nolan | As cited in the questions for consultation: *Would chronic graft-versus-host disease be more likely to occur in people for whom tissue-type matched donors may be more difficult to identify, for example people from a Black, Asian or minority ethnic family background?*<br><br>To reduce the risk of graft-versus-host disease (GvHD) 8/8 human leukocyte antigen (HLA) matching is preferred; however, the chance of finding a perfect match is low especially for some ethnic groups[9].<br><br>Mismatched HLA donorgrafts can contriibute to a higher incidence of GvHD in transplant *patients. These patients may require treatment and ongoing management of their symptoms and the underlying autoimmune responses that are classified as chronic GvHD.* | Thank you for your comment. The equality issues have been included in the final scope and will be considered by the committee throughout the process of this appraisal. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | *9 - HLA (mis)matching in haploidentical transplantation, A. Hyde - https://aml-hub.com/medical-information/hla-mis-matching-in-haploidentical-transplantation* | |
| | Kings College Hospital London | I could not detect any equality issue | No action required. |
| Other considerations | Sanofi | None | No action required. |
| | Anthony Nolan | None | No action required. |
| | Kings College Hospital London | None | No action required. |
| Questions for consultation | Sanofi | *Where do you consider belumosudil will fit into the existing care pathway for chronic graft versus host disease?*<br>Belumosudil would best fit into the cGVHD care pathway after oral corticosteroids (with or without the addition of CNIs) and at least one other systemic therapy, such as sirolimus or the later addition of a CNI. This would position belumosudil, within its licensed indication, as an alternative to whichever treatment the prescribing healthcare professional selects from the full list of best available therapies discussed above.<br><br>*Have all relevant comparators for belumosudil been included in the scope? Which treatments are considered to be established clinical practice in the NHS for cGVHD?* | Thank you for your responses. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | No. ECP, Sirolimus, pentostatin, rituximab, and imatinib, should be captured alongside mycophenolate mofetil, methotrexate, and pulsed corticosteroids. These are commonly understood to be 'best available therapy' options, which are used individually or sequentially in direct response to how the patient presents with this multi-organ complex condition. Sanofi understands, based on expert insights, that methotrexate and pulsed corticosteroids are rarely used in clinical practice. However, for completeness, and in line with the list of reimbursed treatments within the NHS England commissioning policy, these should remain in the comparator set [1].<br><br>*Would belumosudil be used in people who have had more than 5 previous systemic therapies in NHS practice?*<br>The licensed indication for belumosudil is not limited by the number of prior therapies received [2]. However, by positioning it as an alternative "third line" treatment option (according to the rigid definitions of line of treatment in the NHS England commissioning policy), belumosudil could in practice be relegated to use after at least 5 prior systemic therapies (i.e. corticosteroids, CNIs, sirolimus, and at least two of the second line treatment options) [1]. This does not reflect the clinical study protocols and the licence. The choice of comparators in this appraisal has a direct effect on place in therapy in clinical practice and, as such, the comparator set should be amended.<br><br>*Would belumosudil always be given in combination with other treatments such as but not limited to corticosteroids?*<br>No. The licence for belumosudil does not require concomitant therapy of any sort [2]. Data from the Phase II trials showed a reduction in corticosteroid use amongst those receiving concomitant corticosteroids [3]. | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | *Would belumosudil be given in practice to those whose weight was under 40kg?*<br>Potentially. Royal College of Paediatrics and Child Health (RCPCH) UK growth charts for boys and girls indicate that the 50th centile for 12-year-old boys is just over 36kg and, for girls the 50th centile is 40kg [4]. Therefore, children aged 12 years or more but weighing less than 40kg could plausibly be treated with belumosudil within its licensed indication.<br><br>*Would chronic graft-versus-host disease be more likely to occur in people for whom tissue-type matched donors may be more difficult to identify, for example people from a Black, Asian or minority ethnic family background?*<br>Currently, only 72% of patients from White, Caucasian, backgrounds can find the best possible stem cell tissue match from a stranger. This drops, significantly, to 37% for patients from a minority ethnic background [5]. Mismatched, unrelated donors are consistently reported as a risk factor for cGVHD, which is an iatrogenic complication resulting from AlloHSCT [6,7]. Therefore, it is plausible that cGVHD is more likely to occur in people from a minority ethnic background. The current lack of licensed and reimbursed treatments which are supported by robust safety and efficacy evidence may disadvantage these populations. A NICE recommendation in this therapy area could have a positive impact on people protected by the equality legislation.<br><br>*Would belumosudil be a candidate for managed access?*<br>Belumosudil has been recognised as an innovative treatment option for cGVHD (e.g. through ILAP designation and Project Orbis), and was approved on the basis of a Phase II trial. Considering this, as well as limitations in the current evidence base for cGVHD, Sanofi believes it would be a suitable | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | candidate for managed access, and specifically, as a pilot for rapid entry to managed access (REMA).<br><br>Belumosudil has been designated an ultra-orphan medicine by the SMC and so will enter a period of managed access in Q2 2023. It is likely that this will cause inequalities in access between England and Scotland and so we are particularly keen to engage further with NICE / NHSE to discuss the potential for REMA.<br><br>We have also requested a NICE Office for Market Access (OMA) meeting on the 9th of November to discuss possible options including data collection.<br><br>The following data sources could potentially provide the necessary additional evidence under a three-year agreement to inform a subsequent full technology appraisal:<br>1. Prospective registry data collected through the local BSBMTCT registry. (We are currently evaluating potential options with the registry. A representative of the BSBMTCT will be present at both the scoping meeting and the OMA engagement.)<br>2. Retrospective case notes review of patients with cGVHD treated with belumosudil in Great Britain (UO pathway in Scotland and in England via other access pathways, e.g. REMA or other.)<br>3. Claims data from the US where belumosudil has been in use since July 2021. (Analysis using this data source is planned to construct an external control arm for use in economic evaluation.) | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | *Do you consider belumosudil to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?*<br>Yes. Belumosudil is a first-in-class treatment for cGVHD. It has a unique mode of action (selective ROCK2 inhibition) which works through rebalancing of the immune response, reducing inflammation and arresting fibrosis, and thereby improving or stabilising disease [8]. No other available treatments target both the inflammatory and fibrotic pathogenic pathways in cGVHD. Belumosudil has been studied in a difficult-to-treat population with advanced disease yet demonstrated meaningful clinical improvement irrespective of number or type of organ affected, prior number of treatments, or disease severity [3]. Belumosudil is an oral, once daily tablet which can be administered at home, unlike several of the current alternative treatment options. It therefore has potential to make a significant and substantial clinical impact on cGVHD outcomes in the UK as an alternative treatment option to current clinical practice.<br><br>*Do you consider that the use of belumosudil can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?*<br>In the Phase II ROCKstar study, belumosudil allowed patients with persistent cGVHD manifestations to discontinue or taper corticosteroids and CNI therapies. The mean CS dose was reduced by 50%, while 27% of patients discontinued corticosteroid therapy [9]. Longer term benefits of CS reduction on quality of life, such as reduced infections, cardiovascular disease, and osteoporosis [10], are unlikely to be adequately captured in any QALY calculation. | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | In the ROCKstar study, belumosudil demonstrated clinically meaningful improvements in quality of life as measured using the Lee Symptom Scale (LSS) in 61% of the modified intention to treat population and in 70% of responders [9]. The LSS is a validated instrument which captures cGVHD symptoms and associated quality of life. This disease-specific instrument has not been mapped to a utility value and as such cannot be included in the QALY calculation.<br><br>**References:**<br>1. NHS England. (2017). Clinical commissioning policy: Treatments for GVHD following haematopoetic stem cell transplantation. Available: https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf Accessed: 09/2022.<br>2. MHRA. Belumosudil Summary of Product Characteristics (2022). Available: https://mhraproducts4853.blob.core.windows.net/docs/f2dd1f798bdb88b97ad6b7f77040faaa081faba7. Accessed: 09/2022.<br>3. Cutler C, Lee S, 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): 2278-2289.<br>4. Royal College of Paediatrics and Child Health (RCPCH). UK-WHO growth charts 2-18. Available: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years. Accessed: 09/2022.<br>5. Anthony Nolan. Facts and Stats. Available: https://www.anthonynolan.org/front/facts-and-stats. Accessed: 09/2022.<br>6. Flowers M, Inamoto Y, Carpenter P, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft- | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | versus-host disease according to National Institutes of Health consensus criteria. *Blood*. 2011. 117(11):3214-3219.<br>7. Anasetti C. Use of alternative donors for allogeneic stem cell transplantation. *Hematology Am Soc Hematol Educ Program.* 2015. (1): 220–224.<br>8. Zanin-Zhorov A, Blazar B. ROCK2, a critical regulator of immune modulation and fibrosis has emerged as a therapeutic target in chronic graft-versus-host disease. *Clin Immunol*. 2021. 230:108823.<br>9. Cutler C, Lee S, Pavletic S, et al. Belumosudil for Chronic Graft-versus-Host Disease [cGVHD] After 2 or More Prior Lines of Systemic Therapy [LOTs]: 2-Year Safety Results From the Pivotal Phase 2 ROCKstar Study (KD025-213). Poster presented at EBMT. 2022.<br>10. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy, Asthma & Clinical Immunology*. 2013. | |
| | Anthony Nolan | *Would belumosudil be used in people who have had more than 5 previous systemic therapies in NHS practice?*<br>- As per the ROCKstar study, the cohort did include patients with this many previous lines of therapy, so this may be a consideration for clinical teams.<br><br>*Would belumosudil always be given in combination with other treatments such as but not limited to corticosteroids?*<br>- In most instances, yes, patients would be started with steroids, with a view to weaning them off as with best practice. | Thank you for your responses. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | - A large contingent of patients can become steroid refractory, and require second/third-line therapies and other novel agents.<br><br>*Would belumosudil be given in practice to those whose weight was under 40kg?*<br>- This should be considered in line with published studies, and whether this makes belumosudil prohibtive to under 12s.<br><br>*Do you consider belumosudil to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?*<br>Currently the only proposed ROCK2 inhibitor for GVHD, and can be adminstered orally. This may improve patient tolerance and reduce inpatient periods, as well as number of outpatient appointments. | |
| | Kings College Hospital London | | No action required |
| Additional comments on the draft scope | Sanofi | None | No action required |
| | Anthony Nolan | None | No action required |
| | Kings College Hospital London | Any additional comments on the draft scope- Questions written in appendix B that deserve answers. | Thank you for your comment. The equality issues have been |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | Q: Would chronic graft-versus-host disease be more likely to occur in people for whom tissue-type matched donors may be more difficult to identify, for example people from a Black, Asian or minority ethnic family background?<br><br>A: yes, the use of mismatched donors or alternative donors such as haploidentical siblings or unrelated cord blood units are known risk factors for both acute and chronic GVHD. Patients belonging to ethnic minorities have a potential high risk of developing cGVHD and belumosudil would be a potential life-saving medication. | included in the final scope and will be considered by the committee throughout the process of this appraisal. |

**The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope**

Sickle Cell Society
NPPG
Myeloma UK
MPS Society
Lymphoma Action
Immunodeficiency UK