NICE National Institute for Health and Care Excellence

NICE guidance

Belumosudil for treating chronic graft-versus-host disease after 2 or more systemic treatments in people 12 years and over

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Belumosudil is recommended, within its marketing authorisation, for treating chronic graft-versus-host disease in people 12 years and over after 2 or more systemic treatments. It is recommended only if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Usual first-line treatment for chronic graft-versus-host disease (GVHD) is corticosteroids with or without a calcineurin inhibitor. Second-line treatment is extracorporeal photopheresis, pentostatin, rituximab or imatinib. Treatment for chronic graft-versus-host disease after 2 or more systemic treatments can include imatinib, mycophenolate mofetil, pentostatin, pulsed corticosteroids and sirolimus. In this evaluation, this range of potential treatments is referred to as 'best available therapy'.

Clinical trial evidence suggests that taking belumosudil improves people's symptoms, but it was not compared directly with best available therapy. When compared indirectly, the results suggest that belumosudil improves symptoms more than best available therapy.

The most likely cost-effectiveness estimates are uncertain, but they are likely within the range that NICE considers an acceptable use of NHS resources. So, belumosudil is recommended.

2 Information about belumosudil

Marketing authorisation indication

2.1 Belumosudil mesilate (Rezurock, Sanofi) is indicated for 'the 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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for belumosudil.

Price

2.3 The list price of 30 belumosudil 200-mg tablets is £6,708.00 (excluding VAT; BNF online accessed December 2023).

2.4 The company has a commercial arrangement. This makes belumosudil available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Sanofi, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Unmet need

3.1 Graft-versus-host disease (GVHD) usually occurs after an allogeneic haematopoietic stem cell transplant (HSCT) when donated white T-cells attack the body's own cells. Chronic GVHD typically occurs later after a HSCT. Manifestations typically appear within the first year after an allogeneic HSCT, when immunosuppressive medications are reduced. One of the clinical experts noted that the disease can worsen, then improve and even resolve for some people, albeit with lasting effects on quality of life. Chronic GVHD causes severe morbidity and mortality, mainly because of infections resulting from immunodeficiency, as well as damage to organs such as the lungs and liver. The patient expert recalled their experience living with chronic GVHD. They explained that it had affected their eyes, skin, mouth, gut and lung, and that they could no longer work and had difficulties in managing a social life. They emphasised that chronic GVHD has a significant impact on a person's independence and mental health. The patient expert highlighted that accessing extracorporeal photopheresis is difficult for people with chronic GVHD because travel is extremely physically and psychologically challenging. They noted that people with eye GVHD are unable to drive and cannot take public transport because of the possibility of catching infections and being admitted to hospital as a result. The committee noted that people have to take time off work for extracorporeal photopheresis and recalled the barriers associated with it. The committee concluded that GVHD has a considerable impact on quality of life.

Clinical management

Positioning of belumosudil

3.2 NHS England's Treatments for Graft versus Host Disease following Haematopoietic Stem Cell Transplantation is a clinical commissioning policy issued in 2017. It states that first-line treatment for chronic GVHD should be corticosteroids with or without a calcineurin inhibitor. Second-line treatment should be extracorporeal photopheresis, pentostatin, rituximab and imatinib. Third-line treatment should be mycophenolate mofetil, methotrexate or pulsed corticosteroids. The company presented a treatment pathway for chronic GVHD that it had developed with an advisory board of clinical and health economic experts. This proposed corticosteroids at first line, calcineurin inhibitors at second line, and extracorporeal photopheresis, rituximab, mycophenolate mofetil, sirolimus and imatinib at third line. The company positioned treatment with belumosudil 'as an alternative' to extracorporeal photopheresis, rituximab, mycophenolate mofetil, sirolimus and imatinib. But, the company's submission highlighted that belumosudil is intended to be used as a monotherapy after oral corticosteroids (with or without the addition of calcineurin inhibitors) and at least one other systemic therapy, such as sirolimus or the later addition of a calcineurin inhibitors (although the trials supporting the clinical effectiveness for belumosudil allowed for concomitant therapies; see section 3.3). The EAG proposed a different treatment pathway that it had discussed with clinical experts. The EAG's clinical experts considered first-line treatment to be corticosteroids with or without calcineurin inhibitors, second-line treatment to be extracorporeal photopheresis, and other therapies (such as imatinib, mycophenolate mofetil, pentostatin, pulsed corticosteroids, rituximab and sirolimus), including belumosudil, to be third line. The clinical experts emphasised that calcineurin inhibitors did not represent second-line therapy, and that calcineurin inhibitors have a larger impact in the acute setting than the chronic GVHD setting. One clinical expert said that first-line treatment is corticosteroids, and they would wait to see how a person's condition responds to treatment over the course of 4 weeks, before adding a calcineurin inhibitor or another treatment. They confirmed that they do not use calcineurin inhibitors as a separate line of therapy. In the belumosudil trials (see section 3.3), if someone started a calcineurin inhibitor after 4 weeks of corticosteroids, this counted as second-line therapy. The clinical experts agreed with the EAG's treatment pathway and felt that

belumosudil should be positioned as a third-line therapy, after extracorporeal photopheresis. They noted that access to extracorporeal photopheresis is variable depending on location. They explained that the rising cost of living and the impacts of public transport strikes make it challenging for people to travel to their extracorporeal photopheresis services. They highlighted that although extracorporeal photopheresis is a good option for people with chronic GVHD, people would favour an oral option over having to travel because of the increased risk of catching infections on public transport (see section 3.1). The patient expert explained that at the stage of needing extracorporeal photopheresis, many people will be limited in their mobility from the severity of their skin or lung conditions. They emphasised the psychological impact of living with chronic GVHD and that people would prefer not to travel for extracorporeal photopheresis. The committee noted the high unmet need for a new treatment option after 2 systemic therapies. It concluded that current treatment options are limited, and an oral treatment would be beneficial. It also concluded that it preferred the EAG's treatment pathway.

Clinical evidence

Clinical-effectiveness evidence

3.3 The clinical-effectiveness evidence for belumosudil came from 2 trials: ROCKstar (KD025-213) and KD025-208. The ROCKstar study is an ongoing phase 2, randomised, open-label multicentre trial. It is comparing belumosudil 200 mg once daily with belumosudil 200 mg twice daily. It includes people 12 years and over who have had an allogeneic HSCT and have persistent chronic GVHD after 2 to 5 previous systemic lines of treatment. ROCKstar recruited 152 people in 28 centres across the US. KD025-208 was a phase 2a, open-label, dose-escalation, multicentre study. It compared belumosudil 200 mg once daily, belumosudil 200 mg twice daily, and belumosudil 400 mg once daily in people with chronic GVHD. KD025-208 enrolled 54 people in 7 centres across the US. The people recruited had had an allogeneic HSCT, were aged 18 years and over, and had persistent chronic GVHD that had been treated with 1 to 3 lines of treatment. In ROCKstar and KD025-208, concomitant medications were allowed. The committee considered that the belumosudil trials represented the most

appropriate source of evidence for belumosudil for people with chronic GVHD after at least 2 systemic therapies. The committee concluded that the results of the trials were broadly applicable to the UK.

Effect of belumosudil on the primary outcome

3.4 The primary outcome in ROCKstar and KD025-208 was best overall response rate, defined as the proportion of people who experienced a complete or partial response. Clinical data from ROCKstar and KD025-208 for the belumosudil once daily and twice daily dosages were pooled and analysed for the subgroup of people who had had 2 or more previous lines of therapy. The overall response rate for the combined 200-mg dose was estimated at 73.1%; 69.9% of people had a partial response, and a small proportion had a complete response (3.4%). When considering the pooled efficacy analysis at 3 years (September 2022 data cut for ROCKstar, and the 2 or more previous lines of therapy subgroup for KD025-208), the committee concluded that all doses of belumosudil showed a consistent effect for overall response rate.

The REACH-3 comparator trial

3.5 The clinical-effectiveness evidence for the comparators in the company submission came from the best available therapy arm of the REACH-3 trial. REACH-3 was a phase 3, randomised, open-label, multicentre trial. It compared ruxolitinib 10 mg twice daily with best available therapy (of investigator's choice). It included people who had had an allogeneic HSCT, were aged 12 years and over and who had moderate or severe glucocorticoid-refractory chronic GVHD. It was done across 149 centres in 28 countries, including the US and the UK. People who had had 2 or more systemic therapies for chronic GVHD in addition to corticosteroids (with or without calcineurin inhibitors) were excluded. The committee noted that this meant that people in the trial had not had 2 or more previous lines of therapy, and so fell outside of the NICE scope. The EAG's clinical experts had highlighted that best available therapy in REACH-3 reflected what they viewed as established clinical management in the US, so it was likely that additional alternative therapies across the 3 trials would be similar. The committee noted that best available therapy would differ in the UK. For example,

extracorporeal photopheresis is more common in the UK than the US. It concluded that, overall, it is likely that established clinical management was similar across the 3 trials, but it probably differed to UK clinical practice. The committee also concluded that the recruitment criteria for the best available therapy arm in REACH-3 were generally appropriate. But, the committee was mindful that people in this arm were at an earlier stage in the treatment pathway than the people in the belumosudil trials.

Crossover of the REACH-3 trial

3.6 People in the best available therapy arm of REACH-3 who were on corticosteroids (with or without calcineurin inhibitors) at baseline could continue with these treatments throughout the trial. The trial allowed people in this arm to cross over to ruxolitinib on or after week 24 if they did not have or maintain a complete or partial response, had side effects from a control therapy, or had a flare of chronic GVHD. The committee noted that 38% of people in the best available therapy arm crossed over to ruxolitinib on or after week 24. It concluded that this crossover would likely have a large impact on the clinical outcomes measured in the trial for the best available therapy arm.

Patient population

3.7 The population defined in the NICE scope, in line with the belumosudil marketing authorisation, included people 12 years and over (see section 2.1). But, in the ROCKstar and KD025-208 trials, no one between the ages of 12 and 18 years had been recruited at the time of the latest data cut (September 2022). The company highlighted the unmet need in chronic GVHD across all age groups and the biological plausibility of using belumosudil in people aged 12 to 18 years. It noted that it is reasonable and appropriate to align the eligible trial population with the marketing authorisation licence. The EAG could not confirm if adult clinical outcomes would be seen in young people (aged 12 to 18) because there is no efficacy or safety data for belumosudil in this group. Its clinical experts agreed that, from a biological perspective, there is no reason why belumosudil would not work as effectively as it does in adults. The clinical experts agreed that it was plausible for there to be no difference in efficacy in young people and adults. The

committee concluded that although there was a lack of data for belumosudil in young people, the efficacy of belumosudil was likely to be similar in young people and adults.

Naive comparison of belumosudil and best available therapy

3.8 Because the ROCKstar study of belumosudil was an uncontrolled phase 2 study, it did not allow a direct comparison with other treatment options. The company also noted that ROCKstar was done in a population who had had lots of previous treatment (at least 2 previous systemic therapies). So, the company did a systematic literature review to identify studies that could provide comparator data on the clinical efficacy and safety of treatment options for adults with chronic GVHD after an allogeneic HSCT for whom at least 1 previous line of therapy has failed, to enable an adjusted indirect treatment comparison. The company concluded that none of the 24 studies (excluding ROCKstar and KD025-208) identified in the systematic literature review were suitable for an adjusted treatment comparison. Without a control arm and published data for an adjusted indirect treatment comparison, the company used data from the phase 3 REACH-3 trial comparing ruxolitinib with investigator's choice after 1 previous line of therapy (see section 3.5). This allowed a naive direct comparison with currently available treatments to be made. The committee noted that the REACH-3 trial did not provide a complete set of data. It provided data on the endpoints of overall survival, failure-free survival and duration of response, but not time to response or time to treatment discontinuation. The EAG and its clinical experts felt that this was the only feasible option to compare clinical outcomes. But it emphasised the uncertainty associated with naive comparisons of clinical outcomes from different trials. The committee noted that the company had not done a retrospective study in the UK or in another representative population. The company emphasised that the clinical advice it had received had confirmed that the best available therapy arm of REACH-3 was an appropriate comparator. It confirmed that there was no other appropriate natural history data or observational studies other than the REACH-3 trial. The company highlighted that it believed it had used the best source of data available and acknowledged that there were potential uncertainties in this. The EAG noted that out of the 24 studies that had been excluded by the company in the systematic literature review, the REACH-3 trial was a study that had been originally excluded by the

company. The EAG noted that it was reasonable to use the REACH-3 trial, because the best available therapy arm had a larger sample size than the other excluded studies. The EAG also highlighted that other excluded studies often used a single intervention that would not have been representative of the ROCKstar population or did not report key outcomes. The committee concluded that in the absence of more robust comparisons, it had to consider the naive indirect comparison in its decision making.

The company's economic model

Company's modelling approach

3.9 The company's model was based on a partitioned survival model approach and included 3 states (failure free, failure progressed, and death). The model aimed to assess the cost effectiveness of belumosudil compared with best available therapy for treating chronic GVHD after 2 lines of systemic therapy. Within the failure-free health state, people were stratified by treatment response status. That is, whether they had a response (complete or partial) or a lack of response (the 2014 National Institutes of Health definition of lack of response included the criteria of progression, mixed response or unchanged). Also, within the failure-free health state, people could be on or off chronic GVHD treatment. In the failure health state, people were stratified by failure event type (recurrent malignancy or starting a new systemic chronic GVHD therapy). For people whose failure event was a new systemic treatment, they could be on or off treatment. The model included a cycle length of 4 weeks with half-cycle correction over a time horizon of 40 years (lifetime). The committee noted that a partitioned survival model may be too simplistic to capture the trajectory of the condition, because the disease can worsen, then improve and even resolve for some people, albeit with lasting effects on quality of life. There will also be times when a person is on or off treatment. The company noted that, based on its discussions with clinical experts and advisory boards, the chosen modelling approach reflected the disease area and outcomes. The committee concluded that although a partitioned survival model may not have been the most appropriate approach, the company's model was acceptable for its decision making if issues with other modelling assumptions were sufficiently addressed.

Extrapolation of REACH-3 failure-free survival for the best available therapy arm

3.10 In the REACH-3 study, 61 people (38%) in the best available therapy arm crossed over to ruxolitinib on or after week 24 (see section 3.6). The committee had concerns that the best available therapy arm of the Kaplan–Meier curve was not interpretable and not comparable to the belumosudil trials after 24 weeks, because of the impact of crossover. At the first committee meeting, the committee highlighted that the failure-free survival curve in the company model had been extrapolated without any adjustment for that crossover. In response to consultation, the company provided scenario analyses where the failure-free survival Kaplan–Meier data for the best available therapy arm of REACH-3 was truncated at week 24. This was then extrapolated using standard parametric distributions, to improve the committee's understanding of the extrapolations. Extrapolations of the truncated Kaplan–Meier data were then explored using standard parametric survival distributions. The company noted that the gamma distribution provided the best goodness-of-fit statistics and selected it for the base case for the best available therapy arm. The EAG noted that although most of the distributions explored had a good fit to the truncated observed data for best available therapy, many of them resulted in implausible long-term extrapolations lacking clinical validity. For the best available therapy arm, the EAG highlighted that, in addition to the company's preference for the gamma curve, the Weibull curve was also a reasonable choice and had a similar statistical and visual fit to the gamma curve. The committee acknowledged that truncating the Kaplan–Meier data introduced additional uncertainty. But it concluded that in the absence of better data, using the gamma distribution was acceptable for decision making, even though there is uncertainty in the long-term estimates for failure-free survival.

Utility values in the economic model

3.11 Utility values based on response status for the failure-free health states were derived from utility data from ROCKstar (September 2022 data cut), mapped to the EQ-5D-3L. The company used mixed-effect repeated linear regression models to analyse the mapped ROCKstar EQ-5D-3L data. It noted that across all models that had treatment failure as a covariate, the estimates of failure-related

utility were high and so lacked face validity. So, the company estimated a utility value for the failure health state from published data in related disease areas. For the 'failure – recurrent malignancy' health state in the company's model (see section 3.9), the company estimated a utility score as a weighted average based on the utility values of the progression or relapse health states from recent transplant indications (acute myelogenous leukaemia, acute lymphoblastic leukaemia, chronic myelogenous leukaemia and chronic lymphocytic leukaemia). The company assumed that the utility value for 'failure – new chronic GVHD systemic therapy' was equal to the estimated weighted utility for 'failure – recurrent malignancy', based on advisory board opinion. The EAG highlighted that the utility value for 'failure – new chronic GVHD systemic therapy' health state was a key driver of quality-adjusted life years (QALYs) in the model, because people in the best available therapy arm spent most of their time in this health state. The EAG highlighted that there was a high degree of uncertainty around the utility value derived from ROCKstar because of the limited number of observations, but that the utility value estimated by the company for 'failure – new chronic GVHD systemic therapy' was too low. The EAG preferred to use an estimated midpoint value based on Crespo et al. (2012) and an Adelphi disease-specific programme study done by the company. The clinical experts noted that the utility associated with a lack of response and starting a new treatment should be similar. The committee concluded that it would like to see scenario analyses using the midpoint value preferred by the EAG, and using the Crespo et al. (2012) utility value.

Utility value for the 'failure – new chronic GVHD systemic therapy' health state

3.12 In response to consultation, the company did a quality-of-life study and estimated a new utility value for the 'failure – new chronic GVHD systemic therapy' health state. The study included adults diagnosed with chronic GVHD who had at least 2 previous lines of systemic treatment and had ongoing symptoms. This used an EQ-5D-5L questionnaire and responses were mapped to the EQ-5D-3L (17 patients and 8 carers). The company estimated a new utility value for the health state (based only on patient responses) and used this in their revised base case. The company considers the actual figure to be confidential, so it cannot be reported here. The utility value based on both patient and carer

responses was also estimated and explored in a scenario analysis. The EAG preferred to use a midpoint and calculated a revised value based on the utility value from Crespo et al. (2012) and the company's quality-of-life study using data from patients and carers. The committee considered the company's new utility value and the Crespo et al. (2012) utility value (performed by the EAG). It noted that the company's revised utility value may be an underestimation, and the Crespo et al. (2012) utility value may be an overestimation. The committee concluded that it did not have sufficient evidence to have confidence in any one value. In the absence of further data, it considered that the value for the 'failure – new chronic GVHD systemic therapy' health state could be between the 2 values. The committee acknowledged that, overall, this had little impact on the cost-effectiveness estimates.

Disease management costs for the 'failure – new chronic GVHD systemic therapy' health state

3.13 In the company base case, disease management state costs were derived from Hospital Episode Statistics (HES) data. The EAG acknowledged that disease management costs were a primary driver of cost effectiveness in the model, but considered the company's HES study to be thorough, with data reflecting the UK population. The committee noted the company's assumptions for the disease management costs that were differentiated by health state in the model:

- People in the 'failure-free' health state with complete response were assumed to incur the mean cost of HSCTs in people without chronic GVHD in the HES study throughout the time horizon of the model.
- People in the 'failure-free' health state with partial response and lack of response were assumed to incur the mean cost of all HSCTs in people with chronic GVHD in the HES study in the first year. There was then a linear decrease each year to reach the disease management cost of people with complete response in the fifth year. The model assumed that people remaining in the 'failure free' health states incurred the same costs regardless of response status after the fifth year.
- People in the 'failure with a new systemic therapy' health state were assumed to incur the mean cost of HSCT in people with 2 or more records of high-cost

therapy in the HES study.

- For the 'failure with recurrent malignancy' health state, costs were not available from the HES study and so were sourced from NICE's technology appraisal guidance on gilteritinib for treating relapsed or refractory acute myeloid leukaemia.

  The EAG's clinical experts were satisfied with the company's assumptions used to estimate costs from the HES data. The committee acknowledged the challenges of estimating costs using HES data. It noted concerns with the estimates that had been used to inform disease management costs:

- The committee felt that the company's assumption of a constant disease management cost for the 'failure – new chronic GVHD systemic therapy' health state was pessimistic.

- The estimate of the year 1 costs for the 'failure free – partial and lack of response' health state used the mean costs of everyone with chronic GVHD, but the 'failure – new systemic therapy' health state used 2 or more high-cost therapies. The committee noted there was some uncertainty about what treatments people would have had as third-line therapy.

- It was unclear whether the health state costs (for all other health states but recurrent malignancy) excluded the possible costs from recurrent malignancy. The committee noted that if the costs were not excluded, this may introduce bias. In response to consultation, the company provided a scenario removing the proportion of recurrent malignancy disease management costs from disease management costs for the 'failure – new systemic chronic GVHD therapy' health state. The EAG noted that the company's scenario may be reasonable approach to explore the impact of reduction in disease management costs for the 'failure-new systemic therapy health state'. The committee agreed that it was satisfied with the company's scenario.

  The committee also noted the large differences in the annual costs between the 'failure – new chronic GVHD systemic therapy' health state and the 'failure-free with partial response and lack of response' health state. It noted that these had a substantial impact on the incremental cost-effectiveness

ratios (ICERs), and that this was mainly driven by the cost of inpatient stays. The committee asked the EAG to run a scenario in which the disease management cost for the 'failure – new chronic GVHD systemic therapy' health state had a linear decline over 5 years to equal the year 5 'failure-free with partial and lack of response' health state disease management costs. The EAG considered that this scenario may not be clinically plausible and would potentially be biased in favour of best available therapy. The EAG noted that it was clinically plausible that costs could increase because of people starting a new therapy. The committee was aware of the challenges in identifying healthcare resource use from HES data. But it would have liked to see further justification for the company's choice of data, and further justification of the process used to derive the costs for the 'failure – new chronic GVHD systemic therapy' health state, so that they could be further scrutinised. At the first committee meeting, the committee concluded that alternative scenario analyses in which the proportion of people in the 'failure – new chronic GVHD systemic therapy' health state linearly reduced to baseline (that is, the same costs as the 'failure free – partial response or lack of response' health state) would be useful for its decision making.

Company's disease management costs assumption for the 'failure – new chronic GVHD systemic therapy' health state

3.14 In response to consultation, the company supplied scenarios exploring a linear reduction in disease management costs for people in the 'failure – new chronic GVHD systemic therapy' health state over 5 years to the year 5 disease management costs for people in the failure-free (partial response, and lack of response) health states (see section 3.13). The company's scenarios also explored different proportions of people incurring reduced costs. The committee welcomed the scenarios exploring the disease management costs. It would have liked to have seen more detail, for example, splitting the disease management costs by line. The company stated that there is a lack of real-world data to estimate long-term costs for people whose treatment failure is related to a change in systemic treatment for their chronic GVHD. The company also did a survey with 15 clinicians specialising in this disease area. The company stated that, based on the survey, it was clinically implausible that disease management

costs would reduce over time in the 'failure-new systemic therapy' health state, but instead it is likely costs would increase. The committee noted that there was evidence from Schain et al. (2012) suggesting that costs could go down over time rather than remaining high, as was the case in the company's base-case analysis. The company explained that the study by Schain et al. (2012) included a broader range of people not just those at later treatment lines. This study highlighted that people with moderate to severe chronic GVHD spend more time in healthcare, consuming more healthcare resources compared with those with mild chronic GVHD. The committee acknowledged that the study by Schain et al. (2012) could be an informative source, but also noted the views of the clinicians. It concluded that most of the ICERs produced in the scenario analyses showed that belumosudil was dominant (that is, less expensive and more effective than the comparator).

Company's assumption that people in the 'failure – new systemic therapy' health state used 2 or more high-cost therapies

3.15 At the first meeting, the committee noted there was some uncertainty about what treatments people would have had as third-line therapy. In response to consultation, the company explained that treatments considered as high-cost therapy in its analysis informed by HES data included extracorporeal photopheresis, rituximab and ruxolitinib and imatinib. The company noted that it was not possible to identify the use of other, low-cost therapies such as mycophenolate mofetil, sirolimus, and calcineurin inhibitors within the HES database. The company noted that disease management costs for the 'failure – new chronic GVHD systemic therapy' health state represent a population who would have likely had one of these treatments as their third-line therapy. The company also highlighted that it had been conservative in its assumption using the mean chronic GVHD costs in the failure-free health states. This is because it considers people at later treatment lines who therefore accumulate higher costs. The company emphasised that it had used the best available source of data. The EAG commented that the company's approach in assuming 2 or more high-cost treatments for the 'failure – new systemic chronic GVHD therapy' could be considered reasonable and could be a good way of categorising the patients. The committee concluded that this could be an outstanding uncertainty that was not resolvable with the evidence presented to it.

Removal of overall survival benefit for belumosudil

3.16 Overall survival data from the pooled ROCKstar and KD025-208 trials (for belumosudil) and from the best available therapy arm from REACH-3 was immature, with neither dataset reaching the median. In its submission, the company highlighted there was no direct data that showed a relative overall survival benefit for belumosudil compared with best available therapy. The EAG highlighted that, combined with the issue of the naive treatment comparison (see section 3.8), there was substantial uncertainty in the estimated overall survival benefit associated with belumosudil. The EAG also noted that the uncertainty in overall survival because of immature data was increased because people in the best available therapy arm in REACH-3 crossed over to ruxolitinib at 24 weeks (see section 3.6). The EAG preferred to remove the overall survival benefit from the model for belumosudil and noted that doing so excluded another source of unresolvable uncertainty in the model. The company felt that this was reasonable given these circumstances. The EAG explored the impact of including an overall survival benefit in its base case; doing so had a large impact on the ICER, and removing it reduced the company's ICER (post-clarification) so that belumosudil became dominant (that is, it was more effective and cost less). The committee noted that removing the overall survival benefit reduced the time spent in the failure states in the belumosudil arm, substantially reducing costs but minimally reducing the QALYs. In response to consultation, the company provided a model that removed overall survival. The committee concluded that removing overall survival benefit was acceptable in the absence of more evidence.

Removal of response outcomes from model

3.17 The company's model considered response outcomes for people in the failure-free state by assigning different utility according to level of response achieved. The company noted there was uncertainty about the comparability of response outcomes across trials, because the primary endpoint of ROCKstar was best response at any post-baseline assessment, whereas response in REACH-3 was assessed at week 24. The EAG noted that including response in the model potentially added unnecessary complexity. In its submission, the company provided a scenario in which response was removed from the model (people in the failure-free state were not distributed across their response levels). This had

a small impact on the ICER. The EAG felt that the company's scenario was more appropriate. The EAG's clinical experts noted that in clinical practice, failure-free survival is a more clinically relevant outcome. The company agreed with the EAG and its clinical experts. The committee agreed at the first meeting that the EAG's preference for removing response outcomes was appropriate. In response to consultation, the company agreed with the committee's and EAG's preference to remove response outcomes and updated the model. The committee concluded that the updated model was suitable for decision making.

Severity

Data used in the company's QALY shortfall analysis

3.18 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates. To calculate the absolute and proportional QALY shortfall, the company used the base-case total QALYs estimated for the best available therapy arm. The company considers the results of its QALY shortfall analysis to be confidential, so they cannot be reported here. Based on the QALY shortfall analysis, the company estimated that a severity modifier of 1.2 should be applied. The EAG noted that the severity modifier of 1.2 would not apply to the EAG's preferred cost-effectiveness results, because the absolute QALY shortfall was less than 12 and the proportional QALY shortfall was less than 0.85. The committee acknowledged that the condition has a significant impact on quality of life. But it noted it did not have sufficient evidence for the most appropriate source to inform the utility value for the 'failure – new chronic GVHD systemic therapy' health state (see section 3.12). It agreed with the EAG that no severity modifier should apply.

Cost-effectiveness estimates

3.19 Because of the confidential patient access scheme for belumosudil and

confidential comparator discounts, the exact ICERs are confidential and cannot be reported here. In the company's revised base-case ICERs, belumosudil was dominant compared with best available therapy. Additional scenario analyses provided by the company after consultation included:

- extrapolating data from the best available therapy arm of REACH-3 by truncating failure-free Kaplan–Meier survival data at week 24 and extrapolating beyond that point, see section 3.10)
- scenario analyses in which the proportions of people in the 'failure – new chronic GVHD systemic therapy' health state linearly reduce to baseline (for example, 25%, 50% and 75%; see section 3.14).

The committee considered that there was substantial uncertainty associated with the cost-effectiveness estimates for the ICERs produced in the scenario analyses. But it noted that most of the ICERs produced showed that belumosudil was dominant (that is, less expensive and more effective than the comparator). The committee acknowledged that there is some risk that belumosudil is not cost effective in some circumstances, because of uncertainties around the disease management costs (see section 3.14). But overall, based on the evidence it was presented, it concluded that belumosudil was likely a cost-effective use of NHS resources.

Other factors

Equality

3.20 The committee noted that people who have mismatched unrelated donor transplants, and people from minority ethnic backgrounds (who are less likely to find a related donor match), are at a higher risk of developing chronic GVHD. It acknowledged the potential for errors and delays in the diagnosis of skin manifestations (which are a major complication of chronic GVHD) in people with non-white skin, and that current physician-and patient-reported outcome measures may not adequately capture subtle changes. It noted that geographical access to extracorporeal photopheresis services and specialist blood and marrow transplant clinics can be a barrier for people in lower socioeconomic groups who

may be unable to take time off work or afford to travel to appointments. The committee noted these concerns but concluded that they could not be addressed in its recommendations.

Innovation

3.21 The company considered belumosudil to be innovative; it was licensed under the Project Orbis programme and granted an innovation passport by the Medicines and Healthcare products Regulatory Agency (MHRA) in April 2021. The company felt that there were benefits associated with belumosudil that were not captured by the QALY calculation. The company highlighted that some important aspects of extracorporeal photopheresis administration were not included in the QALY calculation, including:

- the disruption and anxiety associated with public or hospital transport for people and their carers attending regular outpatient appointments
- lost workdays for carers attending extracorporeal photopheresis appointments
- the disutility associated with inserting and removing central lines where peripheral venous access was not possible and
- the need for blood transfusions and anticoagulation therapy.

The company noted that these aspects would be avoided by using an oral treatment such as belumosudil. The committee considered if belumosudil was innovative. It did not identify additional benefits of belumosudil not captured in the economic modelling. So, the committee concluded that all additional benefits of belumosudil had already been taken into account.

Conclusion

Belumosudil is recommended

3.22 The committee considered that there was substantial uncertainty in the cost-effectiveness estimates, but that the most likely estimates were within the range NICE usually considers a cost-effective use of NHS resources. So, belumosudil is recommended for treating chronic GVHD after 2 or more lines of systemic treatment.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic graft-versus-host disease and the doctor responsible for their care thinks that belumosudil is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen Smith
Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical and a project manager.

Janet Boadu
Technical lead

Christian Griffiths
Technical adviser

Kate Moore
Project manager

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