NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using belumosudil in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: September 2023

Note that this document is not NICE's final guidance on belumosudil. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using belumosudil in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 25 October 2023
- Second evaluation committee meeting: TBC
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Belumosudil is not recommended, within its marketing authorisation, for treating chronic graft-versus-host disease in people 12 years and over after 2 or more systemic treatments.

1.2 This recommendation is not intended to affect treatment with belumosudil that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by the clinician, the child or young person, and their parents or carers.

Why the committee made these recommendations

Usual treatment for chronic graft-versus-host disease after 2 or more systemic treatments can include extracorporeal photopheresis, imatinib, mycophenolate mofetil, pentostatin, pulsed corticosteroids and sirolimus. In this evaluation, this is called 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. But the results are uncertain.

There are uncertainties in the economic model because of the assumptions it included. Because of the uncertainties in the economic model and clinical evidence, the cost-effectiveness results are not sufficiently robust. Further analyses are needed to address this uncertainty. So, belumosudil is not 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 January 2023).

2.4 The company has a commercial arrangement, which would have applied if the belumosudil had been recommended.

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, as well as the difficulties in managing a social life. They emphasised that chronic GVHD had 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 issued a clinical commissioning policy in 2017: Treatments for Graft versus Host Disease following Haematopoietic Stem Cell Transplantation. This policy 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. The company's submission highlighted that belumosudil is intended to be used as a monotherapy (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 developed 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 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 comparing belumosudil 200 mg once daily with belumosudil 200 mg twice daily in allogeneic HSCT recipients aged 12 years and over with persistent chronic GVHD after 2 to 5 prior systemic lines of treatment. ROCKstar recruited 152 people in 28 centres across the USA. KD025-208 was a phase 2a, open-label, dose-escalation, multicentre study comparing 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 USA. The people recruited were allogeneic HSCT recipients aged 18 years and over with persistent chronic GVHD who had received 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 prior 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 prior 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) in allogeneic HSCT recipients aged 12 years and over with moderate or severe glucocorticoid-refractory chronic GVHD. It was conducted across 149 centres in 28 countries, including the USA 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 prior 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 USA, so it was likely that additional alternative therapies received 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 USA. 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 trial 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 have a large impact on the clinical outcomes measured in the trial for the best available therapy treatment arm.

Patient population

3.7 The population defined in the NICE scope, in line with the belumosudil marketing authorisation, included people aged 12 and over (see section 2.1). In the ROCKstar and KD025-208 trials, however, no one between the ages 12 and 18 years old 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, noting 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 adolescents as 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 in adults. The clinical experts agreed that it was plausible for there to be no difference in efficacy in adolescents and adults. The committee concluded that although there was a lack of data for

belumosudil in adolescents, the efficacy of belumosudil was likely to be similar in adolescents 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 conducted in a heavily pre-treated (at least 2 prior systemic therapies) population. The company therefore 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 prior 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. In the absence of a control arm and published data from which an adjusted indirect treatment comparison could be made, the company used data from the phase 3 REACH-3 trial of ruxolitinib compared with investigator's choice after 1 prior line of therapy (see section 3.5) to allow a naive direct comparison with currently available treatments. 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 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 were no other appropriate natural history data or observational studies other than the REACH-3 trial. The company had sought advice from clinical experts, and noted that there was another

confidential study it had carried out, but because of methodological reasons. 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, as 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 provided that 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. The committee highlighted that the failure-free survival curve in the company model had been extrapolated without any adjustment for that crossover. The committee noted would have liked to see a scenario in which the failure-free survival Kaplan–Meier data for best available therapy arm of the REACH-3 trial was truncated at week 24 and extrapolated to exclude any possible impact from the crossover. The EAG thought that truncating the Kaplan–Meier curve at 24 weeks would likely overestimate the treatment effect of best available therapy. The EAG noted that the base-case estimation of failure-free survival may not reflect an 'unbiased' failure-free survival curve, but felt that it was likely less biased than the scenario suggested by the committee. The clinical experts explained that failure-free survival is not a clinically useful measure because you cannot necessarily use it in clinical practice. The committee noted that the substantial artificial drop in failure-free survival at 24 weeks was likely caused by crossover being allowed from this point. One of the clinical

experts agreed that the failure-free survival curve appeared unnatural, and it would not be expected to see such a large change at a point in time. The company noted that the assumptions were based on clinical opinion and emphasised that the failure-free survival curves that were extrapolated also aligned with the EAG's assumptions. The committee noted the problems with the impact of crossover in the best available therapy arm of the REACH-3 trial. It concluded that a scenario analysis in which the failure-free survival Kaplan–Meier data for the best available therapy arm of REACH-3 is truncated at week 24 and extrapolated would be useful for its decision making. It would like to see joint fit compared with independent fit within REACH-3, and the absolute and incremental mean survival for alternative models applied to belumosudil and best available therapy, in line with the approach in NICE Decision Support Unit technical support document 14. This would improve understanding of the range of plausible extrapolations.

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 lacked face validity. The company therefore estimated a utility value for the failure health state from published data. It did literature searches in related disease areas (indications for the most recent transplants in ROCKstar) and identified utility data for acute myelogenous leukaemia, acute lymphoblastic leukaemia, chronic myelogenous leukaemia and chronic lymphocytic leukaemia. 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 of the most 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 committee acknowledged how the 'failure – recurrent malignancy' health state was derived in the company's model, but noted the EAG's concerns about the utility value for the 'failure – new chronic GVHD systemic therapy' health state (see section 3.12).

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

3.12 The EAG considered the utility value for 'failure – new chronic GVHD systemic therapy' health state to be 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 was concerned that the utility value for 'failure - new chronic GVHD systemic therapy' was too low. At the clarification stage, the company provided utility data for new chronic GVHD systemic therapy and recurrent malignancy (using the September 2022 data cut of the ROCKstar study). The resulting utility value was based on 69 observations from 22 patients, and was similar to the utility value for the failure-free health state (the company considers the actual figure to be confidential, so it cannot be reported here). The company stated that the analysis demonstrated that the utility value for 'failure – new chronic GVHD systemic therapy' lacked face validity. The EAG considered that there was a high degree of uncertainty around the utility value derived from ROCKstar because of the limited number of observations. The EAG preferred to use an estimated midpoint value based on a Crespo et al. (2012) and an Adelphi disease-specific programme study done by the company. The committee highlighted that in the company's analysis of the ROCKstar study, the impact of treatment failure on utility was small and not statistically significant. The committee asked the EAG to run a scenario that assumed the utility value for 'failure – new chronic GVHD systemic therapy' was equal to the utility value for

'failure free - lack of response'. The clinical experts noted that the utility associated with a lack of response and starting a new treatment should be similar. The committee recalled the uncertainty in the utility value for 'failure – new chronic GVHD systemic therapy'. It concluded that scenario analyses using the midpoint value preferred by the EAG, and using the Crespo et al. (2012) utility value, would be useful for its decision making.

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 all patients 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 patients 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.

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 would 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. 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.

Removal of overall survival benefit for belumosudil

3.14 Overall survival data from the pooled ROCKstar and KD025-208 trials (for belumosudil) and from the best available therapy arm from REACH-3 were immature, with neither dataset reaching the median. In its submission, the company highlighted there was no direct data that demonstrated 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, 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. The committee concluded that the EAG's preference for removing overall survival was acceptable in the absence of more evidence.

Removal of response outcomes from model

3.15 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 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 concluded that the EAG's preference for removing response outcomes was appropriate.

Severity

Data used in the company's QALY shortfall analysis

3.16 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 in the absence of further exploration of 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

3.17 Because of the confidential patient access scheme for belumosudil and confidential comparator discounts, the exact ICERs are confidential and cannot be reported here. The company's base-case ICERs were less than £20,000 per QALY gained for belumosudil (all doses) compared with best available therapy. But the committee recalled substantial uncertainty in the clinical evidence and the economic model. It concluded that the following changes to the model and additional analyses could help resolve its concerns:

- excluding overall survival benefit in the model (see section 3.14)
- removing response outcomes from the model (see section 3.15)
- scenario analyses around the utility value for the 'failure – new chronic GVHD systemic therapy' health state; using the midpoint value preferred by the EAG, and using the Crespo et al. (2012) utility value for GVHD progression to explore quality of life in this health state (see section 3.12)

- further justification for the company's choice of categories of people in the HES data, and the description of the process used to derive the costs for the 'failure – new chronic GVHD systemic therapy' health state (see section 3.13)
- 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 3.13)
- 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, following the NICE Decision Support Unit technical support document 14 approach see section 3.10)

Other factors

Equality

3.18 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 were not sufficient to affect its recommendations.

Innovation

3.19 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. It 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 not recommended

3.20 The committee's concerns about the clinical evidence and cost-effectiveness model meant that it was not confident that the results were robust enough for decision making. The committee agreed that further analyses were needed to address this uncertainty. So, belumosudil is not recommended for treating chronic GVHD after 2 or more lines of systemic treatment.

4 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

ISBN: [to be added at publication]