Single Technology Appraisal

Belumosudil for treating chronic graft versus host disease after 2 or more lines of systemic therapy [ID4021]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Belumosudil for treating chronic graft versus host disease after 2 or more lines of systemic therapy [ID4021]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Sanofi**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Anthony Nolan
   b. NHS England Clinical Reference Group
   c. Therakos

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

5. **PMB clarifications for the second appraisal committee meeting**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

National Institute for Health and Care Excellence,
2 Redman Place
London
E20 1JQ

25th October 2023

Re: Belumosudil for treating chronic graft versus host disease after 2 or more lines of systemic therapy [ID4021]

Dear Dr Smith,

Thank you for the opportunity to comment on the draft guidance for belumosudil in the chronic graft-versus-host disease (cGVHD) indication.

The draft guidance highlighted that the Committee has several concerns, and we would like to address these here. To do this, we focus on the following key themes in our response.

- Failure-free survival (FFS) for the best available therapy (BAT) arm.
- Disease-management costs in failure health state.
- Utility values in failure health state.

We have carried out the following activities to respond to these points:

- Truncated the FFS Kaplan-Meier survival curve of the BAT arm in the REACH-3 study at 24 weeks and provided updated parametric curve extrapolations to address the Committee's concerns around the impact of treatment crossover in the study design.
- Conducted interviews with 15 clinicians to test the clinical plausibility of key assumptions in the model.
- Provided EQ-5D-3L data from patients with cGVHD who have experienced failure of at least two prior lines of systemic therapy.
- Updated the economic model to apply model corrections and to enable analyses requested by the Committee.
- Revised the Company base case to incorporate updated assumptions which are more closely aligned to the EAG preferred base case, using the updated model.

We look forward to further discussion at the committee meeting on the 16th November.

Best regards

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1. Executive summary

Revised company base case and model

- We present an update to the company base case which is aligned to the EAG and Committee preferred-base case, except for three parameters: Utility for *failure-new systemic therapy* health state is sourced from UK patient EQ-5D data; subsequent treatment costs and caregiver disutility are applied as in the original base case.
- The probabilistic and deterministic ICERs in the base case are now dominant, which aligns with the EAG preferred base case.
- The model structure has been updated to enable implementation of the Committee's requested scenarios.

Failure-free survival for the BAT arm

- We extrapolated the FFS data from the REACH-3 BAT arm after truncating the KM curve at 24 weeks, at the request of the Committee.
- Applying the best-fitting and most clinically plausible curves to the truncated data resulted in a small increase to mean FFS for BAT, but the resulting ICERs remained dominant when applied in the model.
- However, we consider this analysis to be inherently biased, and less clinically plausible than using the original fitted curves, for the same reasons outlined in the EAG report.

Disease management costs in failure health state

- Patients with recurrent malignancies are unlikely to be captured in the HES study source used to inform disease management costs in this health state. However, we conducted a scenario analysis whereby equivalent costs of recurrent malignancy are removed, and this had minimal impact on the ICER.
- We conducted interviews with 15 clinical experts, all of whom agreed that disease management costs would **increase**, not decrease, over time for patients in this health state, meaning that the requested Committee scenarios are clinically implausible.
- Despite this, we adapted the model to explore these scenarios, and found that all ICERs were below the £20k threshold using the company model.

Utility values in *failure-new systemic therapy* health state

- All 15 of the clinical experts we interviewed confirmed the substantial negative quality of life impact of progressing to failure after three prior lines of therapy.
- We conducted a quality of life study to collect EQ5D data from UK patients with cGVHD after failure of two or more therapies. The resulting utility values reflect the feedback from clinical experts and have been applied to the company revised base case.
- When applying these values to the QALY shortfall analysis in the Company base case, the severity weighting of x1.2 is still achieved.

2. Sanofi revised base case and model

Following discussion with the EAG, the recommendations from the Committee (which have resulted in minor structural changes to the model, See Appendix B), as well as newly available quality of life data from an ongoing patient group survey, we have revised the Company base case. The model inputs are now more closely aligned to those of the preferred EAG base case. The key inputs with an influence on the ICER are summarised in Table 1.

Table 1. Summary of changes to Company revised base case versus EAG preferred base case

Setting/input	EAG preferred base case	Company base case (post-clarification)	Rationale/comments
Overall survival	No survival benefit for belumosudil vs BAT	No survival benefit for belumosudil vs BAT	Aligned with the EAG and committee preferred position
Utility for *failure-new systemic therapy* health state	Midpoint value: [redacted]	[redacted] (SE=[redacted])	Updated with new data from UK cGVHD patients (see Section 5)
Approach to costing of subsequent treatment	Apply costs for maximum 5 years duration (4 weeks for rituximab) for 60% of patients	Apply costs such that 100% of patients spend 60% of their remaining lifetime on subsequent treatment.	Company original position maintained
Caregiver disutility for failure	Same caregiver disutility (-0.045) applied to both *failure-free* and *failure-new systemic therapy* health states	Caregiver disutility increases from -0.045 in *failure-free* health state to -0.142 in *failure-new systemic therapy* health state	Company original position maintained
Response outcomes in model	Removed from analysis	Removed from analysis	Aligned with EAG and Committee preferred position
Concomitant medication costs	Included for belumosudil only	Included for belumosudil only	Aligned with EAG and Committee preferred position
Costs of background therapies	Removed	Removed	Aligned with EAG and Committee preferred position
Time to discontinuation	KM TTD data used for belumosudil, exponential distribution used for BAT	KM TTD data used for belumosudil, exponential distribution used for BAT	Aligned with EAG and Committee preferred position
Accommodation costs for patients on ECP	Removed	Removed	Aligned with EAG and Committee preferred position
Disutility and duration for central line-related infection	Based on disutility for infections and infestations from TA689	Based on disutility for infections and infestations from TA689	Aligned with EAG and Committee preferred position
IV disutility for BAT	Removed	Removed	Aligned with EAG and Committee preferred position

BAT, best available therapy; ECP, extracorporeal photopheresis; IV, intravenous; KM, Kaplan-Meier; SE, standard error; TTD, time to treatment discontinuation.

We acknowledge the clinical rationale for most of the EAG preferred assumptions in the model, including the removal of OS benefit, the addition of concomitant therapy costs, and the removal of response outcomes (Table 1). However, as described in our response to technical engagement, we do not consider the EAG's preferred approach to costing of subsequent treatment to be clinically plausible. We also consider it important to reflect the substantial additional caregiver burden associated with the failure of third line or later cGVHD therapies. We have therefore maintained these assumptions in the revised Company base case, although the absolute impact on the ICER is minimal.

We have also listened to the EAG and Committee's concerns that the utility of patients in the *failure-new systemic therapy* health state was too low in the originally submitted company model. Since the Committee meeting, we have received interim results from a market research survey on quality of life of people with cGVHD disease for which Anthony Nolan provided consultancy and communications support to assist recruitment of UK patients with cGVHD for whom at least two prior therapies had failed. Whilst the analysis is in a relatively small sample, given the paucity of data available in the literature or from our studies, these data are likely to represent the best available evidence for decision-making and are described further in Section 5. Notably, use of this real-world evidence in the model to characterise outcomes for patients treated with BAT lends further weight to our argument that cGVHD at third line or later should qualify for the severity modifier at 1.2 weighting. The analysis of shortfall using the updated utility value of [redacted] (vs the EAG assumption of [redacted]) for the *failure-new systemic therapy* state, is provided in Table 2 below.

Table 2. Summary features of the QALY shortfall analysis

Factor	Value	Reference
Sex distribution	58.0% male	Pooled ROCKstar and Phase 2a
Starting age	53.9 years	Pooled ROCKstar and Phase 2a
QALYs of population without the disease	[redacted]	Calculated by summing the product of the probability of being alive by age in the general population at each cycle of the model using the UK life tables(130) with the half-cycle corrected general population utilities over the model time horizon, adjusted for the model's four-week cycle length
QALYs with BAT	[redacted]	Estimated from the model
Absolute QALY shortfall	[redacted]	Calculated
Proportional QALY shortfall	[redacted]	Calculated
QALY weight based on absolute QALY shortfall	1.2	NICE health technology evaluations: the manual (PMG36)(120)
QALY weight based on proportional QALY shortfall	1.2	NICE health technology evaluations: the manual (PMG36)(120)

BAT = best available therapy; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life year

Based on the QALY shortfall analysis, cGVHD at third line or later meets the severity modifier criteria with a QALY weight of 1.2. This is in line with the significant impact on patients' quality of life described by patients and clinicians.

The cost-effectiveness estimates for both probabilistic and deterministic analyses using the revised Company base case assumptions are presented in Table 3. Full details including the cost-effectiveness acceptability curve (CEAC) and disaggregated results are provided in Appendix A. Further details about the structural changes to the model, which have been applied on request from the Committee to change the modelling of disease management costs, are provided in Section 4.3 and Appendix B.

Table 3. Change in probabilistic and deterministic ICERs from original to revised draft guidance base case

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Probabilistic analysis			
Company base case (post-clarification) WITHOUT severity modifier	[redacted]	[redacted]	3,046
Company base case (post-clarification) WITH severity modifier*	[redacted]	[redacted]	2,539
EAG preferred base case (post-TE)	[redacted]	[redacted]	Dominant
Revised Company base case (draft guidance response) WITHOUT severity modifier	[redacted]	[redacted]	Dominant
Revised Company base case (draft guidance response) WITH severity modifier*	[redacted]	[redacted]	Dominant
Deterministic analysis			
Company base case (post-clarification) WITHOUT severity modifier	[redacted]	[redacted]	3,571
Company base case (post-clarification) WITH severity modifier*	[redacted]	[redacted]	2,976
EAG preferred base case (post-TE)	[redacted]	[redacted]	Dominant
Revised Company base case (draft guidance response) WITHOUT severity modifier	[redacted]	[redacted]	Dominant
Revised Company base case (draft guidance response) WITH severity modifier*	[redacted]	[redacted]	Dominant

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TE, technical engagement.
*The 1.2x severity weighting was applied to both the Company base case and revised Company base case based on QALY shortfall analysis using Company-preferred utilities for the *failure-new systemic therapy* health state.

3. Failure-free survival for the comparator (BAT) arm

The Committee were concerned that the crossover design of the REACH-3 study (whereby patients in the BAT arm could receive ruxolitinib from week 24 subject to response criteria), could have an impact on the clinical outcomes measured in the trial. They considered that the open-label nature of REACH-3 could have led to investigator bias, thus biasing the FFS results used as the comparator arm in the belumosudil economic model. To explore this concern the Committee lead team requested that the EAG comment on truncating the REACH-3 BAT FFS data at 24 weeks. This request was issued very close to the committee meeting and the company was not given the opportunity to perform the analysis or comment ahead of the meeting.

The EAG suggested that truncating the REACH-3 BAT FFS curve at 24 weeks and extrapolating this for use in the economic model has the potential to increase, rather than decrease, the level of bias for the following reasons:

- It is plausible that BAT patients in REACH-3 who were failing prior to the 24-week cut-off did not initiate new treatment and were "switched late" so that they could receive ruxolitinib, while other failing patients could have been "switched early" when ruxolitinib became available. If so, truncating the Kaplan-Meier (KM) curve at 24 weeks would give a clinically implausible overestimation of the treatment effect for BAT.
- The EAG's clinical experts considered that the mean FFS for BAT patients was likely to be around one year, [redacted].
    - This is consistent with the views of the clinical experts who advised Sanofi, although some felt that the FFS curves modelled for REACH-3 BAT would overestimate the time to failure due to treatment switch for patients in belumosudil's licensed indication after two or more prior lines of therapy. In patients at this stage of the treatment pathway, FFS of one year represents a likely maximum, with a mean FFS as low as 3-4 months being more realistic.

We agree with the EAG that this analysis may be inherently biased, but for the purposes of this response we have extrapolated the FFS data from the REACH-3 BAT arm after truncating the KM curve at 24 weeks (the point at which patients were permitted to cross over to ruxolitinib in the REACH-3 trial).

The original BAT FFS extrapolation used a generalised gamma curve in the base case, which was jointly fitted using both arms of the REACH-3 study. The generalised gamma

distribution was selected due to a combination of goodness-of-fit statistics (Akaike information criteria [AIC], Bayesian information criteria [BIC]) and clinical plausibility (including a mean predicted FFS of about 1 year [1.05 years, Table 4]). The gamma distribution actually provided the best AIC/BIC but generalised gamma was retained for the base case as the gamma and generalised gamma curves for BAT were nearly identical (Figure 1) and as generalised gamma was also the distribution used to model FFS for belumosudil. However, after truncating the KM curve for BAT, the fitted generalised gamma curve dropped faster and provided a lower mean predicted FFS (0.85 years). The gamma distribution again provided the best goodness-of-fit statistics and was selected for the base case, although the mean FFS with that curve (1.44 years) was higher than that which would be expected in clinical practice according to the EAG's clinical experts (Table 4). We therefore consider this to be a conservative choice.

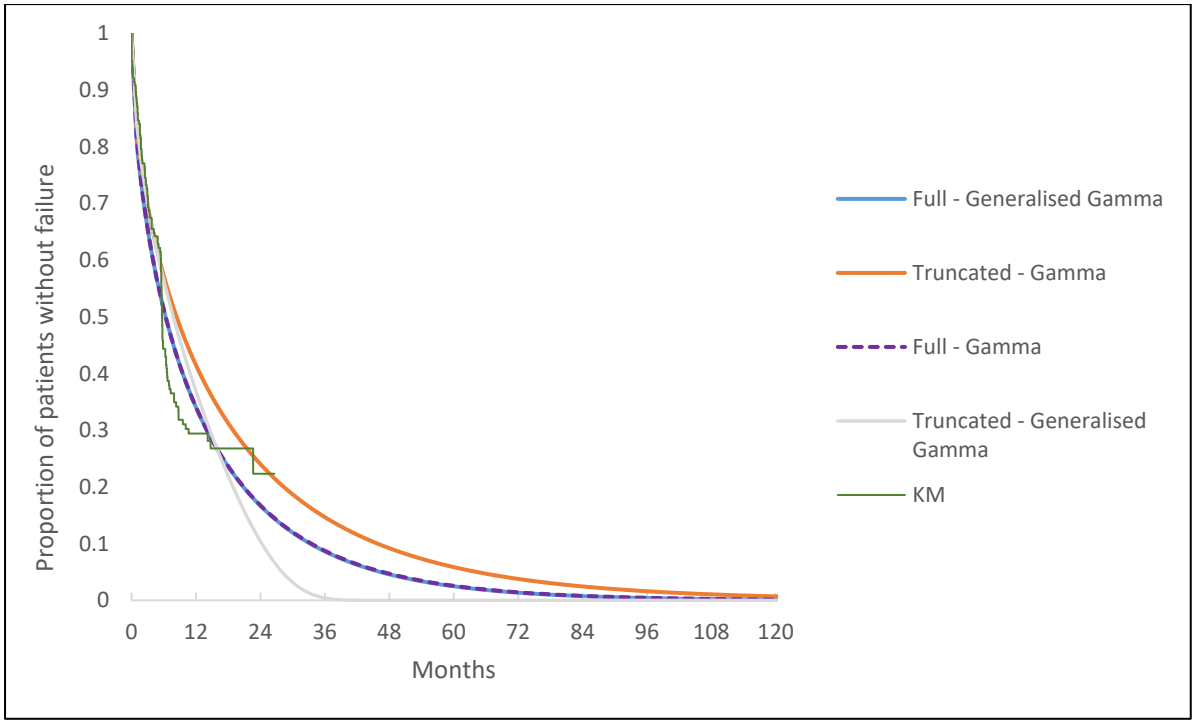
Table 4. BAT FFS: Goodness-of-fit statistics and mean FFS for the fitted distributions

Distribution	REACH-3 full (joint fit)			REACH-3 24-week truncation (joint fit)		
	AIC	BIC	Mean FFS	AIC	BIC	Mean FFS
Exponential	419.9	427.5	0.85 (0.7, 1.02)	224.0	231.6	0.82 (0.64, 1.04)
Weibull	368.6	380.0	1.28 (0.93, 1.91)	187.2	198.6	2.18 (1.16, 4.58)
Gompertz	383.2	394.6	NE	217.5	228.8	NE
Log-logistic	379.2	390.6	NE	192.2	203.6	NE
Log-normal	411.5	422.9	24.69 (9.47, 77.11)	207.1	218.5	401.6 (62.35, 4245.13)
Gamma	366.1	377.5	1.06 (0.8, 1.42)	184.4	195.8	1.44 (0.92, 2.23)
Generalised gamma	368.1	383.3	1.05 (0.78, 1.6)	185.0	200.2	0.85 (0.73, 2.81)*

AIC = Akaike information criteria; BIC = Bayesian information criteria; NE = not estimated.
Cells highlighted in green indicate the parametric models with the two lowest information criteria for each treatment.
* Estimated as restricted mean survival time at 99th percentile of the fitted distribution. No estimate is reported if the fitted distribution does not reach 99th percentile.

Inspection of the best-fitting curves shows that the 24-week truncation did have an impact on the trajectory of the curves, with approximately 7% more patients without failure at 24 months when using the truncated data (with gamma distribution) (Figure 1). Whilst there was negligible difference between generalised gamma and gamma distributions when applied to the full data, for 24-week truncated data these curves diverged considerably, with more favourable FFS results for BAT using the latter distribution.

Figure 1. BAT FFS: Generalised Gamma and Gamma fitted curves based on full KM data versus Generalised Gamma and Gamma fitted curves based on KM data truncated at 24 Weeks



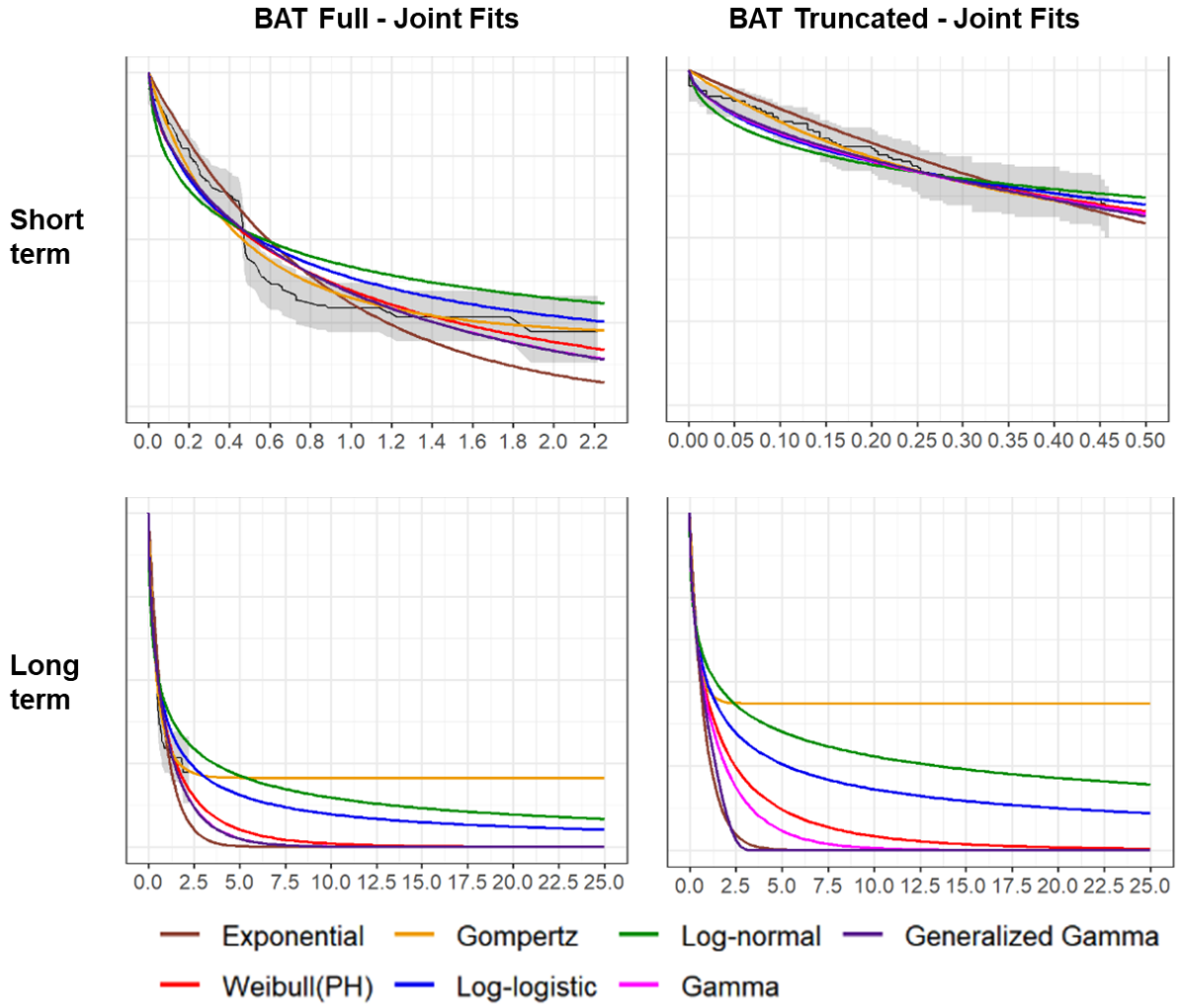
The impact of these updated curves on the ICERs was relatively minor with no change to the direction of the decision. When modelled using Company revised base case assumptions, and applying the best-fitting gamma distribution curve, dominance was maintained (Table 5). Sensitivity analyses show that three of the parametric distributions (Gamma, Generalised gamma, and Exponential) resulted in dominant ICERs, while the Weibull distribution had a higher ICER of £3,082 per QALY gained. Gompertz, Log-logistic, and Log-normal resulted in substantially higher ICERs which were above the cost-effectiveness threshold. However, based on visual inspection of the curves (Figure 2) and clinical expert assumptions around expected mean FFS, these parametric distributions are not clinically plausible.

Table 5. Model results for belumosudil versus BAT using 24-week truncated curve fits from REACH-3

Choice of curve fit for BAT (Joint)	Mean FFS for BAT	Mean LYs (undiscounted) in FF state in model for BAT†	Incremental LYs (undiscounted) in FF state in model (Belumosudil QD Generalised Gamma joint fit vs. …)†	Incremental LYs (discounted) in FF state in model (Belumosudil QD Generalised Gamma joint fit vs. …)†	ICER (discounted) (Belumosudil Generalised Gamma joint fit vs. …)**†
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	3,082
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	693,097
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

NE, not estimated.
* Estimated as restricted mean survival time at 99th percentile of the fitted distribution. No estimate is reported if the fitted distribution does not reach 99th percentile.
**Severity modifier not applied
† Values obtained whilst applying other constraints applicable in the model (i.e., FFS capped by OS, OS for belumosudil made equal to OS for BAT, OS capped by general population mortality).

Figure 2. FFS BAT parametric curve comparison (x-axis in years)



We do not consider the scenario using extrapolated FFS for BAT based on truncated data from REACH-3 to be the most suitable for decision-making since it adds an additional layer of uncertainty and potential bias to the comparator arm, while reducing the clinical plausibility. However, even when this is implemented in the model using most plausible curve fits, the resulting ICER for belumosudil is dominant.

4. Disease management costs in failure health state

The EAG's clinical experts and the clinical experts involved in our advisory boards were satisfied with the assumptions used to estimate costs from the HES data in our submission and considered them to be clinically plausible. However, following the publication of the EAG report, the Committee expressed three key areas of concern about the disease management costs applied to the '*failure-new systemic therapy'* health state in the model:

- Uncertainty about what treatments patients would have had as third-line therapy in the HES study cohort being used to derive costs applied in the model for this health state
- The potential for bias due to recurrent malignancy costs not being excluded from disease management costs for this health state
- The assumption of a constant disease management cost for the '*failure-new systemic therapy*' health state was considered "pessimistic" (compared to the linearly declining costs associated with the *failure-free* health state)

4.1 Justification for the source of disease management costs used in the company submission

HES cGVHD study overview:

We conducted a study using secondary care data from the HES database to estimate disease management costs for the submission model.(1) This study was described in the original company submission (Section B 1.3.1.5) and summarised below.

The HES database contains information on reimbursed diagnoses and procedures from all National Health Service (NHS) inpatient admissions, outpatient appointments and emergency care (EC) attendances in England.(1)

The HES study included data on patients aged ≥12 years with an alloHSCT between 1 April 2017 and 31 December 2020. HES diagnosis data are limited to four-character International Classification of Diseases 10th Revision (ICD-10) codes; however, cGVHD is not identified through a definitive code.(1)

For the purposes of the study to identify episodes of cGVHD, one of the following criteria had to apply:

- Marker of GVHD, defined using ICD-10 code D89.8, ≥100 days after alloHSCT, or

- Marker of GVHD, defined using ICD-10 code D89.8, <100 days after alloHSCT and a subsequent code for a feature of cGVHD, where the cGVHD feature must have occurred after the marker for GVHD, or
- Marker of GVHD, defined using ICD-10 code T86.0 (at any time following alloHSCT) and a subsequent code for a feature of cGVHD, where the cGVHD feature must have occurred after the marker for GVHD.

For comparison, patients with cGVHD were matched to patients who had received alloHSCT but had no evidence of GVHD following the procedure, based on age, gender, time from alloHSCT and type of malignancy.(1) In total, 3,650 episodes of alloHSCT were recorded in patients aged ≥12 years, 821 (22.5%) of which had evidence of cGVHD, 987 (27.0%) had evidence of GVHD but not cGVHD, and 1,842 (50.5%) had no evidence of GVHD. Matching criteria were applied, resulting in 721 episodes belonging to 721 unique patients with cGVHD and 718 unique patients without GVHD, three of whom were re-used as controls.(1)

Application of HES study costs in the model

In the absence of applicable, long-term disease-management cost data from the clinical trials or real-world clinical practice in the UK, disease management costs in the model were primarily estimated based on the results of the HES study. We also applied the assumption, based on clinical opinion gathered at an advisory board and through 1-to-1 interviews alongside a published real-world study, that disease management costs for patients in the *failure-free* health state with PR and LR (i.e. maintaining stable or improving disease) would decrease over time.(3)

Disease management costs were differentiated by health state in the model:

- **Patients in the *failure-free* health state with CR:** assumed to be the mean cost incurred by HSCT patients without GVHD in the HES study throughout the time horizon of the model. For the EAG's preferred scenario which excluded response from the model, this cost is not directly applied.
- **Patients in the *failure-free* health state with PR and LR:** assumed to be the mean cost incurred by all HSCT patients with cGVHD in the HES study in the first year, with a linear decrease in each year to reach the disease management cost of patients with CR in the fifth year. The model therefore assumes that all patients remaining failure-free incur the same costs regardless of response status after the fifth year. For the preferred EAG scenario which excludes response from the model, disease

management costs for all patients in the *failure-free* health state are assumed to be the same as those described above for partial and lack of response.

- **Patients in the failure state with a new systemic therapy**: assumed to incur the mean cost of HSCT patients with two or more records of high-cost therapy in the HES study. Treatments considered as high-cost therapy in the analysis included ECP, rituximab and protein tyrosine kinase inhibitors (i.e., ruxolitinib and imatinib), which were the only identifiable cGVHD therapies within the database. Therefore, disease management costs in the model represent a population who would have likely received one of these treatments as their third-line therapy. It was not possible to identify use of other, low-cost therapies (e.g., MMF, sirolimus, and CNIs) within the HES database.
- **Patients in the failure state with recurrent malignancy:** These were not available from the HES study and so were sourced from TA642 that included the total costs incurred by patients with acute myeloid leukaemia (AML)-related inpatient admissions, ICU, emergency department, outpatient visits, diagnostic procedures, lab tests, and blood transfusions.(2) AML was the most common underlying malignancy in the pooled Phase 2 belumosudil studies. These disease management costs did not include any additional costs associated with cGVHD and so are likely to be underestimated.

The mean follow-up time for patients with cGVHD in the HES study (from the point of alloHSCT) was 17.5 months, compared with 20.6 months for patients without GVHD.(1) Fifty percent of cGVHD patients had less than one year of follow-up. Of these, 241 (67.3%) died, and 117 (32.6%) had an index date less than one year before the study end. The median follow-up for the chronic GVHD patients with less than one year of follow-up and who did not die was 203 days.(1) Therefore, it was necessary to introduce some assumptions on the longer-term disease management costs. If patients have persisted in the FF health state for five years or more, the clinicians we consulted felt the remaining patients represent an enriched cohort who would very likely have ceased treatment due to physician advice or patient preference. It is possible that, for a small number of patients, their cGVHD resolves within this period. Clinicians told us that it is reasonable to assume that these patients would consume less and less healthcare resource over time. This assumption is supported by the study from Schain et al in which costs for cGVHD patients were tracked over time in the Swedish healthcare setting and observed to decrease significantly.(3)

Unlike the *failure-free* health state, patients in the *failure-new systemic therapy* and *failure-recurrent malignancy* states were assumed to attract constant disease management costs

for the duration of the health-state occupancy (i.e., until death). This assumption, which was considered appropriate by the EAG's clinical experts and validated during our advisory boards, has since been further validated through semi-structured interview with other clinical experts, and is described in Section 4.3 below.

4.2 Impact of recurrent malignancy on costs in the failure-new systemic therapy health state

It would not have been possible to accurately identify relapses of malignancy in the HES study for two main reasons. First, since all patients eligible for alloHSCT had a prior malignancy in their data records as an indication for transplant, it was not possible to distinguish these primary cases from subsequent relapses using ICD-10 codes in HES. Similarly, subsequent, unrelated malignancies occurring in patients post-alloHSCT could not be distinguished from prior underlying malignancies in the database. For these reasons, any attempt at reporting recurrent malignancies in these patients would likely overestimate the incidence and we did not exclude such patients from the HES study subgroup on this basis.

The protocol criteria for identifying patients in the *failure-new systemic therapy* health state required patients to have received two or more high-cost drugs. These patients would be unlikely to be prescribed immunosuppressive cGVHD medication following a diagnosis of relapse of malignancy, meaning they would not meet the eligibility criteria for the subgroup of interest.

Nevertheless, we acknowledge the Committee's concerns around the possibility of patients with recurrent malignancies contributing additional costs to the *failure-new systemic therapy* health state, which is modelled separately from the *failure-recurrent malignancy* health state.

It is plausible that a small number of patients in the *failure-new systemic therapy* health state could go on to have relapse, although at this stage of disease the rate would be expected to be very low. The EAG's clinical experts advised that the longer a patient remains relapse-free, the more the risk of recurrent relapse is reduced, but that this was unlikely to be zero after three years following third-line (or later) therapy.

In the belumosudil clinical trials pooled analysis (≥ 2 lines of prior therapy subgroup, mITT, 2022 data cut), [redacted] out of 176 patients ([redacted]%) experienced recurrence of malignancy as a failure event. With this in mind, we have presented a scenario analysis assuming that [redacted]% of patients in the *failure-new systemic therapy* state accrued the same disease management costs as that of the *failure-recurrent malignancy* health state and excluding these patients when estimating the disease management costs to be applied to the *failure-new systemic*

therapy health state (i.e., adjusted annual disease management costs in *failure-new systemic therapy* = [redacted] – [redacted] = [redacted]). This is likely to be an overestimation of relapse events in the HES subgroup analysis, yet the impact on the ICER is small and remains dominant using company or EAG preferred base case assumptions. Deterministic results for this scenario are presented in Table 6.

Table 6. Deterministic results for scenario analysis with [redacted] recurrent malignancy costs subtracted from disease management costs for *failure-new systemic therapy* health state

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company revised base case assumptions (1.2x severity modifier applied)			
Company preferred base case	[redacted]	[redacted]	Dominant
Scenario analysis: Recurrent malignancy costs subtracted from *failure-new systemic therapy* health state	[redacted]	[redacted]	Dominant
EAG preferred base case assumptions (no severity modifier applied)			
EAG preferred base case*	[redacted]	[redacted]	Dominant
Scenario analysis: Recurrent malignancy costs subtracted from *failure-new systemic therapy* health state	[redacted]	[redacted]	Dominant

*EAG preferred base case results differ very slightly from the post-TE ICER. This is because a minor correction was applied in the model engines regarding the construction of the failure health state by cause (see Appendix B). All ICERs presented used the updated company model unless explicitly stated.

4.3 Impact of reducing disease management costs in the failure-new systemic therapy health state

Unlike the FF state, the *failure-new systemic therapy* state is not a single, stable health state; it represents multiple progressions over the late stages of disease from the point of treatment switch until death. Consequently, it is unreasonable to expect a decline in costs over time for patients whose treatment has failed, especially with the more limited choice of effective treatment options available. Indeed, a more plausible approach would be to model an increase in costs as those patients get progressively sicker. However, in the absence of data we considered it more appropriate to model a constant cost of disease management.

As the application of disease management costs to this health state is a key driver of the cost-effectiveness analysis, but data to support the evolution of costs over time is not readily available, we sought the views of 15 clinical experts with experience in the management of cGVHD for the purposes of this response.(4) Because there was not enough time to conduct a formal advisory board, we undertook virtual, unpaid, semi-structured interviews and asked the clinical experts to describe what they observe in their clinical practice. All but three of the

clinicians were happy for their names to be placed on record associated with their comments on this issue.

The survey included 12 consultant haematologists, 1 nurse consultant, and 2 pharmacists specialising in haematology (respondent details in Table 7), with broad geographical representation of treatment centres across England and Wales. A discussion guide based around two simple key themes was followed but the discussion was free-flowing to allow the clinicians to provide a narrative response. (In addition to the question about disease management costs we also asked them about quality of life.(4) This is discussed further in a later section of this response.) The two key themes were:

a) Disease management and healthcare resource use after failure of three or more lines of systemic therapy in cGVHD

b) Quality of life after failure of three or more lines of systemic therapy in cGVHD

Table 7. Clinical expert respondents - personal details shared with respondents' permission

Respondent name, Position and Affiliation
3 x Anonymous Consultant Haematologist*
Dr Chloe Anthias, Consultant Haematologist, Royal Marsden NHS Foundation Trust
Dr Daniele Avenoso, Consultant Haematologist, Kings College Hospital NHS Foundation Trust
Dr Simon Bulley, Consultant Haematologist, The Leeds Teaching Hospitals NHS Trust
Dr Ben Carpenter, Consultant Haematologist, UCLH NHS Foundation Trust
Nick Duncan, Consultant Haematology Pharmacist, University Hospitals Birmingham NHS Foundation Trust
[redacted]
Dr Emma Nicholson, Consultant Haematologist, Royal Marsden NHS Foundation Trust
Chris Salmen, Lead Haemato-Oncology Pharmacist, Royal Marsden NHS Foundation Trust

*3 Clinical experts requested that we maintain their anonymity. All other respondents consented to use of their personal details to be shared and for their quotes to be included in our response to the NICE consultation.

In the clinical expert interviews we conducted, 100% of respondents considered it clinically implausible that disease management costs would reduce over time in the *failure-new systemic therapy* health state. Instead, all 15 clinicians stated that costs would in fact most likely increase over time, due to the increasing level of complications requiring secondary healthcare interventions and ongoing supportive care and monitoring.(4)

For example, one clinician told us…

> *"It is not uncommon for these patients to be in hospital for prolonged periods for management of chronic GVHD e.g. for many months at a time. They will cycle through different types of immunosuppressive therapies, attending clinics at least every couple of weeks, having recurrent hospital admissions… with a huge financial burden for the NHS. Costs would most likely increase over time as they develop increasing co-morbidities and recurrent infective complications as a result of their severe cGVHD." – Dr Emma Nicholson, Consultant Haematologist*

To address their concerns that costs in the *failure-new systemic therapy* health state were too high in our original model, the Committee asked the EAG to explore the impact of reducing costs over the course of five years until patients in this health state attract the costs of a complete responder. This request was made a matter of days before the committee meeting and the company was unable to respond to it.

The EAG considered that the requested scenarios may not be clinically plausible. We agree that it is clinically implausible for this patient population to attract the costs of a complete responder in an earlier line of treatment. In the scenario requested by the Committee, 100% of people who are in the *failure-new systemic therapy* state eventually attract the costs of a complete responder (the EAG considered that this scenario may not be clinically plausible and explored additional scenarios in which varying proportions of patients from 25% to 75% experienced such a reduction in their disease management costs over time in the *failure-new systemic therapy* state). This implies either that late-stage patients for whom multiple treatments fail become significantly easier to treat to the extent that complications associated directly with cGVHD are resolved, or that the NHS drastically reduces its level of care for these patients. Clinicians we interviewed felt this was not supportable, since patients who are at this stage of the disease after the third line of therapy are more likely to be in a state of cyclical interventions in an attempt to control their cGVHD.(4) It is therefore very rare for this group of patients to achieve a complete response within five years. Even within the extremely rare situation where a patient moves to a complete response, the incurred costs would increase rather than decrease because such patients are left with the ongoing complications of cGVHD. For example, clinicians described their own patients currently in their care who required interventions including a lung transplant or a neurosurgical procedure to manage fungal disease from the brain. These situations incur huge costs and imply that the patient journey in this phase of the disease remains extremely complex and the management remains complicated and expensive.

We were told...

> *"'In my service, I have not yet seen a patient who was on their third or fourth line of systemic treatment for cGvHD, who went into complete response"* - [redacted], Consultant Haematologist

Having received the feedback from the clinical community we maintain our original approach to the application of disease costs over time in the model and are aligned with the EAG position that the Committee's requested scenario is unlikely to be clinically plausible, even when applied at the lower end of 25% of patients. Disease management costs **would not** reduce over time in the *failure-new systemic therapy* health state.

However, to satisfy the request of the Committee we conducted further analyses to test their proposed scenario. This required some structural adaptations to the model (detailed in Appendix B) which had not been considered in the original EAG approach, in order to reduce disease management costs in the *failure-new systemic therapy* health state over time. In the EAG analyses, the linear reduction in disease management costs for the *failure-new systemic therapy* health state was applied for all patients from year 1 to year 5 of the model time horizon, regardless of the time at which patients had actually entered the *failure-new systemic therapy* health state. This means that patients in the *failure-new systemic therapy* were assigned an erroneous cost that was based on time elapsed since the start of the time horizon instead of according to the time elapsed since entering the *failure-new systemic therapy* health state. For example, patients who remained in the *failure-free* health state for 4 years in the model would begin to accrue the lower disease management costs corresponding to 5th year with *failure-new systemic therapy* right from the point of transitioning into this health state, rather than accruing the correct, higher costs of 1st year with *failure-new systemic therapy* followed by a decline in costs over the next five years. This is not aligned to the Committee's request and underestimates the overall costs of the *failure-new systemic therapy* health state. Therefore, the ICERs which were originally presented in the EAG's response to the lead team's requested scenarios are substantially higher than those produced using the corrected model incorporating time-dependent costs for *failure-new systemic therapy* implemented via the use of tunnel states (

Table 8).

Table 8. Deterministic results for Committee scenarios with reducing disease management costs in *failure-new systemic therapy* health state

Scenario*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company revised base case assumptions (1.2x severity modifier applied)			
1. Company preferred base case	[redacted]	[redacted]	Dominant
2. Linear decline of *failure-new systemic therapy* disease management costs to f*ailure-free* CR disease management cost	[redacted]	[redacted]	15,226
3. 75% of *failure-new systemic therapy* patients experiencing a linear reduction in disease management cost to *failure-free* disease management cost	[redacted]	[redacted]	5,732
4. 50% of *failure-new systemic therapy* patients experiencing a linear reduction in disease management cost to *failure-free* disease management cost	[redacted]	[redacted]	Dominant
5. 25% of *failure-new systemic therapy* patients experiencing a linear reduction in disease management cost to *failure-free* disease management cost	[redacted]	[redacted]	Dominant
6. 10% of *failure-new systemic therapy* patients experiencing a linear reduction in disease management cost to *failure-free* disease management cost	[redacted]	[redacted]	Dominant
EAG preferred base case assumptions (no severity modifier)			
7. EAG preferred base case*	[redacted]	[redacted]	Dominant
8. Linear decline of *failure-new systemic therapy* disease management costs to f*ailure-free* CR disease management cost (*using original model*)	[redacted]	[redacted]	80,173
9. Linear decline of *failure-new systemic therapy* disease management costs to f*ailure-free* CR disease management cost	[redacted]	[redacted]	64,718
10. 75% of *failure-new systemic therapy* patients experiencing a linear reduction in disease management cost to *failure-free* disease management cost	[redacted]	[redacted]	41,399
11. 50% of *failure-new systemic therapy* patients experiencing a linear reduction in disease management cost to *failure-free* disease management cost	[redacted]	[redacted]	18,079
12. 25% of *failure-new systemic therapy* patients experiencing a linear reduction in disease management cost to *failure-free* disease management cost	[redacted]	[redacted]	Dominant
13. 10% of *failure-new systemic therapy* patients experiencing a linear reduction in disease management cost to *failure-free* disease management cost	[redacted]	[redacted]	Dominant

*EAG preferred base case results differ very slightly from the post-TE ICER. This is because a minor correction was applied in the model engines regarding the construction of the failure health state by cause (see Appendix B). All ICERs presented used the updated company model unless explicitly stated.

In conclusion, the clinical experts we spoke to unanimously agreed that the Committee's requested scenario of reducing disease management costs was not clinically plausible and was not reflective of their clinical experience. This was also the view of the EAG.

Nonetheless we have updated the economic model to allow for incorporation of time dependency in the application of *failure-new systemic therapy* state costs and presented scenario analyses according to the request of the Committee.

In the company revised base case, the ICER remains below the £20k threshold for all the scenarios with reducing disease management costs. Using preferred EAG assumptions, the ICER remains below the threshold with up to 52% of patients experiencing the linear decline in costs. In reality, as we were told by the clinical experts, it is more plausible that disease management costs would increase, rather than decrease, for patients with treatment failure at this position in the treatment pathway. Therefore, the results from these scenarios should be treated with extreme caution.

5. Utility values in *failure-new systemic therapy* health state

Since there was not enough time to conduct a formal advisory board to test or validate the Committee's requested model scenarios around increased quality of life for patients experiencing treatment failure, we conducted online, unpaid, semi-structured interviews with 15 clinical experts with experience in the management of cGVHD (methods and respondent details are described in Section 4.3).(4)

All 15 of the clinical expert respondents described the *failure-new systemic therapy* health state in the model as one involving, in general, a substantial decline of quality of life for patients year on year. Clinical experts described these patients as generally frail and feeling hopeless due to spending prolonged time in hospital. Treatment failure after three or more lines of therapy represents a highly morbid disease state whereby few effective treatments are available and toxicity and infections are of increasing concern. Of those patients who can no longer be offered treatments for disease management, many will require palliative care. Those who continue receiving cGVHD therapies also accrue significant clinical complications requiring multiple clinical specialists. We were told…

> *"Quality of life in cGVHD patients who fail after three or more lines of therapy gets progressively worse over time. They need more and more physical and psychological help over time and become progressively dependent and frail. There is a marked reduction in the quality of life at the point of treatment failure."* – Dr Daniele Avenoso, Consultant Haematologist

Patients are often isolated from their peers (particularly impacting young people), spending most of their time at home or in hospital, and are reliant on others. Mostly, patients are not able to work, meaning that on top of the direct impact on physical health, this patient population is at increased risk of financial strain and is more likely to require support from caregivers/family members. Two clinicians quoted different patients at this stage of the disease pathway who said that, had they known what cGVHD would be like, they would have chosen not to undergo their lifesaving transplant despite knowing the potentially mortal risk of the prior malignancy.

We conducted a quality of life study under the conditions of market research in collaboration with Anthony Nolan with the objective of better understanding the patient and carer experience of cGVHD.(5) To align this with the *failure-new systemic therapy* health state of interest in the model, the screening criteria ensured that only adult patients diagnosed with cGVHD who had received at least two prior lines of systemic therapy, and had ongoing symptoms, could participate in the research. Part of this (currently unpublished) research involved participants completing an EQ-5D-5L survey either for themselves or - if carers - on behalf of the patient they cared for. Carers were included to maximise the sample size, on the understanding that some patients with more severe forms of cGVHD would not be as responsive to completing, or physically unable to complete, the survey. EQ-5D-5L domain scores were calculated and mapped onto EQ-5D-3L according to NICE Decision Support Unit methodology.

A total of 17 patients and 8 carers were included in the study. Of the 25 unique patients being considered, 21 were male, and the mean age was 49.7 years. Further patient descriptive details are provided in Table 9.

Table 9. Descriptive data for patients included in market research study

	Patients + Carers (all patients represented, n=27)	**Patients only (n=17)**
Mean (median) patient age, years	[redacted]	[redacted]
Mean difference in age between transplant and current age/age of death (median), years	[redacted]	[redacted]
Mean number of systemic cGVHD therapies ever received (median)	[redacted]	[redacted]

As shown in Table 10, patients and carers rated the patient quality of life at this stage in the disease at a mean of [redacted] ([redacted] by patients and [redacted] by carers).

Table 10. EQ-5D Index Scores for patients with cGVHD following two or more prior systemic therapies (as reported by patient or carers)

	EQ-5D-5L			EQ-5D-3L*		
	Mean	SD	Median	Mean	SD	Median
Patients, (n = 17)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carers (n = 8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients and carers (n = 25)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*EQ-5D-5L domain scores calculated and mapped onto EQ-5D-3L using method recommended by NICE Decision Support Unit: https://www.sheffield.ac.uk/nice-dsu/methods-development/mapping-eq-5d-5l-3l

In the absence of alternative data, we had used a utility value for relapsed haematological cancer for this health state in our original model. This utility value of 0.479 was tested and agreed with clinical experts. It is noteworthy that the values observed in the market research reported above do not differ substantially from this and indeed the carer assessment of utility is well aligned with it.

For the following reasons we consider the newly sourced utility values to be more appropriate for use in the model than the current EAG-preferred assumption of [redacted]. The latter was based on the midpoint of a previous economic modelling study (with unverifiable sources) and a small sample from the Adelphi Disease Specific Programme (DSP) study containing data from two UK patients. We recognise that a total of 25 respondents to the market research represents a relatively small sample but this is a rare, debilitating disease and the patients included were chosen to reflect a comparable UK population to that described by the *failure-new systemic therapy* state in the economic model.

The poor QoL reflected in the aggregate utility values of [redacted] (EQ-5D-5L) and [redacted] (EQ-5D-3L) corroborate the patient and clinician testimony and literature evidence that cGVHD treatment failure at third line and later has a severe impact on patients' quality of life. We believe these results are the best available evidence to date for this cohort.

The [redacted] utility value from the market research has been implemented in the revised Company base case. When the lower value of [redacted] is applied, the incremental QALYs increase from [redacted] to [redacted] and the ICER remains dominant (Table 11). When applying either of these values to the QALY shortfall analysis in the Company base case, the severity weighting of x1.2 is still achieved (see Table 2).

Table 11. Deterministic results for scenario analyses using patient EQ-5D data from UK market research study to populate the *failure-new systemic therapy* health-state utility

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company revised base case assumptions (1.2x severity modifier applied)*			
Company preferred base case ([redacted] utility for *failure-new systemic therapy* health state)	[redacted]	[redacted]	Dominant
Scenario analysis: Apply [redacted] utility to *failure-new systemic therapy* health state	[redacted]	[redacted]	Dominant
EAG preferred base case assumptions (no severity modifier)			
EAG preferred base case ([redacted] utility for *failure-new systemic therapy* health state)**	[redacted]	[redacted]	Dominant
Scenario analysis: Apply [redacted] utility to *failure-new systemic therapy* health state	[redacted]	[redacted]	Dominant
Scenario analysis: Apply [redacted] utility to *failure-new systemic therapy* health state	[redacted]	[redacted]	Dominant

*The measured age for the failure-new systemic therapy utility value was updated to 51.1 years in the revised base case to align with the population in the quality of life study.
**EAG preferred base case results differ very slightly from the post-TE ICER. This is because a minor correction was applied in the model engines regarding the construction of the failure health state by cause (see Appendix B). All ICERs presented used the updated company model unless explicitly stated.

6. References

1. Sanofi. Data on File. HES Report - The clinical and economic burden associated with chronic graft-versus-host disease following allogeneic haematopoietic stem cell transplant in England; Version No.: 01.00. 2022.
2. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]. Committee Papers. TA642. 2020.
3. Schain F, Batyrbekova N, Liwing J, Baculea S, Webb T, Remberger M, et al. Real-world study of direct medical and indirect costs and time spent in healthcare in patients with chronic graft versus host disease. The European journal of health economics : HEPAC : health economics in prevention and care. 2021;22(1):169-80.
4. Sanofi. Data on file. NICE post-draft guidance clinical expert interviews. 2023.
5. Sanofi, Synergy. Data on file. cGVHD Impact on QoL. Quantitative Stage Research. Draft Report. 2023.

7. Appendix A – Revised base case results

Base case probabilistic cost-effectiveness analysis results

Table 12. Revised company base-case probabilistic results (PAS, without severity modifier)

Outcome	Belumosudil	BAT
Total costs	[redacted]	£ 246,978
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental LYs	[redacted]	
Incremental QALYs	[redacted]	
ICER (£/QALY)	Dominant	
INHB (£20,000/QALY)	[redacted]	
INHB (£30,000/QALY)	[redacted]	
INMB (£20,000/QALY)	[redacted]	
INMB (£30,000/QALY)	[redacted]	

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year; INHB = incremental net health benefit; INMB = incremental net monetary benefit

Table 13. Revised company base-case Probabilistic Results (PAS, with severity modifier [1.2 QALY weight])

Outcome	Belumosudil	BAT
Total costs	[redacted]	£ 246,978
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental LYs	[redacted]	
Incremental QALYs	[redacted]	
ICER (£/QALY)	Dominant	
INHB (£20,000/QALY)	[redacted]	
INHB (£30,000/QALY)	[redacted]	
INMB (£20,000/QALY)	[redacted]	
INMB (£30,000/QALY)	[redacted]	

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year; INHB = incremental net health benefit; INMB = incremental net monetary benefit

Base case deterministic cost-effectiveness analysis results

Table 14. Revised company base-case deterministic results (PAS, without severity modifier)

Outcome	Belumosudil	BAT
Total costs	[redacted]	£ 246,432
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental LYs	[redacted]	
Incremental QALYs	[redacted]	
ICER (£/QALY)	Dominant	
INHB (£20,000/QALY)	[redacted]	
INHB (£30,000/QALY)	[redacted]	
INMB (£20,000/QALY)	[redacted]	
INMB (£30,000/QALY)	[redacted]	

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; INHB = incremental net health benefit; INMB = incremental net monetary benefit; LY = life year; QALY = quality-adjusted life year

Table 15. Revised company base case deterministic results (PAS, with severity modifier [1.2 QALY weight])

Outcome	Belumosudil	BAT
Total costs	[redacted]	£ 246,432
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental LYs	[redacted]	
Incremental QALYs	[redacted]	
ICER (£/QALY)	Dominant	
INHB (£20,000/QALY)	[redacted]	
INHB (£30,000/QALY)	[redacted]	
INMB (£20,000/QALY)	[redacted]	
INMB (£30,000/QALY)	[redacted]	

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; INHB = incremental net health benefit; INMB = incremental net monetary benefit; LY = life year; QALY = quality-adjusted life year

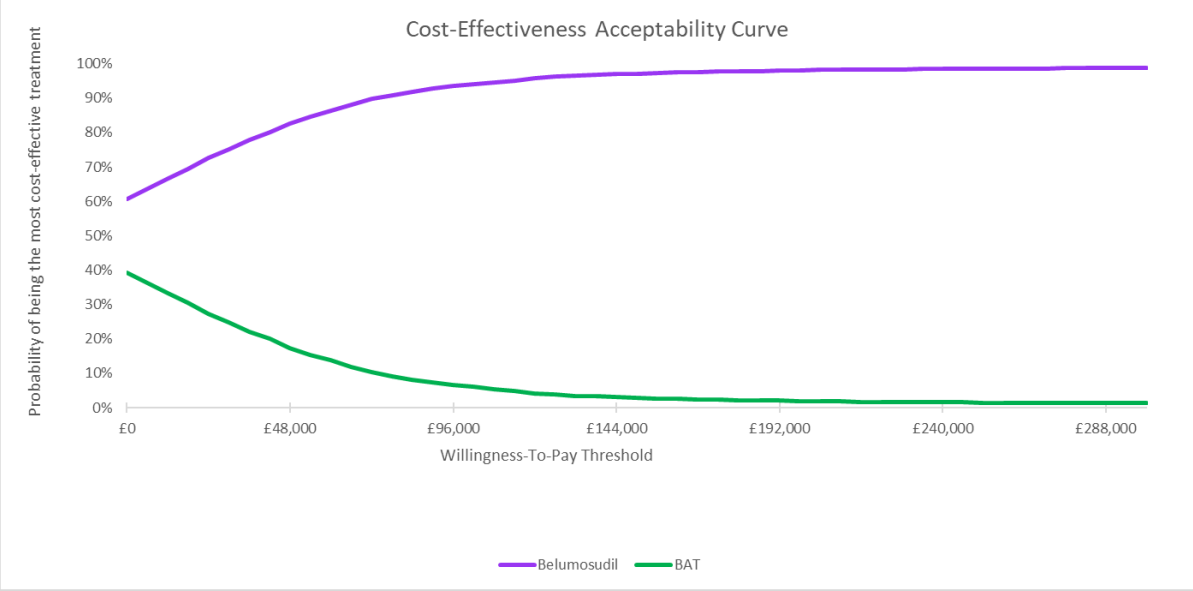
Probabilistic sensitivity analysis

Figure 3. Probabilistic results on the cost-effectiveness plane (PAS, without severity modifier)

[redacted]

[redacted]

Figure 4. Cost-effectiveness acceptability curves for belumosudil vs. BAT (PAS, without severity modifier)



BAT = best available therapy; PAS = patient access scheme

One-way deterministic sensitivity analysis

Figure 5. Tornado diagram of ICER (incremental cost per QALY gained) for belumosudil vs. BAT (PAS, without severity modifier)

BAT = best available therapy; BID = twice daily; cGvHD = chronic graft-versus-host disease; ECP = extracorporeal photopheresis; FFS = failure-free survival; ICER = incremental cost-effectiveness ratio; OS = overall survival; PAS = patient access scheme; PR = partial response; QALY = quality-adjusted life year; QD = once daily; Tmt = treatment; TTD = time to treatment discontinuation
Notes: FFS Parametric Fit – Parameter 1 = mu (Generalised Gamma distribution); FFS Parametric Fit – Parameter 2 = sigma (Generalised Gamma distribution); FFS Parametric Fit – Parameter 3 = Q (Generalised Gamma distribution); FFS Parametric Fit – Parameter 4 = treatment coefficient; OS Parametric Fit – Parameter 1 = rate (exponential distribution); OS Parametric Fit – Parameter 2 = treatment coefficient; TTD Parametric Fit – Parameter 1 = mean (log-normal distribution); TTD Parametric Fit – Parameter 2 = standard deviation (log-normal distribution); TTD Parametric Fit – Parameter 3 = treatment coefficient

8. Appendix B – Model structural adaptations post first Committee Meeting

❖ 1) Minor correction applied in model engines regarding reconstruction of Failure health state by cause:

- Added new column for "Cycle Probability of Death from Failure" (column AZ)
- Updated formulas in columns BB:BC ("Failure - New cGvHD Systemic Therapy"; "Failure - Recurrent Malignancy")
- (Note: columns AW, AX, AY are now obsolete ("Incident Failure (without cap)"; "Incident Failure - New cGvHD Systemic Therapy (without cap)"; "Incident Failure - Recurrent Malignancy (without cap)")
    - We have retained them in the model but applied a different background formatting to denote that these columns are not used anymore.

❖ 2)a) Addition of new settings to conduct analyses requested by NICE's lead team:

- **Truncating KM data at 24 weeks for FFS for BAT**:

- Created new selection in Efficacy!G21 (and corresponding index in Lists!L11)
- Added new section in FFS Parameters!AK253:BB286 for the parameters of the extrapolated curves based on truncated data
    - Updated formulas in FFS Parameters!I260:M285 to pick the appropriate values depending on whether truncated or full KM data are used

- **Time-dependent costs in Failure - New cGvHD Systemic Therapy health state:**

- Created new selection in Costs!G226 (and corresponding list in Lists!I235:I236 and corresponding selection in Lists!L235)
- Created new input field in Costs!G227 for proportion of patients to whom the reduction in costs over time applies
    - (Added macro for hiding/unhiding depending on these two selections)
- Added new input table with time-dependent inputs (costs per year in different periods) for Failure - New cGvHD Systemic Therapy in Costs!G335:K335
    - Added corresponding range in Parameters tab, rows 1249 to 1253
    - (And updated description for parameter corresponding to constant costs in Parameters!I1248)
- Added table of corresponding calculated time-dependent costs per model cycle for Failure - New cGvHD Systemic Therapy in Costs!H246:L246
    - Added corresponding range in Parameters tab, rows 1276 to 1280
    - (And updated description for parameter corresponding to constant costs in Parameters!I1275 as well as the formula for inclusion in the DSA in AA1275)
- In model engines:
    - Added section with time-dependent costs per cycle in EH16:EH20
    - Added calculations of "**tunnel states**", i.e., of proportions of patients at each cycle who are in their 1st year in the Failure – New cGvHD Systemic Therapy health state, proportions of patients who are in their 2nd year in that health state, etc.
        - This involved adding the following new columns:
            - Columns N:Q (for number of cycles to track)
                - Note: calculations in these new columns use two new constants (NumFullCyclesIn1Year and Approx1YearInFullCycles) that were added to Parameters!K21:K22

- Column BA (“Cycle Probability of Surviving from Failure”)
- Columns BJ:BT (columns BJ:BM for proportions of patients who will move to their 2nd year/3rd year/etc. in the Failure – New cGvHD Systemic Therapy health state at the end of each cycle; columns BO:BT for the proportions of patients who are in their 1st year/2nd year/3rd year/etc. in the Failure – New cGvHD Systemic Therapy health state at each cycle)
- Columns CL:CP (half-cycle corrected values for proportions of patients who are in their 1st year/2nd year/3rd year/etc. in the Failure – New cGvHD Systemic Therapy health state at each cycle)

▪ This also involved adding a user-defined function in VBA, which is used (in columns BJ:BM) to simplify the calculations needed in the worksheet itself: see the ’TunnelState’ function in the ’Functions’ module in VBA

- Updated formulas for calculation of disease management costs at each cycle in the Failure – New cGvHD Systemic Therapy health state in EH30:EH812

❖ 2)b) Other features added to simplify replication of EAG’s base case settings:

- **Choice of using KM curve for TTD for belumosudil:**

- Created new selections in Efficacy!G141 and G142 (and corresponding indices in Lists!L13:L14)
  - (Updated worksheet macro for hiding/unhiding depending on these selections, as well as formulas for hiding/unhiding in Efficacy!A146, A157:A159 and for labels in cells F146 and F159)
- In K-M Estimates tab:
  - Updated label in cell BL6
  - Added a new section for “Time to treatment discontinuation (TTD) - calculations for use when "KM Curve" approach is selected for TTD” in columns CP:DH
  - Updated formulas in TTD Param Belu!J40:K823 to pick the appropriate values depending on whether the “use KM data” option is selected or not
  - Added rows for random numbers and multipliers for TTD KM curves for belumosudil (this is for PSA and DSA purposes) in the Parameters tab, rows 202 to 205.
  - (Also updated the formulas for inclusion in the DSA for TTD curve parameters in Parameters!AA166:AA173)

- **Time-point after which to assume same cycle probability of death for belumosudil as for BAT:**

- For convenience, moved the cell to specify the number of years after which the cycle probability of death for BAT is applied to belumosudil from the Parameters sheet to Efficacy!G123 (and marked it as user-modifiable)
  - (Updated worksheet macro for hiding/unhiding depending on this selection)
  - (Also updated label in Efficacy!F122)

- ***Also updated the inputs for proportions of patients on concomitant medication for belumosudil, to use data from the 2022 data cut (in Costs!I159:K160)***

❖ 3) Using the version containing all the updates detailed above, the model may be set up to the EAG base case as follows (numbers 1 to 12 below represent all the changes made sequentially by the EAG to arrive at their base case in their report):

- 1. 'No' in Settings!G16
- 2. '0' in Efficacy!G123
- 3. 'Yes' in Settings!G91; '0%' in Costs!G162:H162 and J162:N162 (and likewise in row 174)
- 4. '0%' in Costs!G159:H160 and L159:N160 (and likewise in rows 171:172)
- 5. 'Yes' in Efficacy!G141 and G142
- 6. 'Exponential Fitted to Reported Median Duration' in Efficacy!G149
- 7. '0%' in Costs!G126; '0' in Costs!G131
- 8. 'Apply Costs for a Given Duration' in Subsequent Tmt!G27; '260' in Subsequent Tmt!G31:H33, G35:H35, J31:J33, J35
- 9. '0.608' in Utilities!G14
- 10. '-0.045' in Utilities!G172; '0.057' in Utilities!H172
- 11. '-0.22' in Utilities!G134; '14' in Utilities!I13412. '0' in Utilities!G155:I155

NICE National Institute for Health and Care Excellence

Belumosudil for treating chronic graft-versus-host disease after 2 or more systemic treatments in people 12 years and over [ID4021]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 25 October 2023. Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Anthony Nolan

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NICE National Institute for Health and Care Excellence

Belumosudil for treating chronic graft-versus-host disease after 2 or more systemic treatments in people 12 years and over [ID4021]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
Name of commentator person completing form:	[redacted]

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Belumosudil for treating chronic graft-versus-host disease after 2 or more systemic treatments in people 12 years and over [ID4021]

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1	**3.1** ***"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."*** Anthony Nolan believes that the committee may have misinterpreted the clinical evidence here as it is likely that patients' cGvHD is, by definition, chronic and therefore unlikely to be in a position where it resolves itself. From our patients' experience, and from clinical expertise, multiple previous treatments lines are likely to have failed for patients who are at the stage of requiring treatments such as belumosudil. Therefore, their cGvHD is unlikely to be improving or on track to resolve itself. The lasting effects on quality of life if cGvHD does resolve are significant, for example, patients can be left with chronic lung conditions because their GvHD has severely impaired lung function, however this is more likely to be the case with patients who have acute GvHD that has resolved, rather than chronic GvHD which continues to worsen patients' baseline health.
2	**3.2 Positioning belumosudil & access to ECP** If the committee agrees with the EAG's treatment pathway that belumosudil is not an alternative to extracorporeal photopheresis, how does the committee intend to manage the difficulty of accessing ECP from the patient perspective, which has also been acknowledged by clinicians? As a patient organisation, we know people struggle to access ECP due to cGvHD-induced immobility, which can be severe. One of our patients has been rendered immobile due to cGvHD-induced fibrosis build up and scleroderma under fascia in legs, rendering them unable to bend their knees sufficiently or to easily transition from straightening to bending knees. They have to access patient transport ambulances in order to go their ECP appointments every 2 weeks. *"I have to be wheeled up the back of the ambulance because I can't support my weight sufficiently enough to go up the step to get into the ambulance, which is quite high and there is usually only a rail on one side. At home on my stairs, I can barely get up and down, but I need both the bannisters. I cannot pull myself out of a car - I can't make the transition from sitting to standing if my knees are that bent, so it can't be a volunteer driver that picks me up and I can't go by taxi."* Therefore, ECP is quite difficult to access and takes a lot of time and effort to get to. Any oral medication for cGvHD would be much easier and more convenient to administer and access.
3	**Psychological impacts of living in a "failure state"** From the patients Anthony Nolan has spoken to, we know that living in state where the treatments they have tried have failed to help manage their conditions adequately can be extremely demoralising. By the time patients need second or third-line treatments, they have already tried multiple treatment options for symptom management. One of our patients said the psychological impact of having used lots of different types of treatments is that "*it gives you hope a lot, and then for weeks nothing happens. It gets very demoralising, and you feel like giving up…I need hope that it will improve".*

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4	**Impacts of unequal access to new treatments** There is a clear inequality in access to innovative and effective treatments internationally, and patients are aware of, and distressed by, this situation. Those living with cGvHD are aware of the multiple treatment options that are available worldwide through various channels such as a Facebook support groups for cGvHD (see: https://m.facebook.com/groups/graftvshost/). As a result, they know of other people around the world who have access to medicines such as belumosudil, but patients in England do not. This can be particularly difficult for them to understand especially when they are hearing from other patients that these new treatments, or a combination of them, are helping to alleviate their cGvHD. Anthony Nolan has heard that it is incredibly frustrating to know someone else who is suffering from the same symptoms as you have been helped but you cannot be because you live in a different place. One of our patients noted how this knowledge has made them feel about the treatments they receive. "*I feel a bit let down by NHS as they gave me a blood marrow transplant which gave me cGvHD symptoms affecting my quality of life and don't have the full resources available to them to improve my situation although they are available in other countries. I feel like I am also now living in a third world country when it comes down to treating health issues."* A decision to not move ahead with belumosudil in England would be particularly painful for transplant patients, especially with the knowledge that the same therapy, for the same indication would be available elsewhere in the UK. There's only one thing worse than not having a treatment option for your condition, and that's knowing there is an effective treatment, but you are unable to access it.
5	**3.16 Severity Modifier** Anthony Nolan believes a severity modifier should be applied to this condition because it was noted within the committee meeting by an expert clinician that patients' quality of life living with chronic GvHD can be the same as living with the active malignancy that required them to undergo a transplant in the first instant. While some cGvHD conditions can be less severe, for those that have been rendered immobile the psychological and life impacts are life-altering. As mentioned in previous comments, patients can feel like "giving up", and the knowledge that though they no longer have the malignancy, but they now are living a life where they have lost jobs, or have been left by partners, and have no active life to speak of is demoralising to the point of extreme depression. Some of the patients we support have had to access long-term therapy and psychological support to come to terms with the new conditions of their lives, because they were under the impression that a stem-cell transplant would mean they could go back to their life's pre-cancer, but their cGvHD has essentially meant this is not an option. One of our patients who is immobile has said that they are "*completely cut off from people",* and prior to their cancer the main loves of their lives were *"walking, gardening, DIY, cooking all which require my legs and now I cannot do as I cannot stand much more than ten minutes at a time. I now have to have ready meals delivered to me by supermarket which are not always the healthiest and many meals arrive with sell by dates so close together that I end up throwing some in bin and wasting money."*

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England Blood and Marrow Transplantation Clinical Reference Group

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted], [redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that this recommendation may lead to inequity in access to treatments. There are very few treatments for chronic GVHD and the main treatment that is available is extracorporeal photopheresis. Patients often have to travel a long way to receive this treatment and it involves a significant time commitment (two days every fortnight) so patients can find it challenging to attend if they have work, family or any other commitments. The time-consuming nature of the treatment and long duration of treatment (often years) means that not all patients are

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	able to receive. Belumosudil would have offered an alternative treatment which is much simpler and easier to access. In addition, it would not have the same resource implications .e.g apheresis capacity, one to one nursing that ECP requires.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Therakos (UK) Ltd- Part of Mallinckrodt Pharmaceuticals

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NICE National Institute for Health and Care Excellence

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Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We agree with the statement in section 1.1. that 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.

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NICE National Institute for Health and Care Excellence

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2	We agree with the EAG that the company positioning for belumosudil as a second line treatment did not reflect the current treatment pathway in England. The NHS England clinical commissioning policy (2017) states that first-line treatment should be corticosteroids with or without calcineurin inhibitors, second-line treatment is extracorporeal photopheresis. Third line treatment should be mycophenolate mofetil, methotrexate or pulsed corticosteroids which is the treatment line that should include belumosudil.
3	The ROCKstar study of belumosudil was an uncontrolled phase 2 study, so there was no comparison directly with best available therapy as used in England.

Insert extra rows as needed

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Single Technology Appraisal

Belumosudil for treating chronic graft versus host disease after 2 or more lines of systemic therapy [ID4021]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Comment on recommendations chapter, section 1:

When making a recommendation I think you also have to consider the wider context of this decision. If we have less effective 3rd line treatment options it doesn't just mean that some patients with chronic GVHD will do worse, it can actually determine other aspects of our whole transplant practice. As transplanters of blood cancers, we manipulate the graft versus disease effect of the transplant to try to balance the risks of chronic GVHD and relapse. If compared to other countries we have less effective chronic GVHD treatment then we are are less able to maximise the graft versus disease effect of transplants and we will likely then have higher deaths from relapse as well as higher deaths from GVHD. If we become an outlier in terms of our GVHD management compared to other developed countries we will also become increasingly unable to extrapolate data from those countries regarding any important advances in management because our patients will do worse if they develop refractory cGVHD.

Comment on committee discussion, positioning of belumosudil, section 3.2:

ECP is an important evidence based treatment for patients with chronic GVHD and we routinely use it as second line therapy in our patients. However it is not possible to deliver in all patients due to the following issues. Our sickest cGVHD patients often have poor venous access making ECP impossible without large lumen central venous catheters. These are prone to infection in this heavily immunosuppressed population and catheters have to be removed, reinserted and access becomes technically impossible in some patients. Others develop central venous catheter associated thrombus leading to cessation of ECP. cGVHD patients also often have low blood counts which means they often need to be transfused with red cells/platelets before the procedure or sometimes that it is not possible to achieve the blood levels required for ECP. Finally, the sickest most vulnerable chronic GVHD patients are frequent inpatients (some for many months at a time), which usually means that they miss ECP during

this time. So while ECP is a very valuable treatment, it cannot be assumed that all patients will have access to it.

Comment on committee discussion, Utility value for the 'failure – new chronic GVHD systemic therapy' health state, section 3.12:

As a transplant consultant, my experience is that patients who fail 3 or more GVHD therapies have a declining and very poor quality of life. All available treatments cause them to be heavily immunosuppressed and patients are in and out of hospital wiht recurrent infections. They are often debilitated both from inevitable high dose steroid use over many months, and as a direct consequence of their GVHD (eg malnutrition (if they have gut or oral GVHD), joint problems, very poor exercise tolerance if they have lung involvement. These patients almost always (and very understandably) then develop depression and other psychological problems as a result. They often have several hospital appointments every week, and for most patients attending these becomes their whole existence, the fatigue associated with chronic GVHD is so overwhelming that many patients lose the ability to take part in life beyond being a patient. Most patients in this state cannot work and in some cases their relatives have to stop or reduce working to look after them and therefore there is an additional economic burden which further impacts their quality of life.

Comment on committee discussion, Disease management costs for the 'failure – new chronic GVHD systemic therapy' health state, section 3.13:

In our experience at my transplant centre, patients who fail 3 or more GVHD therapies will almost invariably have increasing healthcare costs. These are the patients that we see admitted for long periods (eg months) due to either debilitation secondary to their GVHD symptoms and treatment (eg steroid myopathy), and recurrent infections related to their heavily immunosuppressed state. Use of high cost antimicrobials and often the need for blood products, expensive investigations and additional therapies eg intravenous immunoglobulin replacement add to this cost. They often require heavy multidisciplinary input (dietician/physio/gastroenterologist/psychologist/respiratory physician)

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Yes

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, this is a first in class oral, outpatient agent. The inpatient stay cost to the NHS has not been adequately taken into account. The inpatient costs of treatment in terms of pharmaceutical costs, medical and nursing care, and bed blocking will be higher than the costs of Belomosidil.

There is no competitor in the refectory setting. Therefore I think the commissioners should reevaluate this agent and take into account the prolonged inpatient stays for this patient group and health care cost of the comorbidities developed secondary to both cGvHD and cGvHD treatment.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Question: 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?

No

Comments:

Belumosudil is a novel, cost-effective, first in class agent which will have huge impact of steroid and ECP refractory chronic Graft verses Host Disease (cGvHD). Up to 30% of all patients who have undergone an allogeneic stem cell transplantation will develop steroid refractory cGvHD, of which about 35% will be refractory to Extracorporeal Photopheresis (ECP). The patients who are refractory to two lines of treatment represent a huge unmet care need in terms of both morbidity and mortality. Steroid and ECP refractory patients are likely to be highly immunosuppressed making them vulnerable to transplant complications - for example my trust have patients treated in high dependency wards for cGvHD for over a year, which is terrible outcome for patients but also has a huge healthcare costs for the NHS vs the potential benefit from an effective oral outpatient agent. Patients with refractory cGvHD will be treated with immunosuppressive agents which makes puts them at high risk of developing complications including, but not limited to:

Cytomegalovirus, Pneumocystis jiroveci pneumonia, invasive fungal infections, pneumococcal pneumonia Infections all recurring inpatient stay with individually dosed aseptic unit compounded intravenous therapy. Resulting in high cost treatment in terms of pharmaceutical costs, medical and nursing care, and bed blocking.
Disease relapse - increasing the risk of mortality and the possibility of the high cost of a second transplant.

In addition many of the patients who suffer from refractory cGvHD will never be able to work and will require full time care from family and friends. Its is unrecognised, but as an oncology pharmacist working in a transplant centre I have heard many patients say that they would have declined their life saving stem cell transplant if they had known that cGvHD would have affected their quality of life as much as it has. Belomosidil is an effective, oral, outpatient medication that will help many of these patients reduce their non-relapse mortality, vastly improve their quality of life and reduce their costs of healthcare by reducing their inpatient stays.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Question: Has all of the relevant evidence been taken into account?

all relevant evidences were taken in consideration. But NICE should be aware of the following points:
- a randomised trial between placebo vs belumosudil in third line setting would not be fair or safe. Steroid refractory GVHD patients in third line have an important burden of symptoms causing organ damage and making life expectancy shorter. A trial that would compare single agent belumosudil vs single-agent placebo would mean that frail GVHD patients would not be treated and therefore NICE would say that the trial falsely supported belumosudil.
The ROCKstar trail has been designed to treat all the patients eligible for it. Also, the eligibility criteria reflected what happens currently to steroid-refractory chronic GVHD.
-the current standard of care in third line setting is toxic. The side effects of the current standard of care expose patients to infections, cytopenia, secondary malignancy and frequent appointments to ECP clinic and haematology clinic for line care
-The current best available therapies are not really modifying the natural history of chronic GVHD.

NICE should consider that REACH trial is not right comparator for ROCKstar study.
Within REACH study:
25% of patients were steroid dependant
40% of patients had only 1 week of steroid therapy before the enrollment.
Based on what is written and on the ROCKstar study inclusion criteria, there is evidence that belumosudil has been offered to the right population.
Also the ruxolitinib decreases its response rate after 4 weeks of therapy and this is suboptimal in this complication.
In ROCKstar study it seems to have a durable response.
Also, the reach trials have more reported cytopenia and infective complications.
In conclusion, the medical literature showed that belumosudil has a role in treating GVHD.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The analysis of NICE underestimates the financial burden of chronic GVHD on NHS.
cGVHD management is complex and associated with greater inpatient and outpatient health care resource utilisation and elevated healthcare costs, even
after patients require current available therapies for third line therapy.
According to a recent study, Patients with cGvHD had a greater mean number of inpatients (IP) admissions (10.0 vs 6.3 ppy), annualised bed days (14.9 vs
7.2 ppy) and outpatient (OP) appointments (29.0 vs 15.5 ppy) than those with no GvHD. Amongst admitted patients, the mean
cost of admission was ~50% higher for patients with cGvHD compared to those with no GvHD (£18,567 vs
£12,468 ppy).
After initiation of third line therapies (HCT/high cost therapies), the mean number of IP admissions was higher (14.6 vs 8.2 ppy) than without HCTs, and
was reflected in the costs (£21,137 vs £15,956 ppy, respectively). There were greater numbers of OP appointments
once patients required HCTs (35.2 vs 26.7 ppy).

I think the information provided by the stakeholders is truly reflective of the financial burden of refractory GVHD on NHS.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

No. NICE should approve belumosudil for steroid refractory GVHD because of:
-efficacy
-safety profile
-positive impact on quality of life
-design of ROCKstar trial

Question: 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?

NICE should consider that ethnic minorities have less possibility to have a fully matched donor for allo-HSCT.
the use of mismatched or alternative donors exposes this patient to a risk of developing chronic GVHD of nearly 50%.
Within the chronic GVHD population, nearly 50% of them will have steroid refractory disease and end up with third-line therapy.

At the current stage, the lack of belumosudil therapy exposes ethnic minorities to the risk of developing a severe complication that lacks an effective therapy in the third line.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

I think the data regarding the true economic cost of management of chronic GVHD failing 3 lines of therapy is lacking/incomplete and this is a signficant long term economic burden to the NHS.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No - see comments below

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Question: 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?

Patients who are of non caucasian ethnic origin are at higher risk of chronic GVHD as they are more likely to have an allogeneic HSCT from a mismatched unrelated donor or a haploidentical or umbilical cord donor.

Patients from a non caucasian ethnic background are at higher risk of chronic GVHD as more likely to have a mismatched allogeneic HSCT donor or haploidentical donor.

Comment on committee discussion, positioning of belumosudil, section 3.2:

'They highlighted that although extracorporeal photopheresis is a good option for people with chronic GVHD' - ECP is not always a good option for chronic GVHD eg in particular for Lung GVHD/joint/fascial GVHD/GI GVHD and liver GVHD the complete response rates to ECP are low. it is most effective for skin/oral/ocular GVHD but for many organ manifestations of GVHD it is either ineffective or takes many months to work. ECP is used widely in these settings because there are no other effective treatment options for steroid refractory or steroid dependent cGVHD so ECP is used

by default in these situations because we have no other better option available to treat our patients.

Comment on committee discussion, Utility value for the 'failure – new chronic GVHD systemic therapy' health state, section 3.12:

For patients with chronic GVHD failing 3 or more lines of therapy - they have an extremely poor quality of life and this has a long term impact on patients and carers and they have to learn somehow to live with this illness and all that that entails. This condition doesn't just spontaneously get better - the majority of patients will never ever return to the quality of life that they had prior to HSCT and for most that is a signficantly lower quality of life compared to patients who never had GVHD or who had chronic GVHD that has responded to treatment. Most patients spend significant periods of time in hospital clinics or as inpatients, for many that are having ECP they spend 2 days/week having ECP, they have the ongoing anxiety about death and complications of their illness and their disease relapsing, the social isolation from their peers and impact on their relationship with their spouse or partners and children, impact on sexual and mental health, impact and change of appearance due to skin GVHD or chronic steroid use, having to undergo multiple invasive procedures such as line insertions, bronchoscopy, endoscopy, colonoscopy frequently throughout their illness. many of the things that most people take for granted such as being able to work, drive, travel abroad, live independently are not easy and sometimes impossible for patients with refractory chronic GVHD. I don't fully understand the model that has been used to show the quality of life for this cohort but it significantly over estimates the quality of life for this group of patients.

Comment on committee discussion, Disease management costs for the 'failure – new chronic GVHD systemic therapy' health state, section 3.13:

Patients with chronic GVHD that fail 3 or more lines of therapy have ever escalating treatment costs and remain a significant economic burden to the NHS long term. For this cohort of patients there are no effective treatment options and for the majority of patients in this setting their cGVHD is a long term health problem that never resolves and very frequently results in new comorbidites as a result of their GVHD treatment or specific organ involvement with GVHD. For those that don't die early as a result of their chronic GVHD, they continue to live with chronic GVHD and the consequences of this life long. Due to lack of access to effective treatments on the NHS, they develop established severe irreversible chronic GVHD that is refractory to further lines of therapy. As a result of prolonged immunesuppression they are at very high risk of recurrent infections. They require years of high cost antifungal and anti viral and anti bacterial prophylaxis to try to reduce this risk of infection. Patients with chronic GVHD are seen by multiple different specialities in addition to their primary HSCT team eg cardiology, renal, respiratory etc. The economic burden to the NHS of chronic GVHD treatment for patients that fail 3 or more

treatment lines is being hugely underestimated here. In addition, England is a significant outlier compared to other countries within the UK, Europe and worldwide - the options that we have available at this time are substandard and inferior compared to what we should be using to treat this condition and we are increasing the risk of treatment related morbidity and mortality to the huge detriment of our patients.

Name	[redacted]
Organisation	Birmingham Centre for Cellular Therapy and Transplantation, University Hospitals Birmingham
Conflict	N/A

Comments on the DG:

Question: Has all of the relevant evidence been taken into account?

In terms of trial evidence of comparators to other therapies yes.
But - the significance of the REACH 3 BAT arm being comprised of patients receiving 2nd line treatment as opposed to 3rd line treatment (or more - as in ROCKSTAR) cannot be underestimated.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

no. As per comments supplied.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

no

Question: 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?

Inherent to the condition of cGvHD is huge heterogeneity, and therefore discrimination.

The patients most in need of Belumosudil will have marked (severe) sclerodermatous chronic GvHD, which makes the delivery of ECP very challenging, including the practicalities of venous access / insertion of semi-permanent lines, and the challenge+ costs of attending units for regular treatment.

I would therefore say that there is significant risk within this assessment of discriminating against patients with severe sclerodermatous and /or lung GvhD for whom the alternative therapies are significantly inferior.

Even when responses are seen with ECP, they take a long time to manifest, during which time patients remain on cocktails of immunosuppressive therapy, and remain at increased risk of death.

Comment on committee discussion, unmet need, section 3.1, "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":

Chronic GvhD is the leading cause of late mortality following allogeneic stem cell transplantation

Comment on committee discussion, positioning of belumosudil, section 3.2, "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 reality is a mixture of both.
Within the NIH consensus approach to clinical trials in cGvHD if CNIs are started within 4 weeks of steroids they are considered to be part of the 1st line treatment. If they are started beyond 4 weeks they constitute a 2nd line of treatment.
This is usually how professionals in this area view them.

Comment on committee discussion, positioning of belumosudil, section 3.2, "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.":

Please see above commentary. I disagree that CNIs should not be considered another line of treatment in this context.

Comment on committee discussion, The REACH-3 comparator trial, section 3.5, "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. T":

Agree - they have received less treatment and may be less morbid.

Comment on committee discussion, The REACH-3 comparator trial, section 3.5, "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.":

except for ibrutinib which is used in USA

Comment on committee discussion, Disease management costs for the 'failure – new chronic GVHD systemic therapy' health state, section 3.13, "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 company's assumption is entirely in keeping with my experience as a cGvhD expert looking after patients in the failed state.

Comment on committee discussion, Cost-effectiveness estimates, section 3.17, "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)":

I do not understand why quartiles have been chosen for the model given that the committee has already seen that even in the setting of the best 2nd line agent (Ruxolitinib - via REACH 3 trial), the CR rate was only 6% following 2nd line treatment.

A huge problem with the overall model is the heterogeneous clinical syndrome of cGvhD, and the fact that
1- not all partial responses are equal, and do not reflect the continued infectious burden patients can face even with PRs if they remain on systemic immunosuppresion.

2- it is not clear how 'burned out' GvHD is reflected in the model.

I am concerned that the committee are considering burned out GvHD within the failure state, and therefore assuming reduced costs accordingly.

In reality these patients do not cycle around treatments, and are frequently transferred to standard allo-SCT follow up, or late effects services.

Reflecting on my own practice I do not consider 'burned out' patients (who by definition can only achieve PR), to remain in the failure state.

Consequently, reduced costs of care, and improved utility number' would only be achieved if patients enter the failure free state or when they die. A 'snap shot' of survival following ECP in the UK (real world audit by UKPS 2018 - Kinsella et al Leuk Lymphoma), found that 98% of patients who failed ECP died. I am not sure that this mortality has been appreciated.

At a recent discussion as part of the Anthony Nolan retreat (6/10/23), attended by BMT directors across the UK), no one recognised a model whereby cGvhD patients in the failure state I describe, cost equal or less than the failure free cohort. In fact the audience were in agreement with a

model that supported continued significant health care resource use and costs.

Comment on committee discussion, Equality, section 3.17, "Equality":

There is a significant problem in acute and chronic GVHD where unlicensed medications (with less randomised evidence) are being commissioned and used in England for these indications (including ECP), whilst agents with licenses are not available or commissioned.

England is consequently a significant outlier internationally where Belumosudil and others (e.g. ruxolitinib) are increasingly being used standardly.

This inequality extends within the devolved Nations - where Scotland and Wales have more access than England, giving rise to a significantly unfair post code lottery of access in the Uk

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Question: Has all of the relevant evidence been taken into account?

I am writing this comment as a parent of a child who has undergone an allogenic stem cell transplant and then gone on to develop chronic graft versus host disease which has failed to respond to 2 or more systemic treatments. I am not a medic or from a scientific background, so I accept I am unable to respond with any authority on the clinical findings in this consultation document.

I have found it difficult to understand fully the data and evidence presented in the report. What I am aware of is that the conclusion of the report is not to recommend Belumosudil as a third line treatment and I think this decision is influenced in part by the cost and the lack of supporting evidence of it having a beneficial effect. I have never commented on a NICE consultation before, so forgive me if I am not following the correct format. I intend to summarise all my comments in one statement. Please let me know if this is not acceptable. I would also be willing to provide more information if required and am very happy to be contacted.

In terms of an Equality Impact Assessment - the result of the decision not to recommend the use of the drug will have a disparate adverse impact on a group of patients who will all share at least one ""protected characteristic"" under the Equality Act 2010 - namely having a disability. This patient cohort is likely to be vulnerable (be that due to their age and/or health condition) and therefore statistically less able to respond to the consultation and also emphasise the negative impact the report's findings will have for them. I therefore think it is vitally important that their voice is heard as part of the

consultation and the Equality Act implications of any decision made given careful consideration.

Please bear in mind that in order to be in the unfortunate position of being an eligible patient for Belumosudil, a patient will have already gone through a significant amount of medical treatment, illness and general suffering. Patients often describe the ordeal of going through a stem cell transplant as like ""going to hell and back"". Often survivors of a stem cell transplant suffer long term mental health struggles due to the trauma of the process and struggle to reintegrate into ""normal life"". The patient's carers (partners, parents and wider family) are also hugely affected by seeing their loved one so gravely unwell and by caring and supporting them to recover. If very sadly the patient then goes on to suffer complications such as GVHD, the physical and psychological impact of this diagnosis on the patient and their wider support network is unimaginable. What is the point of surviving a stem cell transplant and being cancer free, if the patient then has significant ongoing health conditions which severely impact their long term quality of life? The patients and their families would do anything to improve their situation; searching world wide for possible treatment options. I understand that Belumosudil is widely used in the US to treat GVHD and has had positive results. To learn that NICE is not willing to approve this drug is shocking and such heartbreaking news. It takes away some hope for the limited number of patients who might be eligible to be offered this drug. I appreciate that there is a cost involved in approving this drug, but surely this is not a situation where NICE would be opening the flood gates to thousands of patients being prescribed this drug every year? Given that it is only being recommended as a third line treatment option, surely this means that the cohort of eligible patients each year is relatively small. What is NICE's rationale? I appreciate that the cost of a stem cell transplant on the NHS is extremely high. Is it the case that these patients are now regarded as having had their share of the NHS budget, irrespective of their ongoing clinical need for input from the NHS? Patients left untreated are likely to continue to need medical support, treatment and in patient stays in the NHS for the rest of their lives. They may be unable to work (and therefore contribute to the NHS via taxes) nor to live independently, requiring carers to give up their jobs or reduce their hours.
It is not as though by them not being offered Belumosudil, they will not require any further medication or expenditure from the NHS.

Any treatment option which has low side effects and can be taken as an outpatient at home (as opposed to an alternative like ECP) has to be a good option for both the patient and the NHS alike. It offers hope and this is so vitally important for this cohort of patients. Many of whom (like my son) are only at the beginning of their lives and who are desperate to thrive and live as normal a life as possible. How can the NHS claim to be a world leader in health care if it is not prepared to offer a drug which is offered in other western countries? How can it justify effectively abandoning this group of patients and dismissing the significant impact which chronic GVHD has on the sufferer and their families. There are so few effective treatment options

available and when a drug such as Belumosudil arrives on the scene, it is an important development in the research into treating GVHD.

Another issue to raise is that (speaking as a parent of a paediatric patient) without NICE approval, it is not possible for children to access this drug at all in the UK. Even if they are able to privately fund the cost of the drug, we have been told that our regional centre would not be able to administer the drug to us privately, as there is no option to do a ""Hybrid"" model where the patient pays for the drug, but then accesses the NHS for the blood tests and wrap around care. Paediatric patients are not offered oncology care by private healthcare providers in the UK, so essentially by failing to approve the drug, NICE is effectively preventing children from accessing this drug - surely this has Equality Act implications too?

Question: 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?

Yes - please see statement above.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Those provided by the company are much closer to clinical experience than those put forward by the panel.

Comment on committee discussion, unmet need, section 3.1:

There is a very significant unmet need for effective GvHD therapy. Chronic GvHD has a massive impact on patient quality of life with a very large associated healthcare cost not only in terms of medication but also capacity. While additional research is needed there is thought to be health inequality related to both socioeconomic status and ethnicity in terms of ability to access therapies.

Comment on committee discussion, Positioning of belumosudil, section 3.2:

The pathway for patients who have failed second line therapy is very fractured due to lack of commissioned treatments. Many patients receive prolonged and large doses of steroids and multiple different immunosuppressive drugs cycled and/or given in combination. There are

usually repeated hospital admissions with infection and a burden to the patient and carers in terms of outpatient appointments.

Comment on committee discussion, Clinical evidence, section 3.2:

Choice of comparator is very difficult in cGVHD due to variability of treatment used. Data in transplant is lacking and therefore use of REACH 3 data is best available currently, particularly ensuring that with crossover in the trial that truncated data is used. This would potentially be an area for prospective data collection to improve future NICE submissions for treatment of GvHD

Comment on committee discussion, The company's economic model, section 3.8:

Failure free survival is the main endpoint used in trials of therapy in GvHD and is appropriate clinically.

In modelling patients failing treatment, there are massive associated costs related to infection and morbidity as a result of damage caused by GvHD. As examples this week I have seen two patients who failed to fully respond to treatment, one has required a lung transplant and another has had over £20000 of eye surgery to try and preserve sight. They have both had prolonged antibiotics and multiple hospital admissions.

Comment on committee discussion, Conclusion, section 3.19:

This is disappointing for those treating patients with GvHD. I am surprised that the evidence provided was considered inadequate to demonstrate clinical utility. Additionally, components of the health economic models used by NICE to reach a negative conclusion for funding are significantly distanced from clinical experience.

Name	[redacted]
Organisation	Yorkshire Blood and Marrow Transplant Programme
Conflict	N/A

Comments on the DG:

Comment on committee discussion, unmet need, section 3:

We feel that the unmet need here is huge. The committee quite rightly points out that steroids +/- a calcineurin inhibitor, and possibly ECP will form the backbone of GvHD treatment for many patients. When these therapies have been used (and the evidence for ECP is quite variably across studies, particularly the organs that will respond) we would ask what else there is?

The evidence for the other commissioned treatments (rituximab, mycophenolate, pentostatin for example) is weak, and the only other therapy with significant high quality evidence behind it (ruxolitinib) is not available in England for patients without personal wealth or private healthcare insurance.

The evidence for belumosudil is better quality than for the other options we have access to, and shows important features in the trials such as improvement in lung GvHD in some patients, which is perhaps the biggest unmet GvHD need.

Comment on committee discussion, Positioning of belumosudil, section 3.1:

The committee's discussion on whether to treat a calcineurin inhibitor (CnI) as a second line of therapy seems rather academic in some ways, and possibly detrimental to patients in others.

Aside from ECP we can have very little confidence in our GvHD therapies after steroids and a calcineurin inhibitor. If ECP is not a suitable second line therapy for a patient and a CnI does not count as second line, then the result of the positioning suggested by the EAG will be that patients are exposed to toxic and ineffective treatments such as mycophenolate simply as a stepping stone to belumosudil.

Comment on committee discussion, The REACH-3 comparator trial, section 3.4:

REACH-3 was conducted in a patient population significantly less heavily pre-treated for GvHD than those in the ROCKstar trial. We suspect that belumosudil is therefore more efficacious than supposed by comparison with the control arm of REACH-3.

Comment on committee discussion, Utility value for the 'failure – new chronic GVHD systemic therapy' health state, section 3.11:

We are not sure on what basis the committee wishes to suppose utility in the failure state to be equal to utility in the failure free state. Usually the best marker that GvHD is out of control and burdensome to the patient is the wish to start a new line of therapy. We therefore suggest it is not clinically plausible to presume utility to be maintained when moving from the failure free to the failure state. We do not think an argument that the new therapy might stabilise GvHD and maintain or improve utility is justified, as the data seem to suggest that our alternative therapies will be less efficacious than belumosudil.

Comment on committee discussion, Disease management costs for the 'failure – new chronic GVHD systemic therapy' health state, section 3.12:

We believe that patients in the failure state will require significantly more healthcare resource than patients in the failure free state.

Comment on committee discussion, Equality, section 3.17:

The GvHD treatment in which we have greatest confidence (after steroids and a calcineurin inhibitor) is ECP. Those in lower socio-economic groups are less likely to be able to take time off work or afford to travel for ECP, and children of school age miss significant amounts of education in order to travel for ECP. For these groups in particular an oral alternative would be very welcome.

In England we are falling behind other regions of the UK such as Scotland where belumosudil is already available.

We should also bear in mind that given ruxolitinib for treating GvHD is not available in England, a decision not to support belumosudil would mean patients in England not having access to the two GvHD treatments with high quality trial evidence behind them. This puts transplant patients in England at a significant disadvantage to their counterparts in Scotland and most of the rest of the developed world, where one or both of these therapies are available.

In the transplant community we compare our outcomes across the UK and across Europe. If, due to the lack of GvHD treatments available in England, we see survival falling behind the rest of the UK and Europe, this may drive us to change our transplant practice to minimise GvHD risk. The most obvious changes to make would be intensifying GvHD prophylaxis and going back to bone marrow harvests. A move towards bone marrow harvests would be a significant burden both for the healthcare system and for donors, and manoeuvres to reduce GvHD risk usually come at the cost of increased cancer relapse.

Of course belumosudil (and ruxolitinib) have licences for GvHD treatment in England meaning that those with personal wealth or private healthcare insurance can access them. This puts those patients without such access at a significant disadvantage.

Belumosudil for treating chronic graft versus host disease after two or more lines of systemic therapy [ID4021]

EAG critique of the Company response to the draft guidance

November 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135825.

1 Introduction

This document provides the External Assessment Group's (EAG's) critique of the Company's response to the draft guidance (DG) document produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of belumosudil for treating chronic graft versus host disease (cGvHD) after two or more lines of systemic therapy [ID4021].

The Company has provided a revised base case in response to Committee preferences outlined in the DG. Assumptions informing the Company's revised base case are presented in Table 1.

Table 1. Assumptions informing the Company's revised base case and alignment with EAG preferences

Company revised base case assumption	Aligned with EAG/ Committee preferred assumption	Rationale if different to EAG preferred assumption
Removal of OS benefit for belumosudil+BAT.	Yes	N/A
Removal of response outcomes – Company scenario.	Yes	N/A
Concomitant medication costs for belumosudil only.	Yes	N/A
Removal of cost of background therapies.	Yes	N/A
KM TTD data for belumosudil and Exponential distribution for BAT TTD.	Yes	N/A
Removal of accommodation costs for patients on ECP.	Yes	N/A
100% of patients spend 60% of their remaining life on subsequent treatments.	No	Company original position maintained.
Utility value of [redacted] for failure – new cGvHD systemic therapy based on Company survey data.	No	Updated with new data from UK cGVHD patients (Company survey in collaboration with Anthony Nolan)
Caregiver disutility for failure – new cGvHD systemic therapy equal to failure – recurrent malignancy (-0.142)	No	Company original position maintained
Disutility and duration for central line-related infection based on disutility for infections and infestations from TA689	Yes	N/A
Removal of IV disutility for BAT.	Yes	N/A

Abbreviations: BAT, best available therapy; cGvHD, chronic graft versus host disease; EAG, External Assessment Group; ECP, extracorporeal photopheresis; IV, intravenous; KM, Kaplan Meier; N/A, not applicable; OS, overall survival; TTD, time to treatment discontinuation;

The Company also made a correction to the calculation of incident failure events associated with new cGvHD systemic therapy and recurrent malignancy in their updated model. The EAG considers the correction is appropriate and notes its minor impact on the cost-effectiveness results.

The Company's revised base case is presented in Table 2 and the EAG's base case with the Company's correction applied is presented in Table 3. Results reported include the Company's proposed patient access scheme (PAS) discount of [redacted]. A confidential discount is available for rituximab. The source of the confidential price for rituximab is the commercial medicines unit (CMU). As such, the EAG has produced a confidential appendix to this document. Analyses included in the confidential appendix include the Company revised base case results, scenario analyses and EAG base case and scenario analyses.

The EAG considers that the direction of the deterministic and probabilistic results is aligned (Table 2 and Table 3). However, the EAG notes that in the updated model the probabilistic sensitivity analysis (PSA) includes parameters associated with time-to-treatment discontinuation (TTD) Kaplan-Meier (KM) curve that is now used to inform drug acquisition costs for belumosudil in the Company base case (aligned with the EAG preference). As such, total costs for belumosudil based on the PSA are always higher, resulting in reduced incremental costs. Therefore, the deterministic incremental cost-effectiveness ratios (ICERs) are likely to be an underestimate and probabilistic ICERs are more robust for decision-making.

Table 2. Company's revised (post ACM1) base case results (with Company correction) – no severity modifier applied

Interventions	Total Costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
BAT	246,432	[redacted]	[redacted]	-	-	-	-
Belumosudil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
BAT	246,978	[redacted]	[redacted]	-	-	-	-
Belumosudil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ACM, appraisal Committee meeting; BAT, best available therapy; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

Table 3. EAG's base case results (with Company correction) – no severity modifier applied

Interventions	Total Costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							

BAT	235,716	[redacted]	[redacted]	-	-	-	-
Belumosudil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
BAT	236,324	[redacted]	[redacted]	-	-	-	
Belumosudil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ACM, appraisal Committee meeting; BAT, best available therapy; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

In the DG, the Committee requested the Company explore the following uncertainties:

- Extrapolating data from the best available therapy arm of REACH-3 by truncating failure-free Kaplan–Meier (KM) survival data at week 24 and extrapolating beyond that point, following the NICE Decision Support Unit technical support document 14 approach.
- Further justification for the Company's choice of categories of people in the Hospital Episodes Statistics (HES) data, and the description of the process used to derive the costs for the 'failure – new chronic GVHD systemic therapy' health state.
- 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%).
- 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.

In their response to the DG, the Company provided further analysis addressing each of the Committee points and these are discussed further in Section 2 but none of the new analysis informs the Company revised base case.

2 EAG critique of Company's additional analysis

2.1 Failure-free survival for best available therapy from REACH-3

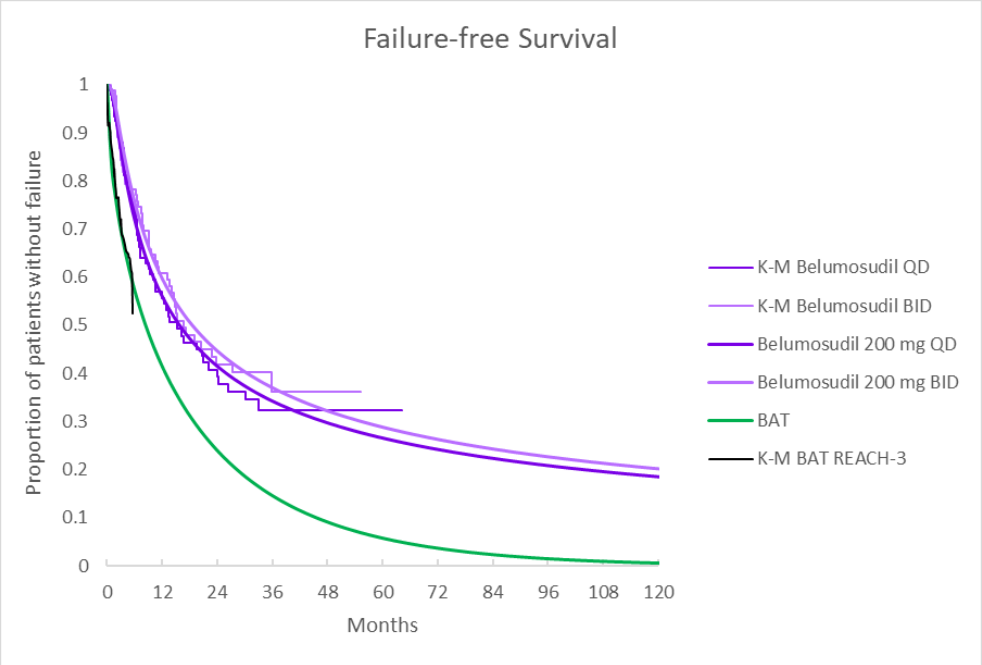
In REACH-3, for patients who did not have or maintain a complete or partial response, had unacceptable side effects from a control therapy, or had a flare of chronic graft versus host disease (cGvHD), crossover from control therapy to ruxolitinib could occur on or after week 24.[1] Additionally, patients in the control group who had a complete or partial response at week 24 could not cross over to ruxolitinib unless they had disease progression, mixed response, or unacceptable side effects from the control therapy.[1] Overall, 38% of best available therapy (BAT) patients crossed over to ruxolitinib on or after week 24. The EAG notes that response in REACH-3 was defined as best overall response (complete or partial) up to week 24 and that failure-free survival (FFS) was defined as relapse or recurrence of underlying disease or death due to underlying disease, non-relapse mortality, or addition or initiation of another systemic therapy for cGvHD, whichever came first.

As REACH-3 was an open-label study, the Committee were concerned that the drop in the Kaplan-Meier (KM) curve for BAT at approximately six months could be due to investigator bias; that is, the investigators inappropriately changing treatment to ruxolitinib for patients in the BAT arm of the trial, resulting in biased FFS results. As such, in the draft guidance (DG), the Committee requested a scenario where FFS KM data for BAT from REACH-3 was truncated at week 24 and then extrapolated for use in the economic model. In their response to the DG, the Company performed the requested analysis.

The Company truncated the FFS KM data for BAT from REACH-3 at week 24 and extrapolations of the truncated KM data were then explored using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma). The Company assessed the fit of each modelled curve against the observed KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the economic model.

For the Committee requested scenario, the Company selected gamma distribution for BAT based on statistical fit and clinical plausibility but maintained the base case generalised gamma distribution for belumosudil 200 mg once daily (QD) and belumosudil 200 mg twice daily (BID) (Figure 1). The mean FFS when using the gamma curve to extrapolate truncated KM data for BAT was [redacted] years.

Figure 1. Modelled failure-free survival – generalised gamma distribution for belumosudil, gamma distribution for BAT (based on truncated REACH-3 data)



The decision support unit (DSU) technical support document (TSD) 14 states that, "*it is important to note that fitting different types of parametric model (for example a Weibull for one treatment arm and a log normal for the other) to different treatment arms would require substantial justification, as different models allow very different shaped distributions*".[2]

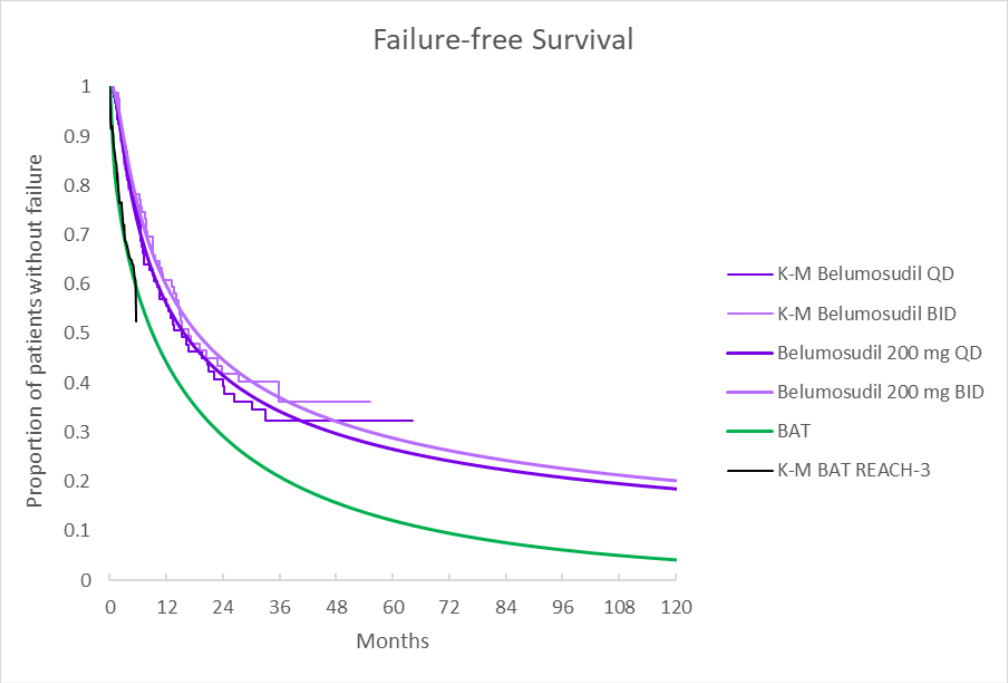
For the scenario, the Company did not justify use of different distributions for the belumosudil+BAT and BAT arms of the model. However, the EAG notes that gamma distribution provided a poor fit to the observed belumosudil pooled data from ROCKstar and KD025-208, and use of the generalised gamma curve for BAT results in mean failure-free survival of [redacted] years, which is more pessimistic than the EAG's base case and may not be clinically plausible.

The EAG explored other parametric distributions for belumosudil+BAT and BAT but while most of the distributions had a good fit to the truncated observed data for BAT, many of the extrapolations (exponential, Gompertz, lognormal, log-logistic and generalised gamma) resulted in implausible long-term extrapolations (lacking clinical validity). For the belumosudil+BAT arm, the best fitted curves were the generalised gamma, lognormal and log-logistic. When using the same distribution for both arms, because of the truncation of the observed BAT data, many of the BAT extrapolations

crossed the belumosudil extrapolations (lognormal, log-logistic and Gompertz), which is considered clinically implausible.

Given that BAT is made up of a number of treatments with different mechanisms of action and belumosudil is the only ROCK2 inhibitor, it may be plausible to assume different distributions for each arm. In the EAG report, the generalised gamma was deemed reasonable for the belumosudil+BAT arm and so maintaining this for the scenario could be considered reasonable. For the BAT arm, the EAG considers that in addition to the Company's preference for the gamma curve, the Weibull curve (Figure 2) is also a reasonable choice and has a similar statistical and visual fit to the gamma curve. The mean FFS when using the Weibull curve to extrapolate truncated KM data for BAT was [redacted] years.

Figure 2. Modelled failure-free survival – generalised gamma distribution for belumosudil, Weibull distribution for BAT (based on truncated REACH-3 data)



Results of the scenario using truncated KM data for BAT from REACH-3 using the gamma and Weibull curves are presented in Section 4.1 and these are incorporated into scenarios including the all the Committee's preferred assumptions, presented in Section 4.2. The EAG advises the Committee to consider the clinical plausibility of patients on BAT remaining failure-free for [redacted] (Company and EAG base case), [redacted] (gamma extrapolation of truncated KM data for BAT) or [redacted] (Weibull extrapolation of truncated KM data for BAT).

2.2 Disease management costs for the failure – new systemic cGvHD treatment

In the DG, the Committee had three main concerns with use of the Hospital Episodes Statistics (HES) data to estimate disease management costs (outlined in Table 4) and requested the Company to provide further justification for their 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. In their response to the DG, the Company attempted to address the Committee's concerns and these are also presented in Table 4, along with the EAG's comments.

The Company provided scenarios addressing the Committee's concerns, described in Table 4 , which the EAG has incorporated into further scenarios which include all the Committee's preferred assumptions, presented in Section 4.2.

Table 4. Committee concerns with HES data, Company justifications and EAG comment

Committee comment on HES data	Company's justification for assumption	EAG comment
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. As such, the Committee requested scenario analyses in which disease management costs for proportions of people in the 'failure – new chronic GVHD systemic therapy' health state linearly reduce to baseline (for example, 25%, 50% and 75%).	The Company stated that there is a lack of real-world data to estimate long-term costs for patients whose failure is related to a change in systemic treatment for their cGvHD. Instead, the Company conducted a survey with 15 clinical experts with experience in the management of cGvHD. The Company's survey found that all the clinical experts considered that 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. As such, the Company considered that assuming a constant costs was a conservative assumption. Nonetheless, the Company supplied scenarios requested by the Committee which explore a linear reduction in disease management costs for incident patients in the failure – new cGvHD systemic therapy health state over 5 years to the year 5 disease management cost for 5 failure-free PR/LR patients. The Company's scenarios also explored different proportions of patients incurring reduced costs, as per the Committee request (25%, 50% and 75%). Results of the scenarios are presented in Section 3.	The EAG highlights that the year 5 failure-free PR/LR disease management cost in the Committee's requested scenario is assumed to be the same as the disease management for complete responders. As such, there is an inherent assumption in the scenario that over five years, patients in the failure – new cGvHD systemic therapy health state will accrue the same health state costs as a patient who is failure-free and has a complete response to treatment (i.e. their cGvHD has resolved). Furthermore, it is unknown what percentage of failure patients who start a new treatment will experience a resolution in their cGvHD or how long it will take before they experience another failure event. However, in the EAG's base case, life years spent in the failure-free health state for BAT patients is approximately [redacted] and is unlikely to be longer than that when patients progress to their next therapy. In the DG, it was 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. As such, the EAG considers it may be an optimistic assumption that disease management costs for patients who have failed at least

		three lines of treatment would reduce. Nonetheless, the Company's scenarios which estimated a linear reduction in costs for different proportions of incident patients in the failure – new chronic GVHD systemic therapy health state appropriately explores the impact of this assumption on the cost-effectiveness results.
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.	The Company explained that treatments considered as high-cost therapy in the HES analysis included ECP, rituximab and protein tyrosine kinase inhibitors (i.e., ruxolitinib and imatinib), which were the only identifiable cGvHD therapies within the database. Disease management costs for failure – new cGvHD systemic therapy, which are restricted to 2 or more high-cost therapies, represent a population who would have likely received one of these treatments as their third-line therapy. The Company note it not possible to identify use of other, low-cost therapies (e.g., MMF, sirolimus, and CNIs) within the HES database. The Company did not comment on the assumption that disease management costs for the failure-free partial and lack of response health state was based on the mean first year costs for all patients with cGvHD but noted that all assumptions for disease management costs were based on clinical expert opinion obtained from an advisory board and 1-to1 interviews.	The marketing authorisation restricts the use of belumosudil to patients who have received at least two prior systemic therapies. In the DG, the clinical experts considered that first-line treatment would be corticosteroids with or without calcineurin inhibitors (low-cost treatment) and second-line treatment to be ECP (high-cost treatment). Therefore, at third-line (which is where the Committee considered belumosudil would be in the treatment pathway), patients might have already had one high-cost treatment. However, it was acknowledged in the DG, that access to ECP is dependent on location and for people with cGvHD travel is extremely physically and psychologically challenging. In the DG, it was noted that manifestations of cGvHD typically appear within the first year after an allogeneic HSCT, when immunosuppressive medications are reduced. Therefore, the EAG considers that for the failure-free partial and lack of response health state, the Company's restriction to the mean first-year costs for all cGvHD patients will likely capture a patient's first year treatment pathway which may consist of mostly low-cost treatments and ECP for those who are able to access it. However, it is likely that for many patients, high-cost third-line treatments

		(such as imatinib, rituximab and sirolimus) will be their first high-cost treatment. Thus, assuming two or more high-cost treatments for the failure – new systemic cGvHD therapy could be considered reasonable.
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 Company stated it was not possible to identify relapses of malignancy in the HES data as they were unable to distinguish primary cases from subsequent cases due to the recording of malignancy in patient records. Additionally, subsequent, unrelated malignancies occurring in patients post-alloHSCT could not be distinguished from prior underlying malignancies in the database. However, the Company explained that because the protocol criteria for identifying patients in the failure-new systemic therapy health state required patients to have received two or more high-cost drugs, patients with recurrent malignancy would be unlikely to be prescribed immunosuppressive cGvHD medication, meaning they would not meet the eligibility criteria for the subgroup of interest. Nonetheless, the Company provided a scenario exploring removing a proportion of recurrent malignancy disease management costs ([redacted] based on pooled recurrent malignancy data from ROCKStar and KD025-208) from the disease management costs of the failure – new systemic cGvHD treatment health state. Results of the scenario are presented in Section 3.	The EAG considers that the Company's justification is reasonable, especially considering that the definition of costs associated with the failure-new systemic therapy health state required patients to have received two or more high-cost drugs and so would likely exclude patients who have had a recurrent malignancy (as upon recurrence of malignancy, treatment for cGvHD stops and treatment for the malignancy begins). However, the Company's scenario which removes a proportion of costs that potentially relate recurrent malignancy may be a reasonable approach to explore the impact of a reduction in disease management costs for the failure-new systemic therapy health state.

Abbreviations: alloHSCT, allogenic haematopoietic stem cell transplant; cGvHD, chronic graft versus host disease; CR, complete response; DG, draft guidance; ECP, extracorporeal photopheresis; HES, hospital episode statistics; HSCT, haematopoietic stem cell transplant; LR, lack of response; PR, partial response.

2.3 Utility value for the failure – new systemic cGvHD treatment

As part of the DG, the Committee considered that there was uncertainty around the utility value for the failure – new cGvHD systemic therapy health state and concluded that the EAG's base case assumption using the midpoint value of 0.608 based on data from the Company's Adelphi disease specific programme (DSP) study (0.52) and from Crespo *et al.,* (0.696) as well as the EAG's scenario only using the Crespo *et al.* utility value was useful for decision-making.[3]

In their response to the DG, the Company did not explore the Committee preferences for the utility value for the failure – new cGvHD systemic therapy health state as part of their revised base case. Instead, the Company conducted a quality-of-life study (QoL) in collaboration with Anthony Nolan, to estimate a new utility value for the failure – new cGvHD systemic therapy health state.

For the QoL study, the Company included adult patients diagnosed with cGvHD who have received at least two prior lines of systemic treatment and had ongoing symptoms. Participants (or carers on behalf of the patient they cared for) completed the EQ-5D-5L questionnaire and responses were mapped to the EQ-5D-3L. Descriptive data for patients included in the study are presented in Table 9 of the Company's response to the DG. Based on the QoL study, the Company estimated a new utility value for the health state ([redacted]), which is based only on patient responses, and used this as part of their revised base case. The utility value based on both patient and carer responses (which may include more severe patients as carers are likely to respond on their behalf) was estimated to be [redacted] and this is explored in a scenario analysis, presented in Section 3.

The EAG considers that the Company's QoL study is a cross-sectional survey and so captures a patient's quality of life at just one point in time and this is the same for the Company's Adelphi DSP study. However, the number of responses informing the Company's utility estimate from the QoL study is substantially larger (25 participants) compared to the Adelphi DSP study (10 participants). The EAG is unclear if all participants in the Company QoL study were from the UK, but given that it was in collaboration with Anthony Nolan, it is likely respondents are UK-based.

The EAG considers calculating a midpoint utility value that includes data from Crespo *et al.* is still valid as the utility value from the Company QoL has limitations and may not accurately reflect the utility value for a patient who has a failure event due to a change in treatment. As such, the EAG calculated a new midpoint utility value of [redacted] based on the utility value from Crespo *et al.,* (0.696) and the Company's QoL study using data from patients and carers ([redacted]). Scenario analysis results

using the revised mid-point value, as well as exploring the Company's base case utility value of [redacted] and [redacted] are presented in Section 4.1 and incorporated into further scenarios which include the all the Committee's preferred assumptions, presented in Section 4.2.

2.4 EAG assumptions not resolved by the Company

In their revised base case, the Company has maintained their position on the calculation of subsequent treatment costs and the caregiver disutility for failure – new cGvHD systemic therapy (assumed to be equal to failure – recurrent malignancy [-0.142]). As no new evidence has been put forward for the Company's assumptions, the EAG has maintained its preferred approach to subsequent treatment costs and the caregiver disutility for failure – new cGvHD systemic therapy (assumed to be equal to failure-free [-0.045]) and includes these in the scenarios exploring the Committee's preferred assumptions. For a critique of these two issues, please refer to the EAG report, Sections 4.2.6.5 and 4.2.7.9.

3 Company scenario analysis

Table 5 presents the results of deterministic scenarios (without the severity modifier applied) explored by the Company in their response to the draft guidance (DG). The External Assessment Group (EAG) considers that the direction of the deterministic and probabilistic results is aligned (Table 2 and Table 3). However, the EAG notes that in the updated model the probabilistic sensitivity analysis (PSA) includes parameters associated with time-to-treatment discontinuation (TTD) Kaplan-Meier (KM) curve that is now used to inform drug acquisition costs for belumosudil in the Company base case (aligned with the EAG preference). As such, total costs for belumosudil based on the PSA are always higher, resulting in reduced incremental costs. The Company did not provide the results of their scenarios using PSA and due to a paucity of time, the EAG was unable to provide PSA results for the scenarios. Therefore, the Company's deterministic incremental cost-effectiveness ratios (ICERs) are likely to underestimate the probabilistic results.

Table 5. Results of the Company's deterministic scenario analyses – no severity modifier applied

	Results per patient	Belumosudil	BAT	Incremental value
0	**Company revised base case**			
	Total costs (£)	[redacted]	246,432	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
1	**Gamma extrapolation of truncated FFS KM data for BAT from REACH-3**			
	Total costs (£)	[redacted]	237,995	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
2	**Weibull extrapolation of truncated FFS KM data for BAT from REACH-3**			
	Total costs (£)	[redacted]	221,361	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	3,082
3	**Disease management costs associated with recurrent malignancy ([redacted]) removed from the disease management costs for failure – new systemic cGvHD treatment health state**			
	Total costs (£)	[redacted]	240,396	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
4	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 100% of patients**			
	Total costs (£)	[redacted]	191,724	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]

	ICER (£/QALY)	-	-	18,271
5	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 75% of patients**			
	Total costs (£)	[redacted]	205,401	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	6,879
6	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 50% of patients**			
	Total costs (£)	[redacted]	219,078	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
7	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 25% of patients**			
	Total costs (£)	[redacted]	232,755	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
8	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 10% of patients**			
	Total costs (£)	[redacted]	240,962	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
9	**Utility value for the failure – new cGvHD systemic therapy health state based on patient and carer responses from the Company quality of life study ([redacted])**			
	Total costs (£)	[redacted]	246,432	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
Company scenarios applied to the EAG base case				
0	**EAG base case**			
	Total costs (£)	[redacted]	235,716	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
1	**Disease management costs associated with recurrent malignancy (4%) removed from the disease management costs for failure – new systemic cGvHD treatment health state**			
	Total costs (£)	[redacted]	229,679	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
2	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 100% of patients**			
	Total costs (£)	[redacted]	181,008	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	64,718

3	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 75% of patients**			
	Total costs (£)	[redacted]	194,685	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	41,399
4	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 50% of patients**			
	Total costs (£)	[redacted]	208,362	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	18,079
5	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 25% of patients**			
	Total costs (£)	[redacted]	222,039	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
6	**Linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 10% of patients**			
	Total costs (£)	[redacted]	230,245	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant

Abbreviations: BAT, best available therapy; cGvHD, chronic graft versus host disease; CR, complete response; EAG, External Assessment Group; ECP, extracorporeal photopheresis; FFS, failure-free survival; ICER, incremental cost-effectiveness ratio; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; QALY, quality adjusted life year; TTD, time to treatment discontinuation.

4 Additional analysis conducted by the EAG

This section presents additional scenarios explored by the External Assessment Group (EAG) including combined scenarios incorporating Committee preferences from the draft guidance. Due to time constraints, the EAG was unable to produce probabilistic results for the EAG scenarios and combined Committee requested scenarios. The direction of deterministic and probabilistic results (Table 2 and Table 3) are coherent with one another. However, as mentioned previously, the probabilistic sensitivity analysis (PSA) now includes parameters associated with time-to-treatment discontinuation (TTD) Kaplan Meier (KM) curve that is used to inform drug acquisition costs for belumosudil. As such, total costs for belumosudil based on the PSA are always higher, resulting in reduced incremental costs. Therefore, the deterministic incremental cost-effectiveness ratios (ICERs) are likely to underestimate the probabilistic results.

4.1 EAG scenario analysis

As mentioned in Section 2.3, the EAG updated its estimation of the midpoint utility value for the failure – new cGvHD systemic therapy health state ([redacted]) and results are presented in Table 6. In addition, the EAG ran the following scenarios:

- Utility value for failure – new cGvHD systemic therapy of:
  - 0.696 from Crespo *et al.*[3]
  - [redacted] based on patients only from the Company's quality-of-life (QoL) study.
  - [redacted] based on patients and carers from the Company's quality-of-life (QoL) study.

Table 6. Results of the EAG's deterministic scenario analyses

	Results per patient	Belumosudil	BAT	Incremental value
0	**EAG base case**			
	Total costs (£)	[redacted]	235,716	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
1	**Midpoint utility value of [redacted] for failure new cGvHD systemic therapy utility value**			
	Total costs (£)	[redacted]	235,716	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
2	**Utility value for failure – new cGvHD systemic therapy of 0.696 from Crespo *et al.*[3]**			
	Total costs (£)	[redacted]	235,716	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
2	**Utility value for failure – new cGvHD systemic therapy of [redacted] based on patients only from the Company's quality-of-life (QoL) study.**			
	Total costs (£)	[redacted]	235,716	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
2	**Utility value for failure – new cGvHD systemic therapy of [redacted] based on patients and carers from the Company's quality-of-life (QoL) study.**			
	Total costs (£)	[redacted]	235,716	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant

Abbreviations: BAT, best available therapy; cGvHD, chronic graft versus host disease; EAG, External Assessment Group; ECP, extracorporeal photopheresis; ICER, incremental cost-effectiveness ratio; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; QALY, quality adjusted life year; QoL, quality of life; TTD, time to treatment discontinuation.

4.2 Scenarios incorporating Committee preferences from the draft guidance

In the Company's revised base case, the following Committee assumptions were included:

1. Excluding overall survival benefit in the model.
2. Removing response outcomes from the model.

However, the following Committee preferred scenarios, not included in the Company revised base case, were aligned with the EAG's base case and a scenario around the EAG base case, presented in Section 4.1:

3. 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*. utility value.

As mentioned in Section 2.4, there are two areas where the Company and the EAG disagree, and these are around the calculation of subsequent treatment costs and the caregiver disutility for failure – new cGvHD systemic therapy (assumed to be equal to failure – recurrent malignancy [-0.045]). As no new evidence has been put forward by the Company for their assumptions, and no Committee preference was outlined in the draft guidance (DG), the EAG has maintained its preferred approach and uses its base case to combine Committee requested scenarios.

The following combination of scenarios was explored by the EAG for Committee consideration:

1. Weibull extrapolation of truncated failure-free survival (FFS) Kaplan Meier (KM) data for best available therapy (BAT) from REACH-3.
2. Gamma extrapolation of truncated FFS KM data for BAT from REACH-3.
3. Weibull extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free complete response (CR) disease management cost – 75% of patients.
4. Weibull extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 50% of patients.
5. Weibull extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 25% of patients.
6. Gamma extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 75% of patients.
7. Gamma extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 50% of patients.
8. Gamma extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 25% of patients.

Table 7. Combined Committee requested deterministic scenarios

	Results per patient	Belumosudil	BAT	Incremental value
0	**EAG base case (including and revised midpoint utility value of [redacted] for failure new cGvHD systemic therapy utility value**			
	Total costs (£)	[redacted]	235,716	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
1	**Weibull extrapolation of truncated FFS KM data for BAT from REACH-3**			
	Total costs (£)	[redacted]	212,806	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	39,759
2	**Gamma extrapolation of truncated FFS KM data for BAT from REACH-3**			
	Total costs (£)	[redacted]	228,077	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
3	**Weibull extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 75% of patients.**			
	Total costs (£)	[redacted]	180,015	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	115,444
4	**Weibull extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 50% of patients.**			
	Total costs (£)	[redacted]	190,945	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	90,216
5	**Weibull extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 25% of patients.**			
	Total costs (£)	[redacted]	201,876	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	64,987
6	**Gamma extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 75% of patients.**			
	Total costs (£)	[redacted]	190,043	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	60,102
7	**Gamma extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 50% of patients.**			
	Total costs (£)	[redacted]	202,721	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	36,161
8	**Gamma extrapolation of truncated FFS KM data for BAT from REACH-3 and linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 25% of patients.**			
	Total costs (£)	[redacted]	215,399	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	12,221

Abbreviations: BAT, best available therapy; cGvHD, chronic graft versus host disease; CR, complete response; EAG, External Assessment Group; ECP, extracorporeal photopheresis; FFS, failure-free survival; ICER, incremental cost-effectiveness ratio; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; QALY, quality adjusted life year; TTD, time to treatment discontinuation.

5 Severity modifier

Based on their revised base case, the Company estimated total QALYs of [redacted] for best available therapy (BAT), which results in a severity modifier of 1.2 being applicable to the analysis. Table 8 presents the Company's base case results with the 1.2 severity modifier applied.

Table 8. Company's revised (post ACM1) base case results (with Company correction) – 1.2 severity modifier applied

Interventions	Total Costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
BAT	246,432	[redacted]	[redacted]	-	-	-	-
Belumosudil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
BAT	246,978	[redacted]	[redacted]	-	-	-	-
Belumosudil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ACM, appraisal Committee meeting; BAT, best available therapy; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

The EAG's base case remains unchanged (except for an update to the midpoint utility value for failure new cGvHD systemic therapy utility value) and total QALYs of [redacted] for BAT were estimated, resulting in a severity modifier of 1 being applicable to the analysis. The EAG notes that combined Committee requested scenarios presented in Table 7 resulted in total QALYs for BAT that were all higher than the EAG's estimate. As such, the severity modifier applicable for all combined Committee requested scenarios was 1.

6 References

1. Zeiser R, Polverelli N, Ram R, Hashmi SK, Chakraverty R, Middeke JM, et al. Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. *The New England journal of medicine* 2021; **385**: 228-38.

2. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. NICE Decision Support Unit, 2011.

3. Crespo C, Pérez-Simón JA, Rodríguez JM, Sierra J, Brosa M. Development of a population-based cost-effectiveness model of chronic graft-versus-host disease in Spain. *Clin Ther* 2012; **34**: 1774-87.

In preparation for appraisal committee meeting 2 (ACM2) for belumosudil for treating chronic graft versus host disease (cGvHD) after two or more lines of systemic therapy [ID4021], NICE requested the External Assessment Group (EAG) to run some additional scenarios.

The additional requested scenarios were as follows:

- Utility value of 0.696 from Crespo *et al.* applied to the company revised base case.
- The hospital episodes statistics (HES) estimate for cGvHD patients with first high-cost therapy ([redacted]), presented in Table 4 of the company submission, for the failure-free first year health state cost. Table 1 presents the costs used for the scenario. Scenarios exploring the assumption of linear decline in the failure-free health state cost to the year 5 failure-free complete response health state cost are also provided.

Results of the scenario analyses around the company and EAG base cases are presented in Table 2 and Table 3.

Table 1. Disease management health state costs for committee requested scenarios

Health states	Mean cost per cycle per year					Source
	1st year	2nd year	3rd year	4th year	≥5th year	
Failure-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	HES database. Chronic GVHD patients with first high-cost therapy (Table 4 of the CS)
Failure - New cGvHD systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	First year cost is the same as the company base case with a linear decline down to the ≥5th year cost for failure-free (CR/PR/LR)

Abbreviations: cGvHD, chronic graft versus host disease; CS, company submission.

Table 2. Committee requested scenario analysis around the company base case

	Results per patient	Belumosudil	BAT	Incremental value
0	**Company revised base case**			
	Total costs (£)	[redacted]	246,432	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
1	**Utility value for failure – new cGvHD systemic therapy of 0.696 from Crespo *et al.*[3]**			
	Total costs (£)	[redacted]	246,432	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
2	**Failure-free health state cost assumed to be cost of first high-cost therapy from HES**			
	Total costs (£)	[redacted]	250,389	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
3	**Scenario 2 + linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 100% of patients**			
	Total costs (£)	[redacted]	195,681	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	21,460
4	**Scenario 2 + linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 75% of patients**			
	Total costs (£)	[redacted]	209,358	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	10,068
5	**Scenario 2 + linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 50% of patients**			
	Total costs (£)	[redacted]	223,035	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
6	**Scenario 2 + linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 25% of patients**			
	Total costs (£)	[redacted]	236,712	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant

Abbreviations: BAT, best available therapy; cGvHD, chronic graft versus host disease; CR, complete response; EAG, External Assessment Group; ECP, extracorporeal photopheresis; FFS, failure-free survival; ICER, incremental cost-effectiveness ratio; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; QALY, quality adjusted life year; TTD, time to treatment discontinuation.

Table 3. Committee requested scenario analysis around the EAG base case

	Results per patient	Belumosudil	BAT	Incremental value
0	**EAG base case**			
	Total costs (£)	[redacted]	235,716	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
1	**Failure-free health state cost assumed to be cost of first high-cost therapy from HES**			
	Total costs (£)	[redacted]	239,672	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant

2	**Scenario 1 + linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 100% of patients**			
	Total costs (£)	[redacted]	184,964	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	69,929
3	**Scenario 1 + linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 75% of patients**			
	Total costs (£)	[redacted]	198,641	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	47,041
4	**Scenario 1 + linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 50% of patients**			
	Total costs (£)	[redacted]	212,318	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	24,152
5	**Scenario 1 + linear decline of failure-new systemic therapy disease management costs to failure-free CR disease management cost – 25% of patients**			
	Total costs (£)	[redacted]	225,995	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	1,264

Abbreviations: BAT, best available therapy; cGvHD, chronic graft versus host disease; CR, complete response; EAG, External Assessment Group; ECP, extracorporeal photopheresis; FFS, failure-free survival; ICER, incremental cost-effectiveness ratio; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; QALY, quality adjusted life year; TTD, time to treatment discontinuation.