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External Assessment Group Report
Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia

EAG addendum: review of D120 data cut

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1 DESCRIPTION AND CRITIQUE OF NEW CLINICAL EVIDENCE

1.1 EAG summary of the company's new data cut for efficacy and safety outcomes

The company reported that an analysis of efficacy and safety data had been performed at Day 120 post-marketing authorisation application (the D120 data cut) in response to a request by regulatory authorities. The analyses were therefore not pre-specified in the statistical analysis plan and the database lock for the analyses was 16th April 2023. At the D120 data cut-off, 59 patients were enrolled in CLIMB THAL-111, 54 of which had received exa-cel (this was 48 in the original submission). Updates for other data sets and stages used in the CLIMB studies are presented in Table 1.

Table 1 Patient analysis sets for the new and previous data cuts

Study stage	CS data cut (IA2) September 2022	D120 data cut April 2023
Enrolled Set	59	59
Safety Analysis Set (SAS)	59	59
Started the conditioning regimen	48	54
Full Analysis Set (FAS)	48	54
FAS beyond initial RBC transfusion washout period*	44	53
PES	27	42
Completed CLIMB THAL-111 and enrolled in CLIMB-131	8	23

Notes: Enrolled Set - all enrolled patients who signed informed consent and met eligibility criteria. SAS - all patients who started the mobilisation regiment. FAS - all patients who received exa-cel infusion. PES - all patients who had been followed least 16 months after exa-cel and for at least 14 months after completion of the RBC transfusions washout period.

1.1.1 Efficacy outcomes

The median follow-up duration after exa-cel infusion was 22.8 months (range: 2.1 to 51.1) months). Forty-two patients had at least 16 months of follow-up after exa-cel infusion and were evaluable for the PES at the D120 data cut. Following infusion with exa-cel, 92.9% of patients (39 of 42 patients, 95% CI: 80.5%, 98.5%) in the PES achieved transfusion independence at 12 months (TI12). This proportion is slightly larger than in the previous data cut (IA2: 88.9%). The same increase was observed for TI6.

All 39 subjects in the D120 PES who achieved TI12 remained transfusion independent; the mean duration of transfusion independence was 23.6 months, ranging from 13.5 to 48.1 months. Mean HbF levels and total Hb levels remained constant compared to the levels reported for the IA2 data cut.

At Month 24, mean serum ferritin levels were similar across the data-cuts. No update was provided for levels of liver iron content or cardiac iron content (T2*).

1.1.2 Safety outcomes

Table 2 summarises safety data from the TDT safety set reported in the original CS (N=48) and from the D120 data update up to M24 (N=54) and after M24 (N=23). In the data update, no new or worsening haematological disorders were reported, and no new malignancies or deaths. The SAE occurring in CLIMB-131 was influenza and was not related to the treatment.

Table 2 Safety data from exa-cel infusion to M24 and >24 M[1]

	TDT safety set		**Data update**		**TDT safety set**	**Data update**
	Exa-cel to M24 (N=48)		**Exa-cel to M24 (N=54)**		**> M24 CLIMB THAL-131 (N=9)**	**> M24 CLIMB THAL-131 (N=23)**
	Any grade	**Grade 3–5**	**Any grade**	**Grade 3-5**	**Any grade**	**Any grade**
No. of patients, n (%)						
≥ 1 AE	48 (100%)	41 (85.4%)	54 (100%)	48 (89%)		
≥ 1 SAE	17 (35.4%)		19 (35%)		1 (11.1%)	1 (4.3%)
≥ 1 AE (possibly) related to exa-cel	13 (27.1%)			14 (25.9%)	0	0
≥ 1 SAE (possibly) related to exa-cel	2 (4.2%)			2 (3.7%)	0	0
New or worsening haematological disorders	42 (87.5%)		0		0	0
Key: AE, adverse event; SAE, serious adverse event.						

1.1.3 Summary

The new D120 April 2023 data cut indicates a slightly improved rate of transfusion independence at 12 months and a continuing persistence of effect in patients who achieve TI12. Mean HbF levels and total Hb levels remained constant across the data-cuts, as did mean serum ferritin levels. The lack of an update on results for liver iron content and cardiac iron content is concerning though.

2 DESCRIPTION AND CRITIQUE OF NEW ECONOMIC EVIDENCE

2.1 Updated cost-effectiveness model parameters

The company detailed a number of parameters updated in the economic model to reflect the D120 data cut. These are detailed in Table 3 below.

Table 3 Updated model inputs

Parameter	Description of change	Previous value (IA2)	Updated value (D120)	Justification
CEA model input changes				
Age (years)	Updated mean baseline cohort age to D120	21.4	21.3	D120 data available
Weight ration	Updated weight ratio of TDT/general public to D120	0.76	0.77	D120 data available
Females (%)	Updated % of females in modelled cohort	52.1%	50.0%	D120 data available
Proportion <18 years old	Updated % of cohort < 18 years old	33.3%	35.2%	D120 data available
Annual transfusions per patient	Updated annual frequency of RBCTs per patient	16.4	16.5	D120 data available
Annualised unit of RBC transfusions	Updated annualised units of RBCTs per patient	35.3	36.4	D120 data available
Treatment withdrawal	Updated to reflect latest clinical and efficacy data (D120)	4.0%	5.3%	D120 data available
Initial engraftment success rate	Same as above	100%	100%	D120 data available
Proportion achieve TI	Same as above	92.6%	100%	D120 data available
Proportion achieve TR	Same as above	7.4%	0%	D120 data available

2.2 Health related quality of life

The company provided updated patient-reported outcome scores for the D120 data cut. The company describe how at baseline, the D120 health utility scores in CLIMB THAL-111 were 0.89 in the PES population. This contrasts to 0.87 based on the data used in the original submission. For the PES patients with 24 months of follow-up, the magnitude of gain over 24 months in health utility scores at D120 was 0.04 (n=19), less than the gain observed in patients in the original submission (0.07 (n=8). Updated patient-reported outcome scores were also provided for the other outcome measures included

in the original report. The EAG note that all patient reported outcome scores reported by the company showed numerical increases in quality of life scores, but none of these were statistically significant.

The EAG's preferred assumptions included a utility decrement associated with the condition equal to the difference in health utilities between the baseline PES score and an age-matched general population value of 0.940 reported by Ara and Brazier 2010. The EAG's preferred utility decrement in the original report was [redacted]. Using the data from the D120 data cut, the decrement used in the analysis is [redacted] and as a result, the EAG considers it appropriate to update the preferred EAG base-case assumptions to reflect this.

2.3 Treatment effectiveness and extrapolation

2.3.1 Transfusion dependence

The D120 data cut updates the proportion of the patients who achieve TI status from 92.6% to 100%. As per the original CS, TI status in the economic analysis is defined *post hoc* and is inconsistent with primary and secondary outcomes defined in CLIMB THAL-111. This definition means three patients who do not meet the TI12 criteria for transfusion independence are classified as transfusion independent in the economic analysis.

As noted in the EAR, the EAG considers the use of the *post hoc* definition of transfusion status to be inappropriate. The EAG prefers to use the TI12 primary outcome to inform the proportion of patients achieving transfusion independence. Using the data from the D120 data cut, the proportion of patients achieving transfusion independence increases from 88.9% (24/27) to 92.8% (39/42). The EAG has updated the preferred EAG base-case assumptions to reflect this new data.

2.3.2 Engraftment success and graft durability

The D120 data cut increases the number of patients who have completed 24 months follow from 8 to 23. There were no engraftment rejections (failures) and no recorded events of loss of transfusion independence. The available evidence continues to support the assumptions of a permanent treatment effect in patients achieving transfusion independence. As per the IA2 data cut, direct evidence remains limited by the small sample size and short duration of follow-up.

3 UPDATED ECONOMIC MODEL

The company updated the model to include data at the D120 cut-off based on the availability of updated CSR data and/or post-hoc analysis following the clarification stage. The company also updated DCEA inputs based on the company's clarification response to the EAG requests. The results presented in this section reflect these modifications to the base-case.

3.1 Results of the updated company base-case analysis

The cost-effectiveness results for the company's base-case analysis are presented in Table 4 and Table 5

Table 4 Base-case results with 1.5% discount rate (deterministic)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years						

Table 5 Scenario results with 3.5% discount rate (deterministic)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years						

3.2 Results inclusive of DCEA reweighting

The company base-case results and scenario analysis inclusive of severity and DCEA re-weighting are presented in

Table 6. These results are presented in NHB form as the DCEA weighting assumes that the NICE threshold represents the health opportunity cost forgone from displaced healthcare services.

Table 6 Company base case results inclusive of DCEA reweighting

Scenarios	NHB at £30,000			
	Base-case	Severity weighted	DCEA weighted	DCEA and severity weighted
Company base-case (1.5% discount rate)	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case (3.5% discount rate)	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: NHB, net health benefit; DCEA, distributional cost-effectiveness analysis				

3.3 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 7 updates scenario analysis presented in the EAR accounting for the D120 update and revised company base case.

Table 7 EAG's additional scenario analysis

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
Company base case	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Modelling no complications	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Costs and outcomes from exa-cel withdrawal	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Baseline prevalence of osteoporosis and diabetes based on CLIMB THAL-111	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Baseline iron levels based on CLIMB THAL-111	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Frequency of blood transfusions based on Shah et al., 2021	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. 3.5% Discount rate	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Align transfusion independence to the TI12 primary outcome in CLIMB THAL-111*	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8 (a). Relapse based on published values from Santarone et al. 2022	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 (b). Relapse based on US ICER report	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Assuming 5 years to iron normalisation	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Iron normalisation in patients with low iron levels	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11 (a). SMR of 2.5 for TD patients	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11 (b). SMR of 2 for TD patients	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12. 1.4% mortality risk for myeloablative conditioning	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13 (a). [redacted] utility decrement*	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13 (b). 0.1 utility decrement	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13 (c). 0.15 utility decrement	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14. No infertility-related decrements	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15. Use of eMIT costs	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16. No health state costs	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17. Multiplicative age-adjustment	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Scenario has been updated following the D120 data cut							

3.4 EAG's preferred assumptions

The cumulative impact of the EAG's preferred assumptions on the base-case are presented in Table 8 and Table 9. The EAG base-case adopts the following scenarios described in the EAR:

- Scenario 1: Alternative assumptions mortality associated with complications,
- Scenario 2: Costs and outcomes from exa-cel withdrawal,
- Scenario 5: Frequency of blood transfusions based on Shah et al., 2021,

- Scenario 6: Using a 3.5% discount rate,
- Scenario 7: Aligning the definition of transfusion independence to the T12 primary outcome in CLIMB THAL-111,
- Scenario 9: Assuming 5 years to iron normalisation,
- Scenario 11: Assuming an SMR of 2.5 for TD patients,
- Scenario 13: HRQoL decrement of [redacted] relative to the general population (updated based on D120 data),
- Scenario 15: Use of eMIT costs,
- Scenario 17: Multiplicative approach to age-adjustment.

Table 8 EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
Company base-case	5.1.1.1	[redacted]
1. Modelling no complications	4.2.2	[redacted]
2. Costs and outcomes from exa-cel withdrawal	4.2.2	[redacted]
5. Frequency of blood transfusions based on Shah et al., 2021	4.2.4	[redacted]
6. Using a 3.5% discount rate	4.2.5	[redacted]
7. Aligning transfusion independence to the T12 primary outcome in CLIMB THAL-111*	4.2.6	[redacted]
9. Assuming 5 years to iron normalisation	4.2.6	[redacted]
11. Assuming an SMR of 2.5 for TD patients	4.2.6.5	[redacted]
13. HRQoL decrement of [redacted] relative to the general population*	4.2.7	[redacted]
15. Use of eMIT costs	4.2.8	[redacted]
17. Multiplicative approach to age-adjustment	4.2.7.4	[redacted]
*Scenario has been updated following the D120 data cut		

Table 9 EAG preferred base-case

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.4.1 Additional scenario analysis on the EAG's base case

Additional scenario analysis on the EAG's base case is presented in Table 10.

Table 10 Results of scenario analyses on the EAG alternative base case analysis

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
EAG base case	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.5% Discount rate	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on published values from Santarone et al. 2022	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on US ICER report	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.4% mortality risk for myeloablative conditioning	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4 DISTRIBUTIONAL COST-EFFECTIVENESS ANALYSIS

This section utilises the updated DCEA inputs based on the company's clarification response and the updated model at the D120 cut-off. The results presented in this section reflect these modifications to the base case. As discussed in Section 8 of the EAR, the distribution of the share of health opportunity costs was incorrectly calculated based on the distribution of the female population rather than the total population reported in the publication, therefore the EAG has implemented the correction in this section. The EAG also uses ONS data for the general population proportions, which shows that IMD quintiles should represent around 20% of the total sample population. The reasons for this are discussed in Section 8 of the EAR.

The NHB results of the DCEA scenario analyses described at a discount rate of 1.5% at £20,000 and £30,000 are presented in Table 11 and Table 12, respectively, using the EAG's preferred approach of using the equally distributed equivalent (EDE) NHB. Results with the Atkinson parameter value of 3.5 applied are also included. The results from the EAG preferred DCEA approach (Scenario 19 in the EAR) are presented in Table 13 and Table 14 at £20,000 and £30,000, respectively.

Table 11 EAG preferred DCEA inputs at a £20,000 threshold (updated model)

Scenarios	Individual level incremental NHB at £20,000 (1.5% discount rate)	
	Base-case	EDE
Company base-case	[redacted]	[redacted]
Corrected DCEA company base-case	[redacted]	[redacted]
Corrected DCEA company base-case with an inequality aversion parameter value of 3.5 applied	[redacted]	[redacted]

Table 12 EAG preferred DCEA inputs at a £30,000 threshold (updated model)

Scenarios	Individual level incremental NHB at £30,000 (1.5% discount rate)	
	Base-case	EDE
Company base-case	[redacted]	[redacted]
Corrected DCEA company base-case	[redacted]	[redacted]
Corrected DCEA company base-case with an inequality aversion parameter value of 3.5 applied	[redacted]	[redacted]

Table 13 EAG scenario 19 (updated model): summary measures of impact on health distribution at a £20,000 threshold

Social welfare index	SoC	Exa-cel
Mean health (inequality aversion = 0)	[redacted]	[redacted]
Slope index of inequality	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 11)	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 3.5)	[redacted]	[redacted]
Incremental EDE* (inequality aversion = 3.5)	[redacted]	
Change in SII* (x 1000)	[redacted]	
Individual level incremental EDE NHB	[redacted]	

Abbreviations: EDE, equally distributed equivalent health; SII, slope inequality index
*The higher the EDE the better
*As EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality
*A positive change in SII indicates an increase in inequality after the intervention

Table 14 EAG scenario 19 (updated model): summary measures of impact on health distribution at a £30,000 threshold

Social welfare index	**SoC**	**Exa-cel**
Mean health (inequality aversion = 0)	[redacted]	[redacted]
Slope index of inequality	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 11)	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 3.5)	[redacted]	[redacted]
Incremental EDE (inequality aversion = 3.5)	[redacted]	
Change in SII * 1000	[redacted]	
Individual level incremental EDE NHB	[redacted]	

Abbreviations: EDE, equally distributed equivalent health; SII, slope inequality index
*The higher the EDE the better
*As EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality
*A positive change in SII indicates an increase in inequality after the intervention

The results for scenario 19 with the updated company inputs are presented in a health equity impact plane as shown in Figure 1 and Figure 2. The equity impact plane shows the relationship between the cost-effectiveness of an intervention (shown on the vertical axis) and its impact on health inequality (shown in the horizontal axis). Both figures show that exa-cel falls in the southwest quadrant, indicating that the intervention is both cost-ineffective and inequality increasing.

Figure 1 Health equity impact plane at 1.5% discount rate (EAG analysis on updated model)

Figure 2 Health equity impact plane at 1.5% discount rate (EAG analysis on updated model)

4.1.1 EAG base case analysis

The impact of updated parameters on the EAG preferred base case (described in Sections 6.4 and 8.1 of the EAR) is presented in Table 15 and Table 16 at £20,000 and £30,000, respectively.

Note that the NHB results for the EAG preferred base-case in the equivalent tables in the main EAG report (Tables 33 and 34 of the EAR) were incorrectly derived from the base-case results sheet of the model rather than the EAG additional analysis sheet, resulting in marginally higher NHBs. The results in this section have been updated accordingly.

Table 15 EAG DCEA exploratory analysis at £20,000 (updated model)

Scenarios	NHB at £20,000	
	Base case	EDE*
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

Table 16 EAG DCEA exploratory analysis at £30,000 (updated model)

Scenarios	NHB at £30,000	
	Base case	EDE*
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

EAG corrections

Following the D120 update the EAG has identified errors in the implementation of Scenario 2 and 7. Results for EAG Scenario 2 were calculated incorrectly using the treatment withdrawal rate from IA2, while Scenario 7 did not recalculate the proportion of TR patient correctly. Table 1 reflects the EAG Scenario 2 results with the treatment withdrawal rate updated to the D120 data cut. Table provide results for scenario 7 updated to reflect the response rate after the TR phase following the D120 update.

Table 1 EAG additional scenario analysis, Scenario 2

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years						

Table 2 EAG additional scenario analysis, Scenario 7

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years						

EAG's preferred assumptions

The results presented in Table 3 and Table 4 are equivalent to Table 8 and Table 9, respectively, in the updated efficacy and safety data cut addendum, incorporating the corrections to Scenario 2 and Scenario 7.

Table 3 EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
Company base-case	5.1.1.1	[redacted]
1. Modelling no complications	4.2.2	[redacted]
2. Costs and outcomes from exa-cel withdrawal	4.2.2	[redacted]
5. Frequency of blood transfusions based on Shah et al., 2021	4.2.4	[redacted]

6. Using a 3.5% discount rate	4.2.5	[redacted]
7. Aligning transfusion independence to the T12 primary outcome in CLIMB THAL-111*	4.2.6	[redacted]
9. Assuming 5 years to iron normalisation	4.2.6	[redacted]
11. Assuming an SMR of 2.5 for TD patients	4.2.6.5	[redacted]
13. HRQoL decrement of [redacted] relative to the general population*	4.2.7	[redacted]
15. Use of eMIT costs	4.2.8	[redacted]
17. Multiplicative approach to age-adjustment	4.2.7.4	[redacted]
*Scenario has been updated following the D120 data cut		

Table 4 EAG preferred base-case

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Additional scenario analysis on the EAG's base case

The results presented in Table 5 are equivalent to Table 10 in the updated efficacy and safety data cut addendum, incorporating the corrections to Scenario 2 and Scenario 7.

Table 5 Results of scenario analyses on the EAG alternative base case analysis

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
EAG base case	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.5% Discount rate	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on published values from Santarone et al. 2022	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on US ICER report	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]				

1.4% mortality risk for myeloablative conditioning	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG base case DCEA analysis

The results presented in Table 6 and Table 7 are equivalent to Table 15 and Table 16, respectively, in the updated efficacy and safety data cut addendum, incorporating the corrections to Scenario 2 and Scenario 7. Note that this correction resulted in differences in the EAG base case NHBs and the respective EDE values.

Table 6 EAG DCEA exploratory analysis at £20,000 (updated model)

	NHB at £20,000	
Scenarios	**Base case**	**EDE***
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

Table 7 EAG DCEA exploratory analysis at £30,000 (updated model)

	NHB at £30,000	
Scenarios	**Base case**	**EDE***
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		