Title: Exagamglogene autotemcel for treating sickle cell disease- appendix with additional scenarios

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Jo Parsons (Assistant Professor), Martin Connock (Honorary Senior Research Fellow), Xavier Armoiry (Honorary Senior Research Fellow and Professor) and Amy Grove (Professor) reviewed and critiqued the clinical effectiveness evidence. Martin Connock reviewed and critiqued the statistics and undertook any additional statistical analyses. Xavier Armoiry reviewed and critiqued the mixed treatment comparisons. Naila Dracup (Information Specialist) critiqued the company's searches and undertook additional searches. Emanuela Castelnuovo reviewed and critiqued the cost-effectiveness evidence and undertook additional economic analyses. Baba Inusa (Paediatric Haematologist) and Elizabeth Rhodes provided expert clinical advice. Peter Auguste (Assistant Professor) reviewed the cost-effectiveness evidence and co-ordinated the project and the report.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

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Content of appendix

In this appendix we outline the EAG's concerns with regards to the company's not related to the company's Markov structure and Markov structural concerns. The structure of this appendix is as follows:

- Concerns not related to Markov structural concerns.
- Impact of non-Markov structural changes to the company's base-case results (without severity modifier)
- Concerns related to the company's Markov structure.
- Changes related to the Markov structure and their impact to ICER

The EAG implemented two groups of changes / modifications:
One set of changes concerns parameters or assumptions that are not related with the Markov structure of the model. These changes affect cost calculations for some drugs, costs and outcomes for the exa-cel cohort and choice of discount rate. These changes have been operated keeping the ***structure of the model as is***. They should be understood not as the EAG base-case but rather, as possible illustrations of the reactivity of the ICER to parameters changes. They remain affected by the overall lack of validity of the model structure.

The second set of changes were an attempt to assess the reactivity of the model structure to changes in the features that the EAG believes inappropriate. These changes should not be interpreted as "fixes" to make the model structure valid; rather, they are a way to test the severe inadequacies highlighted by the EAG, or a way to illustrate why the EAG deems the model structure invalid. Some of these changes show that under the current structure, the model displays behaviours that are hard to interpret. The EAG obtained some indicative ICERs, that at best help to understand the direction of the cost-effectiveness analysis should a proper Markov structure be implemented. In view of the additional analyses undertaken, the EAG reiterates that the model structure appears invalid for the purposes of this STA.

1.1 *Concerns not related to Markov structural issues*

The EAG expressed concerns regarding the following features / model choices:

- Exclusion of 19% of people who received apheresis but not exa-cel
- Exclusion of exa-cel costs for those who have insufficient cells yield.
- Cost of plerixafor (used during apheresis) calculated for the average patient (72kgs in originals model, weight increases in time up to 83kgs, then decreases).

- Cost of blood transfusions with exa-cel and SoC as per Vertex burden-of-illness study.
- Cost of chelation and other drugs calculated by average weight (as for plerixafor).
- Utility for alive state selected- higher than that reported in trial.
- Discount rate of 1.5% on both costs and benefits

1.1.1 Impact of non-related changes to Markov structure to company's results

In Table 1, we report the EAG unrelated to the Markov structure and their impact to the company's base-case results. Results are based on excluding the severity modifier. Considering these cumulative change results in an ICER of approximately [redacted] per QALY.

Table 1: Impact of EAG non-Markov structural changes related to company's base-case results, without severity modifier

Issues, parameters and non-related with Markov structural issues	EAG changes	Company's ICER	Change in company's ICER, vs company's base case	
Base case, company	-	[redacted]	in £	%
Base case, company, updated with EMIT prices	-	[redacted]	[redacted]	[redacted]
Exclusion of 19% people who receive apheresis but not exa-cel	Addition of outcomes for dropouts, who are assigned costs and outcomes as in SoC	[redacted]	[redacted]	[redacted]
Exclusion exa-cel costs for those (approximately 10%) who have insufficient cells yield	Addition of costs of exa-cel for those who do not receive conditioning	[redacted]	[redacted]	[redacted]
	• Minor issue: use of distribution to assess the probability of not having viable quantities of exa-cel (using log normal for CD4+m/kg) - EAG preferred: use in distribution	[redacted]	[redacted]	[redacted]
	Addition of blood transfusion costs for those who do not receive conditioning (exa-cel)	[redacted]	[redacted]	[redacted]
Cost of apheresis calculated for the average patient (72kgs in original model, weight increases in time up to 83kgs then decreases again)	Recalculation of cost of apheresis, using weight distribution for plerixafor	[redacted]	[redacted]	[redacted]
Cost of blood transfusions with SoC as per Vertex BOI study	Recalculation of blood transfusion frequency	[redacted]	[redacted]	[redacted]
Costs of chelation and other drugs calculated by (increasing) average weight	By weight distribution, constant weight	[redacted]	[redacted]	[redacted]
Utility for alive state selected - higher than that reported in trial	Use of trial utility value at 12 months (as per use of VOC rates as in primary endpoint in CLIMB SCD-121)	[redacted]	[redacted]	[redacted]
Discount rate set to 1.5%	Discount rate set to 3.5%	[redacted]	[redacted]	[redacted]
Total, Cumulative changes to company's base case			[redacted]	[redacted]

EAG, Evidence assessment group; ICER, Incremental cost-effectiveness ratio; SCD, Sickle cell disease; SoC, Standard of care; VOC, vaso-occlusive crisis

1.2 *Concerns related to the Markov structure*

The following section presents the issues identified by the EAG with the company's Markov structure.

- Imposed mortality constraints to make cohort 100% over time.
- No rationale for the choice of which sickle cell disease complications are included (e.g., splenic infarction has data but was not considered in the structure)
- States for which there is no evidence of baseline rate and treatment effect – treatment effects are mutated across clinical states with no underpinning clinical rationale – example: is it clinically valid to apply the hazards of pulmonary embolism to clinical events such as "gallstones" and "neurocognitive impairment"?
- Use of vaso-occlusive crisis as a risk equation predictor
- Exclusion of relapse rate. A similar issue concerns the assumption of lifetime benefits with exa-cel.

1.2.1 Impact of changes related to Markov structural issues

In Table 2, we outline the Markov structural issues and the cumulative impact on addressing these changes.

Table 2: Changes related to the Markov structure and impact to company's results

EAG concerns	Concerns explained	Proposed implementation with given model structure	Impact
Starting from cumulative parameter changes (in company's model) (see Table 1)	-	All changes implemented in Table 1	[redacted]
Imposed mortality constraints to make cohort 100% over time.	The ICER reflects alive states that go negative, and consequently, rates of complications that go negative. This means that removing clinical health states (i.e., gallstones, infections etc..) not based on evidence may have an unpredictable effect improving the ICER (i.e., negative utility weight become positive, costs become negative), although for the chronic states this did not happen (see below).	Replace the constraint formula applied to mortality rates in the model.	[redacted]
No rationale for the choice of which sickle cell disease complications are included (e.g., splenic infarction has data but was not considered in the structure)	Most complications are included based on assumptions Splenic infarction can happen in children (literature case reports). The company has done no work in term of locating relevant literature or addressing this endpoint using perhaps clinical opinion.	None	Qualitative issue
States for which there is no evidence of baseline rate and treatment effect – treatment effects are mutated across clinical states with no underpinning clinical rationale – example: is it clinically valid to apply the hazards of pulmonary embolism to clinical events such as "gallstones" and "neurocognitive impairment"?	**Corrective changes should be in the direction of eliminating states for which evidence is not available or clinical opinion has not been sought.** The ICER resulting from the EAG modifications should not be interpreted to mean that this change is favouring SoC, because complication rates in exa-cel are set to zero by definition in the exa-cel-treated in the company's model; as a result, event rates improve, because the EAG added to the exa-cel arm a 19% proportion of people that .turn to SoC as they fail the apheresis-conditioning process in the exa-cel arm. Conversely, outcomes in the SoC arm are heavily driven by longer term complications so SoC picks up the largest benefit from this change. The decrease in event rates in SOC is also not inclusive of chronic states, so likely underestimated	**Issue pertaining to evidence.** The EAG has attempted to delete some of these states (e.g., infections, AKI, gallstones, leg ulcers, CKD) from the model setting the relevant state occupancy to 0s throughout in the exa-cel and SoC arms/acute complications only. This approach could be taken for all chronic events – the impact on the ICER seems to increase (caveated with the rates of people alive becoming positive)	[redacted]
Use of vaso-occlusive crisis as a risk equation predictor	The modification is made challenging because of company's model methods. All states' hazards at baseline and for treatment are geared up with the rate of VOCs embedded in		[redacted]

EAG concerns	Concerns explained	Proposed implementation with given model structure	Impact
	the traces' formulae. Replacing the number of VOCs (0.035 per cycle) with 1 (as is logical, given the use as if in a risk equation) decreases the ICER. Setting this parameter to zero makes the ICER shoot up to [redacted] because the company geared up the VOC rate as a probability and included a term for those who have no VOCs in the "cured" state. This means that one term of the equation serves to apply the baseline rate of events to all the population (1-cohort_m_bvoc) but this also has the effect of setting to zero all acute events in the exa-cel arm, and by reflection to set to zero all biases in the mortality rates underpinning the model. Overall, it is unclear what the differential impact of each of these separate effects amount to, this modification should be taken with extreme care. In addition, this modification is not sufficient to address the mortality issue in the model, which remains affected by overestimation based on background death rates and SCD-specific rates; this also confirms that a quick fix of mortality is unlikely to be feasible or useful given the model structure.		
Exclusion of relapse rate. A similar issue concerns the assumption of lifetime benefits with exa-cel.	-	This requires a time-dependent modification to the model structure, to add rates of people that enter SoC as they relapse or as they lose response. This is very time consuming. The likely impact is that the ICER will increase.	-
AKI, Acute kidney injury; CKD, Chronic kidney disease; EAG, Evidence assessment group; ICER, Incremental cost-effectiveness ratio; SCD, Sickle cell disease; SoC, Standard of care; VOC, vaso-occlusive crisis			

In Figure 1 and Figure 2, we show the cumulative model outputs for people who are alive/dead, in the exa-cel arm and SoC arm, respectively. Vertical axis displaying the percentage of people alive/dead in the model and the horizontal axis is age.

Figure 1:

Figure 2:

As a result of alive state occupancy that goes negative, chronic complication rates (shown in Figure 3 and Figure 4, for exa-cel and SoC, respectively) also goes to negative (i.e., when death rates go above 100%). This occurs around the age of [redacted] years of age in the model for SoC and [redacted] years of age in the model for exa-cel.

Figure 3:

Figure 4: [redacted]