Exagamglogene autotemcel for treating severe sickle cell disease

This is not a HST topic – this STA is being considered by the HST committee due to scheduling and capacity

Slides contain no confidential information

Highly specialised technology committee 10th October 2024, assessing ID4016 as a single technology appraisal - appraisal committee meeting 3

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Exa-cel for treating severe sickle cell disease

- ✓ **Appraisal history**
- ❑ Key issues
- ❑ Cost effectiveness
- ❑ Summary

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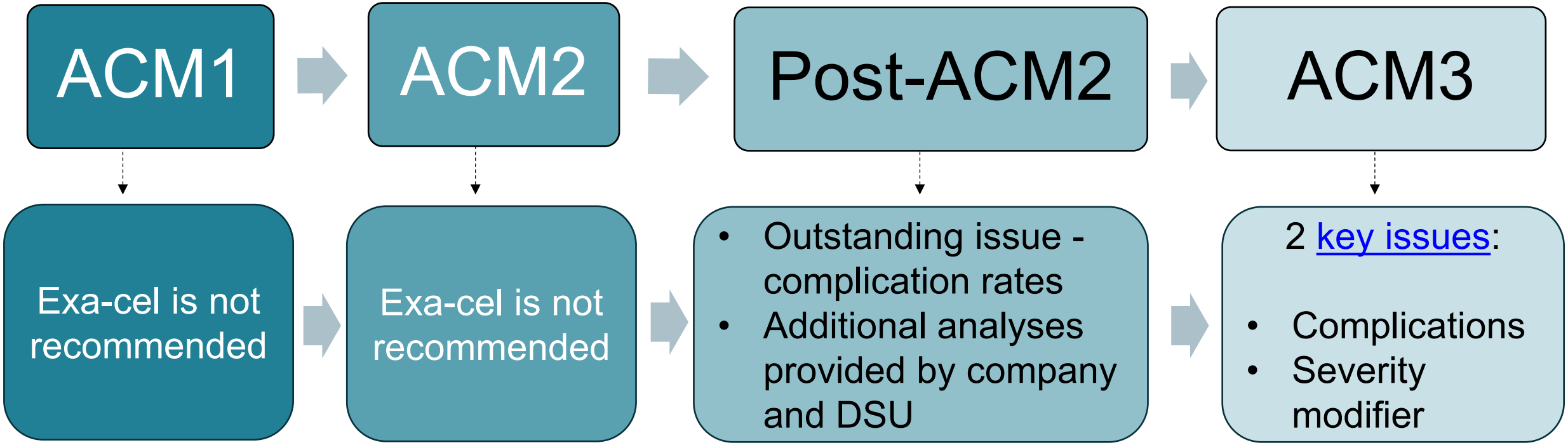
Appraisal history

Marketing authorisation: SCD in patients 12 years of age and older with recurrent vaso-occlusive crises who have the βS/βS, βS/β+ or βS/β0 genotype, for whom HSCT is appropriate, and a human leukocyte antigen matched related haematopoietic stem cell donor is not available



Abbreviation: ACM, appraisal committee meeting; SCD, sickle cell disease; HSCT, hematopoietic stem cell transplant

Exa-cel for treating severe sickle cell disease

- ❑ Appraisal history
- ✓ **Key issues**
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Key issues

Issue	ACM2 conclusion	ICER impact
Source of complication rates • Uncertainty remains about the appropriate rates and application method for inclusion of complications in model • Uncertainty on if the BOI study is representative of people eligible for treatment with exa-cel in the NHS	UK BOI study - 12-35 subgroup complication rates	Moderate
Severity modifier • Cost-effectiveness results for exa-cel and the appropriate severity decision modifier are sensitive to complication values	Severity modifier not met	Large

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Abbreviation: ICER, incremental cost-effectiveness ratio; BOI, burden of illness; ACM, appraisal committee meeting

Complication rates: appraisal history

ACM2 summary

ACM1

Conclusion: most appropriate is Brousse et al. (2023) severe population, but there is uncertainty associated with estimated frequency of SCD complications

ACM2

Conclusion: most appropriate source is the 12-35 years subgroup from the UK BOI study

Post ACM2

- Company submitted new complication analyses using BOI study 12+ years subgroup
- NICE requested input from the DSU on the most appropriate source of complications, and whether implementation underestimates/overestimates the long-term risk of SCD

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Abbreviations: DSU, decision support unit; SCD, sickle cell disease; BOI, burden of illness; ACM, appraisal committee meeting

Key issue: Complication rates (1)

Summary of model data sources

CLIMB SCD-121 - single arm, Phase 1/2/3 study in people aged 12-35 who have severe SCD, [redacted] people from UK

- Severe SCD: ≥ 2 VOCs per year during 2-year period before screening (baseline annual VOC rate: 4.2 per year)
- VOC definition: acute pain, acute chest syndrome, priapism or splenic sequestration needing hospital treatment
- Data used to inform effectiveness of exa-cel arm in model

Vertex unpublished UK BOI study - real world retrospective study of the clinical burden of SCD with recurrent VOCs

- Data from primary care records (CRPD) linked with secondary care data (HES) in England, aged 1-86 years
  - Annual VOC rates (follow-up) by age: 0-11yrs - 2.36; 12-17yrs - 4.92; 18-35yrs - 6.66; 36+ - 7.52
- Disease severity criterion: patient with a SCD diagnosis has ≥ 2 VOCs in the second consecutive year
- VOC definition: primary or secondary diagnosis of SCD with crisis, priapism or acute chest syndrome
- People followed up for mean 4.69 years (SD: 2.86 years; range: 1-11 years)

Summary of modelled complications

- Model tracks people with start age of 21.2 years over lifetime and estimates proportions with complications in each 1-month cycle, assuming acute complications can recur, but chronic complications can occur only once
  - Complication rates impact mostly on the QALYs and costs for SoC group
- UK BOI study informs complication estimates as people age, calculated based on number of events observed and number of years of follow-up per patient from baseline to event/censoring date
  - Recorded complication rates for people aged 0-11yrs, 12-17yrs, 18-35yrs, 36+yrs, and 12-35yrs at baseline

Abbreviations: BOI, burden of illness, SoC, standard of care; QALYs, quality-adjusted life years; VOCs, vaso-occlusive crisis; SCD, sickle cell disease; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics

Key issue: Complication rates (2)

Age and sex distribution for different complication scenarios

Baseline characteristics		Model	CLIMB SCD-121	BOI study	
N		-	43	1117	
Female (%)		44.2	44.2	Overall (2+) population	51.4
				12-35 population	51.2
				12+ population	53.0
Mean baseline age (years) (min-max)		21.2	21.2 (12-34)	Overall (2+) population	24.96 (1-86)
				12-35 population	23.57 (12-35)
				12-35 (aligned with trial)*	23.36 (12-35)
				12+ population	29.17 (12-86)
Baseline age (categorical) N (%)	0-11	-	-	219 (19.6)	
	12-17	-	12 (27.9)	110 (9.9)	
	18-35	-	31 (72.1)	539 (48.3)	
	36+	-	-	249 (22.3)	
Mean annualised VOC rate		4.2**	4.2 (at baseline)	Overall (2+) population	5.84 (follow-up)
				12-35 population	6.37 (follow-up)
Chronic complications at baseline (%)	Pulmonary hypertension	0	0	5.7	
	Chronic kidney disease	0	0	0.7 / 3.0	
	Post-stroke	0	0	-	
	Avascular necrosis	0	27.9	15.5	
	Retinopathy	14.3	14.3	10.7	
	Heart failure	0	0	2.5	
	Neurocognitive impairment	2.9	2.9	1.9	
	Liver disease	0	0	4.3	

***Subgroup aged 12-35 who had no clinical trial exclusion conditions – 51.75% of study population**
****CLIMB SCD-121 baseline VOC rate used as fixed VOC rate overtime in the model**

Abbreviations: BOI, burden of illness, VOC, vaso-occlusive crisis; SD, standard deviation; SCD, sickle cell disease

Key issue: Complication rates (3)

Decision support unit

There are differences between BOI study and CLIMB SCD-121 population (see next slide):

- BOI population is more severe at baseline than trial → higher VOC rate and baseline complications
  - E.g., VOC rate in BOI overall population is higher than CLIMB SCD-121 (5.84 vs 4.2 per year)
  - E.g., Model assumes no baseline comorbidities except 14% retinopathy and 3% neurocognitive impairment, but unclear if BOI study baseline comorbidity is much higher than model or not reported
    - ↳ Applying BOI complication rates may overestimate complication risk for model population
- Mean age of BOI 12-35 similar to CLIMB SCD-121 but data will not reflect age as patients in model get older
- Applying BOI rates assumes 1) population reflects those eligible for exa-cel, 2) observed CLIMB SCD-121 treatment benefit applicable to more severe population
- Overlap between BOI study and CLIMB SCD-121 not reported → not possible to see if matching feasible
  - Unclear which population better represents decision problem

- Which population best represents the target NHS population – BOI study or CLIMB SCD-121?
- What is the most appropriate starting age and sex distribution to use in the model?

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Abbreviation: BOI, burden of illness; QALY, quality-adjusted life years; SoC, standard of care; VOC, vaso-occlusive crisis

Key issue: Complication rates (4)

Company post-ACM2 comments

- Disagree with committee preference to use BOI 12-35 years subgroup, does not reflect decision problem (12+)
- Using entire severe BOI study cohort is more appropriate - captures complications across all ages and better represents disease progression in the model

12–35 complication rates (EAG ACM2 base case)

- Applying 12-35 rates to those aged 12+ significantly underestimates SCD severity over patient's lifetime
  - ↳ Inaccurately reflects disease progression, particularly as modelled SoC median survival is 52 years
- Constant rate applied = when people turn 35+, complications develop at lower rate than would otherwise
  - Complications increase with age and as SCD progresses = underestimates QoL and cost at end of model

Severe SCD (2 yrs +) complication rates (company ACM2 base case)

- More generalisable to UK severe SCD population = captures natural disease progression and risk of complications across all ages (including increase in complication risk with age)

12+ years complication rates (company ACM3 base case)

- Weighted mean complication rates in patients aged 12+ yrs, based on the 12-35yrs and 36+ yrs subgroups
- Matches decision problem and a more accurate reflection of lifelong SCD-related morbidity

Abbreviations: QoL, quality of life; SCD, sickle cell disease; SoC, standard of care; BOI, burden of illness

Key issue: Complication rates (5)

EAG comments

- Major limitation that no systematic review of complication data/studies was conducted by the company
- Still prefer 12-35 population – at least age matches model starting cohort (BOI: 23.6 yrs vs 21.2 yrs)
  - But higher VOC rates and higher baseline burden of disease of BOI cohort may still overestimate SOC complication rates
- License is unrestricted but CLIMB SCD-121 restricted to ≤35 years - no data supporting people aged 35+ yrs
- Agree age-dependent complication rates are reasonable, but data provided is not fit for purpose
- Applying 12+ rates increases model bias and uncertainty – affected by methodological issues
  - Without re-analysis of BOI data, weighted method is more conservative than company's other approaches

Methodological issues:

1. Age group complication rates combined using weights proportional to number of people in BOI age groups
   - Weights applied should reflect model and CLIMB SCD-121 population composition
   - BOI baseline age distribution does not match trial, but age is predictor of complication rates = model rates biased
     - ↳ BOI: 12-17yrs (9.9%), 18-35yrs (48.3%), CLIMB SCD-121: 12-17 years (27.9%), 18-35 (72.1%)
2. Baseline age distribution (model and BOI study) is cross-sectional, but the complication data is longitudinal
   - Complications measured over time as people age, but study did not recorded age at which they occur
     - Average follow-up: 4.7 years

Abbreviation: BOI, burden of illness; VOC, vaso-occlusive crisis; SCD, sickle cell disease

Key issue: Complication rates (6)

EAG comments continued

Implications:

1. Constant complication rate applied in model that includes all ages 12+
   - Amplifies overestimation of complications in earlier cycles (where population and potential bias largest), and downplays underestimation in later cycles
2. 12-35 and 36+ cohort data ≠ data from single population followed up longitudinally from 12 to 35+ years
   - 36+ group has higher VOC than 12-35 – unknown if due to age or other uncontrollable factors
     - ↳ E.g., survivor bias (36+ yrs healthier), or healthcare practice changed (e.g., treatment improved over time and people diagnosed earlier than the older cohort when they were younger)
   - Cannot rule out that 2 cohorts are 'different' for reasons other than just age and rates may be confounded
     - Combining as if 1 longitudinal cohort may introduce uncontrollable biases and increase uncertainty
3. Methodologically flawed to apply separate 12-35 and 35+ rates for different model ages (data longitudinal)
   - 4.7yrs follow-up = data for people aged 31-35 at baseline included in 12-35 and 36+ age group = overlap
   - Applying separate rates using a cut-off double counts complications for cycles relating to 35-40 years
   - Regression model accounting for age at time of complication would allow for matching → data unavailable

Abbreviation: BOI, burden of illness; VOC, vaso-occlusive crisis; SCD, sickle cell disease

Key issue: Complication rates (7)

Decision support unit

- BOI study recorded complication rates for baseline ages 0-11yrs, 12-17yrs, 18-35yrs, 36+yrs, and 12-35yrs
- Ideal analysis: statistical model of relationship between complications and age → need data broken down into narrower age bands and re-analysed according to age at which complications occurred
  - Company: do not have granular level of data e.g., did not record the age at point complications occurred
  - Cannot do further statistical modelling of BOI data to predict complication risks by age
- Ran analyses to further explore impact of age-specific complication rates on exa-cel cost-effectiveness
  - ↳ Different complication rates for specific age bands applied once people reach a particular age in model

1. **12-35yrs and 36+yrs subgroup complication rates**
   - 12-35yrs rates applied to modelled patients until age 36, then 36+yrs rates for all subsequent model cycles
2. **18-35yrs and 36+yrs subgroup complication rates**
   - 18-35yrs rates applied to modelled patients until age 36, then 36+yrs rates for all subsequent model cycles
3. **12-17yrs, 18-35yrs and 36+yrs subgroup complication rates, including lag to account for follow-up**
   - Apply 5-year lag in attempt to align BOI patient age with appropriate time point in modelled age
   - 12-17yrs rates applied to modelled patients until age <23 years, 18-35yrs subgroup rates applied whilst patients aged 23-41 years, then 36+yrs complication rates for all subsequent model cycles
4. **18-35yrs and 36+yrs subgroups complication rates, including a lag to account for follow-up duration**
   - 18-35yrs rates applied to modelled patients until age 41, then 36+yrs rates for all subsequent model cycles

Abbreviation: BOI, burden of illness

Key issue: Complication rates (8)

Decision support unit continued

- None of the available options for incorporating complication rates into the company's model are ideal

EAG ACM2 approach: apply 12-35yrs subgroup data

- Does not account for complications increasing with age as constant rates are applied every cycle
- Data may not reflect complication risks in older ages → ~82% SoC arm predicted to survive beyond age 36

Company ACM3 approach: weighted average of 12-35yrs and 36+yrs subgroup data

- Underlying rates incorporate different effects by age, but applied as constant age-independent rates
- Approach may inflate complication risks for younger patients in model

DSU preferred analysis: 12-17yrs, 18-35yrs and 36+yrs subgroup data, including ~5-year time lag

- Applies age-band specific rates in line with model age - prefer as expect complications to increase with age
- Allows some age-dependence but relies on broad age groups - may mask true age/complication relationship
- Including time lag aims to better reflect age at which BOI complications occur, rather than baseline age
  - ↳ But cannot estimate exact age when complications occurred = likely inaccuracy in model predictions
- Using age-band rates reduces number of patients/events at specific ages e.g., 12-17yrs subgroup (n=110)

Abbreviation: BOI, burden of illness; SoC, standard of care; VOC, vaso-occlusive crisis; SCD, sickle cell disease

Key issue: Complication rates (9)

Modelled acute and chronic complication rates
SoC utility overtime

Company, EAG and DSU apply complication rate data in different ways, based on different age groups

Scenarios	Method	SoC QALYs
Company ACM2 (2+)	Overall population complication rates applied as constant rate each cycle	10.42
EAG ACM2 (12-35)	12-35 age group specific complication rates applied as constant rate applied each cycle	11.00
Company ACM3 (12+)	Weighted average of 12-35 and 36+ rates applied as constant rate each cycle	10.43
DSU scenarios 1	Age dependent, apply rates from each age band until reach equivalent age in model • 12-35yrs and 36+yrs subgroup complication rates	10.50
DSU scenarios 2	Age dependent, apply rates from each age band until reach equivalent age in model • 18-35yrs and 36+yrs subgroup complication rates	10.42
DSU scenario 3	Age dependent, apply rates from each age band until reach equivalent age in model, but includes time lag to account for follow-up and age at time of complication • 12-17yrs, 18-35yrs and 36+yrs subgroup complication rates	10.71
DSU scenario 4	Age dependent, apply rates from each age band until reach equivalent age in model, but includes time lag to account for follow-up and age at time of complication • 18-35yrs and 36+yrs subgroup complication rates	10.61
Literature (ACM2 discussion)	Apply specific complication rates from a variety of literature sources	9.78

Which source and method should be used to estimate complication rates? Consideration of uncertainty: does the preferred scenario for modelling complication rates accurately estimate / overestimate / underestimate?

Abbreviation: DSU, decision support unit, BOI, burden of illness; QALY, quality-adjusted life years; SoC, standard of care

QALY weighting for severity (1)

Link to additional patient, family and carer testimonies

RECAP

ACM2 conclusions:

- Severity modifier did not apply, using committee's preferred BOI study 12-35 subgroup to model complications

Company ACM2:

- Progressive diseases where mortality increases and HRQoL deteriorates substantially over time are unfairly penalised by discounted QALY approach. HST, where undiscounted QALYs are used is more appropriate
- Where case for non-reference discount rate, no discount rate, or 1.5% discount rate should apply in QALY shortfall calculation – in this scenario, 1.7 QALY weight could apply

Other considerations from patient and clinical experts/groups and web comments after ACM1:

- Strongly feel severity for SCD and those living with it has been misjudged and not been fully appreciated
- SCD is a severe condition & patients die very prematurely (early 40s), even with best available treatment
- There are potential gaps in knowledge and evidence concerning SCD severity and the impact on QoL

NICE methods (sections 6.2.12 to 6.2.17):

- Committee will consider the severity of condition, defined as the future health lost by people living with the condition with standard care in the NHS. **Extent of unmet health** need is **reflected within severity definition**
- Expected **SoC QALYs is equivalent** to total QALYs gained with **established NHS practice**
- **Data used** to estimate absolute and proportional QALY shortfall should **focus on specific population** for which the **new technology will be used** and be based on **established clinical practice in the NHS**
- Population **EQ-5D data** and **survival data** used for estimates should be based on **recent and robust source**
- Absolute and proportional shortfall calculations should include **discounting at the reference case rate**

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Abbreviations: SoC, standard of care; QALY, quality-adjusted life year; SCD, sickle cell disease; QoL, quality of life; HRQoL, health-related quality of life; HST, highly specialised technology

QALY weighting for severity (2)

Severity modifier decisions in other technology appraisals

- Decisions about whether the severity modifier is met should take account of all the evidence presented as part of appraisal

TA896 - Bulevirtide for treating chronic hepatitis D

- Committee recognised the limited evidence for hepatitis D, noting NICE's manual states it can accept a higher degree of uncertainty, especially in rare diseases. All but 1 scenario met 1.2 modifier, so committee agreed to apply 1.2 weighting

TA949 - Belumosudil for treating chronic graft-versus-host disease after 2+ systemic treatments in people 12+ years

- Committee acknowledged the condition significantly impacts QoL but noted it did not have sufficient evidence for most appropriate source to inform some health state utility values. It agreed with the EAG that no severity modifier should apply

ID4024 - Vamorolone for treating Duchenne muscular dystrophy – Draft Guidance, appraisal ongoing

- Committee: data used likely overestimated SoC survival, which would have underestimated AS
- Committee: severity calculations sensitive to model assumptions. Considering all evidence available, including expert opinion, the committee concluded that a severity weight of 1.7 was appropriate.

TA981 - Voxelotor for treating haemolytic anaemia caused by SCD (Pfizer is withdrawing voxelotor from market)

- Company and EAG base case did not meet severity modifier - concluded unable to apply 1.2 QALY weighting

Differences from this appraisal: population - people aged 12+ yrs with haemolytic anaemia caused by SCD who are ineligible for, or intolerant of hydroxycarbamide, or hydroxycarbamide alone is insufficiently effective = less severe than CLIMB SCD-121

Considerations:

- *Model start age:* voxelotor company - average age in NHS likely lower than modelled age (licensed for 12+ yrs)
  - EAG: If model built on data significantly different to NHS population, results unsuitable for decision making
- *True QALY loss:* company - people with chronic conditions from early age adapt and report better QoL
- *Rounding up of QALY* shortfall*:* EAG - rounding up to 12 (i.e., when >11.5) is inappropriate and would lower severity threshold
- *Uncaptured severity*: committee concluded that the model may not have fully captured the severity of the disease

Abbreviations: SoC, standard of care; QALY, quality-adjusted life year; SCD, sickle cell disease; QoL, quality of life; AS, absolute QALY shortfall

QALY weighting for severity (3)

1.2 severity modifier met if SoC QALYs ≤10.53

Very narrow range of QALY shortfall values (11.53 – 12.11)

EAG preferred | Company preferred | DSU preferred

QALY weight	Absolute shortfall	Proportional shortfall
x1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

Estimated QALY shortfalls for different scenarios	General population QALEs	Total SoC QALYs	Absolute (proportional) QALY shortfall	Weight
Literature value	22.53	9.78	12.74 (56.58%)	1.2
Company ACM2 base case (severe population, 2+yrs)	22.53	10.42	12.11 (53.74%)	1.2
EAG ACM2 base case (12-35yrs subgroup)	22.53	11.00	11.53 (51.17%)	1.0
Company post-ACM2 - weighted average complication rates (12+yrs)	22.53	10.43	12.10 (53.70%)	1.2
DSU 1: Age-dependent complication rates (12-35yrs and 36+yrs)	22.53	10.50	12.03 (53.39%)	1.2
DSU 2: Age-dependent complication rates (18-35yrs and 36+yrs)	22.53	10.42	12.11 (53.74%)	1.2
DSU 3: Age-dependent complication rates (12-17yrs, 18-35yrs and 36+yrs), including ~5-year lag	22.53	10.71	11.82 (52.46%)	1.0
DSU 4: Age-dependent complication rates (18-35yrs and 36+yrs), including ~5-year lag	22.53	10.61	11.92 (52.90%)	1.0

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Abbreviations: QALE / Y, quality-adjusted life expectancy / year; SCD, sickle cell disease

QALY weighting for severity (4)

Uncertainties in the current model inputs:	SoC QALY impact
Model structure: Appropriate for decision making, but associated with uncertainties (see below)	Unknown
SoC mortality modelling: • Model SoC median survival: 52 years - DG: need validation about most accurate life expectancy • UK BOI study mean death age: 40 years (range: 8-79 years) – only based on 41 / 1,117 people • Company: model overestimates survival in severe SCD population, should be 39-43 yrs (EAG: 43-55 yrs)	Potentially overestimated
Complications: • Concerns complete BOI study population represents a more severe cohort than CLIMB ↳ If BOI more severe = may overestimate complications = underestimate SoC QALYs • Clinical experts ACM1: some significant complications missing from model e.g., acute multi-organ failure If complications underestimated = may overestimate SoC QALYs	Potentially underestimated, alternative scenarios ACM3 Potentially overestimated
Starting age (see next slide): • Model: 21.2 years (CLIMB SCD-121 FAS, age distribution: 27.9% [12-17]; 72.1% [18-35]) • UK BOI study mean age: 24.96 years (2+ years); 29.17 years (12+ years), 23.57 years (12-35 years) • Clinical advisory board: would prioritise treating younger people (aged 18-25). May expand this overtime Proportion aged 36+ would be fit enough to have myeloablation, but excluded from trial	Unknown, younger age = higher QALYs. Impact based on modelling of complication rates
Utilities: • SoC baseline utility: 0.81 - DG: 'suggests severe SCD QoL is reasonable compared to general population' • With complication disutilities applied, QoL declines overtime ([redacted] at baseline, see modelled SoC utility) • DG: 'committee recognised that the EQ-5D may not fully capture the QoL of people with SCD' • Clinical experts: QoL is difficult to capture in congenital conditions and SCD fluctuates in severity	Unknown, but likely to align with complication rates
Baseline VOC rate: likely to be underestimated as only includes VOCs needing treatment in hospital	Potentially overestimated

Abbreviations: BOI, burden of illness, SoC, standard of care; QALY, quality-adjusted life year; SCD, sickle cell disease; QoL, quality of life; VOC, vaso-occlusive crisis; FAS, final analysis set; DG, draft guidance

Severity weighting scenarios (1)

QALY shortfalls scenarios	Total SoC QALYs	Absolute QALY shortfall
Literature value	10.34	1. 13.07
	10.06	2. 12.93
	9.78	3. 12.75
	9.63	4. 12.56
	9.49	5. 12.53
	8.83	6. 12.27
Company ACM2 base case (2+yrs)	11.08	1. 12.33
	10.76	2. 12.23
	10.42	3. 12.11
	10.26	4. 11.93
	10.10	5. 11.92
	9.35	6. 11.75
DSU 1: Age-dependent complication rates (12-35yrs and 36+yrs)	11.37	1. 12.04
	10.94	2. 12.05
	10.50	3. 12.03
	10.25	4. 11.94
	10.04	5. 11.98
	9.03	6. 12.07
DSU 2: Age-dependent complication rates (18-35yrs and 36+yrs)	11.26	1. 12.15
	10.85	2. 12.14
	10.42	3. 12.11
	10.18	4. 12.01
	10.11	5. 11.91
	8.99	6. 12.11

Note: highlighted are scenarios that meet a 1.2 QALY weight. Proportional QALY shortfall not presented, ranged from 51.44% to 58.15% (not near PS severity cut off)

Marketing authorisation: treatment of SCD in people 12 years of age or older

Scenarios 1 & 2 do not reflect data from CLIMB or BOI study. Clinical advisory board: prioritise treating younger people (aged 18-25).

	Scenario	Age (yrs)	Female (%)
1	Younger population 1	15	44
2	Younger population 2	18	44
3	CLIMB SCD-121 (model)	21	44
4	BOI 12–35-year (aligned with CLIMB SCD-121)	23	52
5	BOI 12–35-year subgroup	24	51
6	BOI 12+ group	29	53

Is there the potential for the population to change over time?

Abbreviations: QALE / Y, quality-adjusted life expectancy / year; SCD, sickle cell disease; SoC, standard of care; PS, proportional QALY shortfall

Severity weighting scenarios (2)

EAG preferred | Company preferred | DSU preferred

QALY shortfalls scenarios	Total SoC QALYs	Absolute QALY shortfall
EAG ACM2 base case (12-35yrs subgroup)	11.73 11.37 11.00 10.82 10.64 9.82	1. 11.68 2. 11.62 3. 11.53 4. 11.37 5. 11.38 6. 11.28
Company ACM3 base case - weighted average complication rates (12+yrs)	11.09 10.76 10.43 10.27 10.11 9.36	1. 12.32 2. 12.23 3. 12.10 4. 11.92 5. 11.91 6. 11.74
DSU 3: Age-dependent rates (12-17yrs, 18-35yrs and 36+yrs), including ~5-year lag	11.79 11.37 10.71 10.40 10.21 9.30	1. 11.62 2. 11.62 3. 11.82 4. 11.79 5. 11.81 6. 11.80
DSU 4: Age-dependent complication rates (18-35yrs and 36+yrs), including ~5-year lag	11.40 11.02 10.61 10.40 10.21 9.30	1. 12.01 2. 11.97 3. 11.92 4. 11.79 5. 11.81 6. 11.80
Note: highlighted are scenarios that meet a 1.2 QALY weight. Proportional QALY shortfall not presented, ranged from 49.65% to 55.92% (not near PS severity cut off)		

	Scenario	Age (yrs)	Female (%)
1	Younger population 1	15	44
2	Younger population 2	18	44
3	CLIMB SCD-121 (model)	21	44
4	BOI 12–35-year (aligned with CLIMB SCD-121)	23	52
5	BOI 12–35-year subgroup	24	51
6	BOI 12+ group	29	53

1. Does the model accurately capture SoC utility, mortality and complications? If not, how does this affect SoC QALYs?
2. How should age and sex distribution align with other data sources and committee assumptions in model?
3. Has the severity modifier been met? If so, which QALY weight should be applied?

Abbreviations: QALE / Y, quality-adjusted life expectancy / year; SCD, sickle cell disease; SoC, standard of care; PS, proportional QALY shortfall

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Cost-effectiveness results

EAG preferred | Company preferred | DSU preferred

Exa-cel is above the committee's preferred cost-effectiveness threshold in all scenarios

Option	ICER (with and without severity) 3.5% discount rate	ICER (with and without severity) 1.5% discount rate
Scenario using literature*		
Exa-cel vs SoC	Above £35,000	Above £35,000
Scenario using overall cohort (2+yrs) complication rates*		
Exa-cel vs SoC	Above £35,000	Above £35,000
Scenario using specific age-group complication rates (12-35yrs)		
Exa-cel vs SoC	Above £35,000	Above £35,000
Scenario using weighted average complication rates (12+yrs)*		
Exa-cel vs SoC	Above £35,000	Above £35,000
DSU scenario 1: Age-dependent complication rates (12-35yrs and 36+yrs)*		
Exa-cel vs SoC	Above £35,000	Above £35,000
DSU scenario 2: Age-dependent complication rates (18-35yrs and 36+yrs)*		
Exa-cel vs SoC	Above £35,000	Above £35,000
DSU scenario 3: Age-dependent complication rates (12-17yrs, 18-35yrs and 36+yrs), including ~ 5-year lag		
Exa-cel vs SoC	Above £35,000	Above £35,000
DSU scenario 4: Age-dependent complication rates (18-35yrs and 36+yrs), including ~5-year lag		
Exa-cel vs SoC	Above £35,000	Above £35,000
***Scenarios met severity modifier of 1.2**		

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Abbreviations: QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; DSU, decision support unit; SoC, standard of care

Exa-cel for treating severe sickle cell disease

- ❑ Appraisal history
- ❑ Key issues
- ❑ Cost effectiveness
- ✓ **Summary**

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Decision-making framework (1)

Complication summary

Assumption	Options
Complication literature source	1. Literature (Brousse) 2. BOI study: 2+ population 3. BOI study: 12-35 population 4. BOI study: 12+ population 5. BOI study: age dependent, 12-35 and 36+ yrs 6. BOI study: age dependent, 18-35 and 36+ yrs 7. BOI study: age dependent, 12-75, 18-35, 36+ yrs with lag 8. BOI study: age dependent, 18-35 and 36+ yrs with lag
Severity • Age and sex distribution • Is the SoC QALY value reflective of NHS established practice? • Weight	CLIMB SCD-121 values / BOI values / other Yes / no – if no, what are the uncertainties? 1 / 1.2 / 1.7
Managed access	Yes / No
Uncaptured benefits? - Does committee want to account for any further uncaptured benefits (in addition to health inequalities, innovation and carer QoL)?	Yes / No If yes, what?
Are there any remaining uncertainties?	Yes / No
Threshold - Does committee's preferred ICER threshold remain at £35,000 per QALY gained?	Yes / No If no, what?

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Abbreviations: BOI, burden of illness, QoL, quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care

Decision-making framework (2)

What are committee's preferred assumptions?	Option
What is the committee's preferred ICER? (if this is a range, please state whether the committee want the lower, upper, or midpoint of range to be below threshold)	
Is the ICER below preferred ICER threshold?	Yes / No
If yes, recommend for routine commissioning? (considering uncertainty, inequalities, innovation etc that might impact decision if close to threshold)	Yes / No
If no, could key uncertainties be sufficiently resolved during period of managed access? If so:	Yes / No
Standard NICE appraisal considerations: • Has company made a managed access proposal? Is this considered feasible? • Are any updates or amendments required to the managed access proposal? • Has committee answered the questions in NICE's feasibility assessment? • What is committee's preferred threshold for managed access? • Which ICERs/assumptions represent committee's lower/upper end of uncertainty?	
If not, is chair's action appropriate*?	Yes / No

*That is, if NHSE have indicated they are willing to consider a commercial deal, and the company submit an ICER ≤ committee's preferred threshold using committee preferred assumptions, would committee be happy for the chair to approve this outside of a formal committee meeting?

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Abbreviations: ICER, incremental cost-effectiveness ratio

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Thank you.

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Supplementary slides

Key issue: Complication rates (1)

History of complication issue

RECAP

ACM2 Company

- Base case: unpublished UK BOI study severe SCD population (≥2 VOCs per year ≥2 consecutive years)
  - ↳ More robust and relevant population and VOC definition and study criteria aligns with CLIMB SCD-121
- Alternative: 'Literature' complication source derived from multiple literature sources

ACM2 EAG

- No systematic literature review done of complication data / studies
- Essential to match external populations to model population to avoid substantial overestimation of benefits
  - Preferred source: BOI study - matches model age, but not prior complications or VOC definition
- UK BOI population is more severe than CLIMB SCD-121 and lacks predictive validity for appraisal population
  - BOI baseline VOC rate double the trial, and includes people <12 and >35 yrs (drives complication)
  - Baseline comorbidities higher than model → complication rates represent higher risk of new complication than appraisal population
- Base case: BOI 12-35 subgroup population – baseline age matches model, but may overestimate complication rates because baseline VOC rate and comorbidities still higher than model
  - Approach far from ideal – should match BOI data to CLIMB SCD-121 to align severity with model population

ACM2 conclusions

- High level of uncertainties: literature not derived systematically and BOI study unpublished
- 12-35 years BOI subgroup most appropriate source, but matching trial and BOI data would be informative

Abbreviations: VOC, vaso-occlusive crisis; SCD, sickle cell disease; SoC, standard of care; BOI, burden of illness

QALY weighting for severity (5)

Company preferred | EAG preferred | DSU preferred

Comparison of BOI and CLIMB SCD-121

Age and sex distributions for different scenarios	N	Age (years)	Sex F (%)
CLIMB SCD-121 population (used in model currently)	43	21.2	44.2
Company ACM2 base case (severe population, 2+yrs)	1,117	24.96	51.39
Company post-ACM2 - weighted average complication rates (12+yrs)	898	29.17	53.01
EAG ACM2 base case (12-35yrs subgroup)	649	23.57	51.16
12-35 years with no exclusion conditions (align with clinical trial population)	578	23.36	51.56
DSU 1: Age-dependent complication rates (12-35yrs and 36+yrs)	898	-	-
DSU 2: Age-dependent complication rates (18-35yrs and 36+yrs)	788	-	-
DSU 3: Age-dependent complication rates (12-17yrs, 18-35yrs and 36+yrs), inc lag	898	-	-
DSU 4: Age-dependent complication rates (18-35yrs and 36+yrs), inc ~5-year lag	788	-	-
Literature value	-	-	-
Voxelotor appraisal	-	27.58	58
CLIMB SCD-121 and UK BOI study both had inclusion of people with ≥ 2 VOCs per year in >2 consecutive years			

Abbreviations: QALE / Y, quality-adjusted life expectancy / year; SCD, sickle cell disease

Complication slides

Modelled mean number of acute complications per patient

Highest rate
Lowest rate

Scenarios	Acute kidney injury		Pulmonary embolism		Stroke		Leg ulcers		Gallstones		Infectious and parasitic diseases	
	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC
Literature value	0.10	0.41	0.15	0.61	0.07	0.29	0.71	2.91	0.33	1.34	0.19	0.79
Company ACM2 (2+ yrs) (N=1,117)	1.43	5.84	0.57	2.34	0.07	0.29	2.78	11.40	2.93	11.98	1.78	7.31
EAG ACM2 (12-35 yrs) (N=649)	0.43	1.75	0.21	0.88	0.07	0.29	1.64	6.72	2.35	9.64	1.50	6.14
Company ACM3 (12+ yrs) (N=898)	1.16	4.75	0.51	2.09	0.11	0.45	2.33	9.56	2.45	10.05	1.60	6.54
DSU scenario 1: 12-35yrs and 36+yrs (N=898)	1.68	7.52	0.72	3.21	0.14	0.60	2.83	12.17	2.52	10.42	1.67	6.92
DSU scenario 2: (N=788)	1.72	7.65	0.72	3.21	0.14	0.60	2.94	12.58	2.45	10.15	1.67	6.92
DSU scenario 3: (N=898)	1.35	6.14	0.56	2.57	0.11	0.51	2.36	10.86	2.49	10.03	1.64	6.73
DSU scenario 4: (N=788)	1.41	6.23	0.59	2.62	0.12	0.52	2.66	11.31	2.39	9.87	1.62	6.72

Acute chest syndrome not modelled as included within VOC rate

Complication slides

Modelled mean life years with chronic complications

Highest rate
Lowest rate

Scenarios	Chronic kidney disease		Pulmonary hypertension		Avascular necrosis		Heart failure		Neuro-cognitive impairment		Post Stroke		Retinopathy		Chronic liver disease	
	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC	Exa-cel	SoC
Literature value	2.46	7.57	1.63	5.15	4.49	12.88	4.45	12.8	4.09	8.86	2.13	6.62	7.98	6.25	1.33	4.24
Company ACM2 (2+ yrs) (N=1,117)	1.12	3.59	1.84	5.76	4.17	12.11	1.59	5.01	2.57	4.36	0.47	1.44	10.02	12.28	1.48	4.69
EAG ACM2 (12-35 yrs) (N=649)	0.59	1.90	1.31	4.17	3.25	9.75	0.73	2.36	2.49	4.12	0.47	1.44	9.47	10.76	0.82	2.63
Company ACM3 (12+ yrs) (N=898)	1.07	3.42	1.87	5.86	4.02	11.76	1.48	4.68	2.67	4.69	0.72	2.20	10.11	12.53	1.33	4.24
DSU scenario 1: 12-35yrs and 36+yrs (N=898)	0.97	3.64	1.75	6.16	3.72	11.95	1.30	4.99	2.63	4.75	0.63	2.19	9.90	12.75	1.20	4.38
DSU scenario 2: (N=788)	1.06	3.88	1.90	6.54	3.82	12.14	1.41	5.26	2.61	4.70	0.63	2.19	9.94	12.82	1.18	4.34
DSU scenario 3: (N=898)	0.67	3.09	1.30	5.55	3.33	11.14	0.90	4.13	2.61	4.50	0.37	1.70	9.67	12.01	1.08	3.73
DSU scenario 4: (N=788)	0.93	3.30	1.76	5.90	3.64	11.32	1.22	4.38	2.56	4.46	0.56	1.86	9.78	12.08	1.04	3.70

Web comments

Link to severity | RECAP

Patients, carers, family, clinicians and public comments (1)

Impact of SCD	Current treatments
• Everyday life significant disrupted • Life-limiting, debilitating, unpredictable, and progressive condition • Significantly reduced life expectancy • Severity of SCD worsens overtime • Considerable QoL impact on patients and family • Symptoms e.g., fatigue, chronic pain, organ damage, other life-threatening health complications • Significant negative social, emotional, psychological and physical impact • Affects education, employment, finances • Severity and long-term organ damage has not been fully appreciated	• High unmet need for an effective, well-tolerated treatment • Frequent inpatient treatment interferes with daily life • Current treatments offer temporary relief and do not address underlying cause • Pain relief often fails, exacerbated by delays in following pain relief commissioning requirements, poor care, conflict and confrontation • Other treatment options have been withdrawn • Few African and Caribbean blood donors – need other treatment forms • Care and access to treatment options are extremely limited compared to other inherited conditions

Abbreviation: SCD, sickle cell disease; QoL, quality of life

Web comments

Link to severity | RECAP

Patients, carers, family, clinicians and public comments (2)

Exa-cel	Wider considerations

• Exa-cel should be made available - innovative, one-time and safe treatment
• Long-term benefits:
  ○ reduces hospitalisations, costs and treatment
  ○ improves life expectancy and QoL
  ○ removes clinical, social, and economic burdens
  ○ halts bodily deterioration, enables repairs
• Dramatically change lives of patients and families
• QoL and survival benefits not fully addressed
• More research and data collection needed
• Treatment R&D will stop if always rejected, funding exa-cel will encourage new treatments
• Should be for available for those <12 and >35 years
• No biological mechanism for edited cells to revert
• Want the benefits for future generations
	• Mainly affects African and Caribbean communities – more likely to experience poverty, discrimination, barriers to accessing healthcare
	• Draft recommendation seen as discriminatory and people feel stuck, abandoned and forgotten
	• "Burden of proof" seems higher for SCD community to be taken seriously
	• Should consider factors broader than direct healthcare costs e.g., loss of earnings
	• Little trust in NHS and clinical professionals – lack of understanding and pain often not believed
	• Recognise exa-cel is an expensive treatment
	• Lack of equity and funding for SCD
	• QoL not captured e.g., cultural reasons, nature of SCD and patient adaptations
	• Cure would help to redress some inequalities

Abbreviation: R&D, research and development, SCD, sickle cell disease, QoL, quality of life

Anthony Nolan and the Sickle Cell Society

Link to severity

RECAP

250+ responses from patients, parents, family members, clinicians and others

"My veins are a graveyard, a reminder of the many battles I have fought"

"Traumatic for all involved. Day to day life is a challenge."

"He says [son] it's as if more than one thousand ants are biting his bones from inside at the same time"

"It's a horrific condition, every day is a battle to prevent pain and as some of the triggers are things we have little control over, it's very difficult."

"I wake up every day in pain, and I go to sleep in pain, I have never known a pain-free" life

"It's not just the pain; it's the feeling of being trapped in your own body, unable to escape the torment"

"Living with sickle cell means living with constant fear." "Constant fear – fear of the next crisis, the next hospitalisation, the next brush with death"

"The spectre of a shortened life expectancy looms over me, a grim reminder of the fragility of my existence".

"I am stuck in a corner stagnant with nothing, but a heart full of sadness, and wishing and praying to one day wake up from this terrible nightmare of a life."

"1 in 16 people with SCD die before age of 18"

"Nothing could have prepared me for the sheer magnitude of their [child] suffering"

"All we want is a better quality of life, a pain free life, a long and healthy life"

"It's like a relentless storm that never lets up, slowly wearing you down until you feel like you can't go on. And it's not just the physical toll; it's the toll it takes on your spirit, your hopes, your dreams. I sometimes feel like I want to give up just for the pain to end"

Anthony Nolan and the Sickle Cell Society

Link to severity

RECAP

250+ responses from patients, parents, family members, clinicians and others

"This [exa-cel] would have been literally life saving for people like me who are suffering with this dreadful condition"

"Prospect of Exa-cel gives me hope, a glimmer of light in the darkness of my condition"

"Having SCD is like a death sentence because it comes with daily excruciating bone pain"

"It's difficult to convey as this is an invisible condition. Little awareness. Often, we are misbelieved"

"Patients have learnt to cope with their daily lives because of the lack of education and knowledge surrounding the illness due systemic racism, we've adapted to being unsupported"

"Only 50% of patients with SCD survive beyond their fifth decade"

"Sickle cell sufferers are living in agony in silence, we are not believed, [and] our pain is often disregarded"

"It's discerning when you have to be faced with how much others just don't care"

"[People with SCD] get used to QoL that would be considered restrictive by normal people"
"How I rate my QoL doesn't correlate with the reality of it"

"2013 study (sickle cell anaemia): average life expectancy of 42 years for women and 38 years for men"

"I am always in pain most times and am unable to work, or even enjoy my life"

"Its heart reaching to see the volume of pain they are in and knowing there isn't anything you can do to help them!"

"Severe cases frequent experience excruciating pain, debilitating fatigue, and increased susceptibility to infections and organ damage"

"Whenever we go to the hospital, we are treated differently, sometimes even being sworn at and told to be quiet during a painful sickle cell crisis."

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SoC utility overtime

Complication sources

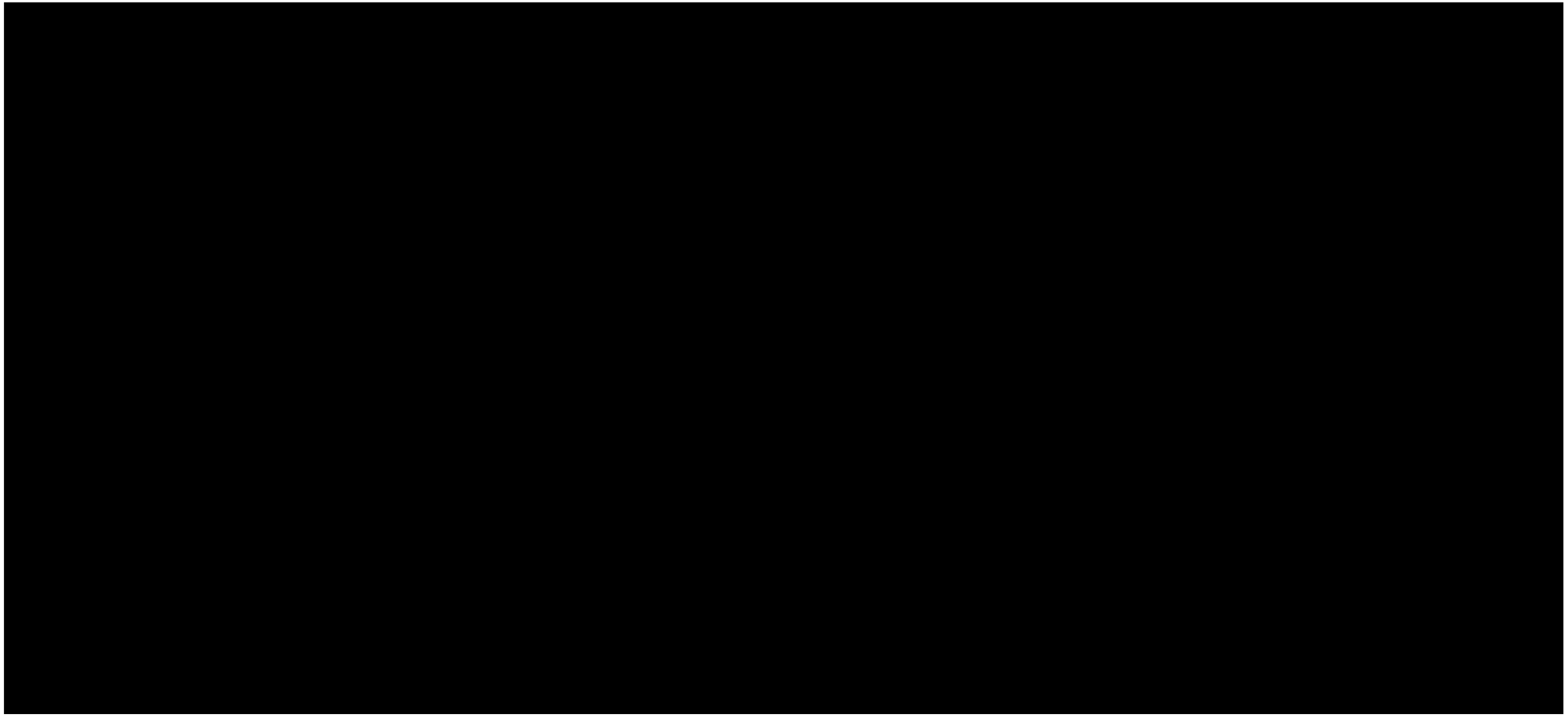
Company and EAG apply complication rate data in different ways, based on different age groups

[redacted]

Abbreviation: DSU, decision support unit, BOI, burden of illness; QALY, quality-adjusted life years; SoC, standard of care

SoC utility overtime

Model uncertainties



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Abbreviations: DSU, decision support unit, SoC, standard of care

QALY weighting for severity (6)

EAG preferred | Company preferred | DSU preferred

QALY shortfalls for different scenarios	Total SoC QALYs	Absolute (proportional) QALY shortfall
EAG ACM2 base case (12-35yrs subgroup)	11.73 11.37 11.00 10.82 10.64 9.82	1. 11.68 (49.90%) 2. 11.62 (50.54%) 3. 11.53 (51.17%) 4. 11.37 (51.24%) 5. 11.38 (51.68%) 6. 11.28 (53.46%)
Company post-ACM2 - weighted average complication rates (12+yrs)	11.09 10.76 10.43 10.27 10.11 9.36	1. 12.32 (52.64%) 2. 12.23 (53.19%) 3. 12.10 (53.70%) 4. 11.92 (53.72%) 5. 11.91 (54.09%) 6. 11.74 (55.64%)
DSU 3: Age-dependent rates (12-17yrs, 18-35yrs and 36+yrs), including ~5-year lag	11.79 11.37 10.71 10.40 10.21 9.30	1. 11.62 (49.65%) 2. 11.62 (50.54%) 3. 11.82 (52.46%) 4. 11.79 (53.13%) 5. 11.81 (53.63%) 6. 11.80 (55.92%)
DSU 4: Age-dependent complication rates (18-35yrs and 36+yrs), including ~5-year lag	11.40 11.02 10.61 10.40 10.21 9.30	1. 12.01 (51.31%) 2. 11.97 (52.06%) 3. 11.92 (52.90%) 4. 11.79 (53.13%) 5. 11.81 (53.63%) 6. 11.80 (55.92%)
Note: highlighted are scenarios that meet a 1.2 QALY weight.		

	Scenario	Age (yrs)	Female (%)
1	Younger population 1	15	44
2	Younger population 2	18	44
3	CLIMB SCD-121 (model)	21	44
4	BOI 12–35-year (aligned with CLIMB SCD-121)	23	52
5	BOI 12–35-year subgroup	24	51
6	BOI 12+ group	29	53

Marketing authorisation: treatment of SCD in people 12 years of age or older

1. Does the model accurately capture SoC utility, mortality and complications? If not, how does this affect SoC QALYs?
2. How should age and sex distribution align with other data sources and committee assumptions in model?
3. Has the severity modifier been met? If so, which QALY weight should be applied?

Abbreviations: QALE / Y, quality-adjusted life expectancy / year; SCD, sickle cell disease; SoC, standard of care