NICE National Institute for Health and Care Excellence

Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant

Lead team presentation

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Company: Medac

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Key clinical issues

1. Is there a clinical need for this treatment and a clearly identifiable patient population?
2. Is its main benefit in reducing transplant related mortality and complications following transplantation rather than an effect on the disease itself, when compared with a reduced intensity regimen?
3. The MC-FludT.14/L Trial II included adults with AML and MDS at increased risk/unfit for standard myeloablative (MAC) pre transplant. Is the population of MC-FludT.14/L Trial II broadly representative of UK clinical practice?
4. Would treosulfan be equally effective in similar patients with other malignant diseases for which alloHSCT is indicated?
5. Is the evidence in children sufficient for them to be included in any recommendation?
6. The trial only compared treosulfan with a reduced intensity regimen There is limited evidence on the comparative effectiveness of treosulfan and fludarabine versus other conditioning regimens particularly standard high-intensity MAC regimens.
    - How does treosulfan differ from other conditioning regimens? Would it be classified as myeloablative at the licensed dose?
    - Would the licensed treosulfan regimen be considered for people who might otherwise receive standard MAC, despite the lack of comparative evidence?
7. The submission does not include any indirect treatment comparison, treosulfan is compared with low dose busulfan only, should it be compared with high intensity regimens?

[redacted]

Treosulfan in combination with fludarabine

Marketing authorisation	Indicated as part of conditioning treatment prior to alloHSCT in adult patients with malignant and non-malignant diseases, and in children with malignant diseases (this appraisal focuses on **malignant disease** only)		
Administration and dose		**Adults with malignant disease**	**Children**
	Treosulfan (intravenous infusion)	10 g/m² body surface area (BSA) per day on 3 consecutive days (day -4, -3, -2) before stem cell infusion (day 0). Total dose is 30 g/m²	10-14 g/m² BSA per day on 3 consecutive days (day -6, -5, -4) before stem cell infusion (day 0). Total dose is 30-42 g/m²
	Fludarabine (intravenous infusion)	30 mg/m² BSA per day on 5 consecutive days (day -6, -5, -4, -3, -2). Total dose is 150 mg/m²	30 mg/m² BSA per day on 5 consecutive days (day -7, -6, -5, -4, -3). Total dose is 150 mg/m²
Mechanism of action	Prodrug of a bifunctional alkylating agent with cytotoxic activity to haematopoietic precursor cells.		

Disease background

- Haematopoietic stem cell transplant (HSCT) is a potentially curative therapy for more than 70 malignant diseases
- UK: most common malignant indications for allogeneic HSCT (alloHSCT) are acute myeloid leukaemia (AML; 36%), acute lymphoblastic leukaemia (ALL; 16%) and myelodysplastic syndrome (MDS) and variants (MPN) (together; 13%). Together these comprise 65%
- AlloHSCT is best performed at early stages of the disease, as soon as complete remission is achieved in patients with high-risk of recurrence
- Remission status at the time of HSCT is an important prognostic factor in the risk of relapse
- Before undergoing HSCT, patients receive a conditioning regimen in order to prepare the patient's marrow for transplantation by ablating it or suppressing it as far as possible. Conditioning treatments are usually chemotherapy alone or chemotherapy associated with radiotherapy

Treatment pathway- HSCT

Selection of patients and collection of stem cells: Eligibility for transplantation assessed, including tissue typing of donors and basic investigations for fitness. Collection of stem cells.

Conditioning therapy: Conditioning therapy prepares the recipient's marrow for transplantation (e.g. myeloablation or immunosuppression)

Transplantation and engraftment: Donor cells are infused intravenously and patients stay in hospital until they recover sufficient neutrophil numbers to reduce the risk of infection (engraftment)

Post-graft immunosuppression and post-transplant follow-up: Monitoring and treatment of complications such as infection and graft versus host disease (GvHD)

[redacted]

Ref: Company's submission, Figure 1

Treatment pathway - Conditioning treatments (1)

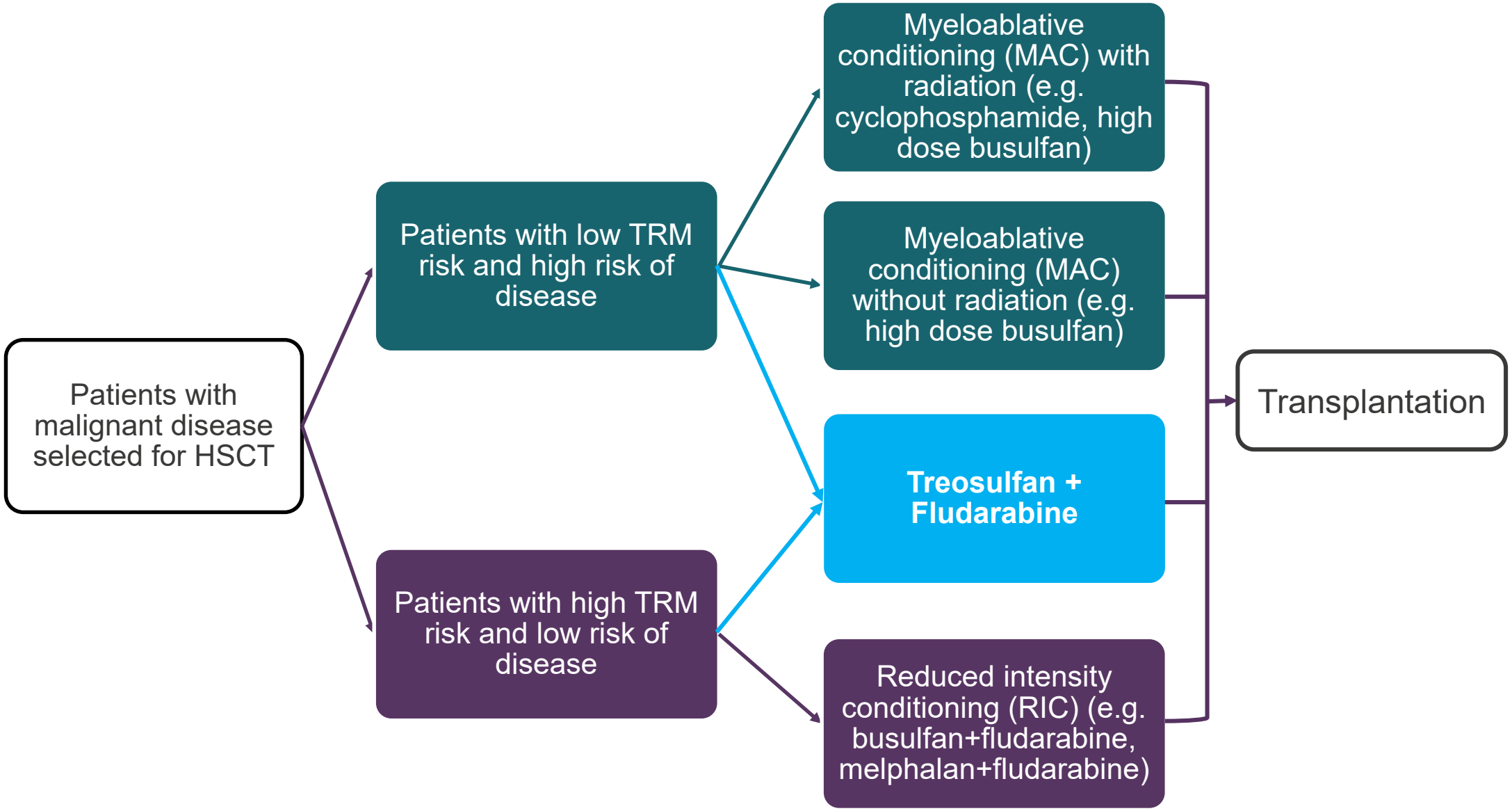
- The decision to conduct HSCT includes several factors besides the underlying disease, and is a fragile balance between risk of relapse/progression and the immediate and late effects of the transplant
- The 3 aims of a conditioning treatment are:
  - To reduce the tumour burden
  - To eliminate the patient's own normal marrow function
  - To suppress the recipient's immune system in order to allow engraftment of stem cells
- The European Society for Blood and Marrow Transplantation (EBMT) recommends that patients with high risk of transplantation related mortality (TRM) and a low disease relapse risk should receive a different conditioning regimen from patients with low risk of TRM and high risk of disease relapse

Treatment pathway - Conditioning treatments (2)

- High-intensity myeloablative conditioning (MAC) and reduced intensity conditioning (RIC) are 2 types of conditioning regimens
  - MAC regimen use total body irradiation and/or high-dose alkylating agents to cause irreversible lowering of all cells (pancytopenia), thereby minimising the risk of disease recurrence and allowing transplant to be accepted
  - RIC regimens use lower doses of total body irradiation or alkylating agents than MAC regimens, resulting in cytopenia which may be reversible
- The company proposes that the licensed treosulfan regimen is a reduced-toxicity regimen (RTC), which is myeloablative, but has lower toxicity than standard MAC regimens.

[redacted]

Treatment pathway – Conditioning treatments (3)



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Ref: Company's submission, Figure 2

Patient and carer perspectives

- Pre-transplant conditioning has significant effect on patient's quality of life, emotional health, and well being.
- Side effects are often experienced in a very severe form, necessitating additional treatment, and in certain cases lead to more extreme treatment-related morbidity
- For many patients, the conditioning phase is more challenging than their previous experience of chemotherapy
- "I was given drugs to prepare me to receive the donation … after first dose, my body started to "rumble" from within my core and culminated in violent shakes that were scary … difficult to articulate how powerful they were."
- "Any drug without side effects would be good." The conditioning phase was "traumatic and a major step back in the recovery process."
- "Really hope new treatments can reduce the suffering for future patients – was not prepared for the agony I was to endure…"
- "It was a tough time and experience, leaving me to this day with many psychological effects". Psychological support should be provided throughout.
- Patients and their families would welcome the introduction of any conditioning regimen with reduced toxicity and side-effect profile.

Decision problem

	Final scope issued by NICE	Evidence used in the model
Population	Adults, children and young people with malignant disease that is in remission before alloHSCT	Adults with AML and MDS that is in remission before alloHSCT
Intervention	Treosulfan with fludarabine	As final scope
Comparators	Standard myeloablative regimens (MAC) - Cyclophosphamide and total body irradiation - Cyclophosphamide and busulfan - Cyclophosphamide and thiotepa - High dose busulfan with fludarabine with or without thiotepa Reduced intensity regimens (RIC) - ***Low dose busulfan with fludarabine*** - Melphalan plus fludarabine	Low dose busulfan with fludarabine
Outcomes	The outcomes measures include: - Overall survival - Event-free survival - Rates of relapse - Success of transplantation (engraftment) - Adverse effects of treatments - Health-related quality of life	Additional including: - non-relapse mortality (NRM)

Clinical evidence - MC-FludT.14/L Trial II

Study design	Randomised, parallel-group, open label, multicentre, international, Phase III non-inferiority
Population	Adults with AML or MDS at increased risk for standard conditioning therapies (not eligible for standard myeloablative conditioning regimens). Increased risk: ≥50 years and/or Hematopoietic cell transplantation co-morbidity index (HCT-CI) score≥2
Intervention	Treosulfan (10g/m^2) x 3 doses with fludarabine (30mg/m^2) x 5 doses
Comparator	Low dose busulfan (3.2mg/kg) x 3 doses with fludarabine (30mg/m2) x 5 doses
Outcomes	Primary endpoint: Event-free survival within 24 months of HSCT Secondary endpoint: Overall survival, non relapse mortality, transplantation related mortality, graft failure, cumulative incidence of relapse
Protocol amendment	*Protocol amendment 03: the treosulfan dose reduced from 3x14g/m^2 to 3x10g/m^2 , as partly unfavourable findings (increased infections after Treosulfan) associated with an imbalanced dosing of treosulfan and busulfan. Results for patients randomised before amendment are not reported in this submission.*

Clinical evidence - MC-FludT.14/L Trial II- Primary outcome

Primary outcome: Event-free survival within 24 months of alloHSCT	Treosulfan + flud. (N=268)	Busulfan + flud. (N=283)
Median follow-up (months)	29.7	29.4
Patients with event	**97 (36.2%)**	**137 (48.4%)**
- Death	35 (13.1%)	56 (19.1%)
Hazard ratio (95% CI)	**0.63 (0.41, 0.97)**	
- Relapse/Progression	61 (22.8%)	72 (25.4%)
Hazard ratio (95% CI)	**0.82 (0.59, 1.16)**	
- Primary or secondary graft failure	1 (0.4%)	9 (3.2%)
Event-free survival at 24 months (95%CI)	65.7% (59.5, 71.2)	51.2% (45.0, 57.0)
Hazard ratio (95% CI)	**0.64 (0.49, 0.84)**	

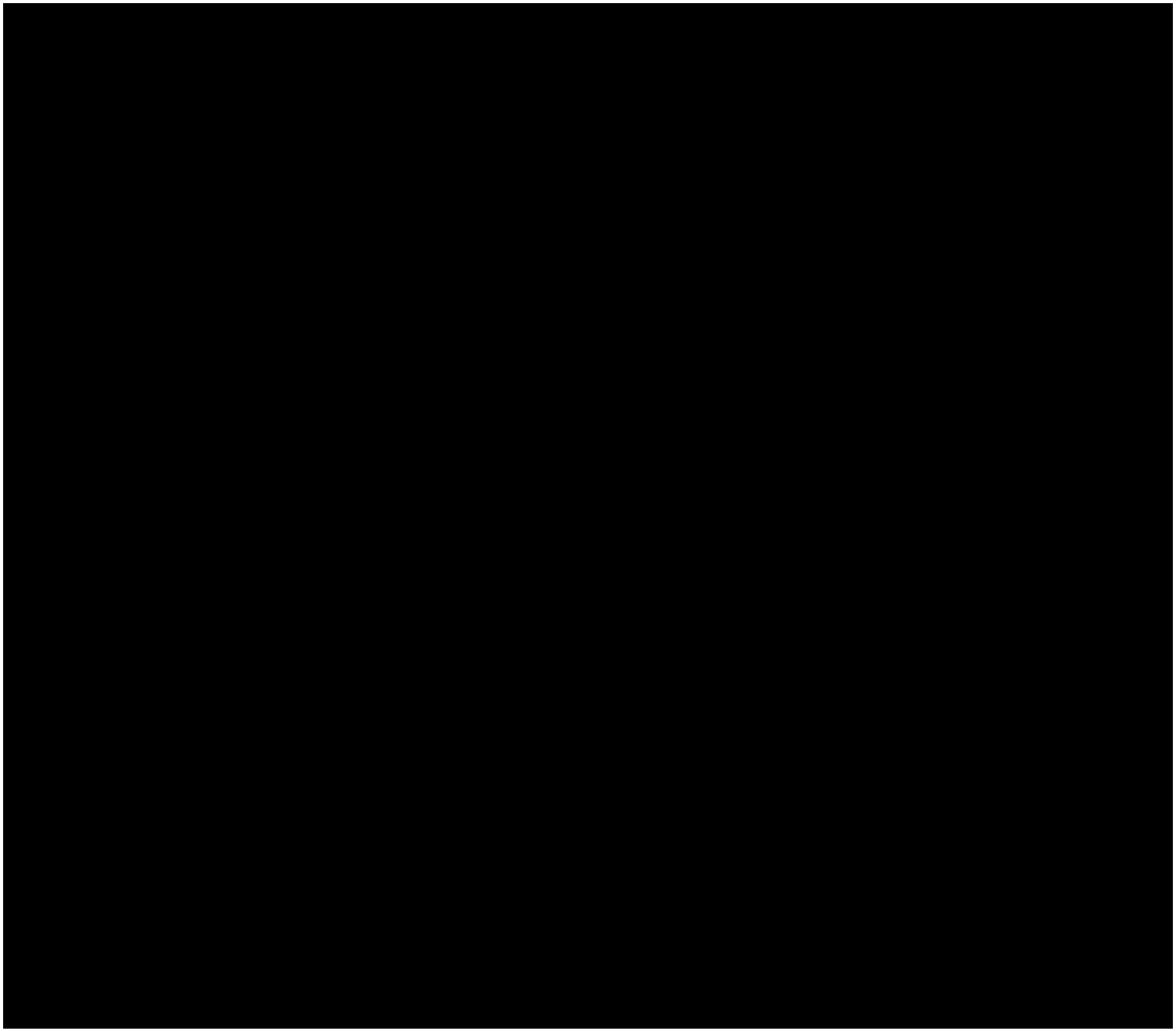
- Event-free survival: composite endpoint - event defined as **relapse, graft failure or death whatever occurred first**
- **Limited benefit** observed on **relapse rates**, the **main benefit** is on mortality, especially **non-relapse mortality** and transplantation-related mortality

[redacted]

Clinical evidence - MC-FludT.14/L Trial II- Secondary outcomes

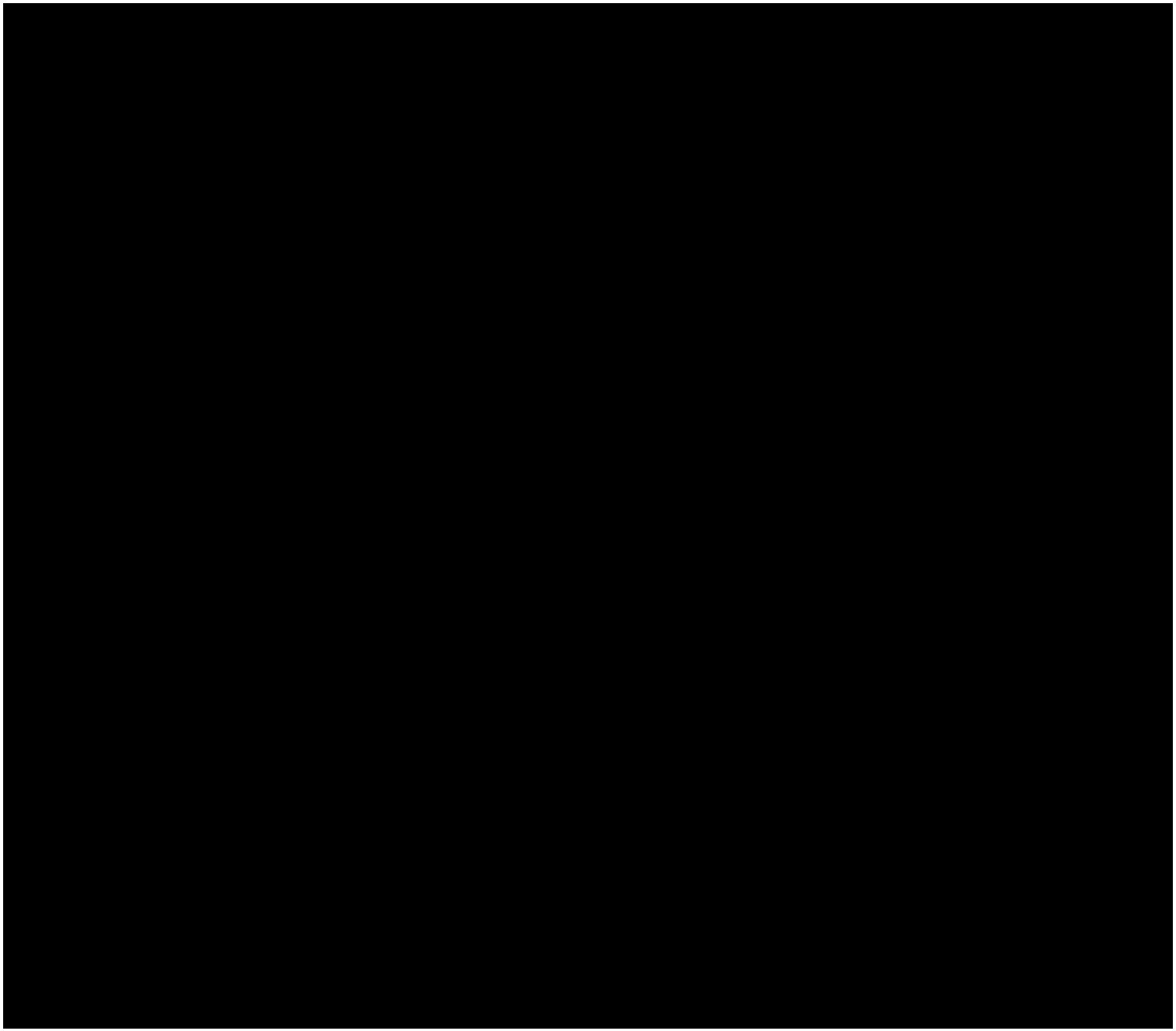
Secondary outcomes	Treosulfan + flud. (N=268)	Busulfan + flud. (N=283)
Overall survival at 24 months (95% CI)	72.7% (66.8, 77.8)	60.2% (54.0, 65.8)
Hazard ratio (95% CI)	**0.64 (0.48, 0.87)**	
Transplantation related mortality at 24 months (95% CI)	12.8% (9.2 to 17.7)	24.1% (19.1 to 30.2)
Hazard ratio (95% CI)	**0.52 (0.34 to 0.82)**	
Cumulative incidence of non relapse mortality at 24 months (95% CI)	12.0% (8.0 to 15.9)	20.4% (15.5 to 25.2)
Hazard ratio (95% CI)	**0.63 (0.41, 0.97)**	
Cumulative incidence of relapse at 24 months (95% CI)	22.0% (16.9, 27.1)	25.2% (20.0, 30.3)
Hazard ratio (95% CI)	**0.82 (0.59, 1.16)**	

Clinical evidence - MC-FludT.14/L Trial II EFS



- Event was defined as relapse, graft failure or death; whatever occurred first

Clinical evidence - MC-FludT.14/L Trial II OS



Clinical evidence – Safety

	Treosulfan (N=270)	Busulfan (N=283)
Treatment emergent adverse events (TEAE)	250 (92.6%)	272 (96.1%)
Serious adverse events (SAEs)		
Any event	23 (8.5%)	21 (7.1%)
Hospitalisation	8 (3.0%)	9 (3.2%)
Death	8 (3.0%)	6 (2.1%)
CTC Grade III IV mucositis (Secondary endpoint)	16 (5.9%)	21 (7.4%)
CTC Grade III IV adverse events (Secondary endpoint)	148 (54.8%)	151(53.4%)

CTC: Common Terminology Criteria

Issue 4: Generalisability of the trial results to the UK population

Background

- No UK patients in MC-FludT.14/L trial. Mean age 59.6 years, mean weight 80.2 kg.
- Trial limited to patients at **increased risk for standard conditioning therapy** (that is, not eligible for standard high-intensity MAC) Defined as 50 or older and/or with a hematopoietic cell transplantation co-morbidity index (HCT-CI) score>2.
- **ERG** agree that alloHSCT **practice** is likely to be **broadly similar** between the UK and other European countries in trial, but uncertain how similar the definition of increased risk for standard conditioning therapy is to the UK definition.

Stakeholder comments

- Company: reasonable to assume that alloHSCT practice in the UK is similar to other European countries, as **50 UK transplant centres** are members of the **EBMT** and work according to the **EBMT guidelines.**
- More than **20 UK experts** were involved in the development of the 2019 EBMT Handbook for HSCT and cell therapies.
- So MC-FludT.14/L trial reflects routine UK practice.

[redacted]

Technical team agree that it is reasonable to assume that alloHSCT practice is similar in England and Wales as with other European countries.

Clinical evidence in children

MC-FludT.17/M (N= 70)	
Design	Prospective, single arm, open-label, multicentre, non-controlled study
Population	Children up to 17 years with haematological malignant disease
Intervention	Treosulfan: i.v. 10, 12 or 14 g/m²/day given prior to fludarabine; Fludarabine: i.v. 30 mg/m²/day days -7 to -3 prior to HSCT. With or without Thiotepa: i.v.
Key results (March 2018 cut-off)	Primary endpoint: Rate of freedom from transplant-related mortality (TRM) at 100 days post HSCT [redacted]% (90% CI: [redacted]) Secondary endpoint at 12 months: - Overall survival: [redacted]% (90% CI: [redacted]) - Event-free survival: [redacted]% (90% CI: [redacted]) - Transplantation-related mortality: [redacted]% (90% CI: [redacted]) - Cumulative incidence or relapse/progression: [redacted]% (90% CI: [redacted]) - Graft failure: no primary graft failure, [redacted] person ([redacted]%) had secondary graft failure

[redacted]

Issue 1: How does treosulfan differ from other alkylating agents used in conditioning regimens? What is the main benefit of treosulfan and is it a standard myeloablative regimen at the dose used in the trial?

Background

- Treosulfan is an alkylating agent proposed as a reduced-toxicity myeloablative regimen (RTC), with lower toxicity than standard MAC regimens.
- Company: main benefit is on the toxicity i.e. the **patients are less likely to die** from the transplant or associated infections, graft vs host disease etc. and it has limited impact on relapse rates. A **reduction in non-relapse mortality** (NRM) is the reason for the overall survival benefit.
- Toxicity in this case relates to bone marrow due to conditioning rather than toxicity in terms of adverse events due to treatment.
- In the trial, treosulfan was administered at a **dose of 10 g/m^2** following a protocol amendment (dose was reduced from 14 g/m^2)

Stakeholder comments

- Company states that treosulfan is a MAC regimen with reduced toxicity. The main benefit of treosulfan compared to other regimen is to provide **better tolerability**, especially versus the busulfan fludarabine regimen, leading to reduced non-relapse mortality.
- The main causes of **non-relapse death** are **infections** (Treosulfan vs. Busulfan: 9.3% vs. 14.1%) and **GvHD** (4.8% vs. 7.4%) Both causes combined: 13.9% vs. 21.5%.
- Treosulfan has limited impact on the relapse rates and according to the company, the effect of treosulfan is mainly on bone marrow toxicity and as a result, is independent of the underlying disease.

[redacted]

Issue 2: To what extent can the trial results be extrapolated to a broader population: other malignancies and children?

Background

- Company submitted evidence from MC-FludT.14/L Trial II - population is **narrower** than marketing authorisation.
- Trial population is adults with **AML** or **MDS.**
- Marketing authorisation refers to **any malignancies** and specifically refers to **children.**

Stakeholder comments

- Company believe trial results are **generalisable to broader population.** Treosulfan main benefit is **reduced toxicity** versus busulfan and fludarabine, which is not impacted by the underlying disease.
- Evidence that treosulfan effect is disease-independent was provided within the large EBMT registry study in patients with multiple myeloma.
- Treosulfan efficacy in children demonstrated in single arm **MC-FludT.17/M trial** (70 children with malignant diseases, dose 10 to 14g/m^2 BSA adapted).
- **ERG**: Evidence submitted can only support assessment of treosulfan and fludarabine in adults with AML and MDS at increased risk for standard conditioning therapies.

[redacted]

Issue 3: The submission focuses on a low-intensity regimen: there is no comparison with high intensity regimens

Background

- Clinical evidence confined to people at **increased risk for standard conditioning therapies** (not eligible for standard myeloablative conditioning [MAC]).
- Increased risk defined as **50 or older** at transplant and/or haematopoietic cell transplantation co-morbidity index **(HCT-CI) score≥2.**
- Comparator **only partially addressed** the NICE **scope** (which included **high-intensity regimens** cyclophosphamide and irradiation, cyclophosphamide and busulfan etc. and **reduced-intensity regimen** melphalan plus fludarabine).
- Evidence is based on **one comparator**, RIC busulfan with fludarabine (comparator in trial).
- There is **no evidence** on the **comparative effectiveness** of treosulfan and fludarabine versus **other conditioning regimens** particularly for standard high-intensity MAC regimens.

Stakeholder comments

- **Company: no consensus** on conditioning regimens for patients not eligible for standard high-intensity MAC regimens. The RIC regimens frequently used currently are low dose busulfan plus fludarabine and melphalan plus fludarabine.
- **ERG:** Evidence sufficient to support assessment of treosulfan vs RIC busulfan but not for assessment vs any other comparators of the scope.

[redacted]

Issue 5: Limited evidence of comparative effectiveness of treosulfan versus other conditioning regimens

Background

- The **only comparative evidence** available for treosulfan and fludarabine is with busulfan and fludarabine in the MC-FludT.14/L trial.
- Company explored 2 approaches for comparative evidence with other regimens;
  - **Registry analyses**: 2 registry studies were analysed to compare patients who received treosulfan in trial to registry patients. Analyses not included in the cost effectiveness modelling.
  - **Indirect treatment comparison (ITC)**: A feasibility assessment was conducted and showed that some ITC were feasible versus busulfan/cyclophosphamide and busulfan/fludarabine (MAC) at 2 years for OS, relapse rate and GvHD incidence.
  - **Company** considered that these ITC outcomes were unlikely to be reliable enough to provide relevant comparative data and **did not include** them in the analyses.

Stakeholder comments

- Company believe that clinicians would consider the evidence to be sufficient to use treosulfan and fludarabine in MAC-eligible patients.
- Company: published retrospective studies from EBMT registry comparing treosulfan and fludarabine to other MAC regimens demonstrate that treosulfan-based regimen is at least as good as other MAC regimens e.g Shimoni et al. concluded that treosulfan and fludarabine is associated with similar low relapse rates as other MAC regimens and similar non-relapse mortality as RIC regimens.

[redacted]

Key clinical issues

1. Is there a clinical need for this treatment and a clearly identifiable patient population?
2. Is its main benefit in reducing transplant related mortality and complications following transplantation rather than an effect on the disease itself, when compared with a reduced intensity regimen?
3. The MC-FludT.14/L Trial included adults with AML and MDS at increased risk/unfit for standard myeloablative (MAC) pre transplant. Is the population of MC-FludT.14/L Trial II broadly representative of UK clinical practice?
4. Would treosulfan be equally effective in similar patients with other malignant diseases for which alloHSCT is indicated?
5. Is the evidence in children sufficient for them to be included in any recommendation?
6. The trial only compared treosulfan with a reduced intensity regimen There is limited evidence on the comparative effectiveness of treosulfan and fludarabine versus other conditioning regimens particularly standard high-intensity MAC regimens.
    - How does treosulfan differ from other conditioning regimens? Would it be classified as myeloablative at the licensed dose?
    - Would the licensed treosulfan regimen be considered for people who might otherwise receive standard MAC, despite the lack of comparative evidence?
7. The submission does not include any indirect treatment comparison, treosulfan is compared with low dose busulfan only, should it be compared with high intensity regimens?

[redacted]

Key cost-effectiveness issues

1. The model is driven by longer time to event as defined in EFS: relapse, graft failure or death whichever occurred first. The effect on disease relapse alone is limited
2. To model mortality the company assumed a “cure point” of 5 years based on the rationale that alloHSCT is potentially curative
   – If patients did not relapse after transplantation, would they be considered cured at 1 year, 2 years, 5 years?
3. Treosulfan dominates busulfan in all analyses, is this sufficient to demonstrate that the treosulfan regimen can be recommended as a cost-effective option for its full licensed indication, which is broader than the model, and compared to the full range of possible treatments?

[redacted]

Cost-effectiveness model

Model type	Partitioned survival model
Population	Patients from the MC-FludT.14/L Trial II – adults with AML or MDS that is in remission before alloHSCT, at increased risk for standard conditioning therapy (that is, not eligible for standard high-intensity MAC)
Intervention	Treosulfan and fludarabine
Comparators	Busulfan and fludarabine
Time horizon	40 years
Model cycle	28 days
Discount rates	3.5% for both costs and outcomes
Utility values	EQ-5D values from literature
Perspective	NHS and PSS

Company's base-case

Overall survival

Event-free survival

Event was defined as relapse, graft failure or death; whatever occurred first

Key model assumptions

Comparators	Low dose busulfan and fludarabine
Concomitant treatments	The same therapies were used concomitantly with treosulfan and busulfan except for phenytoin
Mortality modelling and cure point	• If patients did not relapse 5 years after transplantation, they are considered cured • EFS and OS curves are used until the cure point, then HSCT-specific life tables are used to model mortality.
Health-related quality-of-life	• Utility values based on literature – Clinical trial did not collect HRQoL data
Costs and resource use	• Administration costs are excluded from calculation • Wastage costs are applied, with 100% wastage vial wastage assumed in the base case • All costs associated with adverse events management were incurred in an inpatient setting

Issue 6: Mortality modelling

Background

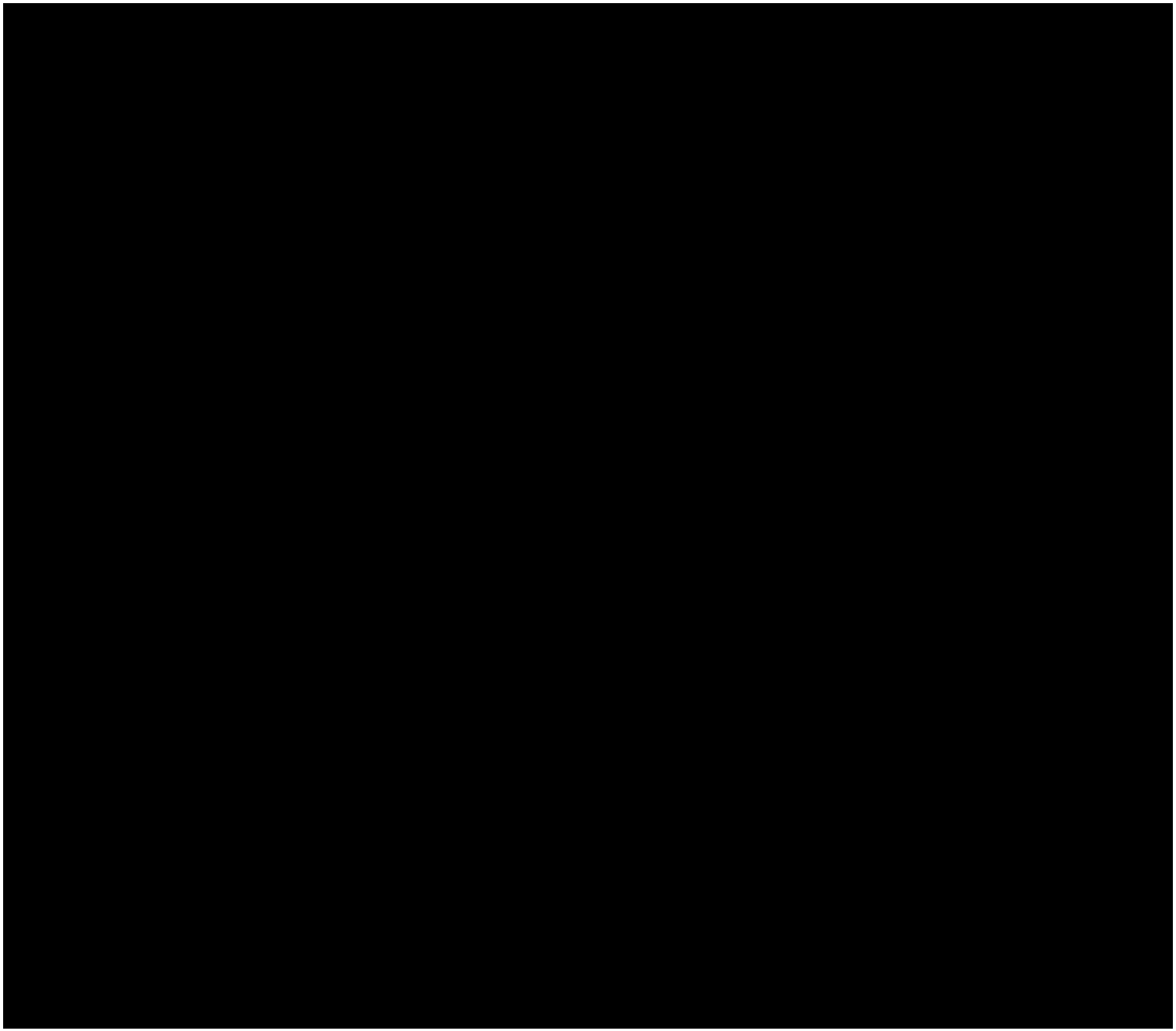
- To model mortality, company used a "cure point" based on the rationale that alloHSCT is **potentially curative.**
- In company's base-case, a fixed "**cure point**" of **5 years** is assumed, based on 2 clinical expert's opinion.
- Company explained that patients who survive alloHSCT for at least 5 years are considered cured.
- The impact of changing the "cure point" was tested by the **ERG**. Results were **similar to the base-case** analysis except when the cure point was assumed to be **one year**, where busulfan was not dominated by treosulfan
- This assumption resulted in treosulfan being dominated by busulfan (incremental costs £2,044 and incremental QALYs -0.03).

Stakeholder comments

- Company stated that there is **consensus among clinical experts** that patients who survive alloHSCT and are disease-free for more than 5 years can be expected to be cured.
- Most survival curves show a plateau at 5 years. In the MC-FludT.14/L trial, it was reached after 40 months.

[redacted]

Clinical evidence - MC-FludT.14/L Trial II OS



ERG corrections and amendments

Issue	Comments
Event-free and overall survival extrapolation	• Company chose a non-mixture cure model (NMCM) lognormal for all analyses and all treatment arms • For OS, ERG prefers to use the NMCM Weibull distribution as NMCM lognormal seem to underestimate OS for busulfan • ERG's preferred model lead to results similar to company's base-case (busulfan dominated by treosulfan). However, it resulted in less cost savings and smaller incremental QALYs
OS and EFS probability calculations	• OS and EFS probabilities were incorrectly calculated using mortality rates instead of transition probabilities. ERG amended calculations, it had a minor effect on the results
Yearly values rescaled to daily values	• Yearly values in the model where re-scaled to daily values using a factor 1/365.25 instead of 1/364
Most recent UK life tables used	• The company did not used the most recent UK life tables, the ERG amended calculation using the 2015-2017 UK life tables

[redacted]

Cost effectiveness results

Scenario	Incremental costs (£)	Incremental QALYs	ICER vs busulfan and fludarabine
Company's base case	-£20,424	0.89	Treosulfan dominates
Company's base after clarification	-£20,329	0.89	Treosulfan dominates
ERG's preferred assumptions			
Cumulative impact of the ERG's preferred assumptions (deterministic)	**-£14,357**	**0.78**	**Treosulfan dominates**
Cumulative impact of the ERG's preferred assumptions (probabilistic)	**-£12,371**	**0.71**	**Treosulfan dominates**

Incremental costs corrected following an update from the company

[redacted]

ERG scenarios – Change in cure point

Scenario	Incremental costs (£)	Incremental QALYs	ICER vs busulfan and fludarabine
ERG's preferred assumptions	**-£14,357**	**0.78**	**Treosulfan dominates**
Cure point			
5 years	-£14,357	0.78	Treosulfan dominates
4 years	-£8,237	0.90	Treosulfan dominates
3 years	-£1,266	1.03	Treosulfan dominates
2 years	-£4,065	0.78	Treosulfan dominates
1 year	£2,044	-0.03	Treosulfan ***dominated***

Incremental costs corrected following an update from the company

[redacted]

Key cost-effectiveness issues

1. The model is driven by longer time to event as defined in EFS: relapse, graft failure or death whichever occurred first. The effect on disease relapse alone is limited
2. To model mortality the company assumed a “cure point” of 5 years based on the rationale that alloHSCT is potentially curative
   – If patients did not relapse after transplantation, would they be considered cured at 1 year, 2 years, 5 years?
3. Treosulfan dominates busulfan in all analyses, is this sufficient to demonstrate that the treosulfan regimen can be recommended as a cost-effective option for its full licensed indication, which is broader than the model and compared to the full range of possible treatments?

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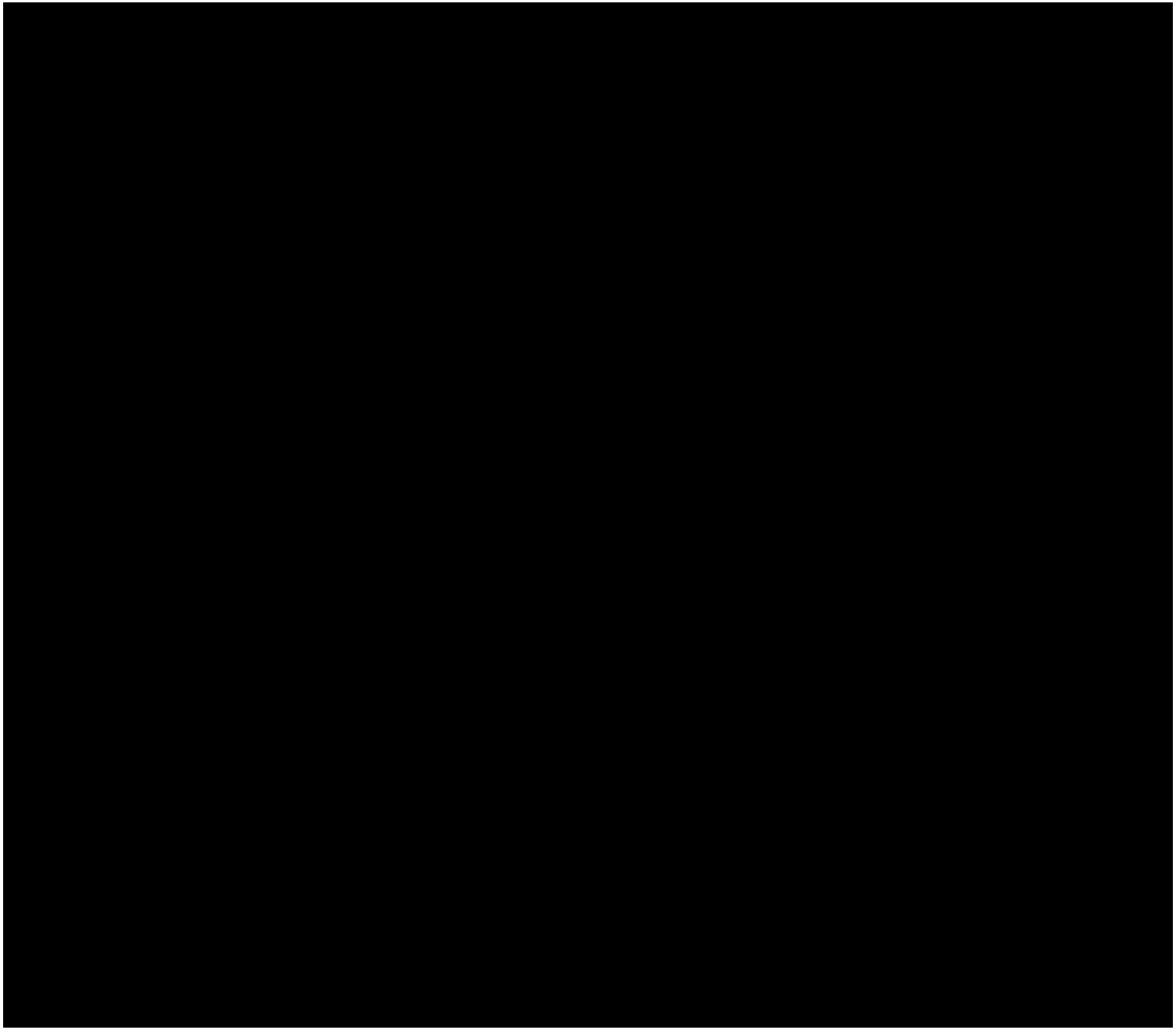
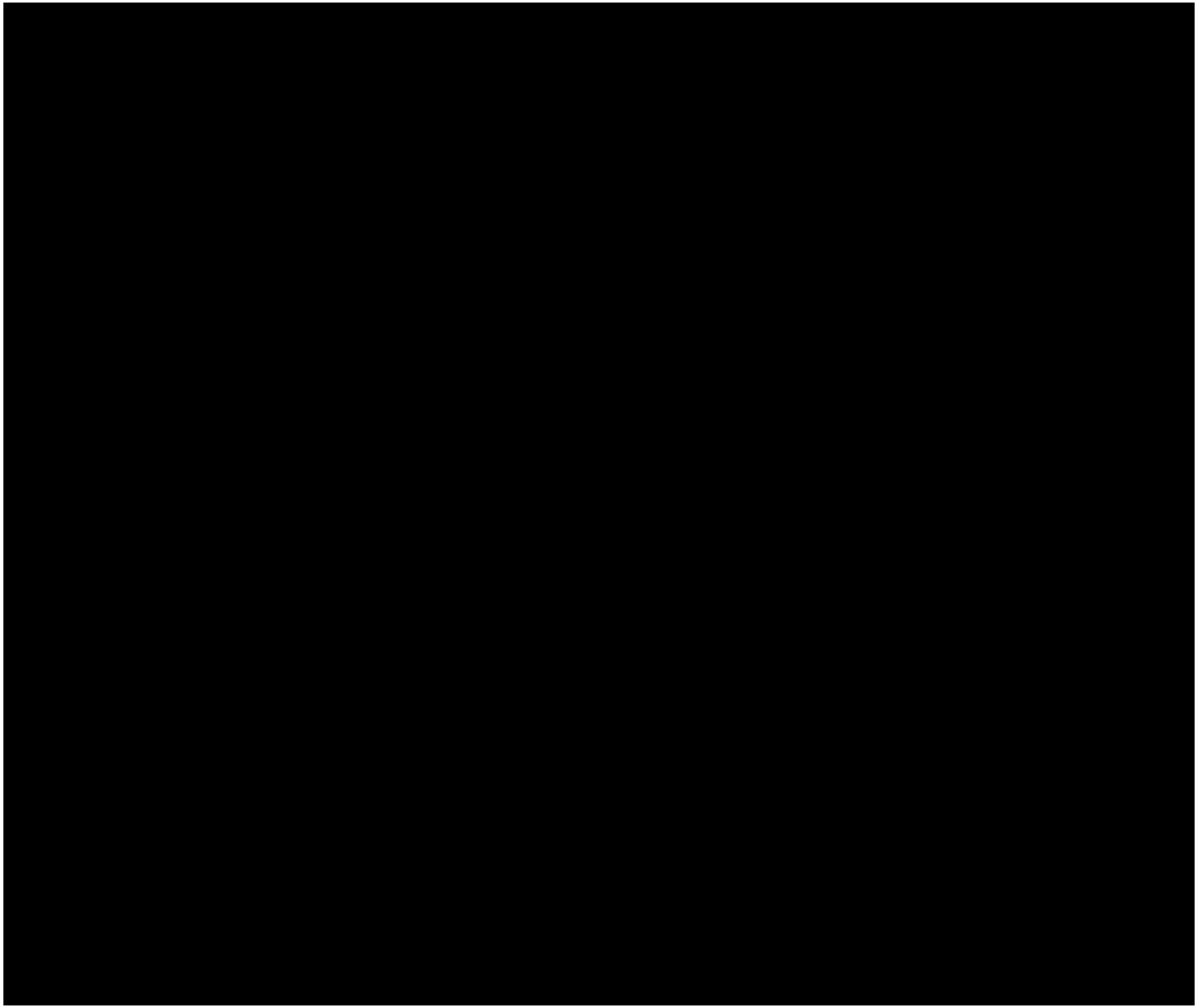
Back-up slides

Causes of deaths in MC-FludT.14/L Trial



Overall survival: Kaplan-Meier vs model extrapolations (ERG base-case)



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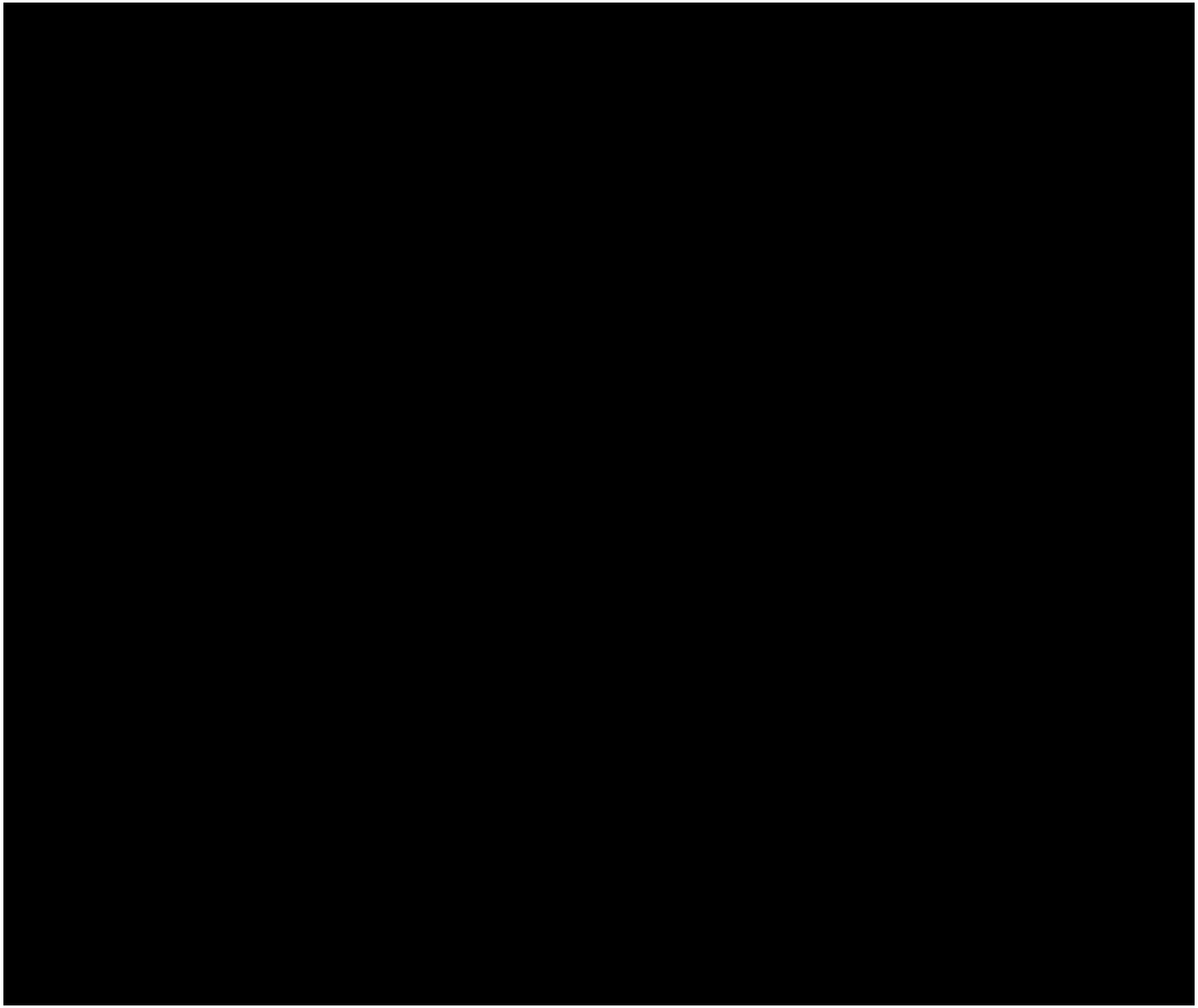
Patient distribution per health state (company's base-case)



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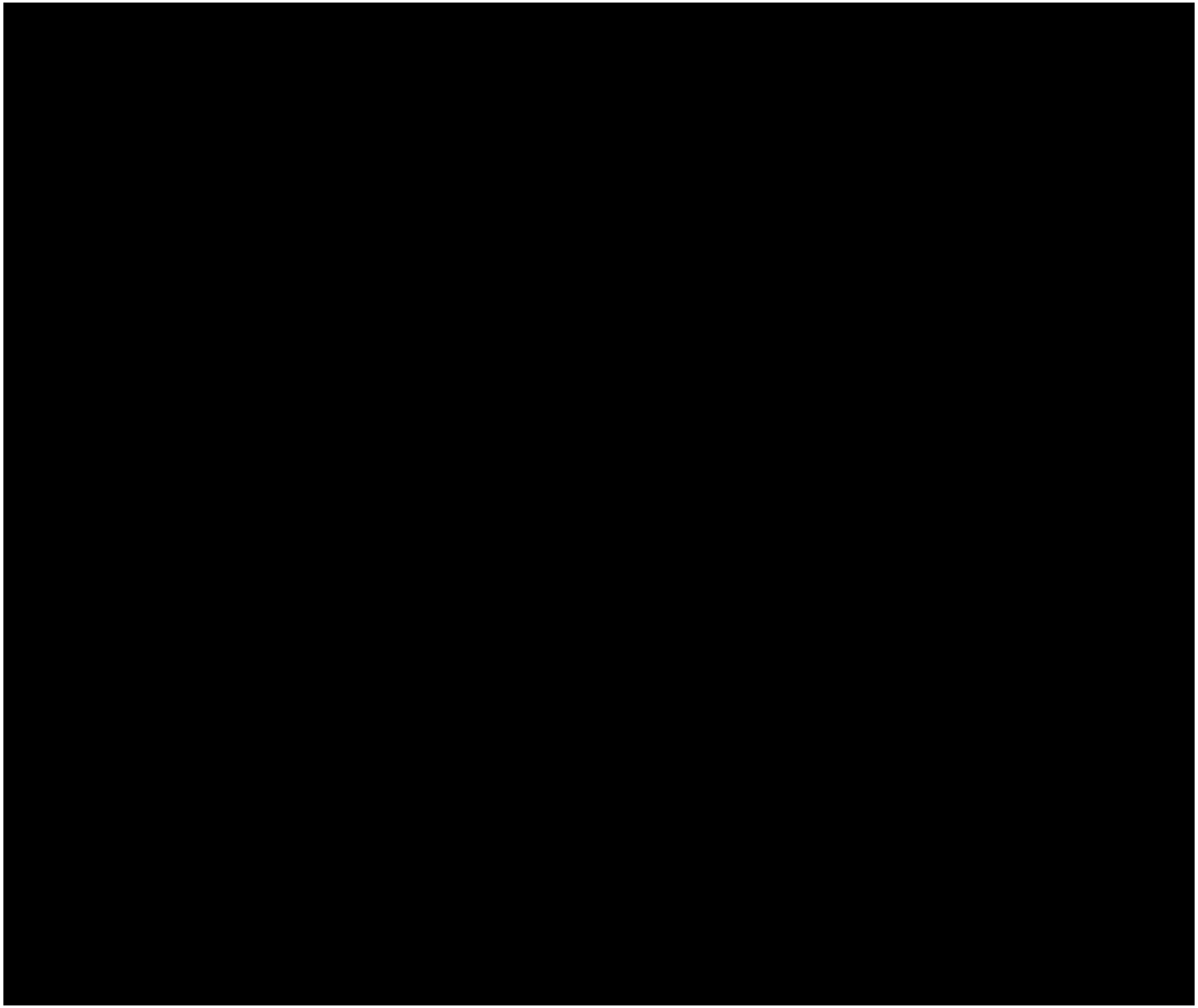
Patient distribution per health state (ERG's base-case)



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Cost effectiveness results

Scenario	Incremental costs (£)	Incremental QALYs	ICER vs busulfan and fludarabine
Company's base case	-£23,759	0.89	Treosulfan dominates
Company's base after clarification	-£23,668	0.89	Treosulfan dominates
ERG's preferred assumptions			
ERG correction of OS and EFS implementation	-£14,492	0.84	Treosulfan dominates
ERG correction of rescaling factor (year to day)	-£14,490	0.84	Treosulfan dominates
Using NMCM Weibull to model OS	-£17,641	0.78	Treosulfan dominates
Using most recent life tables	-£17,689	0.78	Treosulfan dominates
Cumulative impact of the ERG's preferred assumptions (deterministic)	**-£17,689**	**0.78**	**Treosulfan dominates**
Cumulative impact of the ERG's preferred assumptions (probabilistic)	**-£15,857**	**0.70**	**Treosulfan dominates**

[redacted] Results based on the treosulfan price submitted by the company (BNF price)

ERG scenarios – Change in cure point

Scenario	Incremental costs (£)	Incremental QALYs	ICER vs busulfan and fludarabine
ERG's preferred assumptions	**-£17,689**	**0.78**	**Treosulfan dominates**
Cure point			
5 years	-£17,689	0.78	Treosulfan dominates
4 years	-£11,565	0.90	Treosulfan dominates
3 years	-£4,590	1.03	Treosulfan dominates
2 years	-£7,390	0.78	Treosulfan dominates
1 year	-£1,293	-0.03	£47,910/QALY (*ICER of busulfan and fludarabine vs treosulfan and fludarabine*)

[redacted] Results based on the treosulfan price submitted by the company (BNF price)