NICE National Institute for Health and Care Excellence

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Chair's presentation

2nd Evaluation Committee Meeting (11th April 2019)

Highly Specialised Technologies

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ERG: BMJ-TAG

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Company: CSL Behring

Overview

- **Recap (ECM1: August 2018)**
  - The condition
  - The technology
  - Clinical effectiveness and value for money evidence presented at ECM1
  - ECD preliminary recommendations and considerations
- **ECD consultation responses**
- **Company's new evidence submission and ERG comments**
- **Key issues**

[redacted]

Background

The condition

- Alpha1-proteinase inhibitor (A1PI) deficiency causes increased vulnerability to lung damage from toxins (e.g. smoking and pollution)
- Can lead to emphysema

Symptoms of emphysema

- Coughing, wheezing, breathlessness and frequent chest infections
- Repeated exacerbations lead to a decline in lung function
- Walking, speaking and eating become increasingly challenging as disease progresses
- Can reduce life expectancy

Prevalence

- 670 people with emphysema caused by A1PI deficiency in England, A1PI treatment may be considered for ~200–600

Treatment

- Standard therapies for chronic obstructive pulmonary disease (COPD)
  - Aim to delay progression and manage symptoms
  - Do not treat the underlying cause
- Lung transplants can be considered for people with progressed disease

Human alpha1-proteinase inhibitor (Respreeza, CSL Behring)

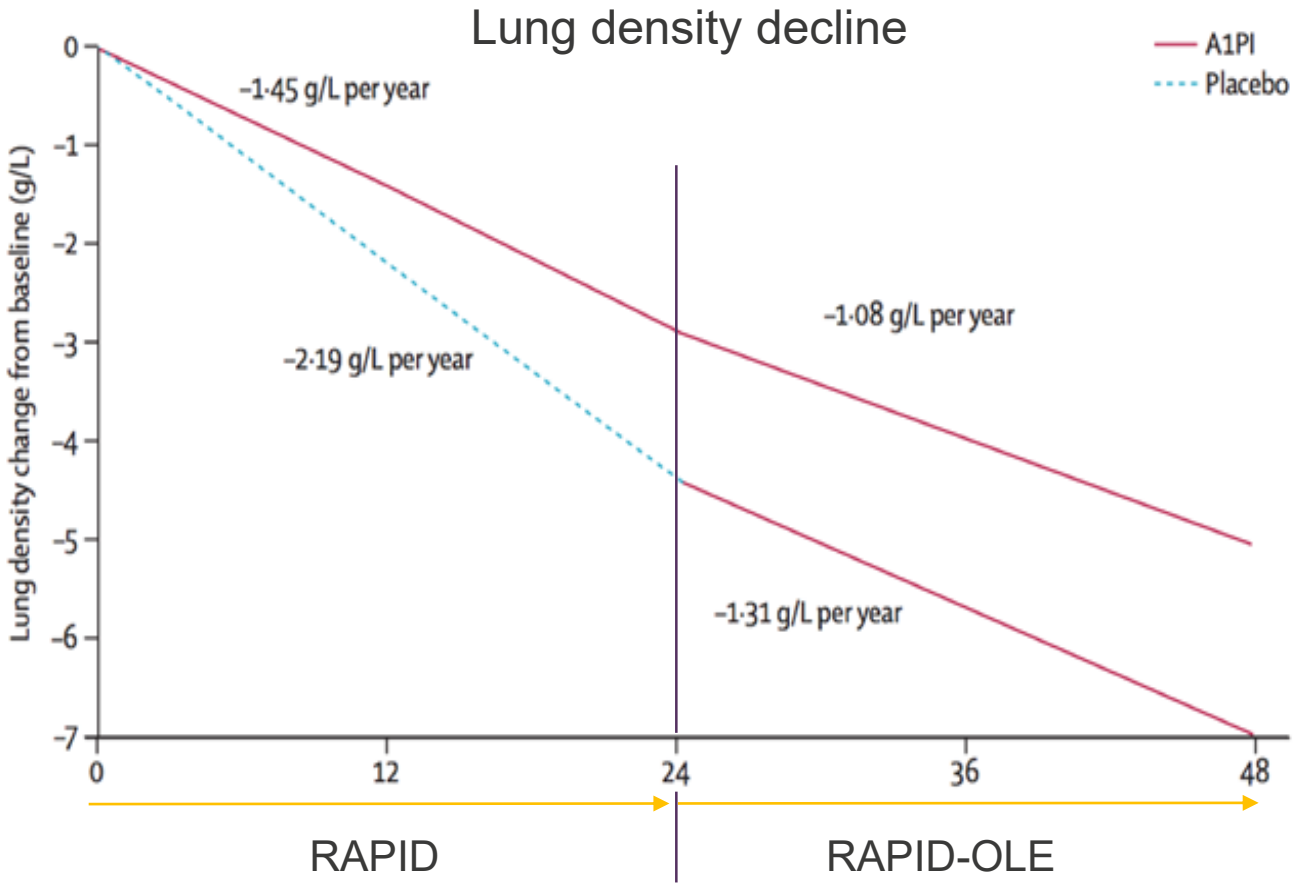
Mechanism of action	Supplements the deficient protein in people with A1PI deficiency
Marketing authorisation	For maintenance treatment, to slow the progression of emphysema in adults: • With documented severe alpha1-proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ) • Under optimal pharmacologic and non-pharmacologic treatment • Showing evidence of progressive lung disease (e.g. lower FEV1 predicted, impaired walking capacity or increased number of exacerbations)
Administration and dosage	Intravenous infusion at 60mg/kg, once weekly
List price	£220 per 1000mg vial – average annual cost per patient: £57,200

Summary of clinical effectiveness evidence

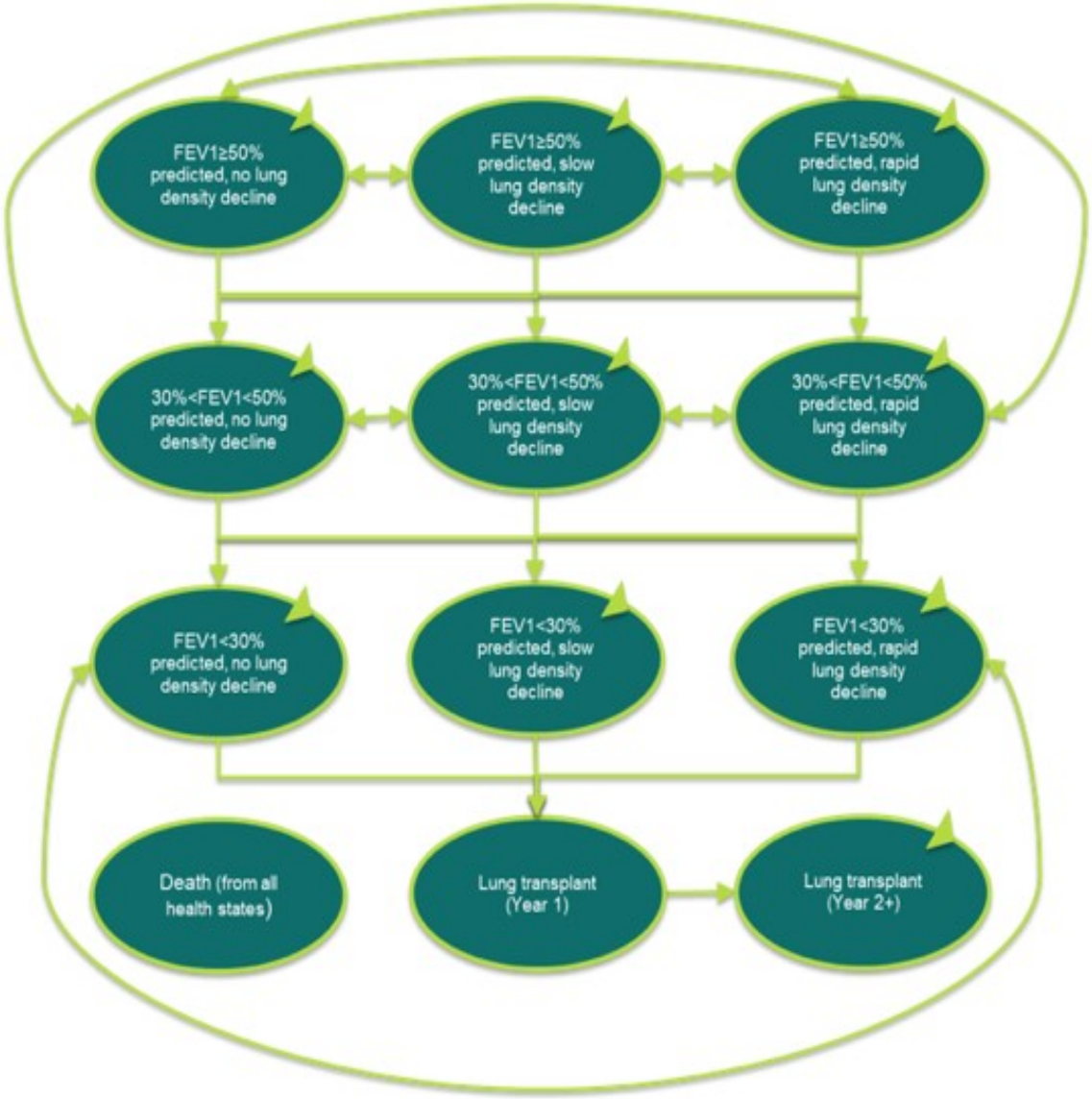
Clinical trial	Observational	Meta-analyses
RAPID RAPID-OLE	ADAPT (UK) NHLBI (US)	Edgar (RAPID + 2 RCTs) Updated Chapman 2009

Results

- Significant reduction in lung density decline with A1P1 treatment vs placebo
- No evidence of benefit in lung function, walking distance or QoL
- A1PI treatment may improve survival, but limitations in the observational evidence



Summary of company's economic model



- Markov model
- 11 health states based on FEV_1% predicted and lung density decline
- 3.5% discount rate, 1 year cycle, 49 year (lifetime) time horizon
- Transition probabilities: RAPID, ADAPT, and the updated Chapman et al. meta-analysis
- Survival using data from RAPID and *Green et al.* (ADAPT)
- Utilities based on FEV_1% predicted and lung transplant

Source: Figure 1 company response to clarification

Summary of evidence – cost effectiveness

	Respreeza		BSC		Incremental		
Description	**Cost**	**QALY**	**Cost**	**QALY**	**Cost**	**QALY**	**ICER**
Company base case	£422,681	6.977	£62,825	5.454	£359,855	1.522	£236,409
ERG exploratory analyses (combined)	£451,319	5.462	£58,157	5.416	£393,162	0.046	£8,573,535

BSC: Best supportive care, **QALY:** Quality-adjusted life year, **ICER:** Incremental cost-effectiveness ratio

ERG's exploratory scenarios

- Transition probabilities: amended meta analysis results
- *Green et al*. (ADAPT) survival data only to model mortality
- Removed stopping rule
- Age cap for lung transplant (65 years)
- Population eligible for lung transplant reduced by 30%
- Alternative survival estimates for lung transplant
- 100% of drug administrations at a specialist clinic

[redacted]

1st committee meeting: clinical evidence

Issue	Committee's consideration
Clinical need	• A1PI deficiency has significant physical and emotional effects on people with the condition and their families • Unmet need for effective treatments
Benefits of treatment	• Slows lung density decline more than placebo • No evidence of benefit on lung function, quality of life or walking distance • May improve survival but limitations in the observational evidence
Patient perspective	• A1PI treatment could protect people from future tissue damage • Could lead to a positive change in behaviour • Potential to delay need for lung transplant
Start/Stop criteria	• Appropriate starting criteria for A1PI treatment not defined • Lifelong treatment with A1PI would be expected

[redacted]

1st committee meeting: economic model

Issue	Committee's consideration
Model structure	• Model could be considered for decision-making
Transition probabilities	• Accounting for the correlation between FEV_1% predicted and lung density decline could reduce uncertainty
Survival	• Mortality remains a critical uncertainty in the model
Lung transplants	• Eligibility for transplant and post-transplant survival uncertain
Utilities	• Utility effects of lung density decline should be presented • Benefit of behaviour change from A1PI treatment not captured • Health effects after transplant appropriately captured • Health effects before the transplant not captured • Carer effects should be considered qualitatively
Costs	• Best supportive care and CT costs should be included

[redacted]

Committee's preferred analysis

Committee's preferred analysis:

- Transition probabilities: applied different results from the updated meta-analysis
- *Green et al.* (ADAPT) survival data only to model mortality
- Removing stopping rule
- Reducing the population eligible for lung transplant by 30%
- Using lower survival estimates after lung transplant
- Using the company's assumption of drug administrations

	Respreeza		BSC		Incremental		
Description	**Cost**	**QALY**	**Cost**	**QALY**	**Cost**	**QALY**	**ICER**
Committee's preferred analysis	£423,330	5.464	£58,162	5.416	£385,167	0.048	£8,069,855

BSC: Best supportive care, **QALY:** Quality-adjusted life year, **ICER:** Incremental cost-effectiveness ratio

Additionally committee concluded:

- High degree of uncertainty around overall survival and survival after transplant
- Accounting for correlation between lung density decline and FEV_1% predicted would reduce uncertainty
- Costs of best supportive care and CT densitometry should be included
- Carer benefits, behaviour change and health effects pre-transplant should be considered

1st committee meeting: key considerations

Issue	Committee's consideration
Value for money	• Most plausible ICER: £8.1 million per QALY gained • Did not meet the criteria for QALY weight
Beyond health benefits	• Condition affects people's economic situations and relationships • Some benefits of treatment not captured in the modelling
Managed Access Arrangement	• Could address uncertainties around starting criteria • Main uncertainties (overall survival, survival after transplant, model structure) might not be resolved or could be addressed without MAA
Population	• Estimates uncertain, expected to increase if treatment available
Equalities	• A1PI treatment is a blood product so may not be used by people of certain religions • A1PI deficiency is commonly found in people of European family origin • No adjustments need to account for the severe and disabling nature of the condition

[redacted]

Evaluation consultation document
preliminary recommendation

Human alpha1-proteinase inhibitor (A1PI) is not recommended, within its marketing authorisation, as maintenance treatment to slow the progression of emphysema in adults with severe alpha1-proteinase inhibitor deficiency.

[redacted]

Key issues for committee consideration

- **Clarifications:**
  - Is the committee happy with the limitations of the observational data?
  - Has the committee received the necessary expert advice?
- **Start/stop criteria:**
  - Should starting/stopping criteria be specified?
  - What is the effect on the population size?
- **Clinical benefits of treatment:**
  - What is the committee's view on the benefit of Respreeza on:
    - Lung function, quality of life, pulmonary exacerbations
    - Survival
- **Economic model:**
  - What are the most appropriate assumptions for the economic model on:
    - Survival
    - Lung transplantation – should it be included, if so how?
    - Transition probabilities
    - Costs, utilities and discount rate
- **Most plausible ICER and application of QALY weighting**
- **Have the benefits of treatment with Respreeza been fully captured**?
- **Any other factors to consider?** (Equalities/Factors affecting the guidance)

ECD: Consultation responses

- Consultee comments from:
  - CSL Behring – including new economic analyses
  - Alpha-1 UK
  - British Thoracic Society
  - Royal College of Physicians
- Clinical expert comments
  - Dr Ravi Mahadeva
  - Professor David Parr
  - Dr Alice Turner
- Web comments
  - NIHR AATD collaborative
- No comment submitted by Department of Health and Social Care

[redacted]

General comments

Recommendation:

- Stakeholders disappointed that Respreeza was not recommended
- Acknowledged the fair process in light of the evidence limitations

Unmet need:

- High level of unmet medical need
- Welcomed recognition that A1PI deficiency has significant physical and emotional effects on people with the condition and on their families

Beyond health benefits:

- Committee failed to recognise the full impact of AATD on patients' and their families' economic situation
  - Including reduced earning potential and associated psychological impact

[redacted]

Points requiring clarification

ADAPT and the UK registry:

- The UK Registry and the ADAPT programme are not synonymous:
  - "ADAPT is a research programme funded by industry - does not offer access to raw data"
  - ADAPT data may be biased due to patient self-selection requiring participation in research
  - "The UK Registry (national register of patients with AATD) should represent a more comprehensive record of AATD patients across England"
  - UK Registry sourced from clinicians across UK, but may contain limited clinical information

BTS SAG:

- Reference to the British Thoracic Society Specialist Advisory Group (BTS SAG) for AATD
- Referred to COPD SAG – no separate group for AATD

NIHR AATD Network:

- A collaboration between centres and experts actively involved in managing AATD
  - Research programme funded by NIHR until 2016
  - ECD comments received (10 clinicians from 7 centres) - proposed starting/stopping criteria

Is the committee happy with the limitations of the observational data?
Has the committee received the necessary expert advice?

[redacted]

Clinical evidence

Start/stop criteria (1)

Committee consideration at 1st meeting:

- Appropriate starting criteria for A1PI treatment have not been defined
- Unlikely to be possible to define stopping rules, so lifelong treatment would be expected

Consultee, clinical expert and web comments:

- Careful patient assessment required to implement and monitor A1PI treatment
- Proposed starting criteria include:
  - ZZ or Znull genotypes
  - Non-smokers
  - Diagnosed emphysema, documented by CT
  - Evidence of decline over at least 4 annual assessments
  - Loss of lung density by >2% per year
- Starting treatment before the onset of severe disability:
  - reduced health care costs
  - less need to consider lung transplantation
- Continuation rule: reduced ‘evidence of decline’ over 4 annual assessments before deciding on continuation

Start/stop criteria (2)

Company:

- Post-hoc analyses from RAPID-OLE including patients who had placebo for 2 years and then switched to Respreeza

Lung density decline during placebo	N	Mean change in lung density on Respreeza (extension study)	95% CI
Not rapid (≤2 g/L/year)	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]

- [redacted]
  - Counterintuitive: people with rapid decline have greatest unmet need
- Clinical judgement may be the most effective approach

Should clinical criteria for starting/stopping treatment be specified?

[redacted]

Secondary outcomes (1)

Committee consideration at 1st meeting:

- There is no evidence of its benefit on lung function, quality of life or walking distance

Company:

- Not possible to measure effects of extended disease progression due to short study time
- Long-term correlations between lung density decline rates and decline in lung function and QOL measurements have been established:

Outcome	Follow-up (years)	Centres	N	Correlation with lung density decline
FEV_1	8	3	51	r=0.41 (p=0.003)
FEV_1	3	1	34	r=0.52 (p=0.001)
FEV_1	2-2.5	3	77	r=0.32 (p=0.007)
FEV_1	4	22	118	r=0.29 (p=0.002)
FEV_1 % predicted	4	22	118	r=0.34 (p<0.001)
FVC	4	22	118	r=0.30 (p=0.001)
SGRQ	2.5	1	22	r=0.56 (p=0.007)
Abbreviations: SGRQ, St. George's Respiratory Questionnaire				

Source: Company response to ECD Table 3

[redacted]

Secondary outcomes (2)

Stakeholder comments:

- CT lung densitometry specifically developed for use as an outcome measure in studies of AATD
- Studies not statistically powered to identify a treatment effect on lung function or health status
  - Conclusions may be misleading
- Patients who have received A1PI treatment have reported significant and life-changing benefits

Patient interviews submitted by Alpha 1 UK

  - *Before treatment patient had difficulties with everyday tasks such as shopping, cleaning, walking short distances and being physically active with her children*
  - *After treatment patient able to return to working part-time which improved financial situation*
  - *After treatment patient able to participate fully in family, social and community life*

[redacted]

Survival

Committee consideration at 1st meeting:

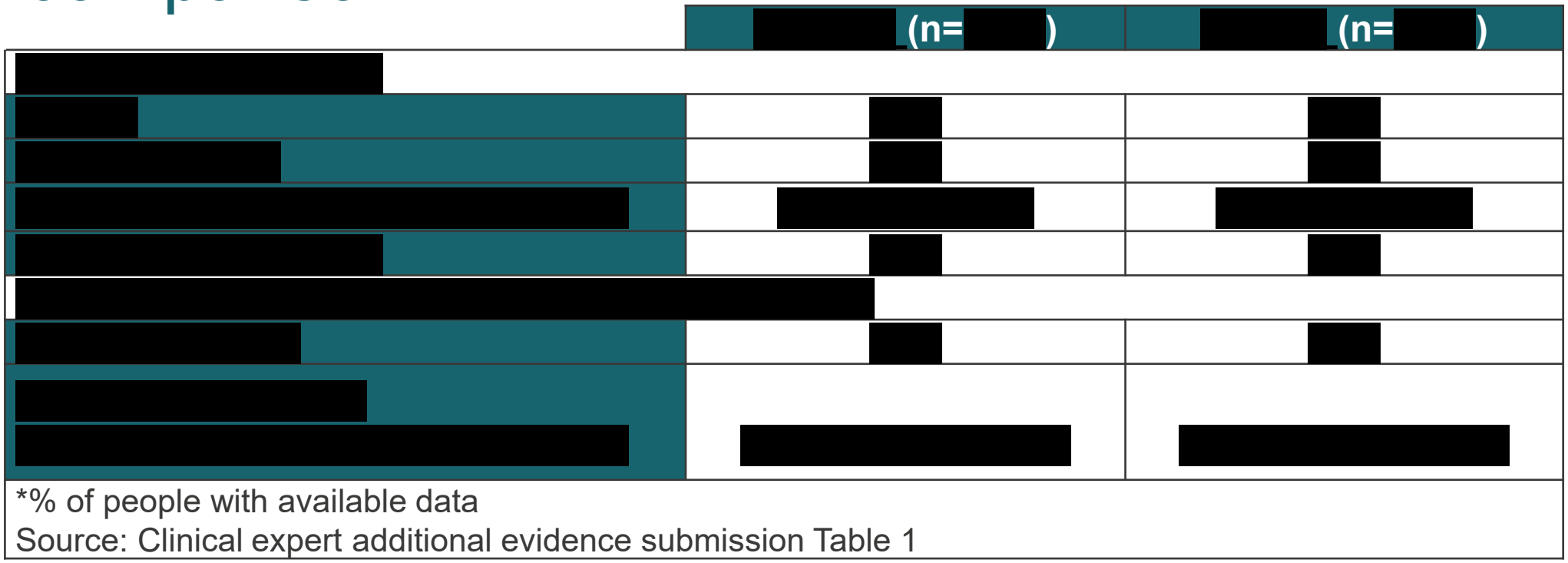
- Not possible to draw conclusions about survival from the RAPID data
- Limitations in the observational evidence, but A1PI treatment may improve survival

Company:

- Real-world evidence comparing outcomes between treated patients in the US [redacted] and untreated patients in the UK [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Survival: baseline characteristics UK/US comparison



*% of people with available data
Source: Clinical expert additional evidence submission Table 1

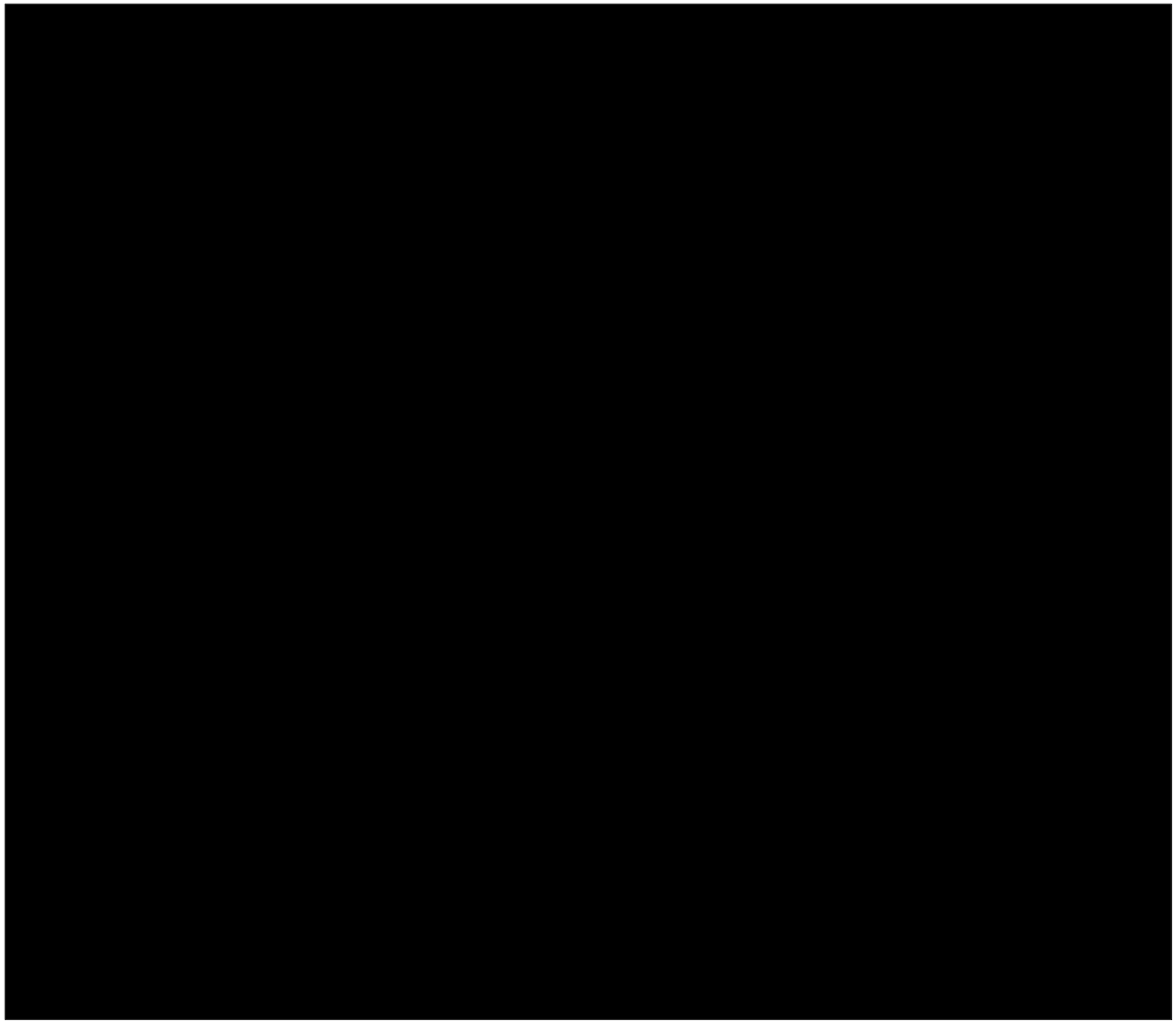
ERG:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Survival: updated analysis

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]



[redacted] Source: Clinical expert additional evidence submission, Figure 1

Exacerbations

Committee consideration at 1st meeting:

- Concern that A1PI treatment may be associated with an increased risk of pulmonary exacerbations

Company:

- No clinical rationale for A1PI treatment to be associated with an increased risk of pulmonary exacerbations
- Compared rates of exacerbations in RAPID with other studies of A1PI deficiency and general COPD

	Annual number of exacerbations	
	RAPID	Alternative studies of A1PI deficient patients*
A1PI treatment	1.70	2.5-7
BSC	1.42	

- Incidence of exacerbations in RAPID was relatively low in both treatment groups, but particularly low in the placebo group

[redacted]

* Lower rates of 1.0 also found in in references cited. Dirksen et al. 2009; Needham & Stockley 2005; Vijayasaratha & Stockley 2008, Vijayasaratha & Stockley 2012

Economic modelling

Survival in the economic model (1)

Committee consideration at 1st meeting:
- Only using data from ADAPT to model survival is more appropriate
- Mortality remains a critical uncertainty in the model

Company's updated survival modelling:

BSC	RAPID (2 years) →	*Green et al.* survival curves by FEV_1, lung density
Respreeza	RAPID / RAPID OLE (4 years) →	*Green et al.* x [redacted]

- Potential double counting of survival benefit:
  - Effect on mortality also captured via reduced lung density decline
- **Survival benefit of [redacted] years** → appears to reflects the [redacted] analysis
- When RAPID removed, survival gain of [redacted] years → does not reflect [redacted] analysis

ERG:
- RAPID/RAPID-OLE data should not be used (immature with few events)
- *Green et al.* data is a source of uncertainty (survival outcomes not statistically significantly related to lung density decline)
- HR from [redacted] does not account for [redacted]
- Applying HR to *Green et al*. data is not robust (differences in the underlying data)

[redacted]

Survival in the economic model (2)

ERG's preferred approach:

- [redacted]
- [redacted]
- [redacted]

  Survival dependent on treatment group not lung density decline and FEV_1% predicted
- Lung transplants removed
  - [redacted]
  - [redacted]

[redacted]

[redacted]

Source: ERG critique of company response to ECD, Figure 4

- ERG's approach gives a survival benefit of [redacted] years (company modelling [redacted] years)

Lung transplants in the economic model (1)

Committee consideration at 1st meeting:
- Not all people with FEV1<30% would have lung transplant

Patient choice

- Majority of UK patients do not undergo lung transplants:
  - limited organ availability and patient choice
- Patient and clinical perspectives not adequately considered by committee

Eligibility for transplant

- FEV_1 <30% predicted as criterion for transplant does not reflect UK clinical practice
  - too early in the treatment pathway
- Company's updated base case assumes 30% of eligible patients do not have a transplant

Utilities

- Company's updated base case includes pre-transplant utility which reflect patients' anxiety while waiting for transplantation
  - weighted average for eligible patients in FEV_1%<30%

ERG:
- 30% reduced eligibility may still overestimate proportion eligible for lung transplants

[redacted]

Lung transplants in the economic model (2)

Committee consideration at 1st meeting:

- Survival after transplant is uncertain. Agreed with the ERGs post-transplant survival estimates (1-year survival rate of 70% and 5-year survival rate of 50%)

Survival after lung transplant

Company: new data supports the company's survival figures

Survival	Model		New data: UK patients with A1PI	
	Company	ERG	Fisher	Stone
1 year	82%	70%	80%	74.2%
5 years	59%	50%	58%	52.9%

ERG:

- No references given for the new data
- *Stone et al.* more consistent with ERG's figures
- ERG prefers to remove lung transplants from the model:
  - Impact depends on how many people have a transplant, when, and the magnitude of health effects
  - Without transplant model captures benefits of Respreeza through survival benefit and utility gain of slowed disease progression

Should lung transplantation be included in the economic model?

- If yes, what assumptions should be made?
- If not, have the benefits of Respreeza been captured?

Transition probabilities

Committee consideration at 1st meeting:

- Meta-analysis results incorrectly applied in the company's analysis
- Committee accepted the ERG's proposed amendment

Company:

- Partly agree with the ERG's approach
- Effect size should apply to ≥50% group – most patients in RAPID had baseline FEV_1 <65%

FEV_1% predicted	Company	ERG	New Company	New ERG
≥50%	18.90	None	18.90	18.11
30–50%	1.28	18.90	18.90	18.11
<30%	n/a	n/a	n/a	n/a

ERG:

- Decline in FEV_1 should be analysed in a population that matches RAPID population
- Reviewed meta-analysis - incorporated both RCTs and observational studies
- Revised treatment effect - mean difference in decline of FEV_1 vs. placebo 18.11 ml/y

[redacted]

Costs in the economic model

Costs

- Company include costs of CT densitometry but best supportive care costs are unchanged

Statutory scheme rebate payments

- CSL Behring is subject to rebate payments: 9.9% in 2019, 14.9% in 2020 and 20.5% in 2021
- Company provide a scenario with statutory scheme rebate deducted from the cost of Respreeza

ERG's critique on costs

- Company replaced consultation costs by FEV_1 (2–4 per year) with single consultation (£149)
- ERG reverted to original and added 1 CT scan (£100)
- ERG added cost of BSC
- Respreeza costs may be underestimated by not using weight distribution from RAPID

ERG's critique on statutory rebate payments

- No updated BIA, rebate payments do not relate to sales volume or growth

Are appropriate costs included in the modelling?

[redacted]

Utilities and discount rate

Company:

Discount rate

- Scenario analysis: alternative discount presented to align with UK Treasury Green Book
  - Discount rate 3.5% for costs and 1.5% for QALYs

Utilities

- Applied age/sex adjusted utilities from original submission scenario to revised base case
- Applied weighted average utility value to FEV_1<30% to account for pre-transplant anxiety
- Scenario analyses explore utility values based on lung density decline status

ERG's critique on discount rate

- NICE's methods guide states the reference case should use 3.5% discount rate for both costs and health effects
- Respreeza does not fulfil the criteria for using the 1.5% discount rate

ERG's critique on utilities

- Approach for adjusting utilities lacked justification, and potentially incorrect
- Green et al. data could have been used to model the relationship between lung density decline and quality of life

[redacted]

Company's revised model assumptions

Transition probabilities	• Treatment effect for FEV_1 30-65% applied to FEV_1≥50% and FEV_1 30-50% states – Scenario analysis: 50% increased/reduced transition probabilities in FEV1 for rapid/no density decline
Lung transplant	• 30% of eligible patients do not receive a transplant, no age limit • Original post-transplant survival estimates (82% and 59%) • Weighted average utility value to account for pre-transplant anxiety – Scenario analysis: no lung transplantation
Utilities	– Scenario analysis: variation in utility values based on lung density decline status
Mortality	• [redacted] from the [redacted] analysis applied to Green et al. data
Costs	• Costs of CT densitometry (1 scan per year) – Scenario analysis: rebate payment deducted from costs
Discount rate	– Scenario analysis: alternative discount rate

[redacted]

Company's revised base case

	Respreeza		BSC		Incremental		
Description	**Cost**	**QALY**	**Cost**	**QALY**	**Cost**	**QALY**	**ICER**
Revised company base case (3.5% discount rate)	£524,220	7.277	£55,230	5.594	£468,991	1.683	£278,615
Revised company base case (alternative discount rate*)	£524,220	8.320	£55,230	6.289	£468,991	2.032	£230,810

BSC: Best supportive care, **QALY:** Quality-adjusted life year, **ICER:** Incremental cost-effectiveness ratio
*3.5% discount on costs and 1.5% discount on outcomes

[redacted] Source: Adapted from Company's additional evidence, Tables 4 and 5

Company's revised model scenario analyses

Scenario			ICER (£/QALY)*
Revised company base case			£278,615
Correlation between FEV_1 and lung density - 50% increased/reduced transition probabilities in FEV_1 for rapid/no density decline		↑	£293,298
Exclude lung transplants		↑	£310,480
Utility increased for no decline in lung density and decreased for rapid decline in lung density	5%	↓	£269,393
	15%	↓	£252,668
	25%	↓	£237,898
Incorporating statutory scheme rebate payments for Respreeza		↓	£264,334

*Company also provided analyses with alternative discount rate using 3.5% rate on costs and 1.5% rate on outcomes: ICER range £200,541 to £265,287

[redacted] Source: Adapted from Company's additional evidence, Table 6

ERG's preferred analysis

	Respreeza		BSC		Incremental		
Description	**Cost**	**QALY**	**Cost**	**QALY**	**Cost**	**QALY**	**ICER**
Company revised base case	£524,220	7.277	£55,230	5.594	£468,991	1.683	£278,615
ERG exploratory analyses (combined)*	£1,031,724	9.690	£58,597	8.190	£973,127	1.500	£648,948

BSC: Best supportive care, **QALY:** Quality-adjusted life year, **ICER:** Incremental cost-effectiveness ratio

ERG's exploratory scenarios

- Removed the adjustment to utilities and corrected error
- Revised meta-analysis (including observational studies) for treatment effect
- Included costs of BSC
- Amended disease management costs and added CT scan
- [redacted] survival analysis used to estimate mortality
- Removed lung transplants

[redacted] Source: ERG critique of company response to ECD, Table 8

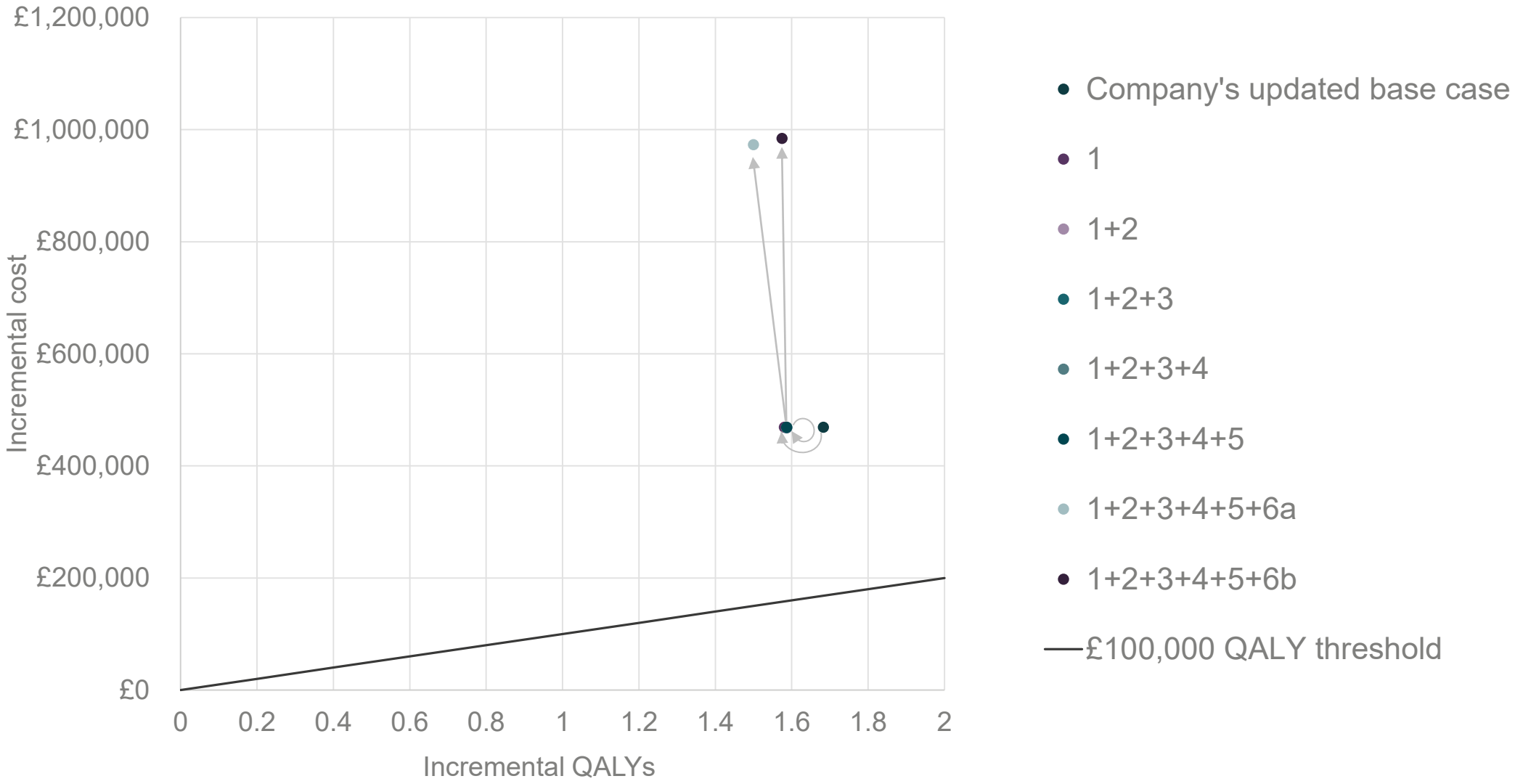
* All ERG analyses use the 3.5% discount rate for costs and health outcomes

ERG exploratory analyses (1)

	ERG's revised scenario analyses	Incremental		ICER (£/QALY)
		Costs	QALYs	
	Company's base case (3.5% discount rate)	£468,991	1.683	£278,615
1	Removing adjusted utilities	£468,991	1.581	£296,642
1+2	Using meta-analysis results for observational studies	£467,855	1.587	£294,818
1+2+3	Including BSC costs in both treatment arms of the model	£469,202	1.587	£295,036
1+2+3+4	Changing the resource for specialist visits so applied based on FEV_1%	£468,716	1.587	£295,360
1+2+3+4+5	Adding the annual cost of a CT scan per patient in both arms	£468,924	1.587	£295,491
1+2+3+4+5+6a	Using the [redacted] survival analysis and removing lung transplants (lognormal)	£973,127	1.500	£648,948
1+2+3+4+5+6b	Using the [redacted] survival analysis and removing lung transplants (gamma)	£984,460	1.575	£625,195

ERG exploratory analysis

Cost-effectiveness plane (cumulative ERG scenarios)



[redacted] Source: produced from ERG scenario model

ERG exploratory analyses (2)

	Transplants included			Transplants removed		
	Incremental		ICER (£/QALY)	Incremental		ICER (£/QALY)
	Costs	QALYs		Costs	QALYs	
All ERG changes to cost, utilities and transition probabilities	£468,924	1.587	**£295,491**	£546,816	1.584	**£345,124**
All ERG changes… + [redacted] survival analysis (lognormal)	£601,861	1.273	**£472,684**	£973,127	1.500	**£648,948**

[redacted]

Revised economic analyses

Assumption	Company base case	Committee preferred	Updated company base case	ERG updated analysis
Transition probabilities	Treatment effect from meta analysis	Amended meta analysis results	Amended meta analysis applied to both ≥30% FEV_1<50% and ≥50%	Revised meta analysis applied to ≥30% FEV_1<50% and ≥50% FEV_1
Survival	RAPID and *Green et al.* data	*Green et al.* (ADAPT) only	RAPID, *Green et al.* and [redacted]	[redacted] only
Lung transplant	1-and 5 year survival 82% and 59%	Lower survival estimates, 30% less eligibility	82% and 59% survival, 30% less eligibility	No lung transplant
Utilities	Non-adjusted	Non-adjusted	Adjusted for age & sex Weighted for transplant	Non-adjusted
Costs	No BSC costs	BSC & CT costs	CT costs, no BSC costs	BSC and CT costs
Discount	3.5% costs and outcomes	3.5% costs and outcomes	3.5% costs and outcomes	3.5% costs and outcomes
ICER	**£236,409**	**£8,069,855**	**£278,615**	**£648,948**

QALY weighting

- ICERs above £100,000 per QALY: recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- Applying a QALY weight: compelling evidence the treatment offers significant QALY gains

Lifetime inc QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal inc)
Greater than or equal to 30	3

	Discounted	Undiscounted
Company submission	1.683	2.369
ERG exploratory analyses	1.500	2.766

[redacted]

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Equalities

- A1PI treatment may not be used by people of certain religions
- A1PI deficiency is a condition mainly found in people of European family origin

Committee:

- Agreed that these could not be addressed within a highly specialised technology evaluation
- Recommendation will apply equally across religions and family origins
- Recognised the severe and disabling nature of the condition
  - no adjustments needed on the grounds of equalities

ECD response:
Patients in England are currently disadvantaged in comparison to other countries where A1PI treatment is available

Uncaptured benefits

- Positive change in behaviour after A1PI treatment - not captured
- Fear and anxiety of people waiting for lung transplants - not captured
  - included in the updated company analysis
- No robust quantitative estimate of carer disutility
  - Committee agreed it would consider the benefit of treatment to families and carers qualitatively

ECD response:
Committee failed to recognise the full impact of AATD on patients' and their families' economic situation
- Including reduced earning potential and associated psychological impact

[redacted]

Key issues for committee consideration

- **Clarifications:**
  - Are committee happy with the limitations of the observational data?
  - Has the committee received the necessary expert advice?
- **Start/stop criteria:**
  - Should starting/stopping criteria be specified?
  - What is the effect on the population size?
- **Clinical benefits of treatment:**
  - What is the committee's view on the benefit of Respreeza on:
    - Lung function, quality of life, pulmonary exacerbations
    - Survival
- **Economic model:**
  - What are the most appropriate assumptions for the economic model on:
    - Survival
    - Lung transplantation – should it be included, if so how?
    - Transition probabilities
    - Costs, utilities and discount rate
- **Most plausible ICER and application of QALY weighting**
- **Have the benefits of treatment with Respreeza been fully captured**?
- **Any other factors to consider?** (Equalities/Factors affecting the guidance)