Public observer slides – no ACIC

Clinical lead team presentation

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

1st Evaluation Committee Meeting
Highly Specialised Technologies, 23 August 2018
Lead team: Sotiris Antoniou, Jeremy Manuel, Sarah Davis
Company: CSL Behring
Chair: Peter Jackson
Evidence review group: BMJ-TAG
NICE team: Thomas Paling, Ian Watson, Sheela Upadhyaya

[redacted]

Key issues for consideration

Clinical effectiveness (1)

- What population would be considered for treatment with Respreeza?
  - What is the likely population size?
  - When would treatment be started and stopped?
  - How would progressive lung disease be defined in clinical practice?

- Are the outcome measures relevant for people with AATD?
  - Is CT densitometry used in clinical practice?
  - What represents a clinically meaningful difference in lung density?
  - Are other outcomes (beyond FEV1 and lung density) of importance to people with emphysema?
  - What is the relationship between lung function and other outcomes (e.g. mortality and pulmonary exacerbations)?

Key issues for consideration

Clinical effectiveness (2)

- What is the committee's view on the clinical effectiveness evidence?
  - Are baseline characteristics suitably balanced across groups in the RAPID studies?
  - Are the meta-analyses informative?

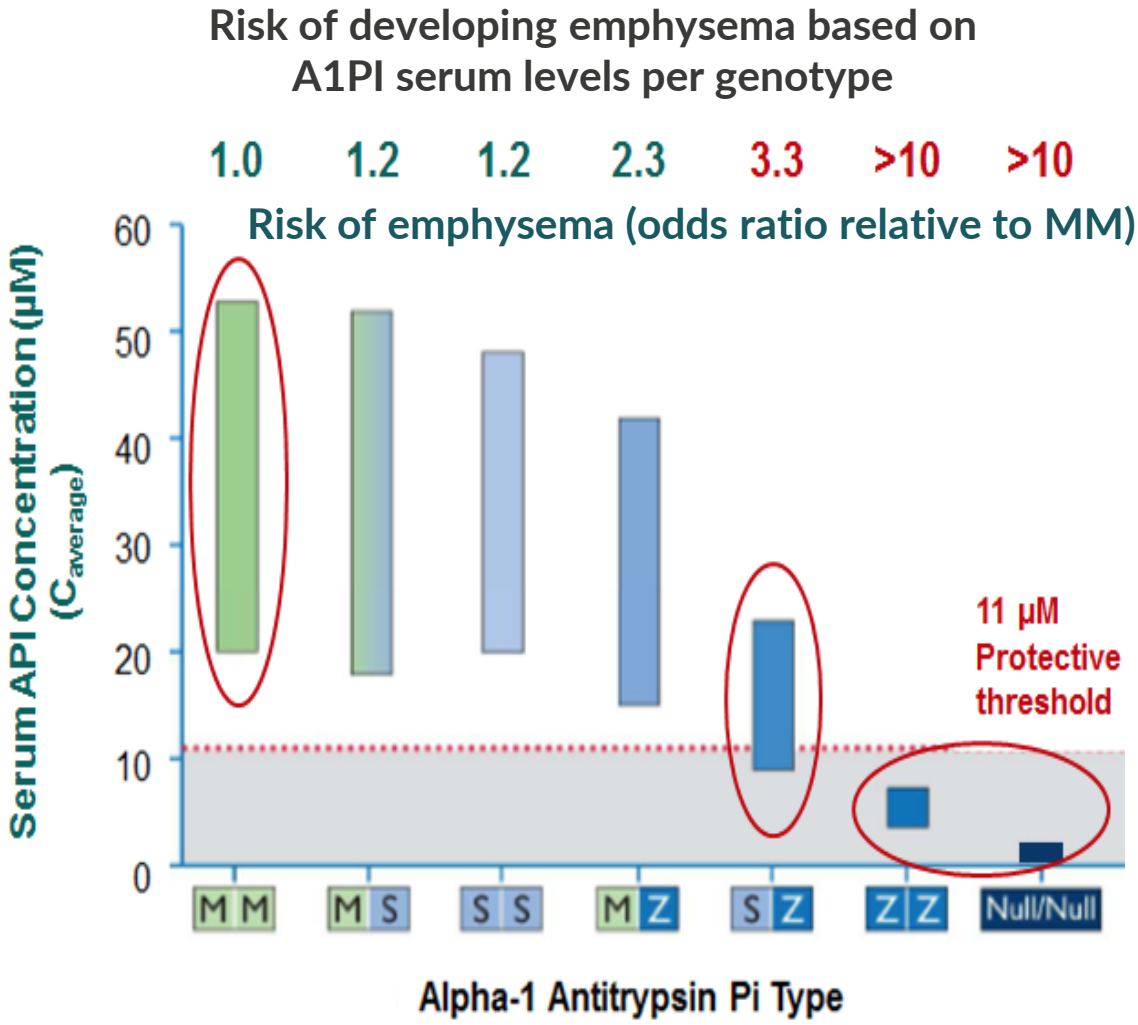
- Does Respreeza provide clinical benefits for people with AATD?
  - What is the committee's view of the clinical and statistical significance of the results of RAPID?
  - Does it provide benefits in lung density, lung function, other outcomes?

Disease background

- Alpha-1 proteinase inhibitor (A1PI) deficiency, aka alpha-1 antitrypsin deficiency (AATD)
  - Rare, genetic disorder which causes low levels of A1PI protein
  - A1PI protects body tissue from damage by protease enzymes
  - Proteases are produced in response to infections and toxins (e.g. smoking, pollution)

- Lack of A1PI makes people more vulnerable to smoke or toxic materials → progressive lung tissue damage
- A1PI <11 µM considered severe AATD
- Development and characteristics of disease vary considerably – interplay between genetics and environmental exposures

[redacted]



Source: figure 2 CS

Population size

- **Company:**
  - Prevalence of symptomatic AATD: 0.99 per 100,000, 80% have clinically significant symptoms requiring treatment

    →670 people with AATD in England

    →Of whom 549 eligible for treatment
- **Clinical expert:**
  - About 1,500 known cases of PiZZ/Znull AATD
  - Of whom about 200 to 250 would be eligible for treatment
- **ERG comments:**
  - Clinical advisers suggested that the population may be larger than estimated by the company (600–700)
  - Availability of a disease-modifying therapy may encourage screening and so increase the population size

[redacted]

Symptoms and complications

- AATD can lead to severe lung disease (emphysema), and liver, skin, and immune system complications
- Emphysema is a long-term progressive disease of the lungs; symptoms include:
  - Breathlessness
  - Persistent chesty cough
  - Frequent chest infections
  - Persistent wheezing
- Shortness of breath and wheezing usually occurs between the ages of 20 and 40
- Repeated exacerbations lead to a decline in lung function
- Decline in lung function reduces quality of life and life expectancy

Current treatment options

- Treatment aims to delay progression of emphysema
- Current treatments provide short-term symptom relief, but do not treat the underlying cause of the condition
- There is no UK guidance on treating AATD
- Currently treatment involves standard therapy for Chronic Obstructive Pulmonary Disease (COPD), such as:
  - Inhaled bronchodilators
  - Inhaled corticosteroids
  - Oxygen therapy
  - Pulmonary rehabilitation
- Lung transplantation can be considered in people with progressed disease

[redacted]

Clinical experts: *Current treatment experience*

There is an unmet need for people with AATD

- Current treatments are only supportive and symptom-based
  - They do not target the underlying disease or prevent progression
  - Breathlessness is only partially alleviated

Clinical management of AATD is heterogeneous between areas

- People attend general respiratory clinics and may not see an expert

Anticipated benefits of disease-modifying treatment

- Preserve lung density
- Delay or prevent the onset of symptoms, disability and mortality
- Could delay or prevent lung transplants

[redacted]

Human alpha 1-proteinase inhibitor
(Respreeza, CSL Behring)

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 as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency
Administration & dose	Intravenous infusion at 60mg/kg, once weekly
List price	£220 per 1000mg vial – average annual cost per patient: £57,200

[redacted]

Source: Company submission

Decision problem: Population and start/stop criteria
Proposed use of Respreeza

Scope	Adults with severe alpha 1-proteinase inhibitor deficiency who have progressive lung disease
Marketing authorisation	"…evidence of progressive lung disease (e.g. lower FEV1 predicted, impaired walking capacity or increased number of exacerbations)"
Company's proposed population	• Severe A1PI (<11µM) and either FEV1/FVC < 0.7 or emphysema demonstrated by CT scan • FEV1% ***30–70%*** • Rapid lung function (measured by FEV1 / D_{LCO}) or lung density decline • Stopping criteria: none proposed
Evidence	*Pivotal study (RAPID):* • Adults (18 to 64yo) with emphysema and severe A1PI deficiency (<11µM) • FEV1% ***35–70%*** *Economic model:* • FEV1% ***>30%***, irrespective of lung density decline • Stopping rule: treatment stops in patients with FEV1% <30%

FEV1%: forced expiratory volume in 1 second, percent predicted

Decision problem: Population and start/stop criteria

ERG comment: proposed use of Respreeza

EMA recommended Respreeza should be used in:

- People with evidence of significant lung density decline

Clinical experts: rapid lung function decline definition is not included in the MA

- Without a definition, anyone with emphysema (and AATD) is eligible for treatment
- However, clinicians will not use Respreeza in people with no decline in lung function

Possible rationale for starting treatment in people with FEV1% <30%

- If ineligible for or awaiting lung transplant
- No alternative treatment options

Stopping rule was not proposed but was applied in the model (when FEV1% <30%)

- Company acknowledged that this was an implementation error

[redacted]

Clinical effectiveness evidence

[redacted]

Clinical evidence summary

RCTs (Respreeza)

RAPID	• 24 month • Double-blinded, placebo-controlled • N=180 (Respreeza=93, Placebo=87)

RAPID-OLE	• RAPID population, 24 month extension
	• Open-label
	• N=140 *(continuing or starting Respreeza)*
	  ○ Early starters = 76 *(on Respreeza in RAPID)*
	  ○ Late starters = 64 *(on placebo in RAPID)*

Key inclusion criteria:

- Adults (18 to 64 years)
- Emphysema and FEV1% 35–70%
- A1PI deficiency (<11µM)

Real-world evidence:

- The ADAPT registry: UK registry of A1PI deficient patients
- NHLBI registry: 37 US centres including 1,129 patients

Meta-analyses:

- Edgar el at: meta-analysis of RAPID studies and 2 other RCTs
- Updated Chapman 2009: meta-analysis of treatment effect across FEV1% groups

[redacted]

Baseline characteristics: *RAPID and RAPID-OLE*

RAPID (Respreeza and placebo)

Characteristic	Respreeza (N=93)	Placebo (N=87)
Mean age, years (SD)	53.8 (6.9)	52.4 (7.8)
Gender (M/F)	52/48	57/43
CT lung density (total), adjusted PD15 g/L, mean (SD)	46.6 (15.6)	49.8 (15.0)
FEV1%, mean (SD)	47.5 (12.1)	47.2 (11.1)
Shuttle walk distance, m, mean (SD)	424.5 (183.0)	435.1 (199.7)
HRQoL (SGRQ symptoms score), mean (SD)	46.5 (22.7)	44.1 (24.8)
Prior medications, n		
Beta-2 agonist / corticosteroids	12	6
Nonsteroidal anti-inflammatory drugs	2	5
Human A1PI (Prolastin)	3	1

Source (RAPID): adapted from table 11 CS

RAPID – OLE (early and late starters of Respreeza)

Characteristic	Early starters (N=76)	Late starters (N=64)
Mean age, years (SD)	56.4 (6.9)	53.3 (7.8)
Gender (M/F)	41/35	38/26
CT lung density (total), adjusted PD15 g/L, mean (SD)	43.1 (14.9)	44.8 (14.1)
FEV1%, mean (SD)	45.0 (12.6)	46.3 (12.0)
HRQoL (SGRQ symptoms score), mean (SD)	47.3 (18.2)	44.0 (16.9)

Source (RAPID-OLE): table 5 ERG report

Clinical evidence

ERG comments

- The overall the risk of bias in RAPID is low
- Notable difference in baseline lung density (46.6 v 49.8 g/L) between groups
  - In the model a 2.0 g/L/y decline in lung density is considered ‘rapid’
- Baseline lung density decline was not measured in RAPID
  - Baseline imbalances could affect the comparison of groups
  - Implications for starting treatment given the company’s proposed starting criteria
- Bronchodilator administration before assessment of FEV1 (as advised for COPD) was not compulsory in RAPID
- RAPID-OLE (observation study) has a higher risk of bias than RAPID

[redacted]

Clinical effectiveness – results

[redacted]

Clinical effectiveness

Overview: RAPID studies results

CT lung density

- Lower annual decline in lung density at TLC with Respreeza than placebo
- Effect was sustained in the extension

FEV1%

- The direction of effect favoured placebo*

Gas exchange (D_{LCO})

- The direction of effect favoured placebo*

Exacerbations

- [redacted] rate of pulmonary exacerbations in the Respreeza arm than placebo

Incremental shuttle walking test (ISWT)

- Larger improvement in walking distance with placebo than Respreeza*

St George's Respiratory Questionnaire (SGRQ)

- Improvement in symptoms at 24 months for people treated with Respreeza

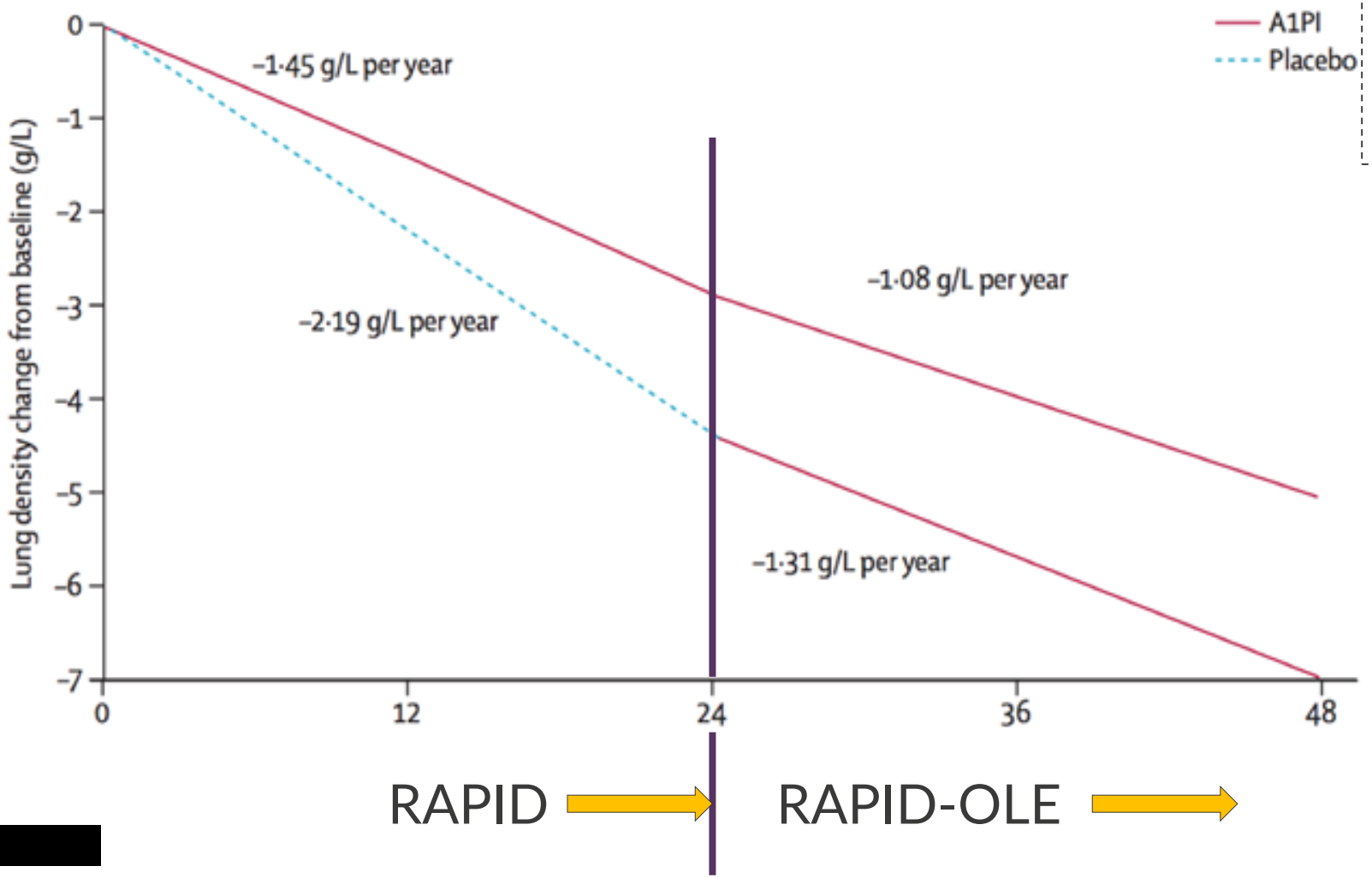
[redacted]

**not statistically significant*

Clinical effectiveness: *RAPID and RAPID-OLE*

CT lung density

Rates of lung density decrease at total lung capacity (TLC)



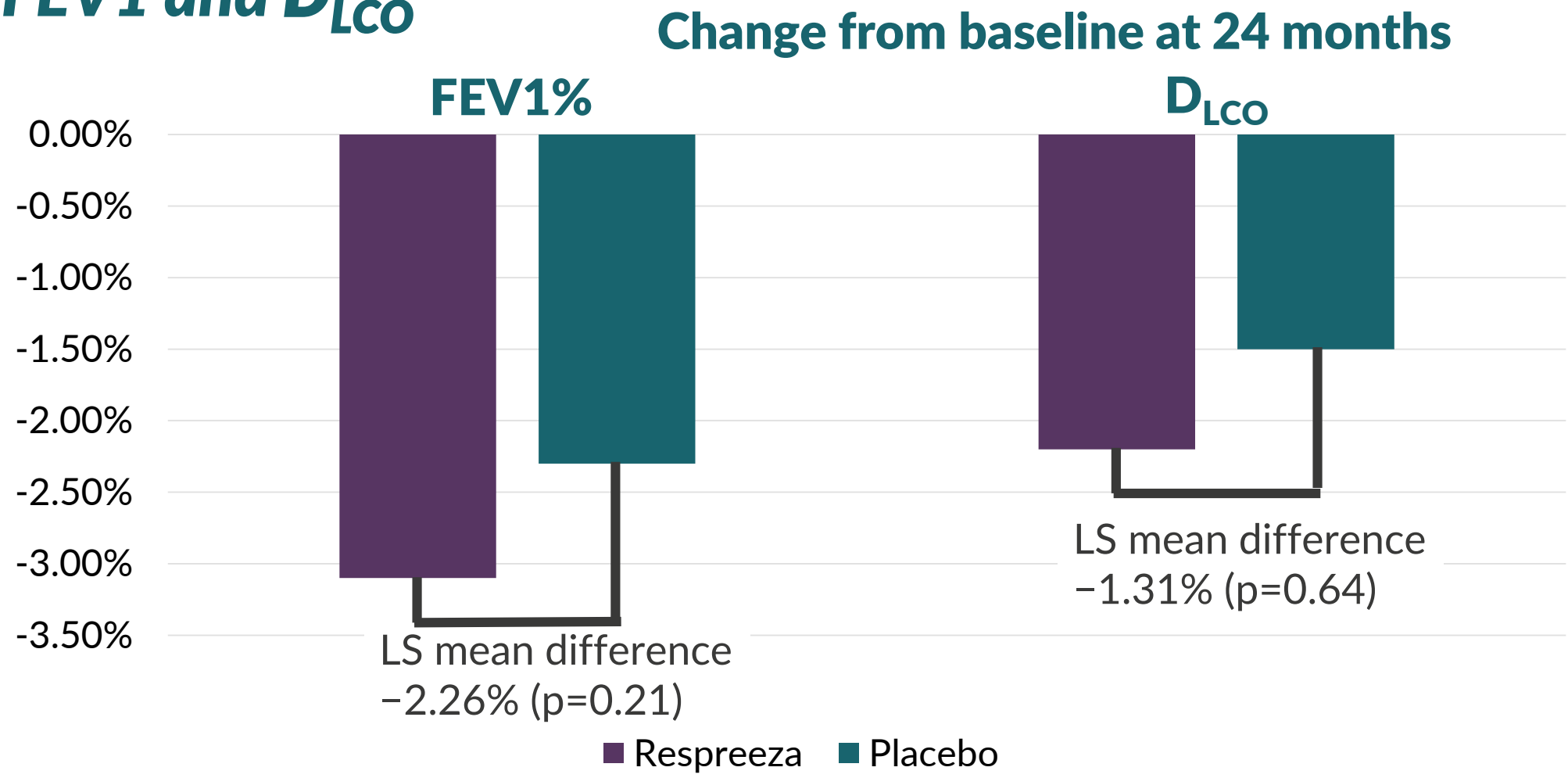
2 g/L/y is considered 'rapid decline' in the economic model

34% reduction in lung density decline at 24 months for Respreeza vs placebo (difference 0.74 g/L/y, p = 0.03, n=180)

Source: Adapted from figure 13 CS

Clinical effectiveness: *RAPID*

FEV1 and D_{LCO}



Larger decline in FEV1% and D_{LCO} with Respreeza than with placebo (not statistically significant)

Source: Adapted from table 22 CS

Clinical effectiveness: *RAPID*

Secondary outcomes: exacerbations

Figure redacted - AIC

[redacted] Source: adapted from company response to clarification (A8)

Clinical effectiveness: *RAPID*

Secondary outcomes: Exercise capacity and quality of life

Outcome	Respreeza (N=93)		Placebo (N=87)		Respreeza vs placebo
	Baseline	Change at 24 months	Baseline	Change at 24 months	Least-square mean difference
Shuttle walk distance (m)	424.5 (183.0)	10.8 (139.8)	435.1 (199.7)	16.1 (101.6)	−13.90 (p=0.48)*
Quality of life (SGRQ)					
Total	44.3 (17.1)	+1.4 (11.1)	42.4 (18.0)	+2.2 (11.7)	−0.19 (p=0.91)*
Symptoms	46.5 (22.7)	−1.4 (16.7)	44.1 (24.8)	+2.0 (20.1)	−1.11 (p=0.67)*
Activity	62.1 (18.6)	+1.7 (12.4)	60.1 (21.4)	+2.6 (13.5)	−0.16 (p=0.94)*
Impact	33.6 (18.4)	+2.1 (14.8)	31.4 (17.6)	+1.8 (12.5)	0.74 (p=0.72)*

Source: adapted from table 22 CS

Shuttle walk distance

- Greater improvement in walking distance for those on placebo compared with Respreeza

SGRQ

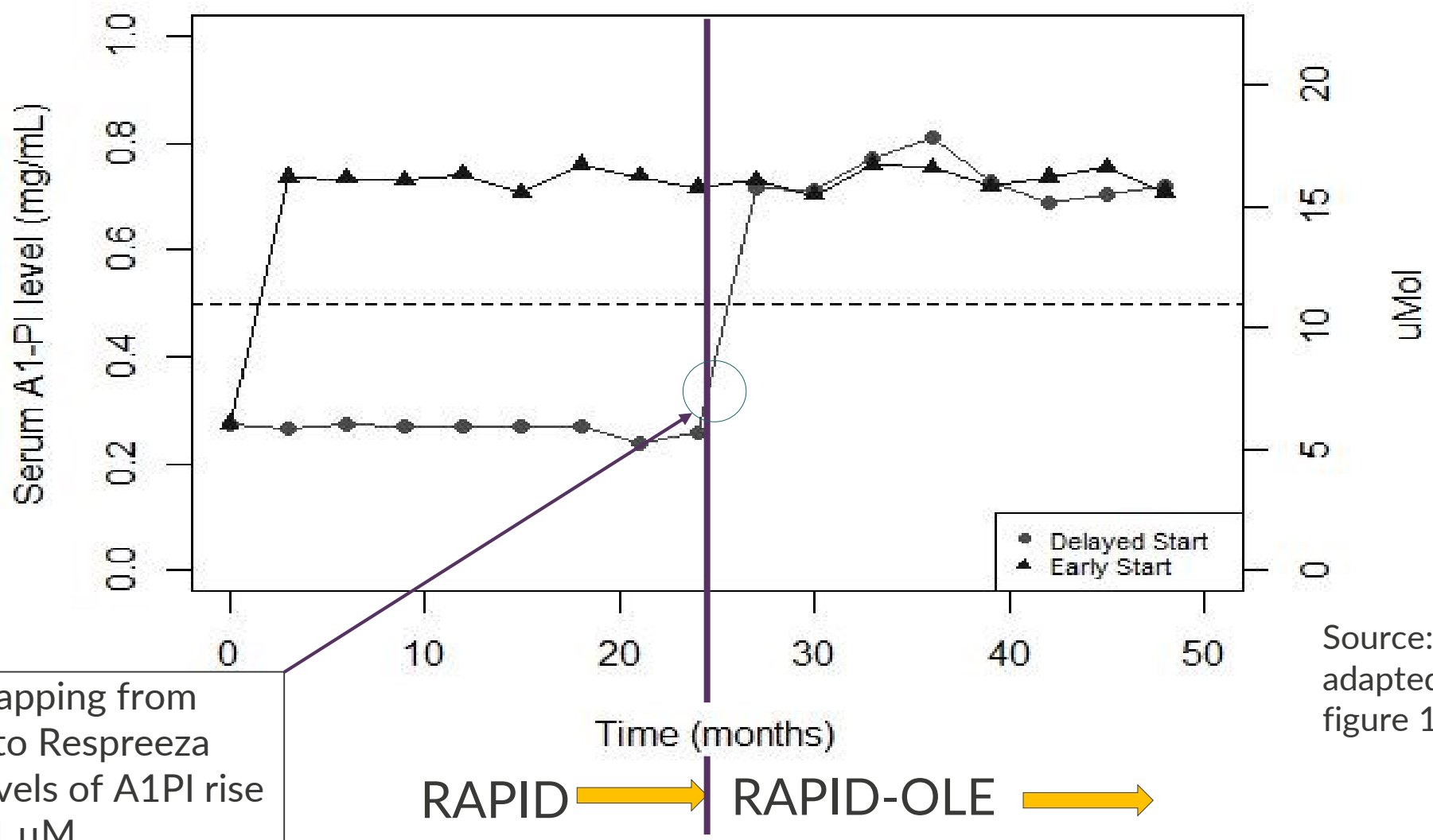
- Higher scores in SGRQ indicate more limitations
- Improvement in symptoms at 24 months for people treated with Respreeza

**Differences are not statistically significant*

Clinical effectiveness: *RAPID and RAPID - OLE*

Secondary outcomes: Change in A1PI blood serum levels

A goal of treatment is to raise the serum levels of A1PI above 11 µM



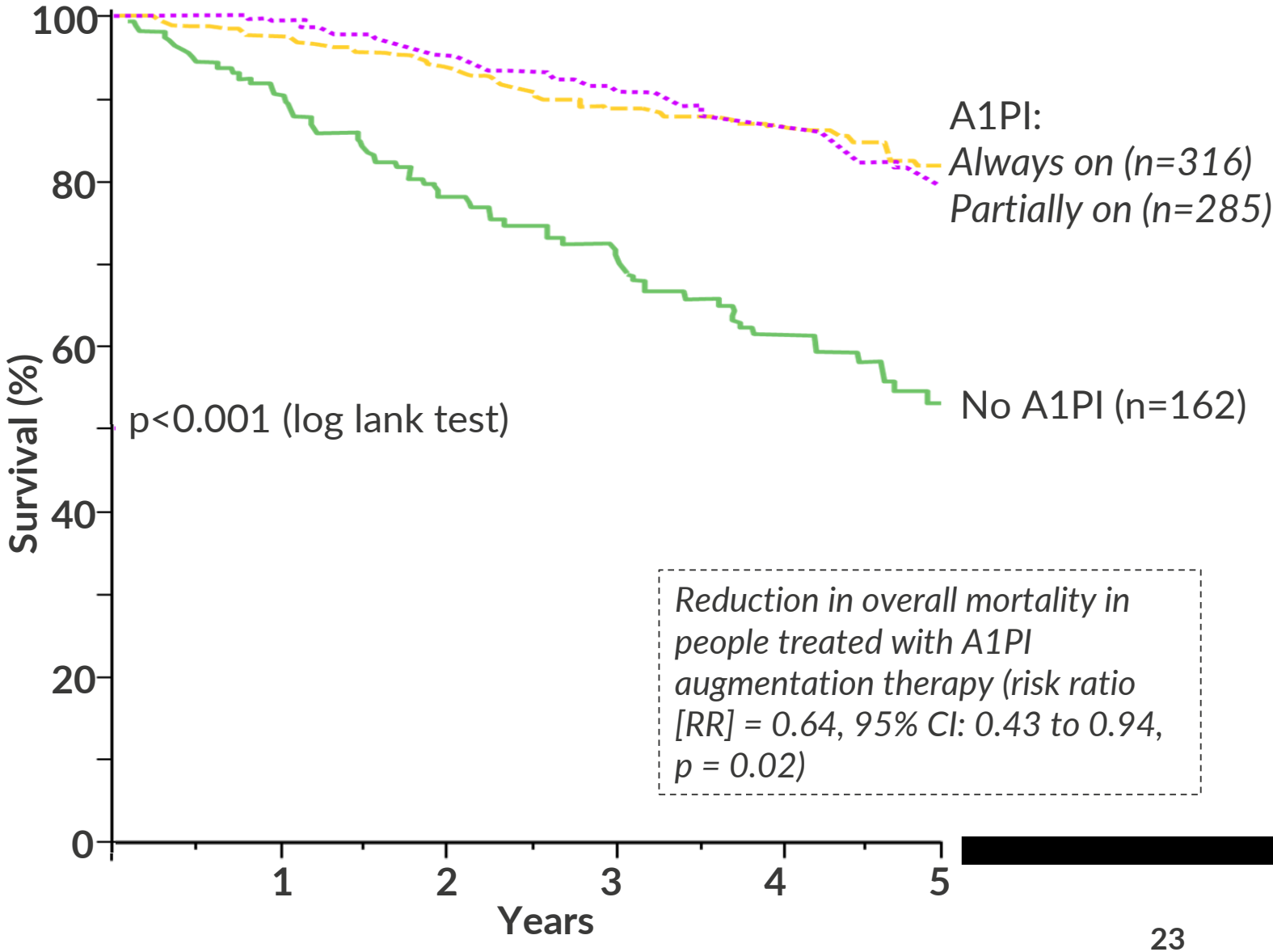
After swapping from placebo to Respreeza serum levels of A1PI rise above 11 µM

Source: adapted from figure 18 CS

Clinical effectiveness: real-world evidence

NHLBI: Mortality risk

- Analysis of 1,048 people with FEV1% <50% using US registry data
- Observational (non-randomised)
- Baseline FEV1% was a major determinant of survival



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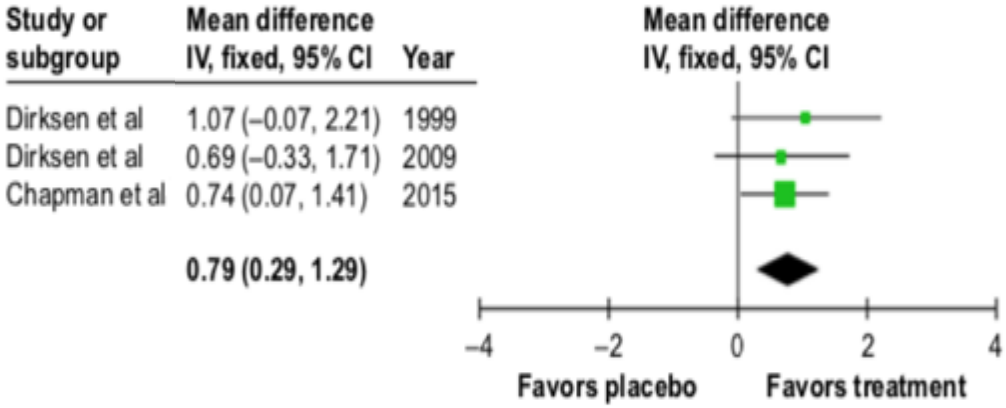
Source: Figure 25 CS (The Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998)

Meta-analysis (1)

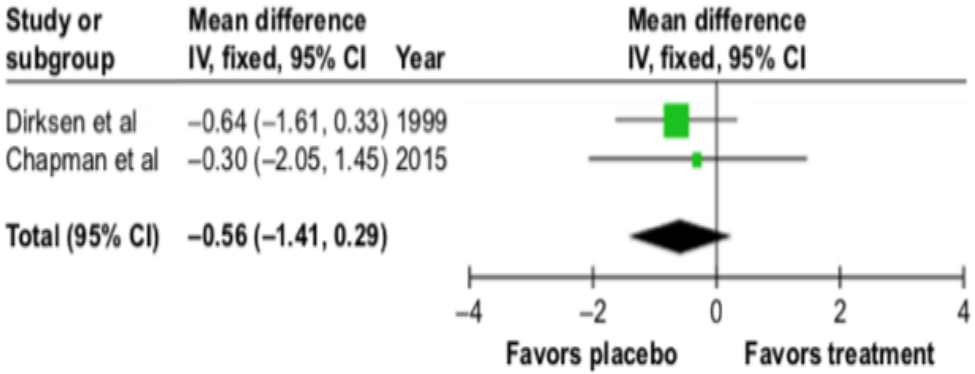
Edgar et al: Lung density, FEV1, exacerbations and quality of life

(RAPID and Dirksen studies)

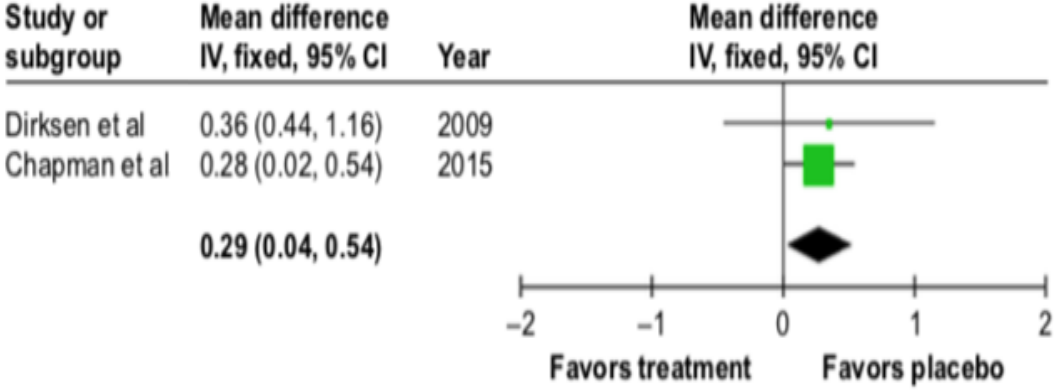
Mean change in lung density



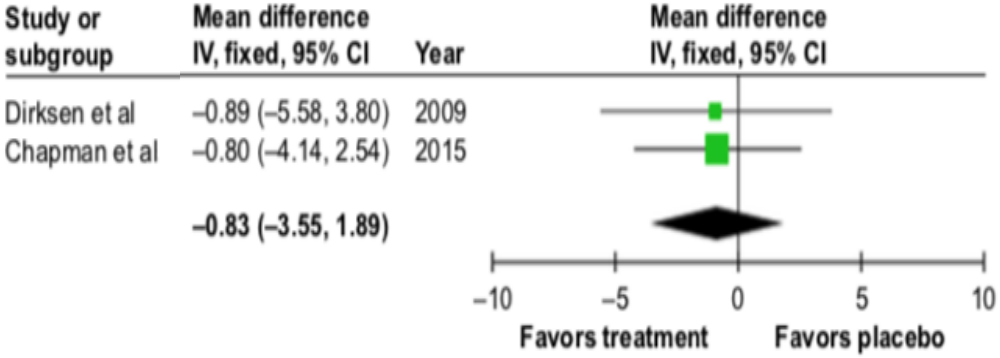
Mean FEV1%



Annual exacerbations



Quality of life (SGRQ)



Source: adapted from figures 20-24 CS

Meta-analysis (2)

Updated Chapman 2009: change in FEV1 stratified by FEV1 category

- Chapman et al (2009) meta-analysis updated to include 3 additional studies (including RAPID)
- The results of this meta-analysis are used in the economic model
- In the updated meta-analysis there is a change in direction of effect to favour placebo over A1PI in people with FEV1 >65%

Source: clarification response question A2

FEV1%	Mean difference in change in FEV1, A1PI vs no treatment (ml/year, 95% CI)
FEV1% <30%	**1.25** (-7.19 to 9.74)
FEV1% 30–65%	**18.90** (6.06 to 31.74)
FEV1% >65%	**-19.30** (-66.4 to 27.85)

[redacted]

Meta-analysis (3)

ERG comment

Edgar et al 2017 meta-analysis:

- Inclusion criteria and baseline characteristics in the included studies were comparable
- Dirksen 1999 and 2009 estimated the effectiveness of Prolastin, not Respreeza
  - Evidence suggests that these A1PIs can be considered equivalent
- Dirksen 1999 used a different dose (250mg/kg every 4 weeks) to the other studies (60mg/kg weekly)
  - Tailing off effect of A1PI serum levels may be observed at the end of the treatment cycle

Updated Chapman 2009 meta-analysis:

- ERG highlighted concerns about how registry data were included and the risk of bias in some studies
  - Advises that the results are interpreted with caution

[redacted]

Adverse events

TEAEs *experienced by > 10% (RAPID)*	Event	Respreeza	Placebo
	Infections and infestations	83%	87%
	Nasopharyngitis	32%	30%
	Respiratory disorders	68%	56%
	Chronic obstructive pulmonary disease (COPD)	32%	23%
	Gastrointestinal disorders	49%	54%
	General and administration site disorders	52%	48%
	Nervous system	49%	49%
	Musculoskeletal and connective tissue disorders	38%	43%

	RAPID study		RAPID – OLE (all Respreeza)	
	Respreeza (N=93), n (%)	Placebo (N=87), n (%)	Early start (N=76), n (%)	Delayed start (N=64), n (%)
Any TEAE	92 (99%)	86 (99%)	76 (100%)	62 (96.9%)
Mild	13 (14%)	16 (18%)	15 (19.7%)	10 (15.6%)
Moderate	54 (58%)	43 (49%)	38 (50%)	33 (51.6%)
Severe	25 (27%)	27 (31%)	23 (30.3%)	19 (29.7%)
Any serious TEAE	28 (30%)	28 (32%)	28 (36.8%)	23 (35.9%)
Death due to TEAE	1 (1%)	3 (3%)	1 (1.3%)	0

Source: adapted from tables 23-25 CS

Key issues for consideration

Clinical effectiveness (1)

- What population would be considered for treatment with Respreeza?
  - What is the likely population size?
  - When would treatment be started and stopped?
  - How would progressive lung disease be defined in clinical practice?

- Are the outcome measures relevant for people with AATD?
  - Is CT densitometry used in clinical practice?
  - What represents a clinically meaningful difference in lung density?
  - Are other outcomes (beyond FEV1 and lung density) of importance to people with emphysema?
  - What is the relationship between lung function and other outcomes (e.g. mortality and pulmonary exacerbations)?

Key issues for consideration

Clinical effectiveness (2)

- What is the committee's view on the clinical effectiveness evidence?
  - Are baseline characteristics suitably balanced across groups in the RAPID studies?
  - Are the meta-analyses informative?

- Does Respreeza provide clinical benefits for people with AATD?
  - What is the committee's view of the clinical and statistical significance of the results of RAPID?
  - Does it provide benefits in lung density, lung function, other outcomes?

Public observer slides – no ACIC

Cost lead team presentation

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

1st Evaluation Committee Meeting
Highly Specialised Technologies, 23 August 2018
Lead team: Sotiris Antoniou, Jeremy Manuel, Sarah Davis
Company: CSL Behring
Chair: Peter Jackson
Evidence review group: BMJ-TAG
NICE team: Thomas Paling, Ian Watson, Sheela Upadhyaya

[redacted]

Key issues for consideration

Cost-effectiveness (1)

- Does the model structure adequately capture the progression of AATD?
  - Is it appropriate to incorporate FEV1% and lung density decline states into the economic model?
  - Is there a relationship between FEV1% and lung density?
  - Are the cut-offs for lung density decline appropriate?
- Are the key assumptions appropriate?
  - Population and starting/stopping of treatment
  - Transitions between health states
  - Mortality (combining RAPID data with registry data)
  - Lung transplant
  - Utility values
  - Costs
- Is the probabilistic analysis suitable for decision-making?

[redacted]

Key issues for consideration

Cost-effectiveness (2)

- What factors affecting the guidance need to be taken into account?
  - Equalities?
  - Impact on the highly specialised service?
- What are the most plausible ICERs?
- Application of QALY weighting?
- Managed access arrangement

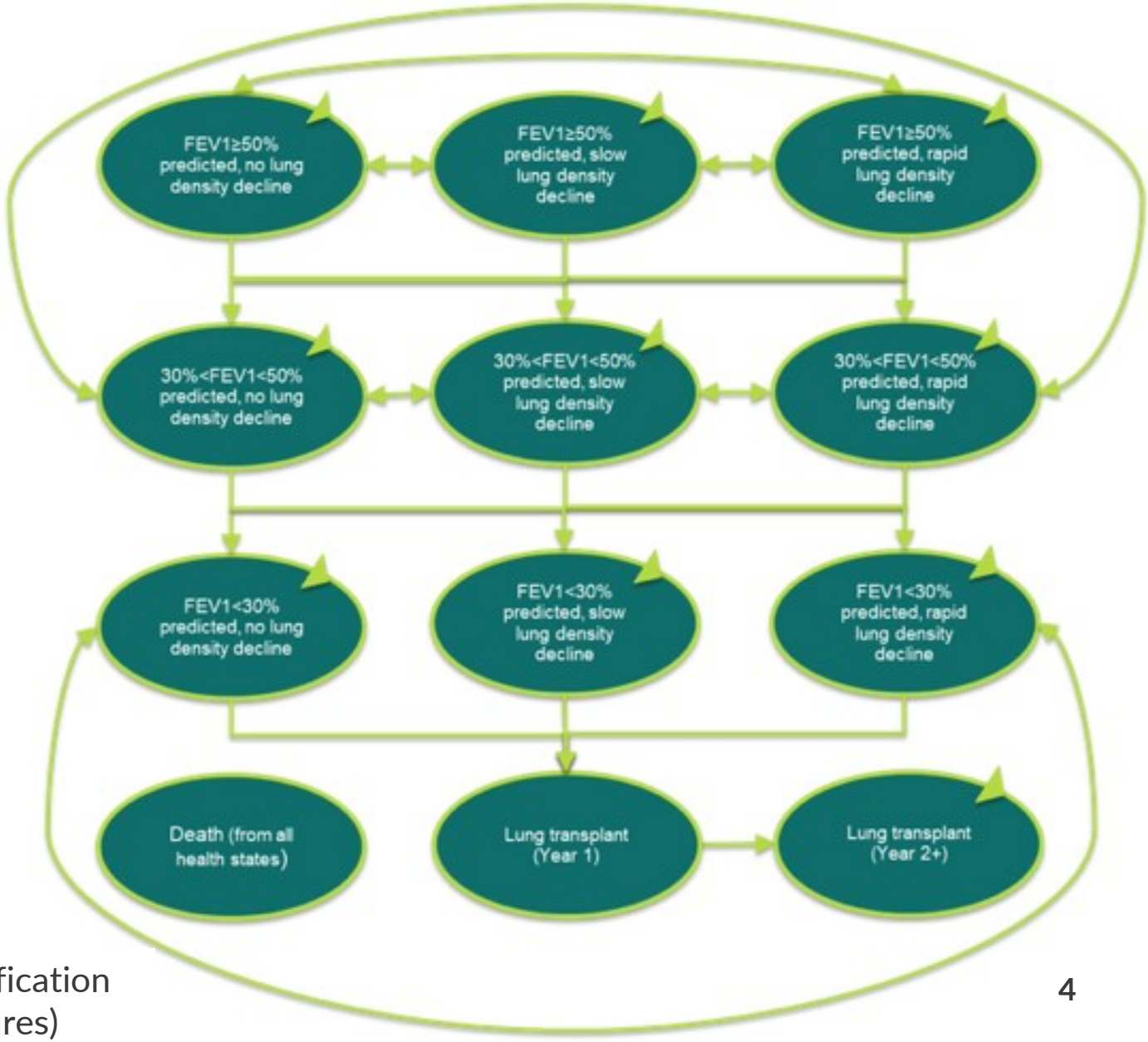
[redacted]

Economic model

Company model structure: State transition model

Lung density decline *(measured by CT scan)*	
No decline (ND)	<0 g/L/year
Slow decline (SD)	0-2 g/L/year
Rapid decline (RD)	>2 g/L/year

Model features	
Discounting	3.5%
Perspective	NHS
Cycle length	One year
Time horizon	Lifetime



Source: Figure 1 company response to clarification
Source: adapted from table 43 (model features)

Economic model: population and start/stop criteria

Starting treatment

- All people in the model start in the FEV1%≥50% and the FEV1% 30–50% states
  - Only people with FEV1% >35% and <70% were included in RAPID

ERG comment:
- The company included a criterion of rapid decline in lung function or lung density in their proposed starting population, but don't implement this in the model

Stopping treatment

- In the model people stop treatment with Respreeza when they move to the FEV1% <30% state; the company acknowledged that this was an implementation error

ERG comment:
- This is not included in the marketing authorisation
- There would be a case to continue Respreeza in people with FEV1% <30% waiting for a lung transplant; explored in scenario analysis

⊙ ***Are the population and start/stop criteria appropriate?***

[redacted]

Economic model

ERG comment

Company model structure (combined FEV1% and lung density health states)

- FEV1% and lung density are correlated but the predictive relationship is uncertain
  - Model does not account for this correlation
- Transitions between FEV1% and lung density states are estimated separately
  - Related outcomes are artificially separated – introduces critical uncertainty
- There is no clinically established threshold for defining CT lung density decline
  - A different model definition (-2g/L/y) of rapid lung density decline could impact the ICER
  - Company cites a study proposing an MCID of -2.89 g/L/y, indicating rapid density decline
  - Clinical outcomes in the model are uncertain and cannot be validated
- Model could have been based on FEV1% alone
- Densitometry is superior to FEV1% but more research is needed to incorporate it in a model

⊙ ***Does the model structure adequately capture the progression of AATD?***
⊙ ***Is there a relationship between FEV1% and lung density decline?***
⊙ ***Are the cut-offs for lung density decline appropriate?***

[redacted]

Transition probabilities

Based on RAPID and UK registry data

Transition probabilities for FEV1% and lung density decline were separately derived

- FEV1% transitions were estimated using 2 different sources of data:
  - BSC: UK registry data used to model transitions
  - Respreeza: Treatment effect estimates from the updated FEV1% meta-analysis used to calculate a relative risk, applied to the BSC transitions
- Lung density decline transitions estimated using RAPID data, adjusted for differences in baseline covariates
  - Lung density decline assumed to remain constant once patients have FEV1% <30%
  - Baseline lung density decline in the FEV1% 30–50%, and FEV1%>50% categories modelled using data (year 0 to 1) from the placebo arm of RAPID

[redacted]

Transition probabilities

ERG comment

FEV1%

- Data source for change in FEV1% for BSC could not be fully assessed
  - The study assessed change using linear regression; linear change is unlikely
  - Implausible to assume the same probability of change in FEV1% regardless of FEV1% status
- Company incorrectly use treatment effectiveness estimates from the meta-analysis

Lung density decline

- Imbalances in baseline lung density (46.6 g/L vs 49.8g/L) are significant
  - Recall that 2/g/L/y decline is considered 'rapid'
  - Baseline lung density linked to mortality and FEV1%; could impact the ICER
- Baseline lung density decline was not captured in RAPID
- RAPID-OLE data included without adjustment for treatment switchers

There is uncertainty in estimation of Respreeza treatment effectiveness

⊙ ***Are the transitions between health states appropriate?***

[redacted]

Mortality

- Mortality data taken from RAPID and RAPID-OLE used to inform the first 2 and 4 annual cycles, respectively
- UK registry data, stratified by rate of FEV1% and lung density decline, used to model mortality for the rest of the time horizon
  - Mortality rates for FEV1% <30% and FEV1% 30–50% assumed to be equivalent
- In addition to the survival gain observed in RAPID, slower FEV1% and lung density decline with Respreeza leads to indirect survival gains

[redacted]

Mortality

ERG comment

- Using RAPID data to model mortality is inappropriate because:
  - Very few mortality events
  - Baseline imbalances
  - No cross-over adjustment in OLE
- Lung density decline (by FEV1%) is not statistically significantly associated with mortality
- When switching from RAPID to registry, company inappropriately allocates people on Respreeza and people on BSC to different points on the survival curves
  - It takes people on Respreeza 2 or 3 years to 'catch-up' to the BSC mortality rate
  - Overestimates survival in the Respreeza arm and underestimates in the BSC arm
- Company assumes equivalent survival in RAPID and the registry, but data are not comparable
- Could have separately estimated survival in the FEV1% 30–50% and FEV1% <30% groups

Modelled overall survival is uncertain

- Predicted mortality is linked to lung density decline, but the relationship between lung density decline by FEV1% group and mortality is not well established
- Only using registry data would reduce uncertainty

⊙ ***Which approach to modelling survival is most appropriate?***

1. ***Combined RAPID and UK registry data***
2. ***Only using UK registry data***

Lung transplant

Eligibility for transplant

- People with FEV1% <30% are eligible for LT, regardless of lung density decline
- Equal probability of receiving a LT, regardless time spent in FEV1% <30%
  - Annual probability 43.8%

Mortality

- Post-lung transplant survival estimates: NHS blood and transplant report (2017)
  - 1 year survival (82%) used to estimate mortality probability in year 1 (16.47%)
  - 5 year survival (59%) used to estimate mortality probability in years 2+ (7.9%)

Post-lung transplant utility values

- Separate utility values are applied for the 1st and subsequent years post transplant
  - Based on weighted average of single and double lung transplant utility values from Anyanwu *et al.* 2001

[redacted]

Lung transplant

ERG comment

Eligibility for lung transplant (LT)

- ERG explored scenarios with reduced rate of eligibility and an age cap of 65 years

Mortality

- Post-LT survival curves should have been included in the model
- Unnecessary manipulation of the data to get 16.47% (should be 18%)
- Expert advice suggested that mortality reporting is poor
  - Post-LT mortality is a key driver - significantly impacts ICER
  - ERG's alternative survival estimates (UK transplant audit and clinical experts):
    - 1-year: 70%
    - 5-year: 50%

Quality of life post-transplant

- Higher post-transplant utilities favour BSC

⊙ ***Is the modelling of lung transplant appropriate?***
  ⊙ ***Eligibility***
  ⊙ ***Survival and quality of life post-transplant***

[redacted]

Health-related Quality of Life (HRQoL)

Data

- No generic measures of HRQoL data were collected in the trials
- Mapping SGRQ (collected in RAPID) to EQ-5D was not appropriate
- Data from UK registry were used to estimate health state utility values

Health state utility values are based on FEV1% categories

- HRQoL assumed to be driven by FEV1%, not lung density decline
  - [redacted]
  - FEV1% explains <50% of the variation in health status – excluding lung density decline from HRQoL estimates is likely to be conservative
- Utility values for each FEV1% health state obtained from the UK registry

[redacted]

Utility values

Economic model health state utility values

Health state	Health state utility value
FEV1% ≥50%	0.79
FEV1% 30–50%	0.63
FEV1% ≤30%	0.51
Post-lung transplant utility values	
LT: year 1	0.76
LT: year 2+	0.77

[redacted]

Source: adapted from table 53 and table 54 ERG report

Company scenario: *carer disutility*

Health state	Utility adjustment
FEV1% ≥50%	5% reduction in carer health related quality of life applied to patients (i.e. a QALY loss of -0.0425 per patient per year)
Post-lung transplant states	
FEV1% 30–50%	10% reduction in carer health related quality of life applied to patients (i.e. a QALY loss of -0.085 per patient per year)
FEV1% ≤30%	

Carer disutility was applied in the death health state, therefore it was continued after death, until the end of the modelled time horizon

Utility values

ERG comment

Generalisability of the source population

- Compared to RAPID, people in registry were older and with increased limitation (higher SGRQ) – i.e. worse quality of life
  - Modelled utility values could be an underestimate in the RAPID population

Omission of lung density decline

- [redacted]
- Modelling health state utility values only on FEV1% is inconsistent with overall rationale for incorporating lung density in the model

Application of age-related utility decrements

- Company's approach lacked justification, and potentially incorrect

⊙ ***Are the utility values appropriate?***

[redacted]

Acquisition and administration costs

Treatment cost item	Value
Acquisition costs	
Price of the technology	£220 per 1000mg vial
Dose	60mg/kg once-weekly
Patient weight	75.9kg
Number of vials required per dose	4.55 (rounded up to 5)
Cost per administration	£1100
Annual acquisition cost per patient	£57,200
Administration costs	
Cost per treatment administration per patient	£44.72
Annual cost per patient assuming 52 administrations per year	£2,326
Total costs	
Annual cost per patient assuming 52 administrations per year	£59,526

[redacted] Source: adapted from table 50 and 51 CS

Other costs

Disease management costs

- The cost of managing COPD used as a proxy for AATD
- Resource costs applied to resource use counts from analysis of ~58.5k UK patients
- Disease management costs were weighted according to exacerbations observed in RAPID

FEV1% state	Cost
FEV1% ≤30%	£4,134
FEV1% 30–50%	£3,674
FEV1% ≥50%	£3,361

Source: disease management costs, adapted from table 57 ERG report

Lung transplant costs

- Lung transplant costs sourced from an evaluation of UK patients (1999), inflated to 2017 costs
- Weighted average of single and double lung transplants

Lung transplant cost item	Value
Proportion of double lung transplants	75%
First year transplant costs	£76,698
Subsequent year transplant costs	£9,260

Source: lung transplant costs adapted from table 54 of the CS

Costs

ERG comment

- The company excluded BSC costs in the model
  - Lung transplant rate and survival differ across arms; BSC costs unlikely to cancel out
  - Excluding BSC underestimates costs associated with Respreeza (small ICER impact)
- If CT scanning will be used, prescribing and monitoring costs should be included
  - Company suggest CT scanning won't be needed in practice – appears inconsistent with need for lung density-based economic model
  - 1 expert considered CT scanning unnecessary
  - Alternative expert: CT scanning is needed to monitor treatment response
  - A study suggested that CT scanning would be more reliable than spirometry for identifying progression requiring A1PI treatment
- Receiving Respreeza at home could be difficult; scenario analysis 100% treated in clinic
- All people assessed for lung transplant eligibility should incur costs
- Full weight distribution in RAPID should be used to model treatment cost
- Exacerbation costs do not fully account for the differences in exacerbations in RAPID

[redacted]

Company base case results

Deterministic base-case ICER

Deterministic	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
BSC	£62,825	5.454			
Respreeza	£422,681	6.977	£359,855	1.522	£236,409

Source: table 6 company response to clarification

[redacted]

Probabilistic analysis

Probabilistic results varying:

- Disease management costs
- Lung transplant costs
- Administration costs and patient weight
- Utilities
- Mortality rates
- FEV1% transitions
- Lung density decline transitions

Probabilistic ICER = £181,879

ERG comment:

- It is unclear why the PSA ICER is lower than the deterministic figure
- Given the uncertainty in the relationship between FEV1% and lung density decline, not correlating these parameters in PSA makes the PSA unreliable

⊙ ***Is the probabilistic analysis suitable for decision-making?***

[redacted]

Company scenario analysis

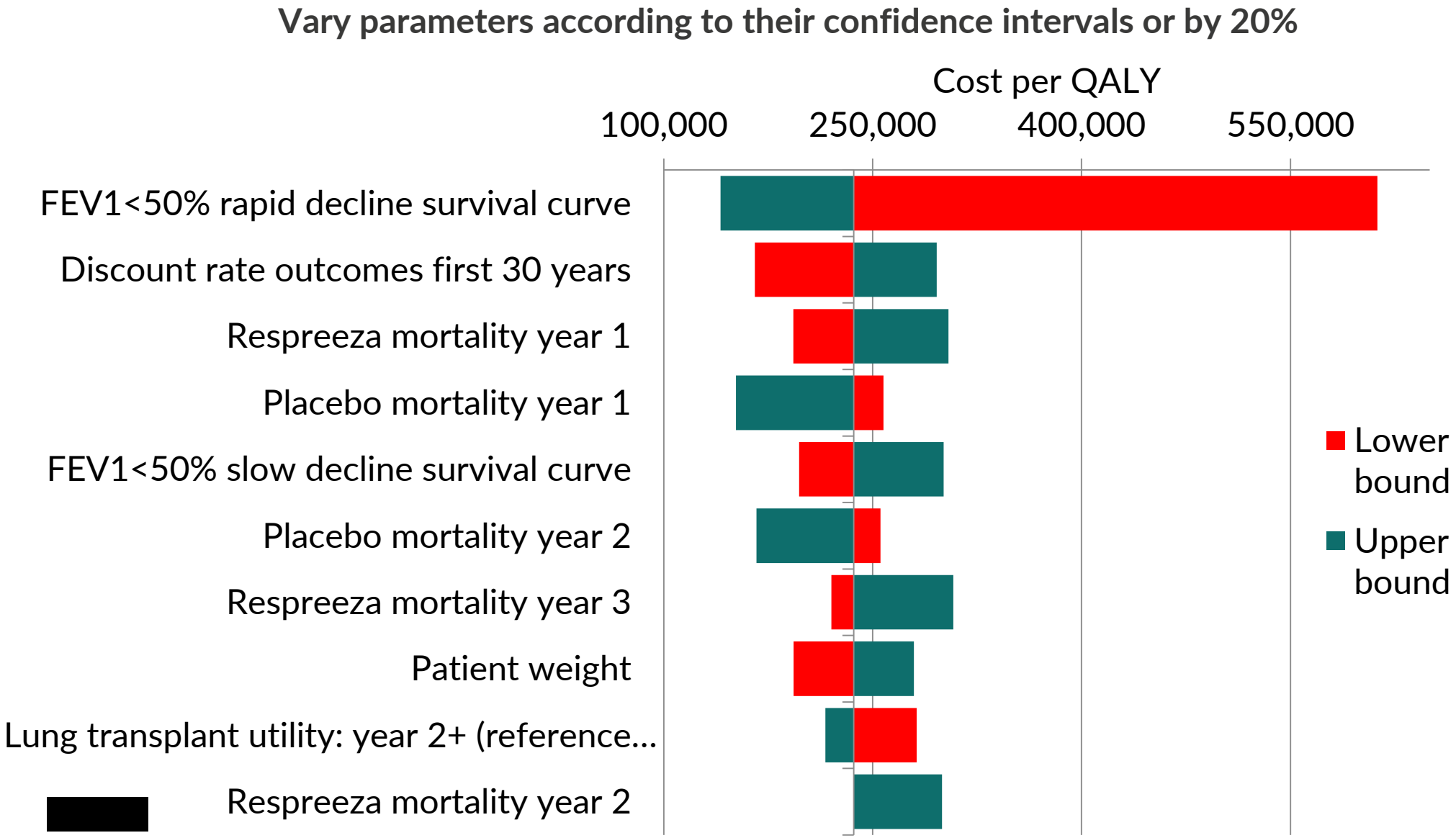
Scenario	Scenario info	ICER (£)
	Company base case	£236,409
1	Discount rate: 1.5% applied to benefits and 3.5% applied to costs	£189,946
2	Mortality data: UK registry survival curves only	£280,942
3	Care giver disutility: *5% QoL reduction in FEV1% >50% health state and post-LT states* *10% QoL reduction in all other health states*	£223,775
4	Adjust utilities by age *Using general population utility decline over time*	£225,638
5	Administration:	
	0% treatment administered at clinic	£234,880
	100% treatment administered at clinic	£240,996
6	Lung density costs and utility: *No decline: 20% increased utilities and 20% decreased cost, and* *Rapid decline: 20% decreased utility and 20% increased cost*	£207,109

Source: adapted from table 7 company clarification response

[redacted]

Company sensitivity analysis

Deterministic



Source: updated company economic model

ERG exploratory analysis

Scenario	Scenario info	Inc costs	Inc QALYs	ICER (£)
	Company base-case	£359,855	1.52	£236,409
	Corrected base-case *Replace the probability of death after transplant (18%, not 16.47%) (slide 12)*	£359,741	1.51	£237,822
1	Using different results from the updated meta-analysis to calculate transition probabilities *(slide 8)*	£383,821	1.21	£317,053
2	Using the UK registry survival data to model mortality *(slide 9)*	£321,815	0.34	£940,871
3	Removing stopping rule for treatment with Respreeza *Receive Respreeza until LT or death (slide 5)*	£419,545	1.51	£277,359
4	Applying an age cap for lung transplant (65 years) *(slide 12)*	£359,308	1.50	£240,298
5	Reducing the population eligible for lung transplant by 30% *(slide 12)*	£360,236	1.57	£230,196
6	Using alternative survival estimates for lung transplant *(slide 12)*	£358,766	1.43	£250,584
7	100% of drug administrations at a clinic *(slide 18)*	£366,723	1.51	£242,438

[redacted]

Source: table 67 ERG report

ERG exploratory analysis

Impact of ERG changes on corrected company base-case

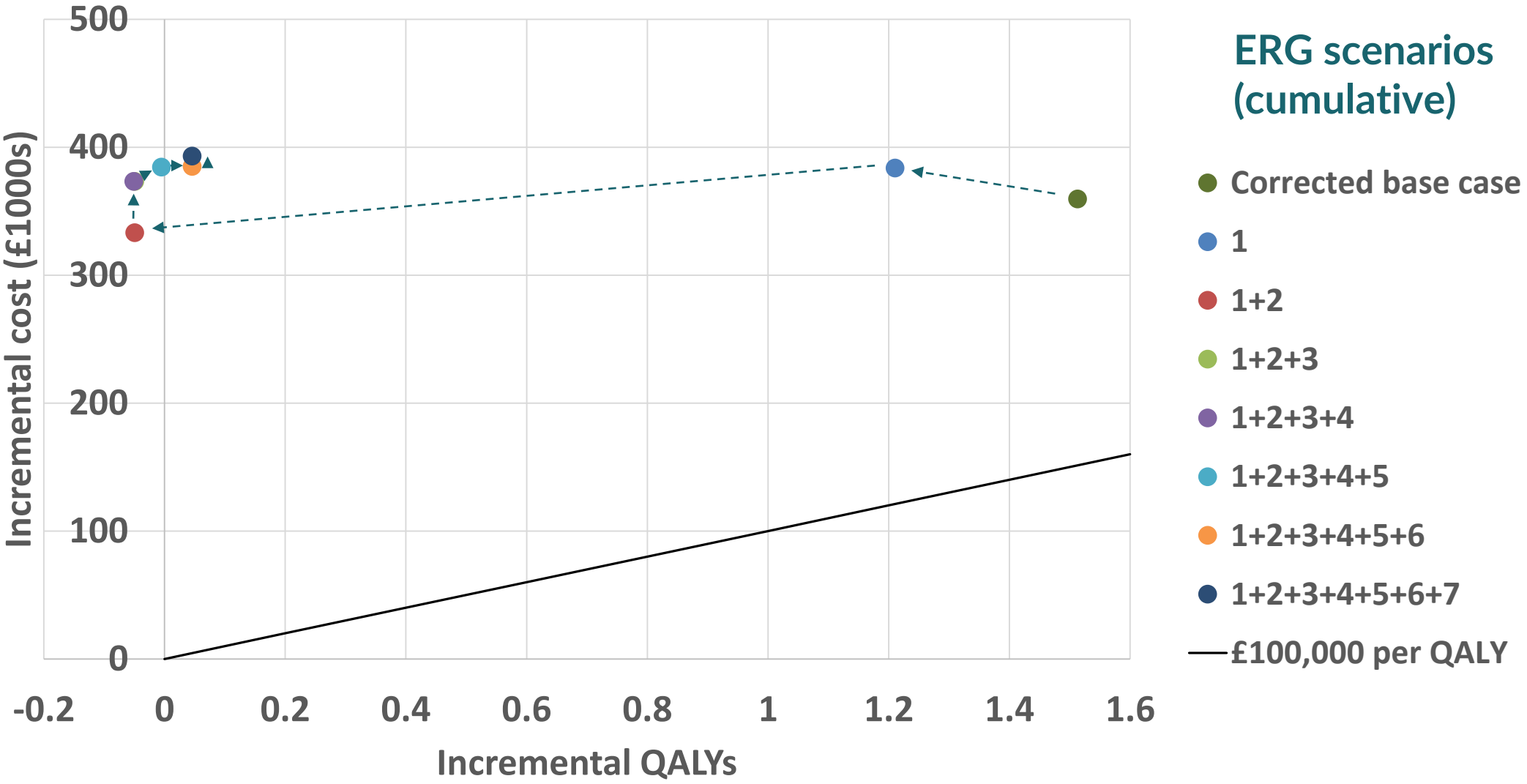
- Analyses added 1 by 1
- Bottom row shows the cumulative impact of all ERG changes

Scenario	Scenario info	ICER (£)
	Company base-case	£236,409
	Corrected base-case	£237,822
1	… + different results from the meta-analysis	£317,053
1+2	… + UK registry survival data	Dominated
1+2+3	… + removing Respreeza stopping rule	Dominated
1+2+3+4	… + age cap for lung transplant (65 years)	Dominated
1+2+3+4+5	… + 30% reduction in population eligible for lung transplant	Dominated
1+2+3+4+5+6	… + alternative survival estimates for lung transplant	£8,399,246
1+2+3+4+5+6+7	… + 100% of drug administrations at a clinic	£8,573,535

Source: table 68 ERG report

ERG exploratory analysis

Cost-effectiveness plane (cumulative ERG scenarios)



[redacted]

Source: produced from ERG scenario model

ERG exploratory analysis
Exploring treatment benefit – lung transplant

ERG analyses highlight the importance of lung transplant to the predicted benefits

- Lung transplant improves QoL and survival
- Therefore a treatment more likely to lead to transplant has greater clinical benefit
- In the model, everyone with FEV1% <30% is assumed to be eligible for LT
  - *Scenarios 1 and 2: **more** Respreeza patients stay in FEV1% 30–50% state → **fewer** transplants → **reduce** cost effectiveness of Respreeza*
  - *Scenario 5: **% of people** eligible for transplant significantly affects results*
  - *Scenario 6: **reduced** survival benefit of lung transplant → staying in FEV1% 30–50% becomes relatively **more favourable** → **improves** cost effectiveness of Respreeza*

This is counterintuitive given the proposal that avoiding transplants is a main treatment benefit

- Effect is driven by the data used to model QoL and survival pre vs post transplant

Key questions

- Is the modelling of lung transplant plausible?
- Are the relative benefits (survival and QoL) in FEV1% 30–50% and post-transplant clinically plausible?
- What is the appropriate clinical threshold for lung transplant?

[redacted]

QALY weighting

- For 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
- To apply the QALY weight, there must be compelling evidence that 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

Scenario	QALY gain	
	Undiscounted	Discounted (3.5%)
Company base case	2.27	1.52
Company scenario (6) with highest QALY gains: *Amending costs and utilities in lung density states (slide 21)*	2.51	1.73
ERG exploratory analysis including all changes	-0.03	0.05
ERG scenario (5) with the highest QALY gains: *Reducing the population eligible for lung transplant by 30%*	2.33	1.57

Source: company economic model and ERG economic model

Budget impact

	Uptake of Respreeza in the incident population	Number of people receiving Respreeza at the start of year	Respreeza plus BSC	BSC	Incremental budget impact
Year 1	50%	48	£3,177,409	£338,499	£2,838,911
Year 2	70%	114	£7,459,423	£674,823	£6,784,601
Year 3	90%	197	£13,024,506	£1,277,109	£11,747,397
Year 4	90%	279	£18,490,128	£2,007,652	£16,482,475
Year 5	90%	357	£23,719,282	£2,778,316	£20,940,966

Source: adapted from table 64 and 65 ERG report (from the updated economic model)

ERG comment:

Cost to the NHS could be higher than that estimated by the company

- The model is based on incident patients, not the prevalent population
- Clinical experts suggested that the company predicted eligible population size (up to 600–700) could rise substantially should Respreeza be approved

Service design and delivery

If Respreeza is recommended changes to NHS service provision would be required

- No national commissioning of specialist assessment services for AATD
- National specialised centres would need to be established to increase capacity
- Specialised centres through the NIHR network exist, but funding and recognition of the service needs to be approved
  - Community network services needed to support clinics assessment of patient suitability and administration needs (self administration or nation centre)
- Centres may not have the equipment needed
  - CT scanning analysis equipment and IV delivery services would be required
- A national guideline would be needed, the NIHR network could provide this

[redacted]

Innovation and equality

Innovation

- Respreeza is the first disease-modifying therapy for AATD

Equality

- Respreeza is produced from human blood – may be a concern for some people with particular religious beliefs
- During scoping, stakeholders noted that there is a disparity in access to treatment across Europe and that AATD occurs nearly exclusively in people with Caucasian family origins – not expected to be equality issues that can be addressed in this evaluation

[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

Managed access arrangement (MAA)

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

[redacted]

Key issues for consideration

Cost-effectiveness (1)

- Does the model structure adequately capture the progression of AATD?
  - Is it appropriate to incorporate FEV1% and lung density decline states into the economic model?
  - Is there a relationship between FEV1% and lung density?
  - Are the cut-offs for lung density decline appropriate?
- Are the key assumptions appropriate?
  - Population and starting/stopping of treatment
  - Transitions between health states
  - Mortality (combining RAPID data with registry data)
  - Lung transplant
  - Utility values
  - Costs
- Is the probabilistic analysis suitable for decision-making?

[redacted]

Key issues for consideration

Cost-effectiveness (2)

- What factors affecting the guidance need to be taken into account?
  - Equalities?
  - Impact on the highly specialised service?
- What are the most plausible ICERs?
- Application of QALY weighting?
- Managed access arrangement

[redacted]

Committee, projector and public observer slides – no ACIC

Lay lead team presentation

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

1st Evaluation Committee Meeting
Highly Specialised Technologies, 23 August 2018
Lead team: Sotiris Antoniou, Jeremy Manuel, Sarah Davis
Company: CSL Behring
Chair: Peter Jackson
Evidence review group: BMJ-TAG
NICE team: Thomas Paling, Ian Watson, Sheela Upadhyaya

[redacted]

Living with the condition

Breathlessness

- Everyday tasks require careful planning
- Breathlessness increases after eating
- Significantly reduces quality of life

"Breathlessness has a major negative impact on all areas of my life"
"When you can't breathe properly life changes"
"I even get out of breath just talking"
"I am almost housebound relying on my mobility scooter to get me out & about"
Breathlessness is "like drowning out of water – or inhaling hot sand"

Other physical issues

"The deleterious effect of AATD on the lungs results in reduced general physical functioning consequent to the shortness of breath"
"I'm barely able to dress myself, it has only taken 5 years to get to this stage"
"My liver and lungs were affected and my physical stamina has gone, things I enjoyed doing are now history to me"

Emotional wellbeing

"I have severe bouts of depression"
"I don't know what the future holds for me I'm too scared to look"

Living with the condition

Social interactions

- Fear of catching colds or infections creates a barrier to social interactions

"I cannot make any arrangements to visit family and friends as I'm always suffering from chest infections"

Expectations and aspirations

- AATD forces people to take early retirement and people limit expectations and aspirations

"My husband was diagnosed in his 30s in 2011, and his health declined so rapidly that he was medically retired in December 2016"

Impact on families and carers

- As lung function declines, there is an increasing dependence on carers

- "It's heart breaking having your family worry about you becoming a nuisance to them seeing the fear in their eyes when you are poorly"
- "The pressures of his ill health have meant my own health has suffered"
- "I have to care for her full-time and am not able to return to work"
- "My husband's condition has changed my lifestyle - loss of independence, loss of income, holidays are difficult as he can't cope with heat, cold or hills"

Diagnosis

- Lack of awareness and knowledge of AATD could contribute to delays in diagnosis
- Delay in accurate diagnosis is distressing and people feel helpless
- In a survey of English people with AATD, ~50% had a diagnosis delay >4 years, nearly 33% reported a delay >10 years

- "I was treated for some years for asthmatic hay fever"
- "Upon receiving the diagnosis of AATD I was told that there was no treatment, no specialists and no further information I could be given, and that I should research the condition on the internet myself."
- "I've lost count of how many doctors it has taken before I was referred to a lung specialist"

[redacted]

Current treatment options

Current treatment is aimed at Chronic Obstructive Pulmonary Disease (COPD)

- Treats the symptoms, not the cause of deteriorating lungs
- Treatments are "'reactive' not proactive"
- Treatments do not protect against future lung damage

Using oxygen is extremely restrictive and embarrassing

- Oxygen-dependence causes anxiety
- Carefully planned is needed to ensure sufficient oxygen supply

Pulmonary rehabilitation helps people cope with breathlessness but access is limited

- Long waiting lists for pulmonary rehabilitation
- The effects are short-term

Lung transplantation is a last resort and a frightening prospect

- Transplantation can lead to other equally debilitating medical problems
- "Many do not make it through the operation"

There is an unmet need for AATD treatments in the NHS

Alpha 1-proteinase inhibitor

An effective therapy would give people their lives back

- A1PI could give people an improved quality of life and independence
- Functional disability may be delayed if disease progression is slowed

The therapy gives hope of living a life not dominated by AATD

- Knowing A1PI slows disease progression improves mental and emotional wellbeing
- "Without this therapy, my health will continue to deteriorate both physically and psychologically at a fast rate"

A1PI cannot fix past lung tissue damage, but it can protect what remains

- Expected to reduce the severity and frequency of exacerbations
- Having regular infusions will have an adverse impact, but this will be offset by the protective effect of treatment

Lung transplantation could be delayed indefinitely

- More lungs could be available for other transplant

"I would expect the therapy to give my lungs the protection from everyday pollutants which my body lacks, to lessen the severity and duration of infectious exacerbations; and to slow my lung function decline enabling me to continue having some quality of life and independence"

[redacted]

Alpha 1-proteinase inhibitor

Benefits of A1PI reported by people with AATD in the US

- Stabilisation of lung function
- Reduction in breathlessness
- Increased/stable general activity levels and reduction of chronic tiredness
- Increased/stable ability to undertake everyday activities
- Improved mobility and independence
- Significant reduction in chest infection frequency and severity
- Reduction in hospital admissions and time off work due to ill-health
- Retention of employed work
- Reduction of dependence on family members and carers
- Improved family, social and sex life due to higher energy levels and less breathlessness
- Ability to participate more actively in family, social and community life
- Improved mental and emotional state for both the patient and family-carers
- Hope that life is extended
- Significantly improved quality of life

Impact of the technology beyond direct health benefits

Patient expert comments

- Due to the debilitating nature of AATD, many people are unable to live a normal life
- AATD can lead to an early retirement which has economic consequences
  - Repreeza could reduce lung density decline and delay retirement
- Reducing lung density decline could allow people to continue with daily life
- "I was professionally successful before AATD forced me to first reduce my working hours and subsequently, to take early retirement due to ill-health"
- "Receiving the therapy would mean I could continue with my limited social life and not become totally housebound. "

Company comments

- There are direct and indirect costs for caregivers
- By delaying the decline in lung density and the need for lung transplantation, Respreeza could reduce a variety of non-NHS government costs
- A German estimate of indirect costs in people with COPD ranged from €11.5k-€19k pppy* and sick days ranged from 24.2-30.8 pppy respectively

**PPPY, per patient per year*

[redacted]