NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Evaluation Report

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Pre-meeting briefing

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Key issues for consideration

Clinical effectiveness

- 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 in clinical practice?
  - 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 (FEV1%, lung density) and other outcomes (such as mortality and pulmonary exacerbations)?
- Who would be considered eligible (and ineligible) to receive a lung transplant?
- 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?

[redacted]

Key issues for consideration

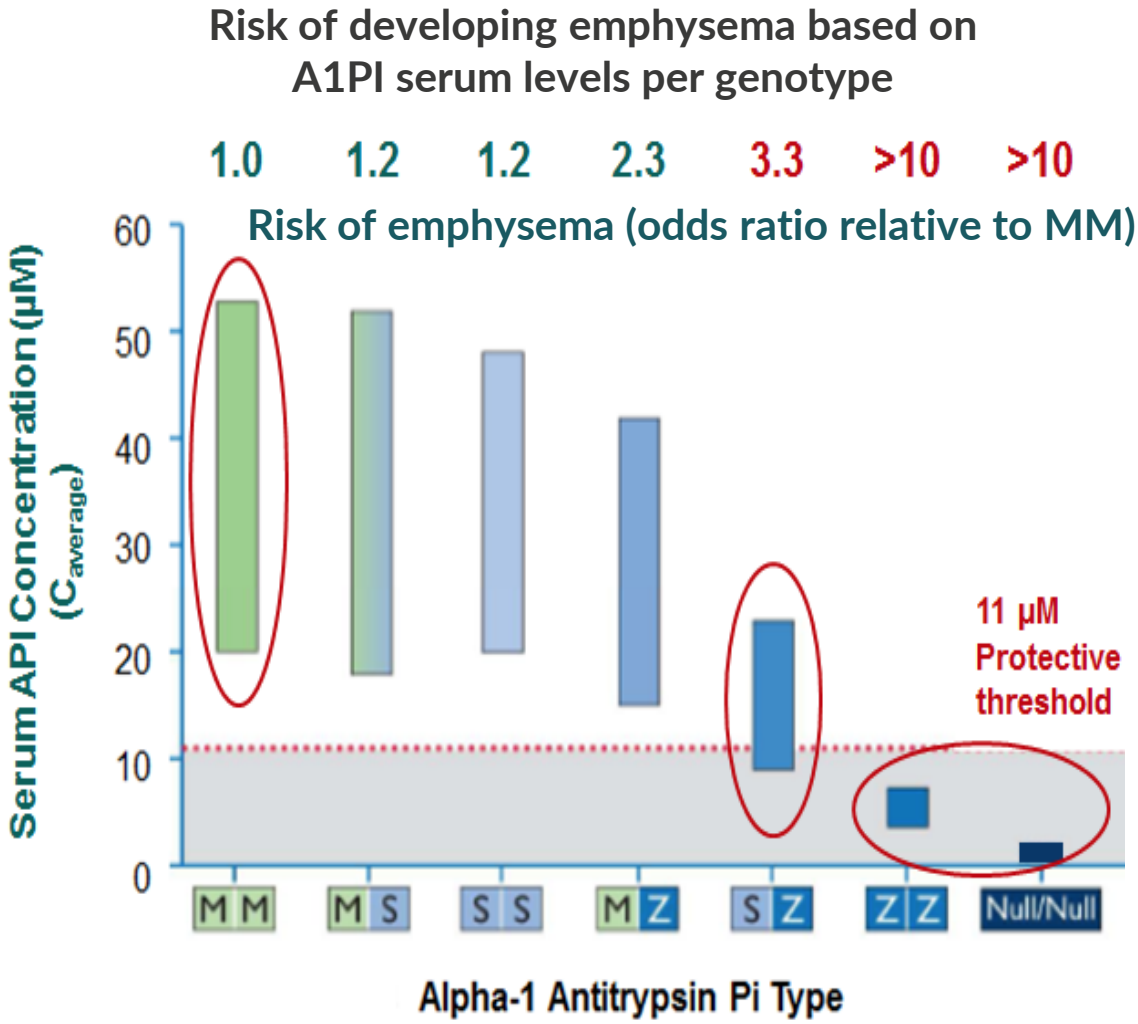
Cost-effectiveness

- 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?
- 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?

[redacted]

Disease background

- Alpha-1 proteinase inhibitor (A1PI) deficiency (also known as alpha-1 antitrypsin deficiency, AATD) is a rare, genetic disorder which causes low serum levels of the A1PI protein
  - A1PI protects body tissue from damage by protease enzymes such as neutrophil elastase
  - These proteases are produced in response to infections and environmental toxins (e.g. smoking, pollution)
- A lack in the protective enzyme (A1PI) makes people more vulnerable to smoke or toxic materials, which leads to progressive damage of lung tissue
- People with A1PI serum concentration <11 µM are considered to have severe AATD
- Development and characteristics of disease vary considerably, suggesting an interplay between genetics and environmental exposures



Population size

- Company estimates the prevalence symptomatic AATD to be 0.99 per 100,000, of whom 80% have clinically significant symptoms requiring treatment
  - Translates to 670 people with AATD in England, of whom 549 would be eligible for treatment
- **Clinical expert comment:** there are about 1,500 known cases of PiZZ/Znull genotype 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 and liver, skin, and immune system complications
  - Most people with AATD present with lung damage
  - Less commonly, people with AATD present with cirrhosis or panniculitis
- AATD can result in emphysema depending on reduced A1PI serum concentrations
- Emphysema is a long-term progressive disease of the lungs, symptoms include
  - breathlessness
  - persistent chesty cough
  - frequent chest infections
  - persistent wheezing
- In people with emphysema due to AATD, shortness of breath and wheezing will usually occur between the ages of 20 and 40 years
- Repeated exacerbations lead to a decline in lung function
  - Quality of life is reduced for people with reduced lung function
- Life expectancy is significantly reduced in AATD as it leads to emphysema and eventually pulmonary failure

Patient perspectives: *the impact of AATD*

Impact on patients

- "The deleterious effect of AATD on the lungs results in reduced general physical functioning consequent to the shortness of breath"
- The effects of AATD often change throughout the progression of the condition
- Breathlessness and lack of oxygen in the blood reduces strength and the ability to be active
- Any physical exertion quickly leads to breathlessness
- Breathlessness is "like drowning out of water – or inhaling hot sand"

Impact on families and carers

- "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"
- "I can't keep a job as I had to keep taking time off to look after my daughter, I have to be her nurse as well as her mum"

Patient perspectives: *living with the condition*

“Breathlessness has a major negative impact on all areas of my life”

- Breathlessness means everyday tasks require careful planning
- Breathlessness increases after eating
- Significantly reduces quality of life
- “I even get out of breath just talking”
- “I am almost housebound relying on my mobility scooter to get me out & about”

Social interaction becomes increasingly difficult and impacts on relationships

- Fear of catching colds or infections creates a barrier to social interactions
- Having difficulty with normal physical activity is causes embarrassment and fear

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”

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

[redacted]

Expert comments: *diagnosis*

Clinical expert comments

- Knowledge and experience of AATD varies greatly
- Misdiagnoses and delayed diagnoses are common
  - There is an average of over 5 years delay until diagnosis
- People are often misdiagnosed with asthma or COPD
- Genetic testing is rarely done in primary care

Patient expert comments

- A lack of awareness and knowledge of AATD could contribute to delays in diagnosis
- Having a delay in receiving an accurate diagnosis is distressing and people feel helpless
  - "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"
- "I was treated for some years for asthmatic hay fever"

[redacted]

Current treatment options

- The aim of treatment is to delay progression of emphysema associated with AATD
- Current treatments provide short-term symptom relief, but do not treat the underlying cause of the condition
- There is no UK guidance on treating A1PI deficiency
- Currently treatment involves standard therapy for Chronic Obstructive Pulmonary Disease (COPD), such as:
  - inhaled bronchodilators; inhaled corticosteroids; oxygen therapy; and pulmonary rehabilitation.
- Lung transplantation can be considered in people with progressed disease

Patient perspectives: *current treatment options*

Current treatment is aimed at COPD

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

Using oxygen is extremely restrictive and embarrassing for such a young person

- Being oxygen-dependent is a constant cause of anxiety
- Everything needs to be carefully planned around ensuring sufficient oxygen supply
- Travel, particularly on aircrafts, becomes challenging with supplementary oxygen

Pulmonary rehabilitation helps people cope with breathlessness but access is limited

- There are long waiting lists for pulmonary rehabilitation
- The effects are short-term

Lung transplantation is a last resort and a frightening prospect

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

There is an unmet need for AATD treatments in the NHS

[redacted]

Clinical experts: *Current treatment experience*

There is an unmet need for people with AATD

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

Clinical management of AATD is heterogeneous between areas

- Most patients attend general respiratory clinics and may or may not see an expert in their condition

[redacted]

Human alpha1-proteinase inhibitor
(Respreeza, CSL Behring)

Marketing authorisation	Respreeza is indicated 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 forced expiratory volume per second (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
Mechanism of action	Human alpha$_1$-proteinase inhibitor is understood to be the primary anti-protease in the lower respiratory tract, where it inhibits neutrophil elastase.
Administration & dose	Intravenous infusion at 60mg/kg, once weekly
List price	£220 per 1000mg vial Average cost per patient per year: £57,200 *(based on 52 administrations per year, for a person of average weight [67–83 kg])*
Treatment course length	Life time

Clinical experts: *A1PI*

Anticipated clinical benefits of A1PI

- Preserve lung tissue and reduce inflammation, slow decline in CT lung density
- Delay or prevent the onset of symptoms
  - May reduce the frequency and severity of exacerbations
  - Improve health related quality of life
  - Improve psychological well being
  - The onset of disability and mortality can be delayed
- Could delay or prevent lung transplants (more lungs could be available for other transplants)

[redacted]

Patient perspective: *A1PI*

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]

Decision problem

	Final Scope	
Population	Adults with severe alpha 1-proteinase inhibitor deficiency who have progressive lung disease	
Intervention	Human alpha 1-proteinase inhibitor* in addition to established clinical management	
Comparator	Established clinical management without alpha 1-proteinase inhibitor	
Outcomes	• incidence, duration and severity of acute exacerbations, including hospitalisation • lung function • symptom control (e.g. shortness of breath)	• change in lung density • exercise capacity • mortality • adverse effects of treatment • Health-related quality of life (for patients and carers

*Scope specifies the intervention as A1PI, and is not specific to Respreeza

- *Although other A1PIs are available in the EU, Respreeza is the only A1PI licensed in England*
- *Data from other A1PIs are presented in the clinical effectiveness evidence*
- *ERG notes a biochemical comparison supports the proposal that A1PIs can be considered equivalent*

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 position (see slide 19):

- Severe A1PI (<11µM) and either FEV1 / FVC < 0.7 or emphysema demonstrated by CT scan
- FEV1% predicted ***30–70%***
- Rapid lung function decline (measured by FEV1 / D_{LCO}) or lung density decline
- Stopping criteria: none proposed

Evidence

- Pivotal study (RAPID):
  - Adults (18 to 64 years old) with emphysema and severe A1PI deficiency (<11µM)
  - FEV1% predicted ***35–70%***
- Economic model:
  - FEV1% predicted ***>30%***, irrespective of lung density decline
  - Stopping rule: treatment stops in patients with FEV1% predicted <30%

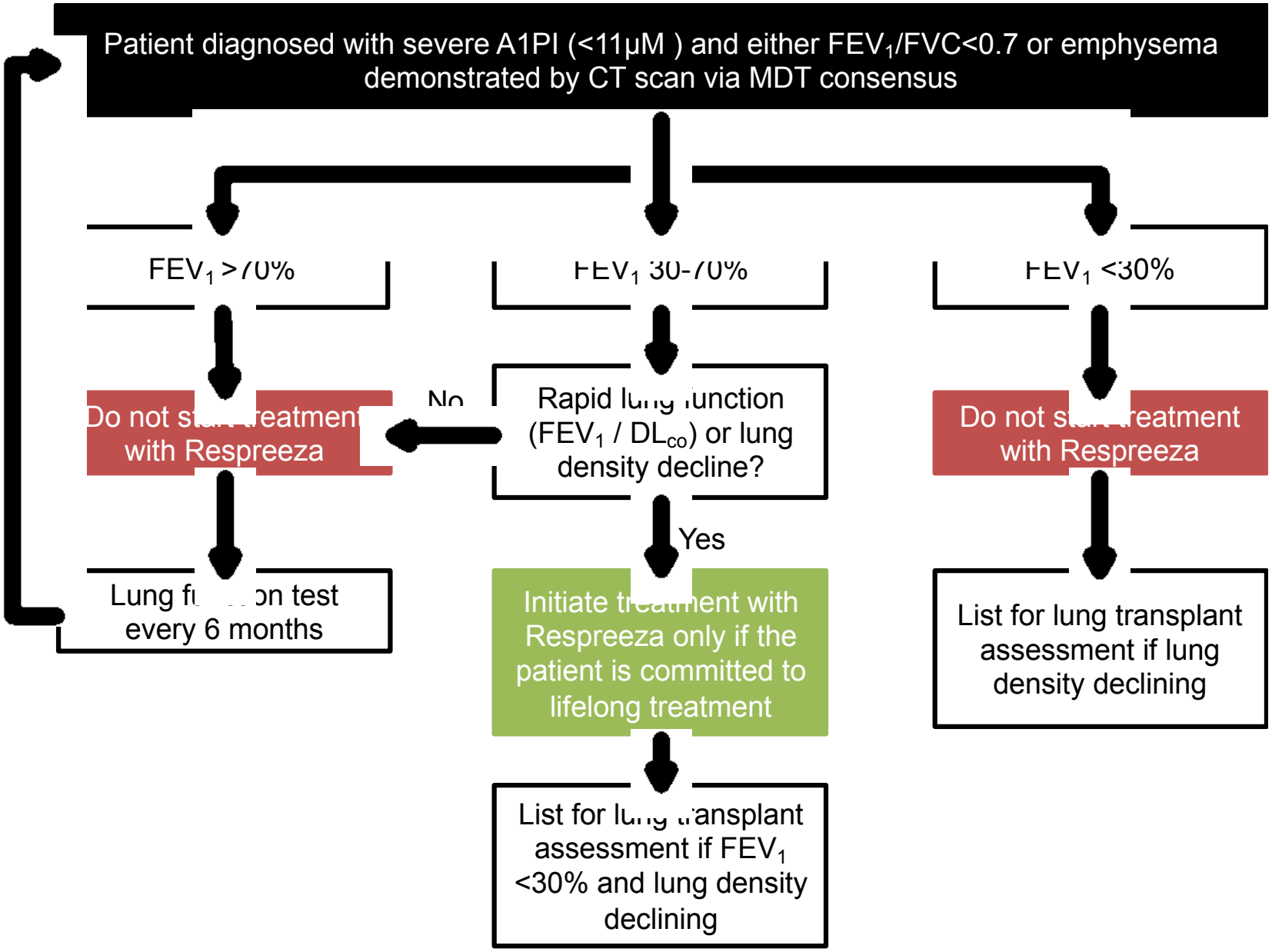
Decision problem: Population and start/stop criteria
Proposed use of Respreeza

ERG comments

- EMA recommended that Respreeza should be used in people with evidence of significant lung density decline
- Clinical advisers generally agreed with proposed position, but noted lack of definition of rapid lung function decline
  - As there is no definition of 'rapid decline' in the proposed starting criteria, anyone with emphysema associated with A1PI may be eligible for treatment
  - Clinical advisers noted that they would not want to give Respreeza to people with no decline in lung function
- May be a rationale for starting treatment in patients with FEV1% predicted <30% (if ineligible for or awaiting lung transplant)
- Stopping rule was not proposed but was applied in the model; may be a case to remain on treatment when FEV1% predicted decreases below 30%
  - *Company accepted that this was an implementation error*

[redacted]

Proposed Respreeza treatment initiation



Clinical effectiveness evidence

[redacted]

Clinical evidence summary

RCTs (Respreeza)

- RAPID
- RAPID-OLE (extension study)

RCTs (other A1PI augmentation therapy)

- Dirksen 1999
- Dirksen 2009 (EXACTLE)

Real-world evidence:

- The ADAPT registry: UK registry of A1PI deficient patients
- National Heart, Lung and Blood Institute (NHLBI) registry: 37 US centres including 1,129 patients

Evidence synthesis and meta-analyses:

- Edgar el at meta-analysis of RAPID (Chapman) studies and Dirksen 1999, 2009
  - Meta-analysis of 3 RCTs comparing augmentation to placebo
- Updated Chapman 2009 meta-analysis (including 3 additional post-2009 studies)
  - Meta-analysis of treatment effect across FEV1% predicted groups

[redacted]

Clinical evidence

Respreeza studies: RAPID and RAPID-OLE

Study	Location, duration, blinding and patient numbers	Primary outcome(s)
RAPID Phase III *RCT*	• 28 centres: Australia, Canada, Europe (0 UK), USA • 24 month • Double-blinded, placebo-controlled • N=180 (Respreeza=93, Placebo=87)	Rate of change in lung density as assessed by CT scan (adjusted PD15)

RAPID-OLE
Phase IV
Observational study
	• RAPID population (without USA residents)
	• 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)*
		Rate of change in lung density as assessed by CT scan (adjusted PD15)

Key inclusion criteria (RAPID):

- Adults (18 to 64 years old)
- Emphysema and FEV1% predicted ≥ 35% and ≤ 70%
- A1PI deficiency (<11µM)

[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% predicted, 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

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% predicted, mean (SD)	45.0 (12.6)	46.3 (12.0)
HRQoL (SGRQ symptoms score), mean (SD)	47.3 (18.2)	44.0 (16.9)

Clinical evidence

ERG comments

- The overall the risk of bias is low in RAPID
- There is a substantial difference between groups in baseline CT lung density (46.6 g/L v 49.8 g/L)*
  - Effect on results is unclear
- Baseline lung density decline was not measured in RAPID
  - Differences in baseline lung density decline could affect the comparability of the groups
  - This also has implications for starting treatment given the company's proposed starting criteria (see slides 17 and 19)
- Bronchodilator administration before assessment of FEV1 was not compulsory in RAPID (advised by GOLD for COPD), this could affect results and meta-analysis
- RAPID-OLE, as an observational study, is associated with a higher risk of bias than RAPID

[redacted]

Study outcomes

CT lung density (primary outcome)

- An independent predictor of mortality
- Correlates with other clinical outcome of disease progression (FEV1 and FEV1% predicted) and health status (SGRQ total score) in people with A1PI deficiency
- Not regularly conducted in clinical practice due to radiological considerations

ERG comment:

- Although there is evidence that CT lung density is a valid measure for assessing emphysema severity, a minimally important difference not yet established
- The extent that decline in CT lung density correlates with other clinical measures (FEV1, FEV1% predicted, D_{LCO}, FEV1/FVC ratio) is uncertain

Secondary outcomes

- FEV1
- D_{LCO}
- Exacerbations
- Exercise capacity (Incremental shuttle walking test [ISWT])
- Quality of life (St George's Respiratory Questionnaire [SGRQ])

[redacted]

Summary of clinical efficacy analyses

Primary efficacy analysis

- Comparison of change in CT lung density (adjusted PD15 combined for TLC and FRC) in people treated with Respreeza vs those on placebo
  - PD15 adjusted: due to natural variations across people a physiological volume correction is needed (PD15). This generates the 15th percentile CT lung density

Mixed model

- Assesses lung density decline across RAPID and RAPID-OLE studies (48 months)
- 'Early starters' of Respreeza compared to 'Late starters'

Meta-analyses

- Edgar meta-analysis of outcomes from Dirksen and RAPID studies (Chapman)
- Updated meta-analysis from Chapman 2009 (include additional post-2009 studies)
- Augmentation therapy compared with placebo

[redacted]

Clinical effectiveness – results

[redacted]

Clinical effectiveness

Overview: RAPID studies results

CT lung density

- Respreeza was associated with a statistically significantly lower annual decline in adjusted lung density at TLC compared with placebo
- The effect of Respreeza in reducing rate of lung density decline is sustained in the extension

FEV1% predicted

- The direction of effect favoured placebo (not statistically significant)

D_{LCO}

- The direction of effect favoured placebo (not statistically significant)

Exacerbations

- The rate of pulmonary exacerbations was higher in the Respreeza arm than placebo

Incremental shuttle walking test (ISWT)

- Larger reduction in walking distance in the Respreeza arm (not statistically significant)

SGRQ

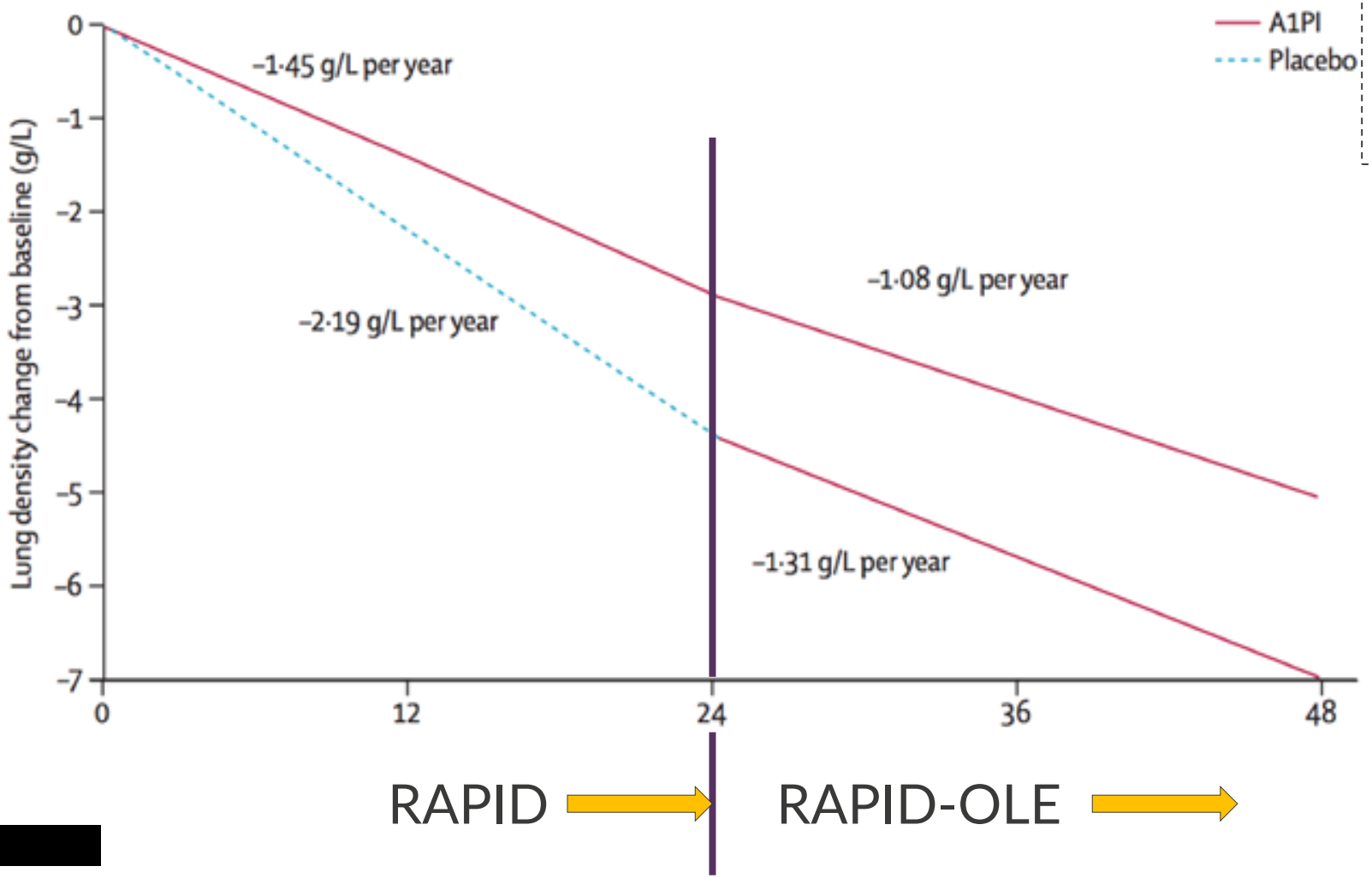
- Improvement in symptoms at 24 months for people treated with Respreeza

[redacted]

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)

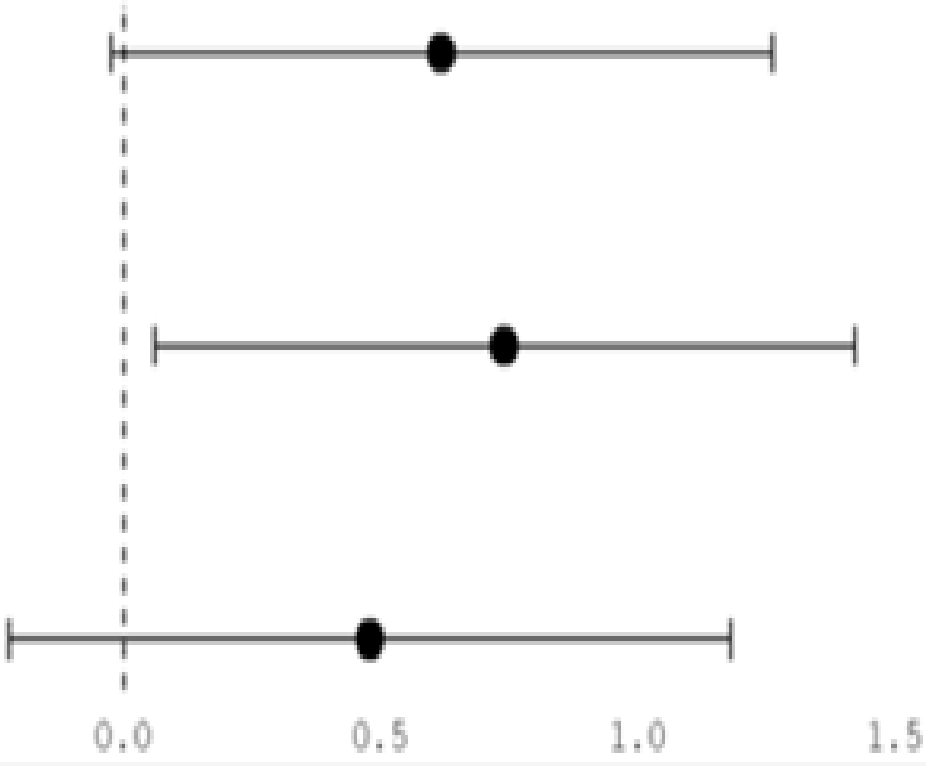
[redacted]

Clinical effectiveness: *RAPID*

CT lung density

TLC is easier to replicate than FRC, and the CHMP endorses it as the optimal method of monitoring disease progression in emphysema

Inspiration state	Treatment difference	P-value*
TLC + FRC	0.618	0.06
TLC	0.740	0.03
FRC	0.478	0.18



Clinical effectiveness: *RAPID*
FEV1 and D_{LCO}

Outcome	Respreeza (N=93)		Placebo (N=87)		Respreeza versus placebo
	Baseline	Change at 24 months	Baseline	Change at 24 months	Least-square mean difference
FEV1% predicted	47.4% (12.1)	−3.1% (10.7)	47.2% (11.1)	−2.3% (13.1)	−2.26%[a] (p=0.21)
D_{LCO} (mL/mm Hg/min)	13.6 (5.3)	−2.2% (18.2)	15.0 (5.6)	−1.5% (19.5)	−1.31%[a] (p=0.64)

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

[redacted]

Clinical effectiveness: *RAPID*

Secondary outcomes: exacerbations

Outcome	Respreeza (N=93)	Placebo (N=87)
People experiencing ≥1 pulmonary exacerbation n (%) (number of events)	[redacted]	[redacted]
1 to 3 exacerbations	[redacted]	[redacted]
4 to 6 exacerbations	[redacted]	[redacted]
>6 exacerbations	[redacted]	[redacted]
People experiencing a moderate exacerbation [a] n (%) (number of events)	[redacted]	[redacted]
People experiencing a severe exacerbation [b] n (%) (number of events)	[redacted]	[redacted]
Hospitalisation	[redacted]	[redacted]

[a] Defined as [redacted]
[b] Defined as [redacted]

[redacted]

Clinical effectiveness: *RAPID*

Secondary outcomes: Exercise capacity and quality of life

Outcome	Respreeza (N=93)		Placebo (N=87)		Respreeza versus 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[a] (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[a] (p=0.91)*
Symptoms	46.5 (22.7)	−1.4 (16.7)	44.1 (24.8)	+2.0 (20.1)	−1.11[a] (p=0.67)*
Activity	62.1 (18.6)	+1.7 (12.4)	60.1 (21.4)	+2.6 (13.5)	−0.16[a] (p=0.94)*
Impact	33.6 (18.4)	+2.1 (14.8)	31.4 (17.6)	+1.8 (12.5)	0.74[a] (p=0.72)*

Shuttle walk distance

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

SGRQ

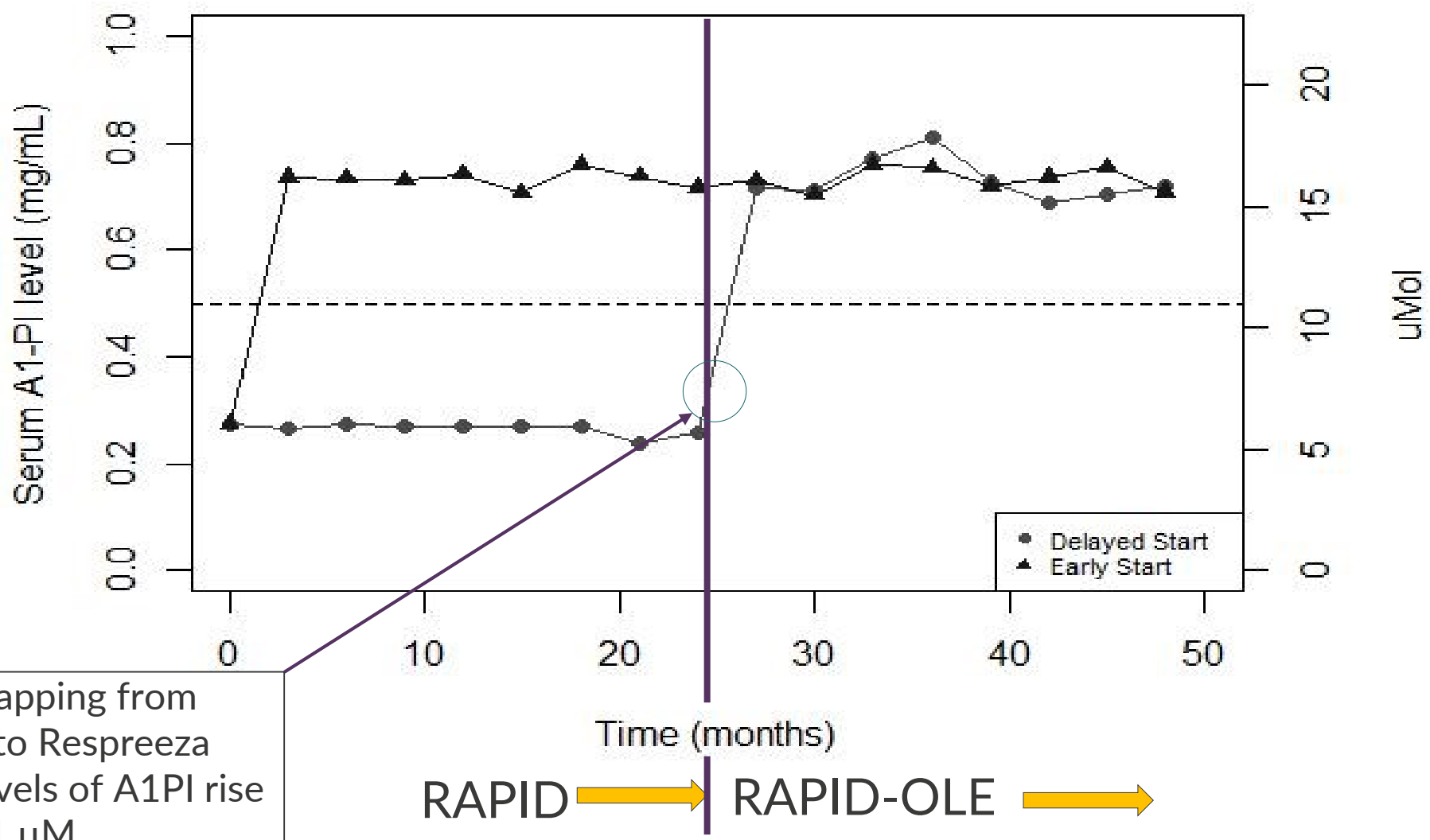
- Higher scores in SGRQ indicate more limitations
- Improvement in symptoms at 24 months for people treated with Respreeza

**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

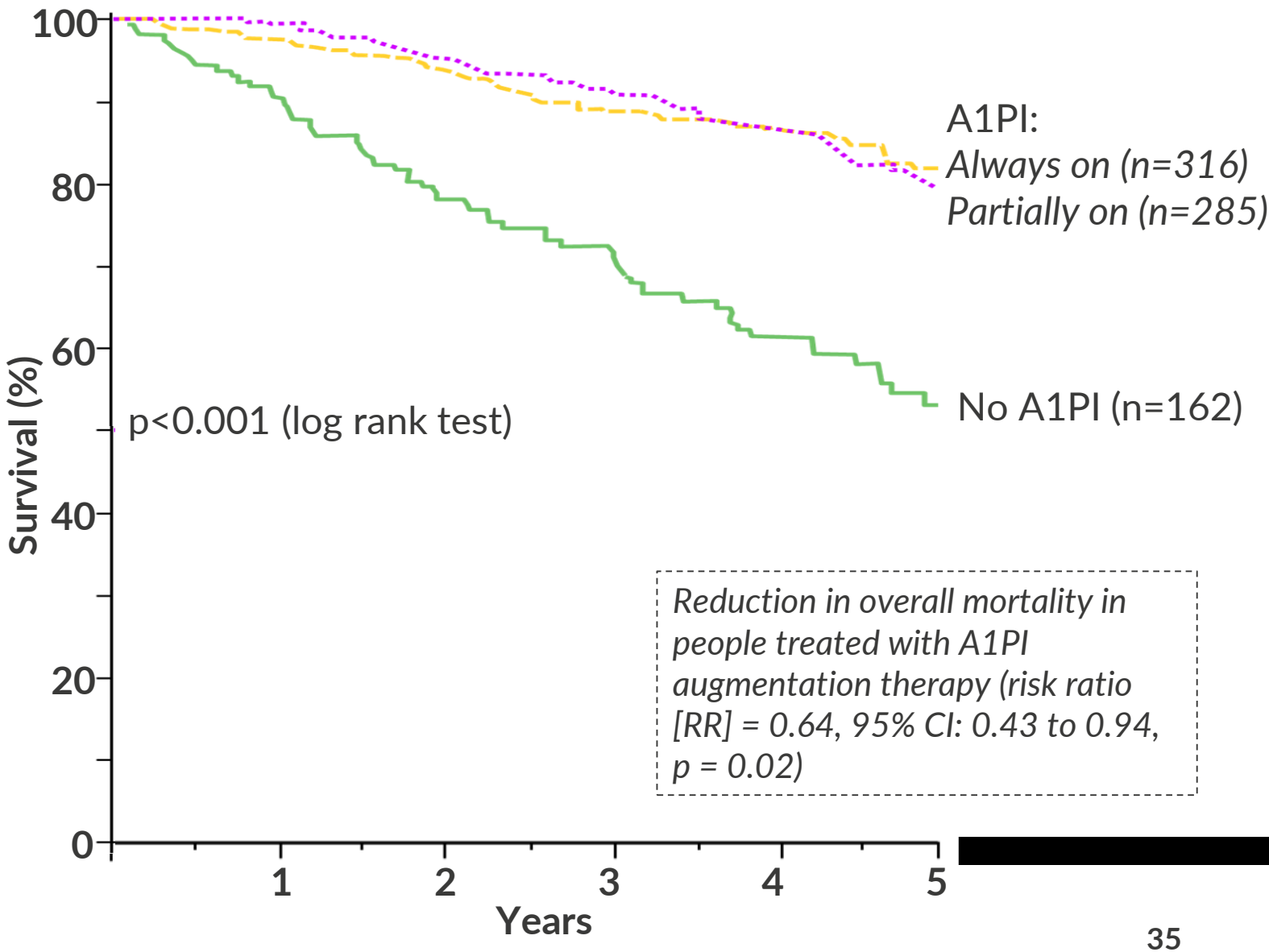


After swapping from placebo to Respreeza serum levels of A1PI rise above 11 µM

Clinical effectiveness: real-world evidence

NHLBI: Mortality risk

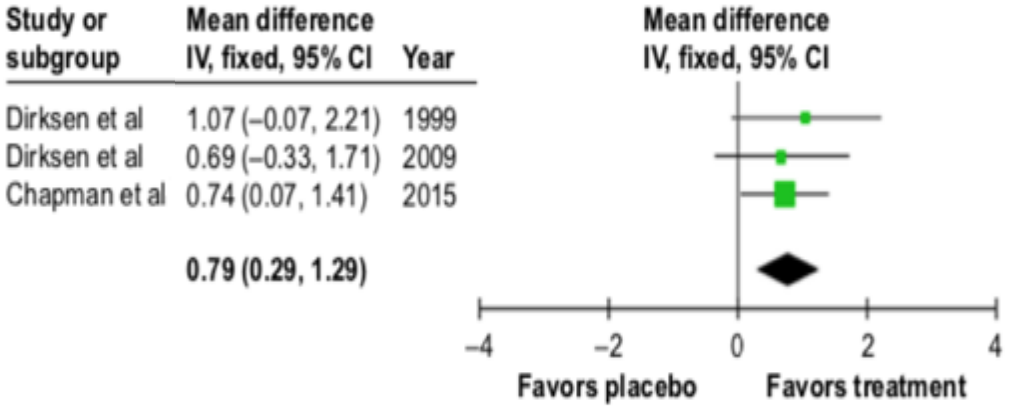
- Analysis of 1,048 people with FEV1% predicted <50% using US registry data
- Groups were not randomised; baseline characteristics were not balanced
- Baseline FEV1% predicted was a major determinant of survival



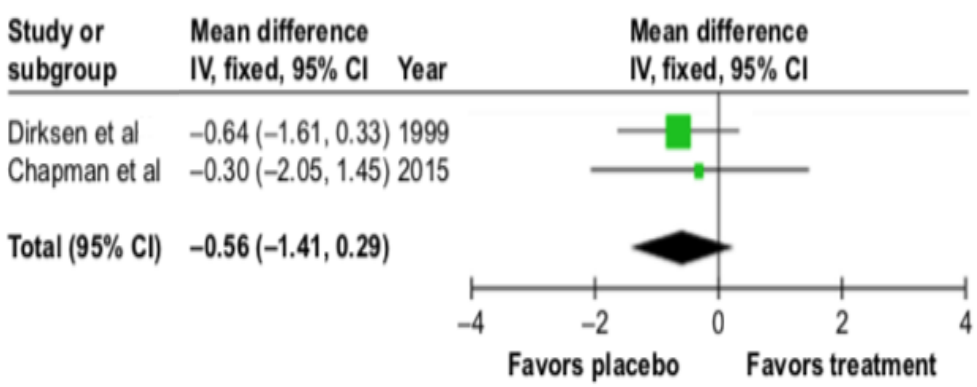
Meta-analysis (1)

Edgar et al meta-analysis: Lung density, FEV1, exacerbations and quality of life (RAPID and Dirksen studies)

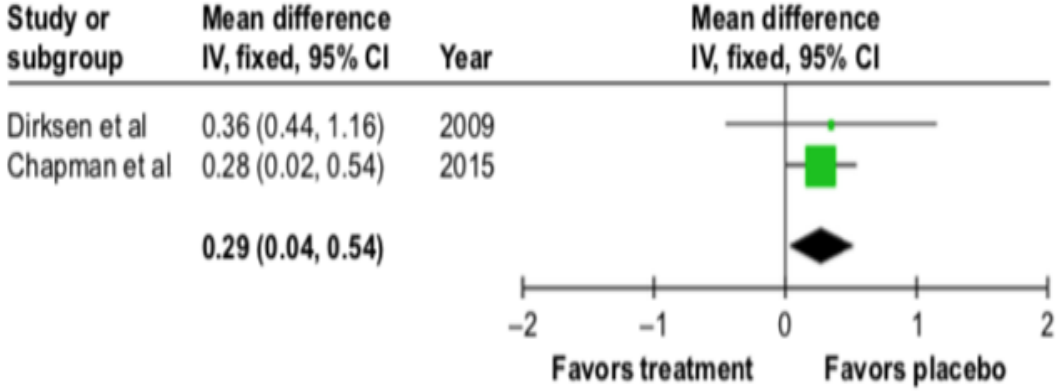
Mean change in lung density



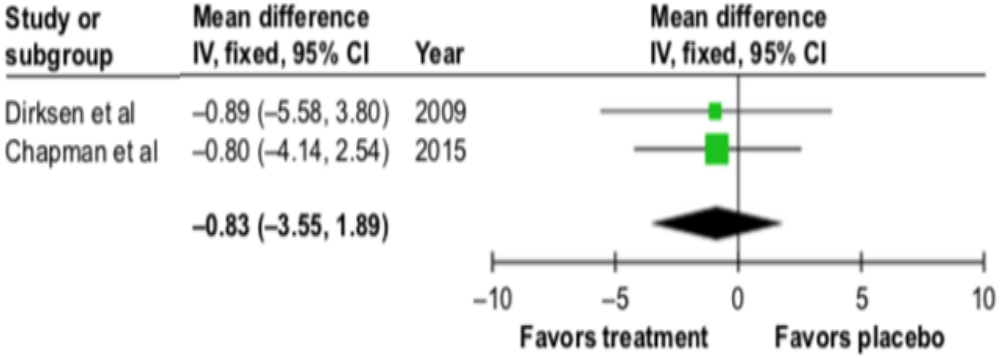
Mean FEV1% predicted



Annual exacerbations



Quality of life (SGRQ)



Meta-analysis (2)

Updated Chapman 2009 meta-analysis: change in FEV1 stratified by FEV1% predicted category

- In response to clarification the company provided an update to the meta-analysis published by Chapman et al (2009), to include 3 additional studies (including RAPID)
- The results of this meta-analysis are used in the economic model
- Results from one of the newly included studies (Tonelli et al 2009) counterintuitively showed that patients having A1PI with FEV1% predicted >65% declined faster than those who did not
  - Other studies did not find a statistically significant decline in people having A1PI with FEV1% predicted >65%

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

Meta-analysis (3)

ERG comment

Edgar et al 2017 meta-analysis

- Inclusion criteria in the included studies were comparable on disease characteristics
  - Baseline characteristics of the populations are comparable
- Dirksen 1999 and Dirksen 2009 assesses Prolastin, not Respreeza
  - There is evidence to suggest 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:

- With the exception of the FEV1% predicted >65% group, the inclusion of additional studies produced similar results to the original analysis (the direction of effect favours Respreeza)
- Given ERG's concerns about how registry data were included and the risk of bias in some studies, ERG advises that the results are interpreted with caution

[redacted]

Adverse events

TEAEs *experienced by > 10% (RAPID)*	Event	Respreeza	Placebo
	Infections and infestations Nasopharyngitis	83% 32%	87% 30%
	Respiratory disorders Chronic obstructive pulmonary disease (COPD)	68% 32%	56% 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

Cost-effectiveness evidence

[redacted]

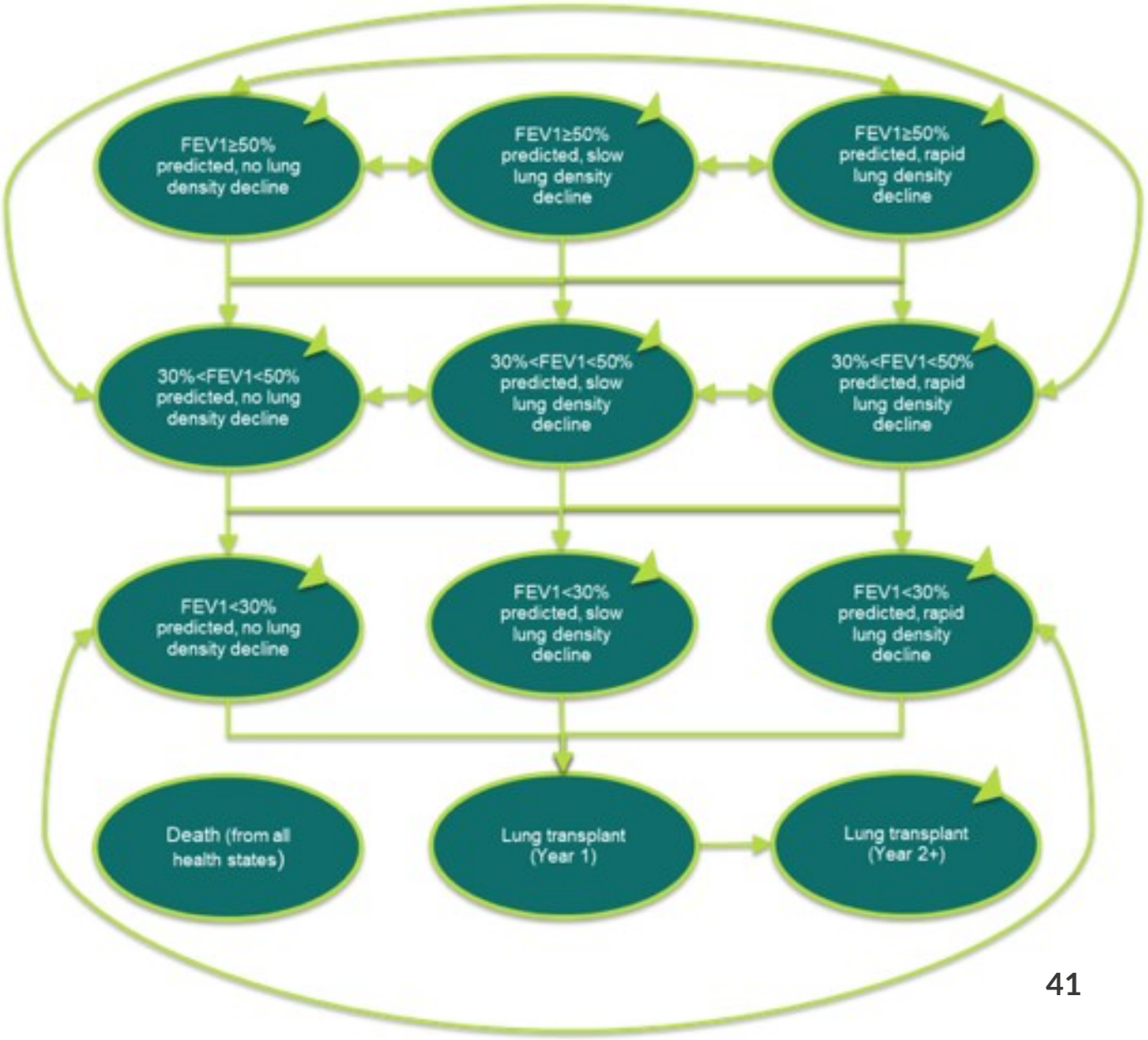
Economic model

Company model structure: State transition model

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

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

[redacted]



Economic model: population and start/stop criteria

Starting treatment

- All people in the model start in the FEV1% ≥50% (ND, SD and RD) and the FEV1% 30–50% (ND, SD and RD) states
  - Only people with FEV1% 35–70% were included in RAPID
- In the economic model treatment is started regardless of lung density decline
  - **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 economic 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
    - For some people with FEV1% <30% there will be no alternative treatment options, therefore, there would be a case to remain on treatment
    - There would be a case to continue Respreeza in people with FEV1% <30% waiting for a lung transplant

[redacted]

Economic model

ERG comment

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

- Evidence suggests that FEV1% and lung density are correlated
  - The correlation between these outcomes is not accounted for in the model
  - The predictive relationship between FEV1% and lung density is uncertain
- Due to limitations with the trial evidence, it was necessary to use alternative evidence to estimate transitions between FEV1% and lung density states separately
  - Related outcomes, FEV1% and lung density, are artificially separated
- There is no clinically established threshold for defining CT lung density decline
  - If the definition of rapid lung density decline used in the company's model were changed, there could be a considerable impact on the cost effectiveness
  - Company cited a study proposing an MCID of -2.89 g/L, indicating rapid density decline
- As a result of this, clinical outcomes in the model are uncertain and cannot be validated
- The company could have based the model on FEV1% alone
  - Costs, quality of life and mortality could all easily be linked to FEV1% states
- Densitometry is a superior measure to FEV in the assessment of emphysema but further research is needed to develop a model incorporating it
- Artificially separating FEV1% and lung density introduces a paramount degree of uncertainty

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 was used to model transitions
  - Respreeza: Treatment effect estimates from the updated FEV1% meta-analysis were used to calculate a relative risk, which was applied to the BSC transition probabilities
- Lung density decline transitions for Respreeza and BSC were estimated using data from RAPID and RAPID-OLE, adjusted for differences in baseline covariates
  - Linear regressions were fitted to different data points to obtain the proportion of patients in each health state and track their transitions between lung density states*
  - Patients with FEV1%<30% do not move between lung density decline states – lung density decline is assumed to remain the same on transitioning to these states
  - Baseline lung density decline in the FEV1% 30–50%, and FEV1%>50% categories was modelled using data from the placebo arm of RAPID (transitions from year 0 to year 1)

Transition probabilities

ERG comment

FEV1%

- The external data source used to estimate change in FEV1% for those on BSC was only available in abstract form so could not be fully assessed
  - Change in FEV1% is unlikely to be linear; the study assesses change using linear regression
  - Assuming the same probability of change in FEV1% regardless of FEV1% status is clinically implausible
- The company incorrectly selected treatment effectiveness estimates from the updated FEV1% meta-analysis when modelling FEV1% decline in the Respreeza arm
  - The treatment effect estimates from the meta-analysis correspond to the effect of slowing FEV1% decline within FEV1% categories, not transitioning between FEV1% thresholds

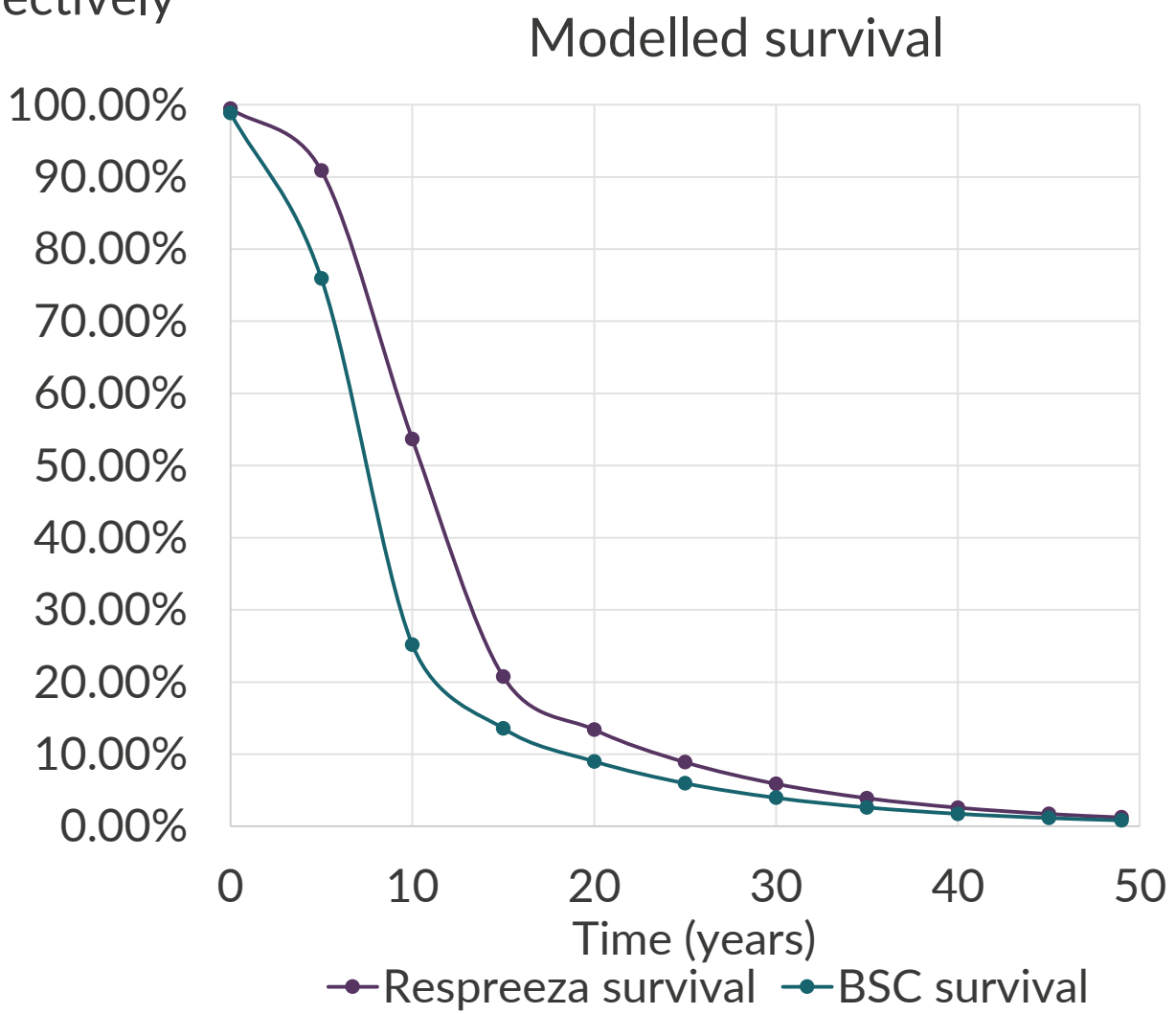
Lung density decline

- Imbalances in baseline lung density (46.6 g/L vs 49.8g/L) are significant in the context of the economic analysis where a 2/g/L/y decline is considered a rapid decline
  - Baseline lung density has been linked to mortality and FEV1%; could impact the ICER
  - Adjustments for imbalances in baseline characteristics excluded baseline lung density
- Baseline lung density decline was not captured in RAPID, it was estimated from post-baseline transitions in the placebo group
- Lung density decline in the FEV1% <30% and FEV1% 30–50% groups could have been modelled separately using data from people who progressed to FEV1% <30%
- Data used from RAPID-OLE includes people who crossed over to Respreeza, without adjustment

There is uncertainty in estimation of Respreeza treatment effectiveness

Mortality

- Mortality data taken from the RAPID study and RAPID-OLE were used to inform the first two and four annual cycles, respectively
- UK registry data, stratified by rate of FEV1% and lung density decline*, was used to model mortality for the remainder of the modelled time horizon
  - An assumption of equivalence in the mortality rates for FEV1% <30% and FEV1% 30–50% groups was made based on the available evidence
- In addition to the survival gain observed in RAPID, slower FEV1% and lung density decline for those treated with Respreeza leads to indirect survival gains



Mortality

ERG comment

- Using RAPID data to model mortality is inappropriate because:
  - There are very few mortality events (5)
  - Concerns around baseline imbalances between the trial arms
  - People in RAPID-OLE cross-over to Respreeza without adjustment
- The data shows that lung density decline is not statistically significantly associated with mortality, when data are analysed by FEV1% category
- When switching from RAPID to registry data, the 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
- The company's approach assumes that survival in RAPID and the registry is the same
  - Therefore no data adjustments when switching from RAPID survival curves to registry curves
  - However, survival data are not comparable (lower in RAPID)
- The company uses FEV1% 30-50% survival data from the registry to model survival for FEV1% 30–50% and FEV1% <30%, when separate survival data are available for both of these groups

Modelled overall survival is uncertain

- Because predicted mortality is linked to lung density decline, but the relationship between lung density decline by FEV1% group and mortality is not well established, OS modelling is uncertain
- Only using registry data to model survival would reduce uncertainty in the modelling of survival

Lung transplant

Eligibility of transplant

- All people with FEV1% <30% are eligible for a transplant, regardless of lung density decline
- There is an equal probability of receiving a lung transplant, regardless of how long people have been in the FEV1% <30% state; with an annual probability of 43.8%

Mortality

- Post-lung transplant survival estimates were taken from the NHS blood and transplant report (2017)
  - 1 year survival (82%) was used to estimate the probability of mortality after transplant in year 1 (16.47%)
  - 5 year survival (59%) was used to estimate survival in subsequent years (7.9%)

Post-lung transplant utility values

- Separate utility values are applied for the first year post transplant and subsequent years
- A weighted average of single and double lung transplants utility values from Anyanwu *et al.* 2001 was used:
  - First year post-lung transplant utility value: based on an average of the utility values from 0-6 months and 6 to 18 months
  - Subsequent year post-lung transplant utility value: based on an average of the utility values from 19 to 36 months and >36 months

Lung transplant
ERG comment

Eligibility of transplant

- The proportion of people eligible for lung transplantation within the FEV1% <30% state could have been further explored with clinical input
  - Everyone with FEV1% <30% is assumed to be eligible for LT
  - An age cap of for transplant of 65 years is explored

Mortality

- Post-lung transplant survival curves should have been included in the model
- The company unnecessarily manipulated the data to get the 16.47%, this should be 18%
- Expert advice suggested that mortality reporting is generally poor
  - Given that post lung transplant mortality is a key driver in the model, differences in these estimates have a substantial impact on the ICER
  - 1-year survival estimate used by the company (82%) is higher than that estimated from a UK cardiothoracic transplant audit (around 70%)
  - 5-year survival estimate used by the company (59%) is higher than the estimate of 50% obtained from clinical experts and the UK cardiothoracic transplant audit

Quality of life post-transplant

- Post-lung transplant utility values (0.76 year 1 and 0.77 year 2 +) are higher than in the FEV1% 30–50% and FEV1% <30% state; higher post-LT utilities favour BSC

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 Ejiofor and Stockley (2015) were used to estimate utility values

Health state utility values are based on FEV1% categories

- HRQoL is assumed to be driven by FEV1%, not lung density decline
  - [redacted]
  - According to another study FEV1% explains less than 50% of the variation in health status. Therefore, excluding lung density decline from HRQoL estimates is likely to provide a conservative estimate of the benefit of Respreeza
- Health state specific EQ-5D utility values, stratified by FEV1% predicted, were obtained from the UK registry
  - FEV1% categories in the study did not match the modelled health states so a weighted average was taken to derive the utility for the FEV1% 30–50% group

[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]

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 Ejiofor and Stockley (2015) were older and with increased limitation (higher SGRT), therefore, they may have worse quality of life
  - Modelled utility values could be an underestimate in the RAPID population

Omission of lung density decline

- [redacted]
  - [redacted]
- The company's decision to model health state utility values only on FEV1% is inconsistent with its overall rationale to incorporate lung density in the model
- An attempt could have been made to identify and incorporate lung density decline into the estimation of utility values

Application of age-related utility decrements

- The company's approach to account for age-adjusted utilities was done without justification, and potentially incorrect

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
Vial size	1000mg
Number of vials required per dose	4.55 (rounded up to 5)
Cost per administration	£1100
Annual treatment cost per patient assuming weekly infusion (excludes cost of administering the infusion)	£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]

Other costs

Disease management costs

- The cost of managing people with COPD was used as a proxy for AATD disease management
- Up to date resource costs were applied to resource use counts from an analysis of ~58.5k UK patients
- To better reflect the average rate of exacerbations from RAPID (between 1.4 and 1.7) disease management costs were weighted according to exacerbations (1, or 2 or more) in the external data source

Lung transplant costs

- Lung transplant costs are a sourced from an evaluation of UK patients (1999)
  - Costs are inflated to 2017
- A weighted average of single and double lung transplant costs is applied in the model

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

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

Costs

ERG comment

- The company excluded BSC costs in the model stating that they would cancel out
  - Different rates of lung transplant and survival across arms means that BSC costs are unlikely to be equivalent
  - As people treated with Respreeza live longer, the costs associated with Respreeza is underestimated in the model; the impact of adding BSC costs is minimal
- If CT scanning will be used, prescribing and monitoring costs should be included
  - The company suggest CT scanning won't be needed in practice – appears inconsistent with need for lung density-based economic model
  - Clinical experts differed: 1 considered CT scanning unnecessary, other would need CT scanning to monitor treatment response
  - A study suggested that CT scanning would be more reliable than spirometry for identifying progression requiring A1PI treatment; less at risk individuals are missed
- Receiving Respreeza at home could be difficult; scenario analysis 100% treated in clinic
- All people assessed for lung transplant eligibility should incur costs
- Treatment cost should have been modelled using the full weight distribution in RAPID
- The company's approach to costing exacerbations has a number of issues
  - The number of exacerbations does not match RAPID
  - Higher number of exacerbations in the Respreeza arm of RAPID are not costed

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

[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 outcomes, not correlating these parameters in PSA makes the PSA unreliable
  - Estimates of the correlation could have been taken from the literature or endpoints of RAPID could have been analysed

[redacted]

Company scenario analysis

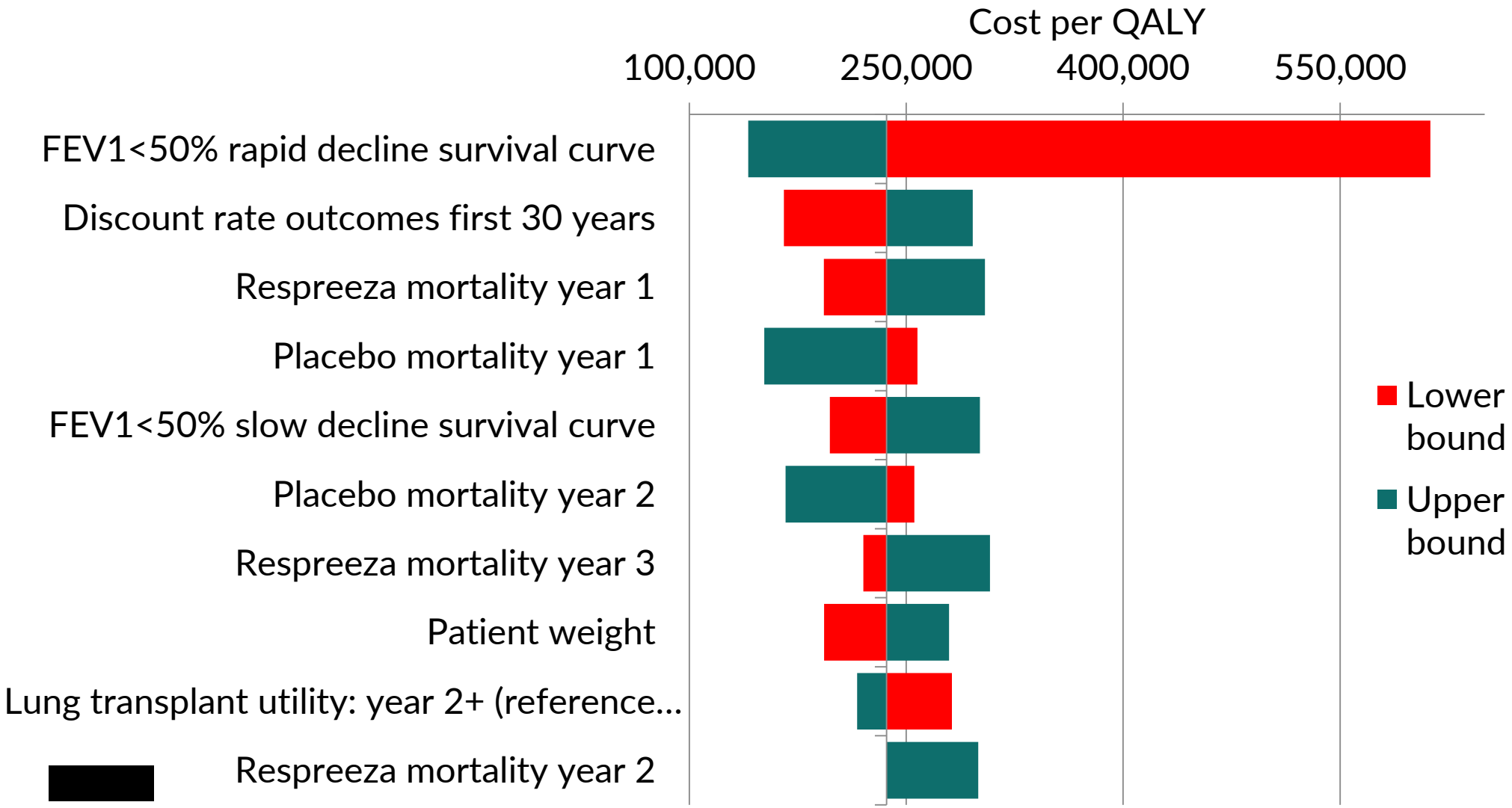
Scenario	Scenario info	ICER (£)
	Company base case	£236,409
1	Discount rate: 1.5% applied to benefits and 3.5% applied to costs	£189,946
2	Mortality data: UK registry survival curves only	£280,942
3	Care giver disutility: 5% QoL reduction in FEV1% >50% health state and post-LT states 10% QoL reduction 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

[redacted]

Company sensitivity analysis

Deterministic

Vary parameters according to their confidence intervals or by 20%



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 48)*	£359,741	1.51	£237,822
1	Using different results from the updated meta-analysis to calculate transition probabilities *(slide 45)*	£383,821	1.21	£317,053
2	Using the UK registry survival data to model mortality *(slide 47)*	£321,815	0.34	£940,871
3	Removing stopping rule for treatment with Respreeza *Receive Respreeza until LT or death (slide 42)*	£419,545	1.51	£277,359
4	Applying an age cap for lung transplant (65 years) *(slide 49)*	£359,308	1.50	£240,298
5	Reducing the population eligible for lung transplant by 30% *(slide 49)*	£360,236	1.57	£230,196
6	Using alternative survival estimates for lung transplant *(slide 49)*	£358,766	1.43	£250,584
7	100% of drug administrations at a clinic *(slide 55)*	£366,723	1.51	£242,438

ERG exploratory analysis

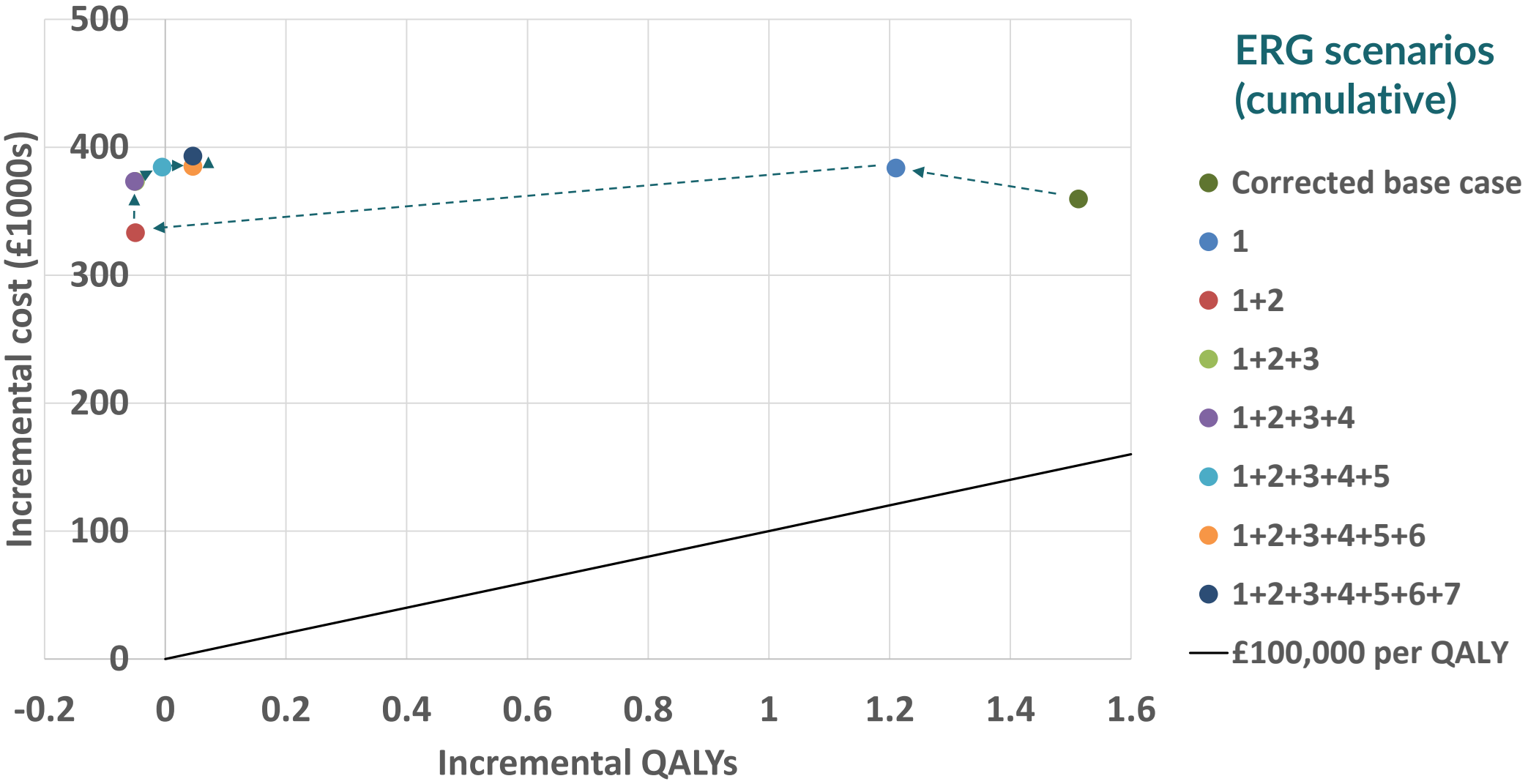
Impact of ERG changes on corrected company base-case

- 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

ERG exploratory analysis

Cost-effectiveness plane (cumulative ERG scenarios)



[redacted]

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 to be eligible 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 (discount rate)
Company base case	2.27	1.52 (3.5%)
Company scenario (6) with highest QALY gains: *Amending costs and utilities in lung density states (slide 58)*	2.51	1.73 (3.5%)
ERG exploratory analysis including all changes	-0.03	0.05 (3.5%)
ERG scenario (5) with the highest QALY gains: *Reducing the population eligible for lung transplant by 30%*	2.33	1.57 (3.5%)

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

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

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 participate in social events

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 and sick days in people with COPD ranged from €11.5k-€19k pppy and 24.2-30.8 pppy respectively

[redacted]

Service design and delivery

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

- There is no national commissioning of specialist assessment services for AATD
- National specialised centres would need to be established to increase capacity to be able to see patients more regularly
  - There are existing specialised centres through the NIHR network but funding and recognition of the service would need to be approved
  - Community network services would be needed to support clinics to assess patient suitability and whether they could self administer treatment or need to attend a national centre
- Centres may not have the equipment needed
  - CT scanning analysis equipment and intravenous 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

Key issues for consideration

Clinical effectiveness

- 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 in clinical practice?
  - 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 (FEV1%, lung density) and other outcomes (such as mortality and pulmonary exacerbations)?
- Who would be considered eligible (and ineligible) to receive a lung transplant?
- 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?

[redacted]

Key issues for consideration

Cost-effectiveness

- 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?
- 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?

[redacted]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Specification for company submission of evidence

May 2018

File name	Version	Contains confidential information	Date
Respreeza NICE HST vFINAL - Revised ACIC [ACIC] Redacted 9July2018	**Final**	**Yes**	**9th July 2018**

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List of abbreviations

Term	Definition
A1PI	Alpha1-proteinase inhibitor
AATD	Alpha-1 antitrypsin deficiency
ADAPT	Antitrypsin Deficiency Assessment and Programme for Treatment
AE	Adverse event
AWMSG	All Wales Medicines Strategy
BSC	Best Supportive Care
COPD	Chronic Obstructive Pulmonary Disease
CT	Computerised Tomography
DL_{CO}	Diffusing capacity for carbon monoxide
EMA	European Medicines Agency
FDI	Foreign Direct Investments
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
HRCT	High resolution computed tomography
HRQoL	Health Related Quality of Life
HRU	Healthcare Resource Utilization
ISWT	Incremental shuttle walk test
ITT	Intention to treat
LABA	Long-Acting Beta2 Agonist
LAMA	Long-Acting Muscarinic Antagonist
LSIO	Life Sciences Investment Organisation
mTLV	Measured total lung volume
NCPE	National Centre for Pharmaco Economics
NE	Neutrophil Elastase
NHS	National Health Service
NIHR	National Institute for Health Research
OLE	Open- label extension
PD15	15^{th} percentile
PFT	Pulmonary function test
PSS	Personal social services
PSSAG	Pescribed Specialised Services Advisory Group
QALY	Quality-adjusted life year
RCT	Randomised Control Trial
SGRQ	St George's Respiratory Questionnaire
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
SQRQ	St. George 's Respiratory Questionnaire
TEAE	Treatment-emergent adverse event
TLC	Total lung capacity
TLV	Total lung volume
UKTI	UK Trade & Investment

Executive Summary

Respreeza® is human alpha1-proteinase inhibitor (A1PI), which is a natural component of the blood that functions to protect the lung tissue from damage by protease enzymes. It is obtained from human blood and works by augmenting the protein that is lacking in patients with A1PI deficiency.

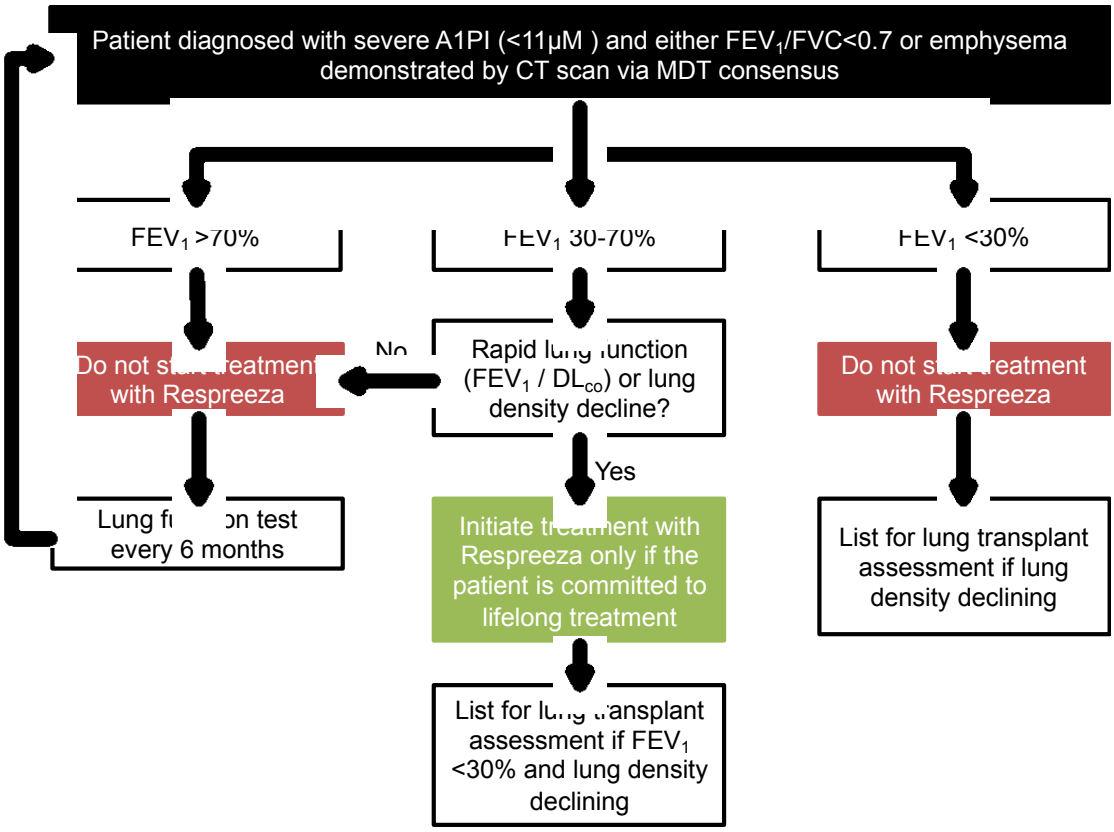
Human A1PI is the primary anti-protease in the lower respiratory tract, where it inhibits neutrophil elastase (NE). Normal healthy individuals produce sufficient A1PI to control the NE and are thus able to prevent inappropriate protein breakdown of lung tissue by NE. However, individuals deficient in endogenous A1PI are unable to maintain appropriate anti-protease defence and experience more rapid protein breakdown of the alveolar walls. This leads to the development of emphysema in patients with severe A1PI deficiency.

Respreeza was granted marketing authorisation by the EMA on 20th August 2015. Respreeza is indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe A1PI deficiency (e.g. genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show continued evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV_1) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency.

Respreeza is available as a 1,000 mg powder and solvent for solution for infusion. It is administered in weekly infusions of 60 mg/kg that will take approximately 15 minutes to infuse. At an average body weight of 75.9kg, this would equate to needing 4.55 vials per week, totalling £57,200 per year when rounding up to the nearest vial. The SPC indicates that initial infusions should be administered under the supervision of a healthcare professional experienced in the treatment of A1PI deficiency, but subsequent infusions can be administered by a caregiver or by the patient.

In light of the patient population in which Respreeza has been studied, it is proposed that Respreeza is used in a subset of patients with severe A1PI deficiency (<11μM), as illustrated in Figure 1. Flowchart illustrating proposed treatment initiation criteria for Respreeza. Patients would only be started on treatment if they have an FEV_1 between 30% and 70% and rapid lung function/density decline and if they are committed to lifelong treatment. Treatment would be ceased if a patient has a lung transplant.

Figure 1. Flowchart illustrating proposed treatment initiation criteria for Respreeza



Nature of the condition

A1PI deficiency is a rare, genetic disorder with low serum levels of the A1PI protein and is the commonest hereditary cause for emphysema. A1PI is found in all body tissues but appears to have primary physiological importance in the lungs, protecting alveolar tissue from proteolytic damage. The deficiency of A1PI predisposes an individual to several illnesses, such as liver and skin disease, and most commonly manifests as emphysema, one of several respiratory diseases known collectively as chronic obstructive pulmonary disease (COPD). In people with emphysema, the lung tissue involved in exchange of gases (oxygen and carbon dioxide) is damaged. Severe A1PI deficiency is a devastating disorder that profoundly impacts patients' quality of life, daily activities and their ability to work and function (Manca et al., 2013, Kaplan and Ries, 2008). Patients have a considerably reduced life expectancy, with studies estimating a life expectancy of 54 to 59 years (Lara and Miravitlles, 2015, National Institute for Health Research, 2014).

Emphysema due to severe A1PI deficiency presents most commonly with shortness of breath and causes progressive difficulty in breathing and a hacking cough (short, dry, frequent cough) (Genetics Home Reference, 2018). Symptoms of shortness of breath and wheezing typically appear at 20-40 years of age. Repeated exacerbations lead to an accelerating decline of lung function, that is associated with reduced quality of life and ability to work and function (Barros-Tizon et al., 2012). Patients experience

severe, suffocating breathlessness in the last years of life, causing a very high burden of disease (Tanash et al., 2010a, Seersholm et al., 1994, Lara and Miravitlles, 2015).

An online survey of A1PI deficiency patients (n=93) and carers (n=69) indicated that A1PI deficiency is a major burden for patients, and for their families and carers (Alpha-1 Alliance, 2013). Many patients felt distressed about losing their independence and becoming a burden for their families, often at a young age, and at a time when they are trying to bring up a family. They also felt anxious about their future and that of their families. Several respondents also reported that the disease affected their social well-being and mental health. Many respondents highlighted the inability to be active and mobile as a result of shortness of breath. As the condition progressed, respondents reported a significant impact on their ability to live a normal and fulfilled life. Many struggled to perform normal everyday activities.

As it becomes difficult for patients to participate in social activities, the burden of care falls on the family which will require further services to maintain a reasonable quality of life for the patient. In order for the family to provide assistance they either have to reduce their hours or stop working due to their caregiving responsibilities, which leads to high indirect and intangible costs (Karl et al., 2017).

The clinical symptoms of A1PI deficiency overlap with asthma and other more common respiratory disorders, and in the absence of specific screening for A1PI deficiency the disorder is often misdiagnosed until the disease has progressed significantly. The delay between onset of first symptoms of A1PI deficiency and receiving a correct diagnosis can be between 6-7 years, contributing to more irreversible lung damage (Rahaghi et al., 2012, McElvaney et al., 1997).

Current treatment consists largely of inhaled therapy with combinations of bronchodilators and corticosteroids to treat the symptoms of COPD as a result of A1PI deficiency. These have limited short-term benefits but do not treat the underlying cause of the condition. In the later stages of the condition, patients usually require oxygen therapy, which imposes further limits on daily activities. End-stage disease may be treated by lung transplantation and/or lung volume reduction surgery, although finding a suitable donor may not always be possible. Respreeza may act to prolong the time to or obviate the need for lung transplant. Therefore, lung transplant and/or reduction surgery should be considered as downstream options within the treatment pathway as opposed to a standalone frontline comparator.

Impact of the new technology

Respreeza has been evaluated in the world's largest randomised, placebo-controlled trial in severe A1PI deficiency (RAPID study) including 180 patients with 2-year follow-up and a subsequent 2-year extension phase. The primary endpoint of this Phase III study was a reduction in computed tomography (CT) measured lung density decline as a validated measure of emphysema. There is consistent evidence demonstrating that CT-measured lung density decline is the most sensitive and appropriate indicator

of disease progression in A1PI deficiency (Chapman et al., 2015, Dirksen et al., 1999, Dowson et al., 2001a, Bakker et al., 2005, Dirksen et al., 2009, Stockley et al., 2010).

The RAPID trial results showed a statistically significant 34% reduction in the annual rate of decline in CT-measured lung density at total lung capacity versus placebo (1.45 versus 2.19 grams/litre/year [g/L/y]; p=0.03). Furthermore, the RAPID extension study showed a 36% reduction in the annual rate of lung density loss when patients were switched from placebo to Respreeza (2.06 versus 1.31 g/L/y; p=0.021).

Thus, Respreeza reduces irreversible loss of lung tissue and therefore modifies the course of the disease, which also provides the potential to prolong the time to or obviate the need for lung transplant. In addition, Respreeza has a well-established safety profile and tolerability similar to placebo. Regarding AEs observed in the RAPID and open-label extension (OLE) trials, headache was the most common TEAE, affecting 37 Respreeza patients and 33 placebo patients, respectively, but with a lower number of events in the Respreeza arm (98 and 105, respectively). Additionally, there were more (≥10) bronchitis, respiratory disorders, nausea and condition aggravated events in the Respreeza group than the placebo group.

A Cox regression analysis of UK registry data has demonstrated that baseline density (p=0.002) and rapid CT density decline (p=0.026) were significantly associated with death, whilst patients whose lung density declined slowly showed a similar trend compared to those not declining (p=0.065) (Green et al., 2014a). An accelerating decline of lung function was also associated with repeated exacerbations in patients as measured by vital capacity and DL_{CO}, in a1-AT deficiency (Barros-Tizon et al., 2012). Exacerbations are a major cause of morbidity and mortality in general COPD (Dirksen et al., 2009). As Respreeza was shown to reduce lung density decline in RAPID, health economic modelling estimates that this will translate into a survival gain of 3 years, equating to a 33% increase in survival compared to best supportive care (BSC).

RAPID was not powered to detect significant between-group differences in other endpoints. However, patients treated with Respreeza had improvements in the St George's Respiratory Questionnaire (SGRQ) symptoms score at 24 months compared with baseline, whereas scores for placebo patients worsened (change from baseline of -1.4 and 2.0, respectively; the difference did not reach statistical significance).

A meta-analysis of RAPID and the only other two placebo-controlled randomised controlled trials in severe A1PI deficiency found comparable results to the RAPID study. The two RCTs tested A1PI augmentation therapy, with initial results revealing that analysis of CT scans showed a trend toward a favorable effect of protease inhibitor treatment, suggesting some protection against loss of lung tissue. Additional results showed that in patients with A1PI deficiency, CT is a more sensitive outcome measure of emphysema modifying therapy than physiology and health status, and demonstrates a trend of treatment benefit from A1PI augmentation therapy. In the meta-analysis of RAPID, A1PI was associated with a significant reduced decline in lung density of 0.79 g/L/year compared with placebo. No significant differences were observed with

treatment in terms of forced expiratory volume in one second (FEV_1), diffusing capacity of the lungs for carbon monoxide (DL_{CO}) or quality of life (measured by the SGRQ) (Edgar et al., 2017).

However, a meta-analysis of 1509 patients from 5 clinical trials found that A1PI was associated with a 26% reduction per year in the rate of FEV_1 decline in patients with FEV_1 30-65% predicted (Chapman et al., 2009). Four of these trials were non-randomised, with three being a1-Antitrypsin Augmentation Therapy vs. no augmentration; the fourth one established results before vs. after commencement of the a1-Antitrypsin Augmentation Therapy dose given weekly. The fifth trial was a randomised control trial comparing 250 mg/kg α1-AT every 4 weeks for ≥ 3 years vs. 625 mg/kg albumin. According to the 26% reduction, it is expected that administration of A1PI will have a significant effect of on FEV_1, but this can only be observed over long periods of time or in very large patient numbers. It is challenging to use FEV_1 as an outcome in clinical trials because it measures the obstruction of airways and not parenchymal tissue loss which is the first to be affected by neutrophil elastase, and the large sample sizes required to observe statistically meaningful improvement in treated versus untreated patients are prohibitive in this rare disorder (Stockley et al., 2010). Similarly, it is challenging to detect reduction in mortality in controlled clinical trials due to low patient numbers reaching terminal respiratory failure or death (Chapman et al., 2009).

Subgroup analysis of patients in the pivotal study using primary and key secondary outcomes has not suggested that there is a group of patients in which the treatment provides greater clinical benefits.

Value for money

A de novo economic model was developed to evaluate the cost-utility of Respreeza (in conjunction with BSC) to BSC alone in the treatment of patients with empysema due to A1P1 deficiency. The analysis was undertaken using a National Health Service (NHS) and personal social services (PSS) perspective using a lifetime time horizon. Outcomes were reported in terms of costs, life years and quality adjusted life years (QALYs). Outcomes were discounted using annual rates of 3.5% in line with the NICE reference case. A scenario explores the use of a 1.5% discount rate for QALYs and a 3.5% discount rate for costs, in line with the recent recommendations in the HM Treasury Green Book.

The model adopted a Semi-Markov structure consisting of eight health states that considered six states of lung density decline stratified by FEV_1 % predicted status, lung transplantation and death. The model was primarily informed by the RAPID study, observations from a UK registry of patients with A1P1 deficiency and supplemented by secondary sources where necessary.

Patients with A1P1 deficiency treated with Respreeza plus BSC and BSC alone were expected to have life expectancies of 10 years and 7 years, respectively, from the baseline age of 51 years. On a per patient basis, the amount of QALYs accrued over

these expected lifetimes are 5.98 and 4.67 QALYs respectively (Section 12.5). Treatment with Respreeza plus BSC therefore offers patients an additional 1.31 years of perfect heath compared to treatment with BSC alone.

Treatment with Respreeza plus BSC and BSC alone resulted in predicted additional costs of £486,950 and £39,001 respectively being incurred by the UK NHS over a patient's lifetime. Hence, treatment with Respreeza corresponds to an incremental per-patient cost of £447,949. The Incremental Cost-Effectiveness Ratio (ICER) is therefore £342,872 per QALY gained. The ICER is reduced to £283,875 per QALY gained if outcomes are discounted to a rate of 1.5%.

One-way and multi-way sensitivity analyses show that the most important parameters affecting the model outcomes is the discount rate applied to health benefits. The ICER is reduced to below £300,000 per QALY gained if either the mortality rate associated with Respreeza was reduced or if BSC increased in the first cycles of the model, and also if average dose and therefore cost of Respreeza was reduced (Sections 12.5.11 to 12.5.14). In the absence of data, caregiver disutility was explored using assumed utility decrements associated with disease progression, however, this had a minimal impact on the overall conclusion.

There are an estimated 549 patients with severe A1P1 deficiency in England whom could benefit from treatment with Respreeza, with 95 incident patients per year. As Respreeza is given in addition to BSC, it was assumed that BSC would not be displaced on the introduction of Respreeza. If uptake of Respreeza was 50% in year one for those starting treatment, the total budget impact at year one would be £2,779,196. If uptake rose to 70% at year two and 90% for years thereafter, the total budget impact would rise to £20,270,814 at year five. This is calculated based on 48 patients treated in year one, rising to 353 patients in year five. The budget impact remains under £20,000,000 in the first three years in the base case budget impact analysis.

Impact of the technology beyond direct health benefits

A substantial portion of the costs (savings) and benefits that will result from treatment with Respreeza are incurred outside of the NHS and personal social services. Due to the severity and chronic nature of emphysema caused by A1PI deficiency, the disease can have a highly significant economic impact on patients, their families, the healthcare service and wider society. As the patients diagnosed are in their third or fourth decade (Greene et al., 2008), an age during which full economic activity is high, they are at risk of not being able to perform at work with the immediate burden falling primarily on their family.

In an online survey of 152 respondents by the Alpha-1-Alliance (Alpha-1 Alliance, 2013), results showed that many respondents were unable to be active and mobile as a result of shortness of breath, and as the condition progresses, there is a significant impact on their ability to live a normal and fulfilled life with difficulties in performing normal everyday activities as they gradually lose independence and cannot maintain

their work (Alpha-1 Alliance, 2013). This inability to maintain employed work has a drastic impact on economic costs and so does the fact that family members will have to either reduced their hours or had stop working because of their caregiving responsibilities.

Patients with A1PI deficiency tend to retire early and have to adjust to physically less demanding jobs. Reducing patients' lung density decline will keep them in a better state of health to enable them to retain full time employment. Patients are typically diagnosed with A1PI deficiency in their thirties and forties, which is generally the peak of a person's career and therefore the age associated with highest pay. An improved health state can be translated to fewer exacerbations and healthcare appointments, reducing the burden on health services, patients and carers.

The SPC indicates that initial infusions should be administered under the supervision of a healthcare professional experienced in the treatment of A1PI deficiency, but subsequent infusions can be administered by a caregiver or by the patient. The value for money analysis assumed that 25% of administration will continue within the specialist setting. The resource implications of alternative approaches for delivery, including homecare administration are presented to inform future discussions with NHS England regarding any commercial agreement. Respreeza will be initiated within the current context of care, by specialists experienced in the management of A1PI deficiency at existing facilities.

Respreeza has shown a statistically significant reduction in the annual rate of decline in CT-measured lung density at total lung capacity versus placebo (34% reduction; p=0.03), which continued in the 2-year extension study. Treatment with Respreeza plus BSC therefore offers patients an additional 1.31 years of perfect health (QALYs) compared to treatment with BSC alone. Respreeza addresses an important unmet public health need, providing the only proven disease-modifying agent that reduces the progression of emphysema due to A1PI deficiency, which is associated with significant morbidity and mortality.

Section A – Decision problem

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table 1. Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	Adults with severe alpha 1-proteinase inhibitor deficiency who have progressive lung disease.	As per scope.Adults with severe alpha1-proteinase inhibitor deficiency (A1PI deficiency, also known as alpha-1 antitrypsin deficiency, AATD) who have progressive lung disease. In clinical practice, the population is defined as: patients with a serum A1PI level < 11 µmol/L. This is typically patients with genotypes PiZZ, PiZ(null) and Pi(null,null). Some patients with genotype PiSZ have severe disease and more than 150 rare variants have been described. Evidence of progressive lung disease can be a lower forced expiratory volume per second (FEV_1) % predicted or DL_{CO} % predicted, impaired walking capacity or increased number of exacerbations as evaluated by a healthcare professional experienced in the treatment of A1PI inhibitor deficiency.	N/A - equivalent

Intervention	Human alpha 1-proteinase inhibitor in addition to established clinical management.	A1PI (Respreeza) in addition to best supportive care (BSC).	N/A - equivalent
Comparator(s)	Established clinical management without alpha 1-proteinase inhibitor, which may include but is not restricted to: • short-acting bronchodilators • long-acting beta2 agonists (LABA) • long-acting muscarinic antagonists (LAMA) • inhaled corticosteroids • oral therapy with slow-release theophylline or a • mucolytic • pulmonary rehabilitation • oxygen therapy • lung transplantation • lung volume reduction	Established clinical management without A1PI as listed in the scope is clinically equivalent to best supportive care (BSC) and so should not be listed as standalone comparators. Most patients with A1PI deficiency will receive a combination of corticosteroids, oxygen therapy and/or bronchodilators to treat the symptoms, which have short-term benefits but do not address the underlying problem of the deficient protein. The placebo arm of the pivotal study is representative of patients receiving BSC. End-stage disease may be treated by lung transplantation and/or lung volume reduction surgery. Respreeza may act to prolong the time to or obviate the need for lung transplant. Therefore, lung transplant and/or reduction surgery should be considered as downstream options within the treatment pathway as opposed to a standalone frontline comparator.	Agreed with NICE and ERG on decision problem meeting call.
Outcomes	The outcome measures to be considered include: • incidence, duration and severity of acute • exacerbations, including hospitalisation • change in lung density • lung function • symptom control (e.g. shortness of breath) • exercise capacity • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)	As per scope. However, it is not feasible to conduct a clinical trial powered to observe statistically meaningful changes in either mortality or health related quality of life in such a rare condition. Such a study would require a larger number of patients than could feasibly be recruited and would have to be conducted over many years to detect significant treatment effects. Therefore, outcomes such as mortality and health-related quality of life will not be based on trial outcomes but derived indirectly using published data.	N/A
Subgroups to be considered	If evidence allows, consideration may be given to subgroups based on the	None.	Subgroup analysis of patients in the pivotal

	characteristics and progression of the disease (including for example, speed of decline, distribution of disease, and frequency of exacerbations)		study using primary and key secondary outcomes has not suggested that there is a group of patients in which the treatment provides greater clinical benefits.
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options	As per scope.	N/A
Impact of the new technology	Listed as 'Clinical Effectiveness' in the final scope • overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)	As per scope.	N/A
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	As per scope.	N/A
Impact of the technology beyond direct health benefits, and on the	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred	As per scope. By delaying the loss of lung density and function, Respreeza is anticipated to prolong patient independence	N/A

delivery of the specialised service	outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise	as well as prolonging the time to or obviating the need for lung transplant. Respreeza will be initiated within the current context of care, by specialists experienced in the management of A1PI deficiency at existing facilities. Home administration is likely. Although Respreeza is expected to reduce caregiver burden, there was limited evidence available to quantify the impact of this and also the costs to patients or costs to society outside of healthcare/PSS.	
Special considerations, including issues related to equality	Listed as 'Other considerations' in the final scope • Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements	A positive review of Respreeza will enable equity of access to licensed treatment for a minority group with a rare genetic disease.	N/A

6MWT=6 minute walk test; ECG=electrocardiography; echo=echocardiography; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; MEP=maximum expiratory pressure; MIP=maximum inspiratory pressure; MVICT=maximum isometric voluntary contraction testing; NHS=national Health Service; PSS=Personal Social Services.

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Respreeza®

Approved name: Human alpha1-proteinase inhibitor

Therapeutic Class: B02AB02 (WHO ATC Code)

2.2 What is the principal mechanism of action of the technology?

The active substance in Respreeza, human A1PI, is a natural component of the blood that functions to protect the lung tissue from damage by protease enzymes. It is obtained from human blood and works by augmenting the protein that is lacking in patients with severe A1PI deficiency (see section 6.1), similar to enzyme replacement therapies in other conditions.

Human A1PI is understood to be the primary anti-protease in the lower respiratory tract, where it inhibits neutrophil elastase (NE). Normal healthy individuals produce sufficient A1PI to control the NE produced by activated neutrophils and are thus able to prevent inappropriate proteolysis (destruction) of parenchymal lung tissue by NE. However, individuals deficient in endogenous A1PI are unable to maintain appropriate anti-protease defence and experience more rapid proteolysis of the alveolar walls starting prior to the development of clinically evident chronic obstructive lung disease in the third or fourth decade (Greene et al., 2008).

2.3 Please complete the table below.

Table 2. Dosing Information of technology being evaluated

Pharmaceutical formulation	1,000 mg powder and solvent for solution for infusion
Method of administration	In homecare or near home setting with self-administration possible
Doses	60 mg/kg body weight administered once weekly
Dosing frequency	Once weekly
Average length of a course of treatment	Not applicable (long-term chronic therapy)
Anticipated average interval between courses of treatments	Not applicable (long-term chronic therapy)
Anticipated number of repeat courses of treatments	Not applicable (long-term chronic therapy)
Dose adjustments	No dose adjustments are recommended in the Summary of Product Characteristics.

Source: (Medicines.org.uk, 2018a)

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Respreeza was granted marketing authorisation by the EMA on 20th August 2015 (marketing authorisation number: EU/1/15/1006/001). Respreeza is indicated 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). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV_1) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency (Medicines.org.uk, 2018a).

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Respreeza is available based on a maximum NHS list price, which was agreed with the Department of Health and Social Care in 2016 (NHS Business Authority, 2018).

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Respreeza was granted marketing authorisation by the EMA on 20th August 2015. Respreeza is licensed in the United States with marketing authorisation granted in July 2003 under the brand name Zemaira, and therefore has been used in the US for 15 years (CenterWatch, 2018). Additionally Respreeza has been approved in multiple countries globally such as Switzerland, Canada, Brazil, Mexico and Australia. CSL Behring is working with US registries to acquire data on long term use of augmentation therapy, which will be made available to NICE. See section 5.1 regarding availability of other (unlicensed in the UK) forms of A1PI in Europe.

3.4 If the technology has been launched in the UK provide information on the use in England.

Respreeza has been used in England off label for patients with panniculitis, a skin condition associated with A1PI deficiency. NICE appraisal and commissioning by NHS England has been delayed since Sept 2015 to allow for PSSAG to designate A1PI deficiency as a highly specialised service. See section 8.6 for more detail.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months

There are no ongoing studies for Respreeza.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

There are no current or planned assessments in the UK.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

A negative outcome based on this evaluation could lead to an adverse impact on people with A1PI deficiency, which is a disabling and life-limiting genetic condition.

5.2 How will the submission address these issues and any equality issues raised in the scope?

A1PI deficiency is a rare disease leading to a lower quality of life and a shorter life expectancy. Respreeza is the first licensed therapy that treats the underlying disease (i.e. by augmenting the missing A1P1) rather than the symptoms of A1PI deficiency.

Other (unlicensed in the UK) forms of A1PI are available in Europe, called Prolastin® (Grifols), and Alfalastin® (LFB). Although manufacturing processes differ, all augmentation therapy is based on raising the A1PI serum concentrations.

If Respreeza is not approved for use in England, this may disadvantage people with A1PI deficiency and limit their chance to live a longer, healthier life. Respreeza is anticipated to prolong patient independence and reduce caregiver burden. It has been shown that patients who receive Respreeza have a decreased decline in lung density, allowing them to prolong the time to or obviate the need for lung transplant. Respreeza will be initiated within the current context of care, by specialists experienced in the management of A1PI deficiency at existing facilities. Home administration is likely. A positive review of Respreeza will enable equity of access to licensed treatment for a minority group with a rare genetic disease, who can already access treatment in the majority of European nations.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Alpha-1 proteinase inhibitor (A1PI) deficiency (also known as alpha-1 antitrypsin deficiency, AATD) is a rare, genetic disorder resulting in low serum levels of the A1PI protein and is the most common hereditary cause for emphysema. A1PI is found in all body tissues, but appears to have primary physiologic significance in the lungs, protecting alveolar tissue from damage caused by proteolytic enzymes (Fregonese and Stolk, 2008). The deficiency of A1PI most commonly manifests as emphysema, a component of chronic obstructive pulmonary disease (COPD), and also predisposes an individual to other illnesses such as liver and skin disease, (Stoller and Aboussouan, 2012, Greene et al., 2008). In people with emphysema, the lung tissue involved in exchange of gases (oxygen and carbon dioxide) is damaged. Natural history studies of severe A1PI deficiency have indicated that it is a devastating disorder leading to a considerably reduced life expectancy, and that emphysema and liver disease are the most common causes of death (Larsson, 1978, Tanash et al., 2010a).

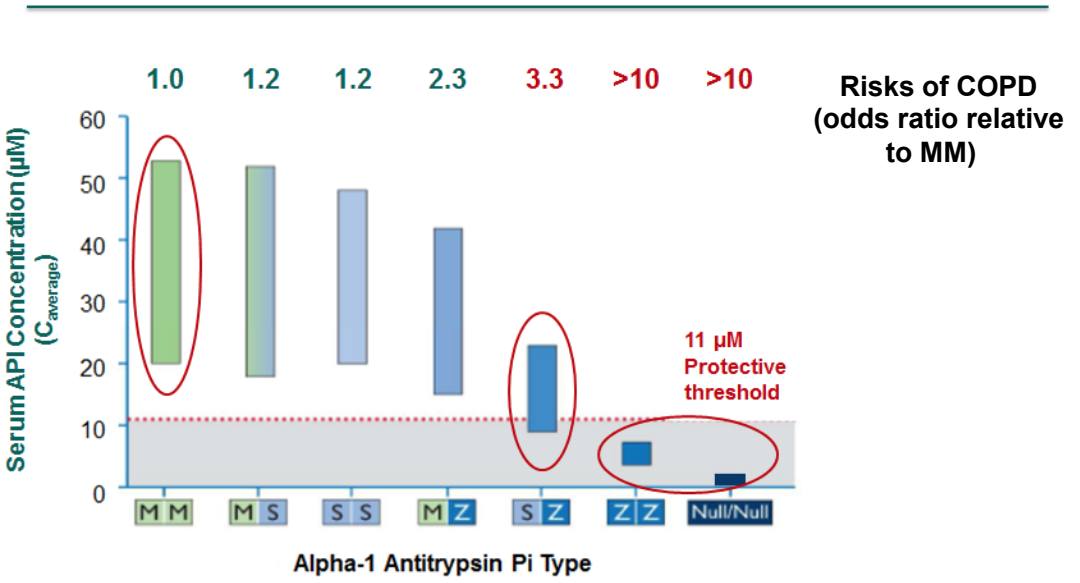
Pathophysiology

In most A1PI deficiency patients, there is a reduced production of A1PI, which leads to progressive degradation of parenchymal lung tissue. In a limited sub-group of patients liver disease may manifest, as an abnormal form of A1PI is produced in the liver which is not secreted into the serum, resulting in apoptosis/necrosis and high juvenile mortality rates (McNab et al., 2012). The main function of A1PI (as outlined in section 2.2) circulating in the bloodstream is to protect body tissue from damage by enzymes, particularly neutrophil elastase, an enzyme that can attack lung elastin and compromise bronchial and alveolar wall integrity (Janciauskiene et al., 2011).

- More than 150 rare functional and defective genetic variants of PiM, the normal gene for A1PI, have been identified. The two most frequent deficient alleles are PiZ (which expresses approximately 10–20%) and PiS (which expresses approximately 50–60% of A1PI) (de Serres et al., 2003).
- Severe A1PI deficiency (A1PI level < 11 μM) includes subjects homozygous or heterozygous for the Z-allele (Russi, 2008), with 95% of clinically affected A1PI deficient individuals having the PiZZ genotype (Stocks et al., 2006).

- The risk of developing emphysema is dependent upon reduced A1PI serum concentrations and not the genotype which results in these reductions. Exclusion by genotype is not supported as it would unfairly exclude A1PI patients with rare genotypes that are not explicitly listed or as of yet undiscovered. The relationship between more common genotypes, resulting serum concentrations and the relative risk to develop emphysema is depicted in Figure 2.

Figure 2. Relative risk to develop emphysema based on A1PI serum levels per genotype



Symptoms

Emphysema due to severe A1PI deficiency presents most commonly with shortness of breath and causes progressive difficulty in breathing and a hacking cough (short, dry, frequent cough) (Genetics Home Reference, 2018). Symptoms of shortness of breath and wheezing typically appear at 20-40 years of age.

Repeated exacerbations lead to an accelerating decline of lung function, which is associated with reduced quality of life and a reduced ability to work and function (Barros-Tizon et al., 2012). Patients experience severe, suffocating breathlessness in the last years of life, causing a very high burden of disease (Tanash et al., 2010a, Seersholm et al., 1994, Lara and Miravitlles, 2015).

Current treatment consists largely of inhaled therapy with combinations of bronchodilators and corticosteroids to treat the symptoms of emphysema as a result of A1PI deficiency. These have limited short-term benefits but do not treat the underlying cause of the disease. In the later stages of the condition, patients usually require oxygen therapy, which imposes further limits on daily activities. Lung transplantation may be needed, but availability of lungs is limited and outcomes are variable although quality of life and lung function improves in survivors (Stoller and Aboussouan, 2012).

Diagnosis

Severe A1PI deficiency is defined as patients with an A1PI level below the "protective" threshold of 11 μM (American Thoracic Society/European Respiratory Society, 2003). Progressive lung disease can be defined as patients with a more rapidly declining lung function (commonly measured by FEV_1, FEV_1 % of predicted, DL_{CO} or DL_{CO} %) or declining lung density (measured by CT scan) compared to aging alone.

In earlier and less severe states of the disease, the clinical symptoms of A1PI deficiency overlap with asthma and other more common respiratory disorders, and in the absence of specific screening for A1PI deficiency the disorder is often misdiagnosed until the disease has progressed significantly. The delay between onset of first symptoms of A1PI deficiency and receiving a correct diagnosis can be between 6-7 years, contributing to more irreversible lung damage (Rahaghi et al., 2012, McElvaney et al., 1997).

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

Between 1 in 1600 and 1 in 5000 new born babies have A1PI deficiency, but not all will develop emphysema (NIHR Horizon Scanning Centre, 2014). Based on a disease registry in the West Midlands, it is estimated that 670 people in England have emphysema caused by A1PI deficiency (Miravitlles et al., 2010). About 540 of these people (80%) will have clinically significant and progressive emphysema that requires treatment, yielding an estimated prevalence rate of 1:123,284 UK residents (NIHR Horizon Scanning Centre, 2014).

Similar incidence rates of symptomatic A1PI patients are found in registries and real life data across Europe: 1:80,620 in Germany based on approximately 1,000 treated A1PI patients, 1:165,075 in France based on approximately 400 treated A1PI patients, 1:113,376 in Belgium based on a national registry of 55 A1PI patients (Hutsebaut 2015).

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

Emphysema due to severe A1PI deficiency is a serious and chronic disorder, which significantly reduces life expectancy. The annual mortality from A1PI deficiency is estimated to be 3.5%, predominantly due to emphysema (72%) and cirrhosis of the liver (10%) (Caspi A. and Losseff M., 2010) . In a survival analysis of 397 patients with severe A1PI deficiency, the overall median survival age was 54.5 years with no

significant difference between men and women (Seersholm et al., 1994). In a recent Spanish registry analysis of 343 patients, the mean age at death was 59 years (Lara and Miravitlles, 2015). In a Swedish registry study, the mean age at death was 67 years; main causes of death were respiratory diseases including respiratory failure and infections (Tanash et al., 2010a).

The Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) is the UK registry for A1PI deficiency patients, established in 1996. People with A1PI deficiency are referred to ADAPT by their GP or hospital consultant, or are identified by screening (Holme, 2011). Patients attend a single centre (Birmingham) and undergo annual assessment of clinical health, lung function, health status, comorbid disease, and exacerbations, using a range of validated questionnaires and nursing and medical review (Pillai et al., 2014). All patients are untreated apart from supportive care, as there are no licensed treatments for A1PI deficiency in the UK.

Analysis of survival data from this registry shows that lower lung density and rapid lung density decline are associated with higher mortality rates.

In the analysis of mortality, all A1PI replacement therapy-naive patients with ≥2 quantitative CT scans ≥1 year apart were selected and subsequent deaths and lung transplants noted (Green et al., 2014a). [redacted] Total decline in lung density and time between scans determined the annual rate of decline per patient, and was divided into 3 categories: no decline (no change), slow (0-2g/L/year) and rapid decline (>2g/L/year).

[redacted] Clinical characteristics of the patients are detailed in .

Table 3: Clinical characteristics of analysed patients from the ADAPT registry

[redacted]

In the analysis of only patients with whole lung density decline recorded, 27 had died and 1 was transplanted and excluded from further analysis. Cox regression demonstrated that baseline density (p=0.002) and rapid CT density decline (p=0.026) were associated with subsequent death, whilst patients whose lung density declined slowly showed a similar trend compared to those not declining (p=0.065) Figure 3 (Green et al., 2014a).

Figure 3. Cox regression curves from UK registry of A1PI deficiency patients with whole lung density recorded, showing impact of density decline on survival (Green et al., 2014a)

Figure 4. Cox regression curves from UK registry of A1PI deficiency patients with whole or upper lung density decline recorded, showing impact of density decline on survival

Figure 5. Cox regression curves from UK registry of A1PI deficiency patients with whole or upper lung density decline recorded and an FEV_1 30-50% predicted, showing impact of density decline on survival

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

Patients with A1PI deficiency experience significant impairment in their health related quality of life (HRQoL). A1PI deficiency is characterised by progressive emphysema which can be debilitating and causes considerable morbidity. The main symptom that patients experience is extreme breathlessness on minimal activity e.g. light housework, showering and dressing, walking and climbing stairs which results in severe restrictions on patients' ability to undertake everyday activities and lead a normal life. Frequent exacerbations often result in hospitalisation. Patients' mobility and independence is severely reduced, with many patients becoming housebound, dependent on supplementary oxygen and reliant on carers at advanced stages of the disease.

The disease and its consequences impact on leading a fulfilled family and social life as patients become increasingly unable to go out with friends, play with their children, or to travel. Patients' severe breathlessness also impacts on their ability to have intimate relationships.

A loss of friends and social isolation, paired with patients worrying about not being able to look after their children, providing for their families and becoming a burden to others commonly leads to mental health issues among patients with A1PI deficiency.

An online survey was conducted by the Alpha-1 Alliance (a coalition of leading clinicians in the field and patient groups with A1PI deficiency) from November 2012 to August 2013 (Alpha-1 Alliance, 2013). The survey (n=162) included leading clinicians, English patients, their families and carers, 93 responses were submitted by patients and 69 by patient members or carers. The vast majority of patient respondents were reported to suffer from the most severe form of A1PI deficiency, with the genotype PiZZ. Respondents were asked to detail how their health problems reduce their ability to work, or to take part in recreational and social activities. The survey indicated that A1PI deficiency is a major burden for patients, and for their families and carers. Many patients felt distressed about losing their independence and becoming a burden for their families, often at a young age and at the time they are trying to bring up a family. They also felt anxious about their future and that of their families. Several respondents also reported that the disease affected their social well-being and mental health. Many respondents highlighted the inability to be active and mobile as a result of shortness of breath. As the condition progressed, respondents reported a significant impact on their ability to live a normal and fulfilled life. Many struggled to perform normal everyday activities.

To understand how A1PI deficiency affects everyday life, a patient's wife described how her husband's condition evolved through time (Alpha-1 Awareness UK, 2018)

"Steve was 42 and at that time he was playing football 3 times a week, was a keen swimmer and enjoyed cycling and weight training.

Three years later in 1999 we moved in together – we had both been married before and had 3 sons between us. Within a couple of weeks I noticed he had a persistent cough so insisted he went to the doctors where he was diagnosed with COPD. Steve's cough continued and he started to struggle with his breathing when playing football and soon had to stop. Then he had to stop cycling and swimming.

Two years later Steve had to give up work – this hit us hard financially and I would be lying if I didn't say that I started to resent him for smoking when he was younger and getting this terrible illness that had affected us so much. I couldn't believe how quickly my fit husband had suddenly become "old" and it was really brought home to me when I watched his 78 year old father up ladders cutting our trees while Steve stood holding the ladders.

In 2008 I was on a train travelling to London for a meeting when I got a call from my 16 year old Son asking me what medication Steve was on as the paramedic needed to know! I was 10 minutes from Peterborough so got off and headed straight back to Darlington – it was the longest journey ever. When I got to the hospital I was told that Steve's lung had collapsed and as he only had very limited capacity in his other lung he had suffered heart failure but had been resuscitated. His lung kept collapsing and he spent Christmas and New Year in hospital. Steve was diagnosed with Alpha-1."

An observational, cross-sectional study was conducted in patients with emphysema due to severe A1PI deficiency (phenotype PiZZ, n=35) and a control group of COPD (n=61). The study showed that the relationship between severity of lung disease and HRQoL, both generic and specific, is stronger in emphysema associated with A1PI deficiency than it is in smokers with COPD (Manca et al., 2013).

In a survey of 398 patients with A1PI deficiency, 75.3% of respondents with severe deficiency reported at least one adverse effect: 44.4% retired early, and 19.1% changed to a physically easier job. The duration of diagnostic delay correlated with the degree of adverse psychosocial effects (Stoller et al., 1994).

Exacerbations occur frequently and are associated with significant disease burden in patients with A1PI deficiency. During a 1-year follow-up study of 922 subjects with A1PI deficiency, 91.5% experienced at least one exacerbation (mean 2.4 exacerbations per subject, median 2, and mean duration 17 days per episode, regardless of the definition used). Most exacerbations were categorised as severe by symptoms and moderate by healthcare resource utilisation (HRU) criteria. Subjects with frequent exacerbations had the worst baseline HRQoL scores, as well as more physician visits, emergency room visits, and hospitalisations (Campos et al., 2009)

In a study of 77 patients with A1PI deficiency, health status was assessed using the St. George ‘s Respiratory Questionnaire (SQRQ). Patients showed markedly impaired HRQoL at baseline based on the SGRQ scores (Dirksen et al., 2009).

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Currently the burden of care for A1PI deficiency patients on family members is high as many patients are housebound, have restricted mobility and are unable to self care. Carers often need to reduce or give up work to be able to care for the patient. Some family members and carers experience resultant mental health issues.

Patients diagnosed with A1PI often have young children and the condition impacts on the ability of their children to have a normal childhood. Parents are unable to play in the park with their children and day trips or family holidays are often cancelled at the last minute due to exacerbations. In addition children often have to assume a carer role for their parent.

While A1PI is delivered intravenously and family members may need to accompany patients on weekly trips to secondary care for treatment this is not seen as an undue burden as it provides an opportunity for close patient monitoring

Patients with A1PI deficiency treated with Respreeza have a 34% slower rate of lung density decline compared to those receiving placebo (-1.45 g/L in years versus -2.19 g/L, p = 0.03) (see Section 9). This will allow patients treated with Respreeza to slow their rate of progression and thereby prolong their independence and delay the worsening of their condition and the need for lung transplantation. This could also translate into a decrease in psychological distress and fatigue.

Due to the severity and chronic nature of the disease, emphysema caused by A1PI deficiency can have adverse economic effects for patients, as well as for the healthcare service and wider society. Patients are typically diagnosed with A1PI deficiency in the third or fourth decade (Greene et al., 2008), an age when many people are at full economic activity. As described in Section 7.1, an online survey of 162 UK respondents clearly demonstrated the severe difficulties experienced by people with A1PI deficiency in maintaining employed work and usual social activities, adversely impacting their quality of life (Alpha-1 Alliance, 2013). Reducing patients’ lung density decline is expected to enable them to retain employment and social participation for longer.

A decrease in the rate of disease progression and the subsequent need for lung transplantation is likely to have a positive impact on the psychological distress and caregiving burden of family and carers.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are no UK -specific guidelines on the treatment of A1PI deficiency. UK clinicians, who are experts in the management of A1PI deficiency, have stated that standard COPD therapy is the only treatment currently available for A1PI deficiency patients in the UK. The relevant NICE guideline is 'Chronic Obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update) (CG101), June 2010'. This was published before the results of the trial of Respreeza were available. The recommendations include:

- Smoking cessation
- Change of profession to remove workplace irritant exposure
- Influenza and pneumococcal vaccination
- Short or long-acting bronchodilators
- Inhaled corticosteroids
- Combination therapy
- Pulmonary rehabilitation
- Long-term oxygen therapy
- Early antibiotic and steroid therapy during acute exacerbations of COPD

In late 2016 the ERS guidelines were updated based on the RAPID program results and the recent licensing of Respreeza to delay disease progression in A1PI patients. These guidelines specifically recommend genetic screening of COPD patients to identify A1PI patients and subsequent treatment of A1PI patients with augmentation therapy (Miravitlles et al., 2017)

The American Thoracic Society guidelines have not been updated since 2003, however an independent review of augmentation therapy has been recently published by a group of US pulmonologists/A1PI experts which recommends augmentation therapy for A1PI patients with FEV_1 ≤65% predicted and to treat necrotising panniculitis (Sandhaus et al., 2016)

The Canadian Thoracic Society has also published guidelines which support the use of augmentation therapy in A1PI patients with an FEV_1 30-80% predicted. (Marciniuk et al., 2012)

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Respreeza will be used in conjunction with symptomatic treatments (inhaled bronchodilators, steroids, oxygen, etc.) for those patients with severe A1PI deficiency with ongoing evidence of progressive lung disease, who meet the criteria given in Section 8.1.

Currently, the treatment for COPD is the same regardless of whether or not patients have A1PI deficiency.

- NICE Clinical Guideline 101 recommends that people with COPD should be provided with help to stop smoking and should be offered pneumococcal vaccination and an annual influenza vaccination. It also recommends initial treatment with short-acting bronchodilators (NICE, 2010).
- For people who remain breathless or have exacerbations despite using short-acting bronchodilators as required, NICE clinical guideline 101 recommends a sequence of inhaled treatments. These treatments may include a long-acting beta2 agonist (LABA), a long- acting muscarinic antagonist (LAMA) or inhaled corticosteroids, alone or in combination. Some people may have oral therapy with slow-release theophylline or a mucolytic (NICE, 2010).
- Additional treatment options include pulmonary rehabilitation (a multidisciplinary programme of supervised exercise training and education), oxygen therapy and, for those with severe disease, lung transplantation. With the exception of smoking cessation, current treatments for emphysema/COPD caused by A1PI deficiency aim to alleviate symptoms and do not slow down the progression of the disease.

NICE Clinical Guideline 101 does not recommend replacement therapy for people with emphysema due to A1PI deficiency. At that time, there was no licensed treatment available in the UK. It notes that people with A1PI deficiency should be offered referral to a specialist centre to discuss the clinical management of this condition (NICE, 2010).

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

There are no UK-specific guidelines on the treatment of A1PI deficiency as standard COPD therapy is the only treatment currently available for A1PI deficiency patients in the UK. This is described in Section 8.1.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

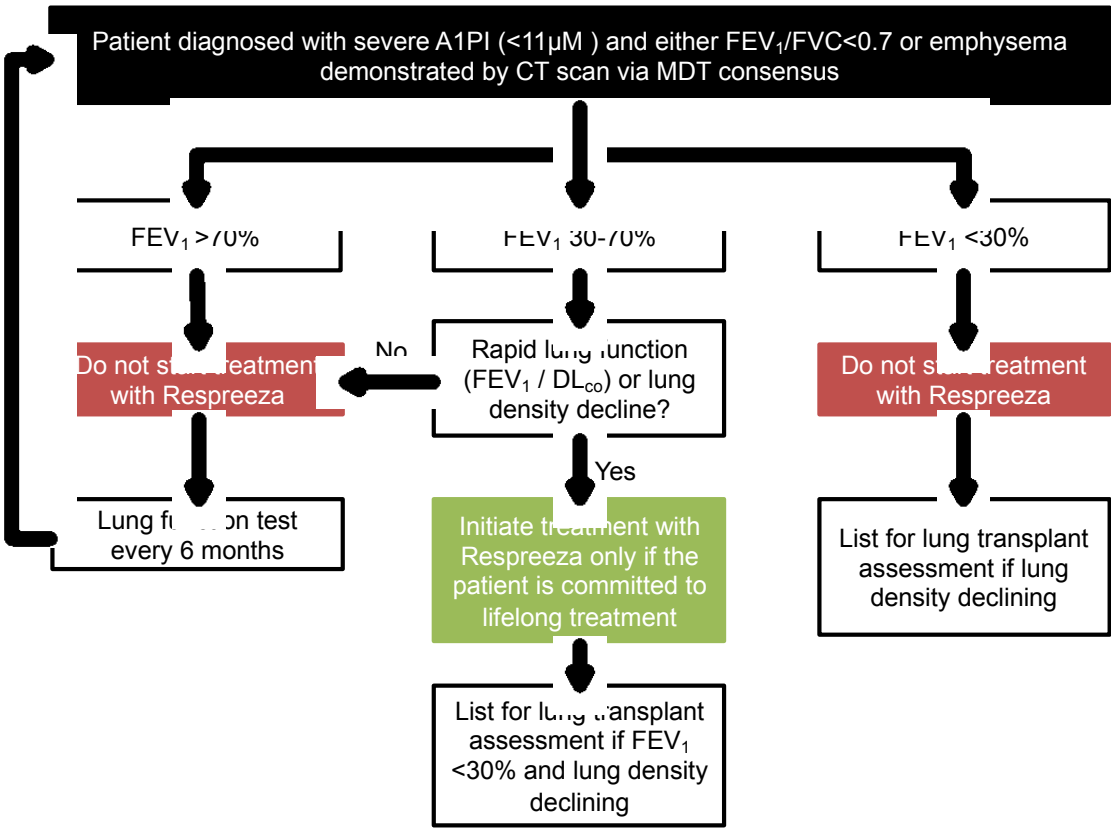
Respreeza will be used in conjunction with symptomatic treatments (inhaled bronchodilators, steroids, oxygen, etc.) for those patients with severe A1PI deficiency and evidence of ongoing progressive lung disease.

Severe A1PI deficiency is recognised as patients with an A1PI level below the "protective" threshold of 11 μM (American Thoracic Society/European Respiratory Society, 2003). Progressive lung disease can be defined as patients with a declining lung function (measured by FEV_1 or DL_{CO}) Therefore, Respreeza should be initiated in patients who meet **all** of the following criteria:

- diagnosis of severe A1PI deficiency (<11μM)
- FEV_1/FVC<0.7 (indicating airways obstruction) or emphysema demonstrated by CT scan via multi-disciplinary team consensus
- FEV_1 30-70% predicted
- rapidly declining lung function (FEV_1 % or DL_{CO} %), or lung density decline.

These treatment initiation criteria are illustrated in Figure 6.

Figure 6. Flowchart illustrating proposed treatment initiation criteria for Respreeza



8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Respreeza is an innovative technology. It is the first in class and the only proven disease-modifying agent for A1PI deficiency, a rare genetic disease that is associated with significant morbidity and mortality. Until the development of Respreeza there was no effective licensed treatment option, and no treatment that addresses the underlying cause of the disease. Based on the provided budget impact and cost effectiveness analyses, treatment poses a low financial impact and leads to prolonged survival and retained quality of life in patients with a burdensome and life-limiting condition. It also increases the likelihood that eligible patients will be able to benefit from a lung transplant, by managing their condition until a donor can be found.

Treatment of A1PI deficiency may act as a catalyst for long-term benefits to the NHS based on increased research and innovation, especially the multi-systemic elements of the disease such as respiratory, hepatology, transplantation, genetics, dermatology, renal and paediatrics.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

A new highly specialised service for individuals with severe A1PI deficiency is required.

Responsibility for the delivery of clinical services for patients with A1PI deficiency are being transferred to NHS England. In March 2018, the Department of Health and Social Care's Prescribed Specialised Services Advisory Group (Prepared by the PSSAG Secretariat) published recommendations to ministers. Relating to A1PI deficiency (but not relating to A1PI augmentation), PSSAG suggested changes to the delivery of clinical services for patients (Prepared by the PSSAG Secretariat, 2018). In 2017, PSSAG had recommended that this should become a directly commissioned service. Ministers have accepted this recommendation but agreed to NHS England's request for more time to prepare for a transfer. As such, NHS England is continuing to work towards becoming the responsible commissioner from April 2019.

The service would have two key aims:

1. Provide a specialist multidisciplinary service for the diagnosis and management of individuals with severe A1PI deficiency across England
2. Reduce morbidity and mortality due to severe A1PI deficiency, and ensure equity of access to specialist care for all patients with severe A1PI in England

The service is anticipated to be specifically for patients who have confirmed severe A1PI deficiency (with severely reduced A1PI serum concentrations – confirmed by a blood test) including those transitioning from paediatric clinics. These individuals would be referred to the specialist centres for assessment and risk stratification. Three to five specialist centres would commission existing secondary care service providers to operate as spokes for some elements of the patient's pathway.

The specialist centres would undertake a range of diagnostic tests at initial assessment to determine which pathways are most appropriate for the patient based on clinical risk. The specialist centres would provide:

- integration and coordination of all aspects of clinical care through multidisciplinary teams, which would comprise respiratory, hepatology, transplantation, genetics, dermatology, renal and paediatric services
- annual reviews for low risk patients, to track disease progression and direct appropriate pathways of care
- quarterly reviews for high risk patients to guide the use of licensed treatment
- elective in-patient management for the small proportion requiring this
- expert multidisciplinary clinics including respiratory, hepatology, transplantation, genetics, dermatology, renal and paediatrics
- personal management plans for each patient based on risk stratification and improve patient experience and outcomes

- support for local providers through shared care arrangements and provide specialist advice tailored to individual patients' requirements
- specialised transition clinics, elective inpatient care, a phone advice line, and develop a personal management plan for each patient
- links to genetic, hepatology and paediatric hepatology, dermatology, renal and transplant networks
- tightly controlled access to licensed treatment and future effective therapies for the most appropriate patients
- identification of family relatives to prevent activities such as smoking early on before progressive lung disease ensues?

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

Respreeza requires no specific monitoring for safety or efficacy. The monitoring of patients will not change from current monitoring under best supportive care, which includes measurement of A1PI levels and genotyping. Therefore, Respreeza will not require any additional appointments or tests above standard best supportive care. See section 6.1.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies or infrastructure above that in the service specification described in section 8.6 are anticipated to be needed. To meet the service specification each specialist centre will require a respiratory consultant, nurse specialist, respiratory physiologist and administrative support as well as access to multidisciplinary team support from hepatology, radiology, physiotherapist, transplantation, genetic counsellor, dermatology, renal and paediatric colleagues.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Not applicable.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

Whilst the brand name for the intervention being considered is Respreeza, other equivalent brands of A1PI are licensed outside of the UK. Other forms of A1PI are available in Europe, but unlicensed in the UK, includes Prolastin® (manufactured by Grifols) and Alfalastin® (manufactured by LFB). Although manufacturing processes differ, all augmentation therapy is based on raising the A1PI serum concentrations. Consequently, a comprehensive review of the evidence base for augmentation therapy, including but not limited to Respreeza, is reported to support this submission.

Two systematic literature reviews (SLRs) of effectiveness of treatments for A1PI deficiency have recently been published (Edgar et al., 2017, Gøtzsche and Johansen, 2016, Gotzsche and Johansen, 2010). Edgar et al included a broad range of study types and any treatment used for severe A1PI deficiency, but primarily focused on randomised controlled trials (RCTs). Gøtzsche et al specifically reviewed RCTs of A1PI replacement therapies compared to placebo or no treatment. Both SLRs found the same three RCTs and conducted a meta-analysis.

Whilst RCTs can provide the most reliable source of evidence, in light of the rarity of A1PI deficiency, we did not limit the evidence base for this submission to only RCTs. Therefore, the Edgar et al SLR was considered a more appropriate review than Gøtzsche et al. The protocol for the search is available in the PROSPERO database:

www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015019354

Since this search was conducted in April 2015, we conducted an update SLR based on the same search strategy as used by Edgar et al (Figure 7). The study question was defined according to the population, intervention, comparator, outcome and study (PICOS) framework (Table 5). The systematic search, which was based on a combination of MESH terms and free-text, was conducted on MEDLINE and EMBASE on 9th April 2015, and an updated search was conducted for 9th April 2015 to 11th April 2018 (Appendix 17.1.4). Additional hand searches of the Centre for Reviews and Dissemination, Cochrane library, conference websites and clinical trials registries were conducted (Appendix 17.1.5) for full search strategy).

Titles and abstracts (where available) yielded from the search were screened for relevance by two reviewers independently. Disagreements were resolved by discussion between the two relevant reviewers, involving the third reviewer where required. Hard copies of relevant articles were obtained and assessed against the full selection criteria using two independent reviewers. One reviewer extracted data from any included studies, which was checked by the other reviewer.

Table 4. Outcome measures and treatment effects of identified studies

Outcome measure	Treatment Effect	Reference
CT lung density preservation	1.07 g/L/y (p=0.07), (n=56)	(Dirksen et al., 1999)
	0.86 g/L/y (p=0.07), (n=77)	(Dirksen et al., 1999)
	0.84 g/L/y (p = 0.006), (n=119)	(Stockley et al., 2010)
	0.74 g/L/y (p=0.03), (n=180)	(Chapman et al., 2015)
	0.75 g/L/y (p=0.021), (n=140)	(McElvaney et al., 2017)
Reduced mortality	Significantly lower mortality rate p<0.001 log rank test, (n=763)	(The Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998)
FEV_1 preservation	13 mL/yr, all subjects, (n=1509) 18 mL/yr, FEV_1 30-65% predicted, (n=398)	(Chapman et al., 2009)
Long term correlations between lung density lung function and quality of life	FEV_1, r=0.286 (p=0.002), (n=118) FEV_1 % predicted, r=0.338 (p<0.001, (n=118) FVC, r=0.296 (p=0.001), (n=118)	(McElvaney et al., 2017) 4 years, 22 centers
	FEV_1, r=0.52 (p=0.001), (n=34)	(Parr et al., 2006) 3 years, 1 center
	FEV_1, r=0.32 (p=0.007), (n=77)	(Dirksen et al., 2009) 2-2.5 years, 3 centers

	FEV_1, r=0.41 (p=0.003), (n=51)	(Stolk et al., 2015) 8 years, 3 centers
	SGRQ, r=0.56 (p=0.007), (n=22)	(Stolk et al., 2003a) 2.5 years, 1 center

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Unpublished early phase clinical trials of Respreeza conducted by CSL Behring are reported in section 9.3.1. and were provided by the company.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table 5. Selection criteria used for published studies

Inclusion criteria	
Population	Adults suffering from severe A1PI, circulating level of A1PI <11μmol/L and/or a genotype consistent with such levels (eg, PiZZ, PiZNull with or without a diagnosis of COPD.
Interventions	Treatment for A1PI-related lung disease including any method of treatment that has been accepted in peer-reviewed literature
Outcomes	No restrictions were placed on outcome measures.
Study design	Observational (i.e. registries) Cohort studies RCTs
Language restrictions	None
Search dates	Original search conducted by (Edgar et al., 2017): up to 9th April 2016 Update SLR commissioned by CSL Behring: 9th to 11th April 2018
Exclusion criteria	
Population	• Liver Disease • Panniculitis • Children
Interventions	No restriction
Outcomes	Outcomes must have been reported <3 months after initiation of therapy
Study design	• Animal • Individual case study reports • Letters • Comment articles • Reviews • Epidemiology

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 7. PRISMA flow diagram from Edgar et al., 2017

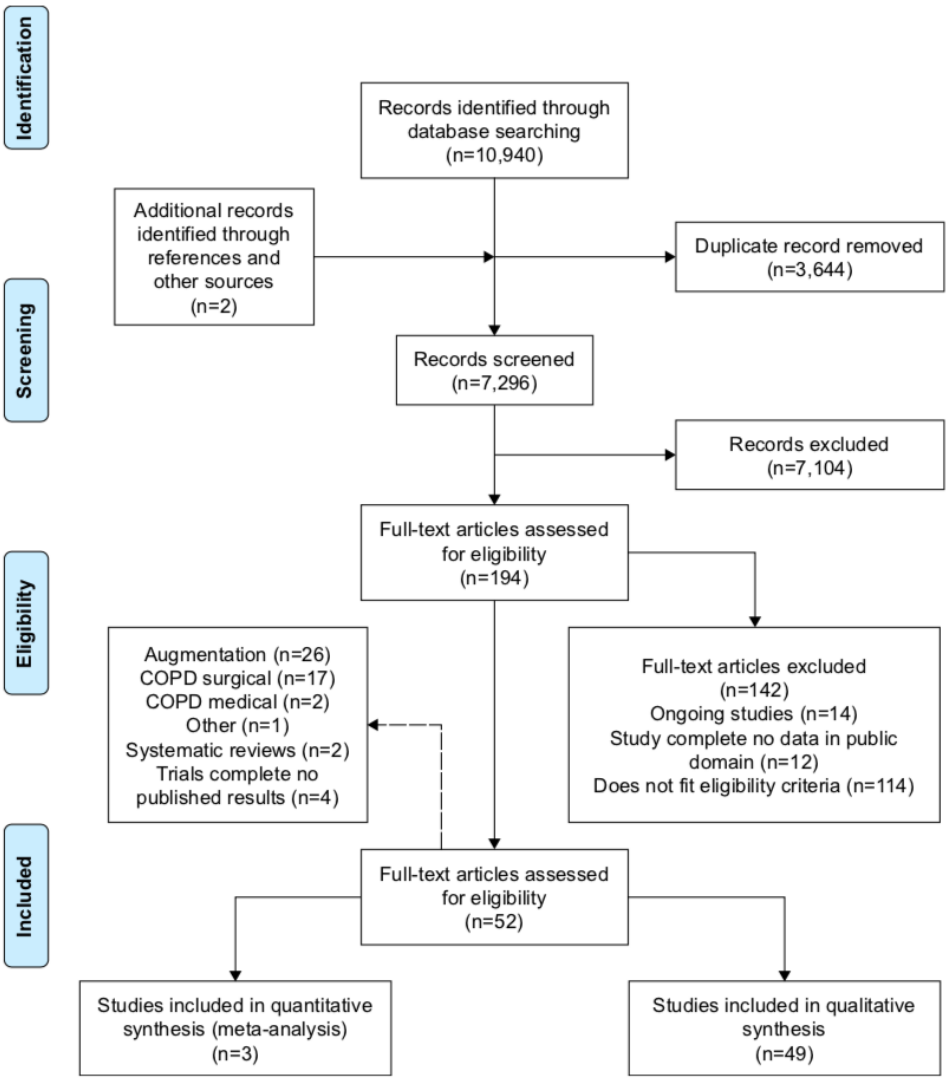
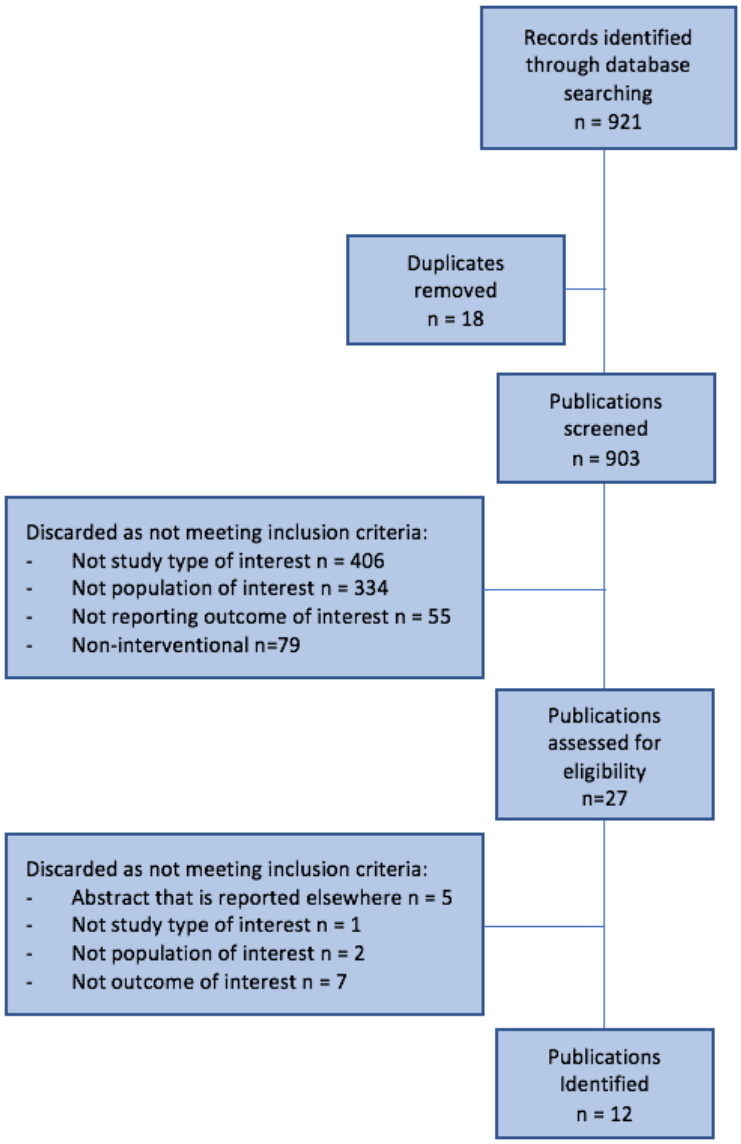


Figure 8. PRISMA flow diagram with results from updated SLR commissioned by CSL Behring



Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

A specific search strategy of unpublished studies was not used.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Three unpublished Phase I or II studies have evaluated the safety and efficacy of Respreeza:

- Study 101, a phase I study assessing the safety, tolerability and pharmacokinetics of Respreeza (15, 30, 60 and 120 mg/kg single IV dose)
- Study 1002, a phase Ib study assessing the bioavailability of Respreeza 60 mg/kg IV single dose (n=9) compared to Prolastin 60 mg/kg IV single dose
- Study 201, a phase II study assessing the steady-state serum trough levels and safety of Respreeza 60 mg/kg IV/week for 26 weeks followed by a 7 week to 22-week treatment extension (n=9)

These studies were biochemical efficacy studies that were not designed to capture the clinical efficacy of Respreeza. These three studies were therefore excluded.

9.3 Complete list of relevant studies

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2. .

Edgar et al conducted a broad search of all treatments for A1PI deficiency, including A1PI (referred to as augmentation therapy), COPD medical management and COPD surgical management (including lung transplantation). The relevant intervention considered in this submission is only A1PI so results of studies of COPD medical and surgical management found by Edgar et al, and in the update SLR, are not considered in the tables below.

RCTs of Respreeza are detailed in Table 6. Placebo-controlled RCTs of other brands of intravenous A1PI are detailed in Table 7 and Table 8.

RCTs comparing doses or formulations of A1PI as detailed in the supplementary appendix of Edgar et al, are not re-reported here. Furthermore, the update SLR found RCTs of new formulations of A1PI: an inhaled therapy (Brantly et al., 2017

) and a liquid A1PI (Barker et al., 2017). Respreeza is administered intravenously and these alternatives may not have comparable efficacy and safety and thus were excluded from the tables. These studies are not informative of the decision problem, which includes intravenous A1PI compared to best supportive care (i.e. no treatment).

Table 6. List of Respreeza RCTs

Primary study reference	Study Number (Status)	Population	Intervention	Comparator	Endpoints
Stocks et al. (2006)	Study 2002, Phase III (completed)	Men and women with A1PI deficiency	Respreeza 60 mg/kg IV/week for 24 weeks (n=29)	Prolastin 60 mg/kg IV/week for 10 weeks, then subjects (n=43) switched to Respreeza 60 mg/kg IV/week for a further 14 weeks (n=14)	**Primary** Bioequivalence of steady- state trough serum A1PI levels and maintenance of such levels above the protective threshold of 11μM **Secondary** Safety and tolerability and confirmation of increase in A1PI in the epithelial lining fluid of the lower lung.
Chapman et al. (2015)	Study 4001, RAPID, Phase III (completed)	Subjects with A1PI deficiency	Respreeza 60 mg/kg/week body weight for 24 months	Placebo 60 mg/kg/week body weight for a period of 24 months (n=87).	**Primary** Progression of emphysema, assessed by the decline of lung density, measured by CT. **Secondary** Exercise capacity respiratory symptoms, pulmonary exacerbations.
(McElvaney et al., 2017)	Study 3001, RAPID extension (OLE), Phase IV (completed)	Non-US subjects with A1PI deficiency who completed study 4001	Respreeza 60 mg/kg body weight/week IV for 2 years (n=76) Upon entry to the extension study, patients who were randomised to placebo in RAPID were switched to Respreeza ("Delayed Starters"); patients randomised to Respreeza in RAPID continued to receive Respreeza for another 2 years ("Early Starters"). Full data of the two years were available from Early Start subjects (n=40) and Delayed Start subjects (n=39).		**Primary** Progression of emphysema, assessed by the decline of lung density, measured by CT. **Secondary** Exercise capacity respiratory symptoms, pulmonary exacerbations.

Table 7. List of placebo-controlled RCTs of other brands of intravenous A1PI

Primary study reference	Population	Intervention	Comparator	Endpoints
Dirksen 1999	Inclusion criteria was PiZZ phenotype; moderate to severe emphysema; FEV_1 30% - 80% of predicted. N= 58, recruited from both the Danish and Dutch AATD Registries.	AAT Augmentation (n=28) 250mg/kg body weight intravenously infused every 4 weeks. Minimum treatment duration of 3 years.	Placebo (n=28) Human albumin in an isotonic solution 625mg/kg body weight infused every 4 weeks. Minimum treatment duration of 3 years.	Lung Function - FEV_1, SVC, KCO, DL_{CO} and patient-administered serial spirometry Annual rate of decrease in lung density measured by CT scan.
Dirksen 2009	Inclusion criteria was AAT -serum concentrations <11μM; ≥18yrs; ≥1 exacerbation in past 2 years; post bronchodilator FEV_1 ≥25% and ≤80% predicted with FEV_1/FVC ratio ≤0·70; Normal Spirometry could be included if KCO was ≤80%; Weight 42kg-92kg. N=82, with 77 randomised across 3 sites in Denmark, Sweden and the UK.	AAT Augmentation (n= 35) Prolastin: 60mg/kg body weight intravenously infused weekly. 2 year treatment. Additional optional 6 month open label extension study.	Placebo (n= 32) 2% human albumin infused weekly. 2 year treatment. Additional optional 6 month open label extension study.	Lung Density Pulmonary Exacerbations Lung Function - FEV_1, DL_{CO} and KCO Mortality Quality of life – SGRQ Adverse events

Table 8. List of non-RCTs of all A1PIs (shaded rows are from Edgar et al, unshaded rows are from update SLR)

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
Weber 1987 Uncontrolled Observational	PiZZ AATD, clinical evidence of progressive emphysema, non-smoking.	N= 10 Three centre study in Germany with average pre inclusion follow up of 2·5 years. Of the completers: Mean Age (yrs.) (SD): 48 (5) Sex (male) n (%): 7 (70)	AAT Augmentation (n=10) AAT Augmentation: AAT 60mg/kg body weight intravenously infused weekly. Up to 18 months treatment.		Biochemical – achieved a-priori serum AAT trough levels. Adverse Events – Safe and well tolerated Lung Function – No Change in lung function
Wewers 1987 Controlled Observational	PiZZ AATD, Clinical evidence of destructive lung disease.	N=30 Single centre recruitment from National Heart, Lung and Blood Institute (NHLBI), USA. Mean Age (yrs.) (SEM): Int: 46 (Prepared by the PSSAG Secretariat)	AAT Augmentation (n= 21) AAT Augmentation: AAT 60mg/kg body weight intravenously infused weekly. Up to 6 months treatment.	Control = 9 No intervention participants with PiMM phenotype, normal levels of AAT	Lung Function – No changes in lung function observed over the 6 months. Adverse Events – No severe adverse reactions observed. Only 4 “important” adverse events Biochemical – Biochemical efficacy in raising Serum and fluid in the epithelial lining of the lungs AAT trough levels($p<0·0001$), Serum and fluid in the epithelial lining of the lungs anti-neutrophil elastase($p<0·0001$).

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
		Cont: 28 (3) Sex (male) n (%): Int: 18 (85·7) Cont: 6 (66·7) Mean FEV_1 % predicted (SEM): Int: 37 (3) Cont: n/a			
Schmidt 1988 Uncontrolled Observational	AATD PiZZ phenotype with COPD	N= 20 Recruited from 3 sites in Germany. Mean Age (yrs.) (SD): 46·6 (7·6) Sex (male) n (%): 15 (75) Mean FEV_1 L(SD) n=17: 1·1(0·32)	AAT Augmentation (n= 20) AAT (Cutter Biological of Miles Inc., Berkeley, California) 60mg/kg body weight intravenously infused weekly. Up to 6 months treatment.		Adverse Events – Well tolerated and safe. Biochemical – Effective at augmenting circulating serum AAT.
Barker 1994 Uncontrolled Observational/ Retrospective chart review.	AATD PiZZ phenotype.	N= 14 Recruited from NHLBI National AAT Registry USA.	AAT Augmentation (n=14) Prolastin 60mg/kg body weight intravenously infused every 4 weeks. 48 months		Adverse Events – Similar safety profile to previously reported data. Lung Function –No statistical differences before and after treatment

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
		Mean Age (yrs.) (SD): 50 (6·16) Sex (male) n (%): 10 (71·4) Mean FEV_1 L (SD): 1·11 (n/a)			
Miravitlles 1994 Uncontrolled Observational	Plasma AATD <35% of normal, PiZZ PiNullNull or PiZNull, non smoker, aged 18-75, clinical/radiological evidence of Emphysema and compatible PFT's(FEV_1<80 % and/or RV>140% of predicted).	N= 13 Recruited from single centre in Italy. Of the completers: Mean Age (yrs.) (SD): 46·6 (9·4) Sex (male) n (%): 6 (46·1) Mean FEV_1 % predicted (SD): 26 (9.3)	AAT Augmentation (n= 13) Prolastin 60mg/kg body weight intravenously infused every week for four weeks then 240mg/kg body weight intravenously infused every four weeks. Minimum treatment duration of 3 years.		Adverse Events – Safe and well tolerated. Biochemical – 3 of 16 participants did not achieve a 'protective' level of AAT. Lung Function – Insufficient data for statistical analysis.
Barker 1997 Uncontrolled Observational	AATD serum AAT levels of <50 mg/dL and PIZ genotype; airflow obstruction with an FEV_1<75% of predicted;	N= 23 Patients referred from 4 states across the USA. Mean Age (yrs.) (SD): 51·1 (7·2)	AAT Augmentation (n=23) Prolastin-C 120 mg/kg body weight every 2 weeks for a total of 9 infusions over a period of 16 weeks. A 10th infusion was administered at week 20, 4 weeks later. 20 month study duration.		Adverse Events - No patient required interruption or discontinuation of infusion. There were no other deaths or serious adverse events. Biochemical – No participants maintained AAT levels >80mg/dl >7 days. Lung Function - FEV_1, FVC. No clinically or significant changes

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
	non/ex-smoker >1year; AAT augmentation therapy > 6 months prior to study entry.	Sex (male) n (%): 18 (65·2) Mean FEV_1 1 L(SD): 1·22 (0·56)			
Schwaiblmair 1997 Uncontrolled Observational.	AAT PiZZ, PiSZ phenotype; clinical evidence of destructive lung disease.	N= 20 Single centre recruitment in Germany. Mean Age (yrs.) (SD): 48·8 (1·8) Sex (male) n (%): 11 (55) Mean FEV_1 % predicted (SD): 41·7 (3·1)	AAT Augmentation (n= 20) AAT Augmentation: 60mg/kg once a week. Minimum treatment duration of 3 years.		Adverse Events – Safe and well tolerated. Biochemical – Mean Serum AAT adequately augmented. Lung Function - FEV_1, FVC, TLCO, MEF50, RV, TLC at 12, 24 and 36 months. No changes
Seersholm 1997 Observational Controlled study.	PiZZ or AAT serum level <12 µmol·L; either FEV_1 <65% predicted or annual decline in FEV_1>120mL; non/ex-smoking at enrolment; recipient of AAT augmentation therapy ≥1 yr.;	N= 295 Recruited from 25 centres across Germany and from the Danish AATD Registry Mean Age (yrs.) (SD): Int: 46 (Prepared by	AAT Augmentation (n= 198) Prolastin: infused weekly at 60 mg/kg body weight Mean follow up duration 3·2±1·6 years.	Control (n= 97) Normal clinical treatment with no AAT augmentation therapy Mean follow up duration 5·8±3·4 years.	Lung Function – 22ml/yr. Slower decline in FEV_1 in treatment group across all patients(p=0·02). No significant difference in change in FEV_1 between the treated group and the untreated group among the patients with the lowest and the highest FEV_1 % pred. In patients with initial FEV_1 of 31–65% predicted, significantly lower rate of decline in FEV_1 among the treated patients (p= 0·04).

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
	≥2 spirometries ≥1yr apart. performed during the treatment period; index cases; >25 yrs. of age at entry.	the PSSAG Secretariat) Cont: 45 (10) Sex (male) n (%): Int: 142 (71·7) Cont: 55 (56·7) Mean FEV_1 % predicted (SD): Int: 37 (14) Cont: 42 (10)			
The Alpha-1-Antitrypsin Deficiency Registry Study Group 1998 Observational Controlled study	>18 yr. of age; either AAT serum <11mMol or PiZZ genotype.	N= 1129 Patients from NHLBI AATD Registry USA. 1048 patients used in Survival analysis (no demographics) & 927 used for FEV_1 slope analysis. Of the 927: Mean Age (yrs.) (SD): Int Grp 1: 46 (11) Int Grp 2: 47 (10) Cont: 43 (12)	AAT Augmentation (n= 747 in two groups: 1)390 always received therapy, and 2)357 partly receiving therapy while in the Registry) Prolastin 60mg/kg body weight intravenously infused weekly. Up to 7 years follow up.	Control (n= 382) Normal care naive to AAT augmentation	Lung Function – Overall change in FEV_1 was not significantly different between groups. Subgroup into GOLD disease severity by FEV_1 decline is slowest in those receiving augmentation p=0·03. Survival – Across all patients no changes. Those with FEV_1<50% saw significantly higher ($p < 0·001$) mortality in subjects who never as opposed to sometimes or always received augmentation therapy.

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
		Sex (male) n (%): Int Grp 1: 227 (58·1) Int Grp 2: 206 (57·9) Cont: 187 (49·1) Mean FEV_1 % predicted (SD): Int Grp 1: 37 (Prepared by the PSSAG Secretariat) Int Grp 2: 41 (21)			
Wencker 1998 Uncontrolled Observational	>18 yrs.; AATD; FEV_1<65% predicted, or annual decline of FEV_1>120 mL; non/ex-smoker >3 months prior to the first infusion.	N= 443 Patients from 25 centres throughout Germany. Mean Age (yrs.) (SD): 47 (9) Sex (male) n (%): 292 (65·9) Mean FEV_1 % predicted (SD): Exsmokers:35·5 (14·8)	AAT Augmentation (n= 443) Prolastin 60mg/kg body weight intravenously infused weekly. Registry study and treatment duration varied.		Lung Function - FEV_1 decline showed no differences. Subgroup analysis observed those with FEV_1<30% predicted had a significantly slower rate of decline of FEV_1 than those with FEV_1>30% predicted. Adverse Events – Safe and well tolerated.

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
		Non-Smokers: 42·2 (18·2) Of 287 patients included in FEV_1 Longitudinal follow up: Mean Age (yrs.) (SD): 46 (9) Sex (male) n (%): 187 () Mean FEV_1 % predicted (SD): 36·3 (15·2)			
Wencker 2001 Observational Controlled study	AATD serum levels , 35% of normal regardless of phenotype; FEV_1≤65% predicted or decline in FEV_1 of 120 mL/yr.; non-smokers or ex-smokers >3 months.	N= 96 Data taken from the Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenkrankungen (WATL) Germany. Baseline demographics: Mean Age (yrs.) (SD): Int: 44·3 (8·6)	AAT Augmentation (n= 96) Prolastin: 60mg/kg body weight intravenously infused weekly. Mean follow-up after start of augmentation was 50·2 (30·2) months.	Control (n=96) Control group was the same cohort with data taken from at least the year prior to commencement of treatment. Mean follow-up before augmentation was 47·5 (28·1) months.	Lung Function - FEV_1 declined significantly slower (p=0·019) after starting therapy - 34·3±29·7(SD)mL/yr. than prior to therapy with AAT augmentation -49·2± 60·8 mL/yr.

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
		Sex (male) n (%): Int: 62 (64·6) Mean FEV_1 % predicted (SD): Int: 41·0 (17·3)			
Stoller 2003 Observational Controlled study	Age >18 years; serum AAT level 11 mol/L; or a ZZ or Znull phenotype;	N= 1129 Patients were from the NHLBI AATD Registry USA. Mean Age (yrs.) (SD): 47 (9) Sex (male) n (%): 292 (65·9) Subgroups - always (Grp1), partly (Grp2) or never (Grp3) receiving AAT therapy: Mean Age (yrs.) (SD): Grp 1: 48 (9) Grp 2: 47 (10) Grp 3: 45 (12) Sex (male) n (%): Grp 1: 226 (58) Grp 2: 204 (57)	AAT Augmentation (n= 747 in two groups 1) 390 always received therapy, and 2) 357 were partly receiving therapy while in the Registry) AAT60mg/kg body weight intravenously infused weekly. Follow up 3·5-7 years.	Control (n=382) Normal care naive to AAT augmentation	Adverse events – Participants receiving weekly infusions reported a higher rate and severity of AE's than those treated every 2 to 3 weeks (p=0·020 and p=0·003) or monthly (p=0·001 and p=0·014). But compared to literature safe and well tolerated

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
		Grp 3: 197 (52) Mean FEV_1 % predicted (SD): Grp 1: 37 (Prepared by the PSSAG Secretariat) Grp 2: 37 (21) Grp 3: 65 (37)			
Campos 2009 Uncontrolled Observational	AATD;- members of AlphaNet (a not-for-profit health management company responsible for co-ordinating services for subjects with AATD), AAT augmentation recipient; presence of obstructive lung disease	N= 1062 Participants were members of AlphaNet USA. Of the 922 eligible: Mean Age (yrs.) (SD): Int: 54·5(9·6) Sex (male) n (%): Int: 485(52·6) Mean FEV_1 % predicted (SD): Int: 37·5 (19)	AAT Augmentation (n=922) Augmentation type and duration not available· All had been established on treatment for 12 months prior to inclusion to study.		Health Status - No clinically significant changes in SGRQ Exacerbation Rates – oldest sub group had significantly lower exacerbations (p<0·05) Health Care Utilisation - No differences pre and post treatment
Campos 2009 Uncontrolled Observational	AATD;- members of AlphaNet, AAT augmentation recipient; presence of	N= 1062 Members of AlphaNet USA. Of the 922 eligible:	AAT Augmentation (n=) Prolastin: intravenously infused data on dosing and frequency was unavailable.		Health Status - No clinically significant changes in SGRQ Exacerbation – No significant differences in frequency.

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
	obstructive lung disease	Mean Age (yrs.) (SD): Int: 54·5(9·6) Sex (male) n (%): Int: 485(52·6) Mean FEV_1 % predicted (SD): Int: 37·5 (19)			
Tonelli 2009 Observational Controlled study	AATD PIZZ genotype; ≥2 post bronchodilator FEV_1, ≥6 months apart.	N=164 The Alpha-1 Foundation DNA and Tissue Bank. Multiple sites across the USA Mean Age (yrs.) (SE): Int: 61·3(0·7) Cont:65·1(1·9) Sex (male) n (%): Int: 59(47·6) Cont: 20(50) Mean FEV_1% predicted (SE): Int: 43(Prepared by the PSSAG Secretariat) Cont: 77(5)	AAT Augmentation (n=124) The augmentation therapy used was predominantly weekly intravenous Prolastin 60mg/kg/week (88% of patients) but also Aralast and Zemaira. Insufficient data on dosing and frequency. Patients were on their own Rx and study team had no input. Mean follow up of 41·7 months.	Control (n=40) Usual care no augmentation therapy	Lung Function - statistical difference (p=0·05) in FEV_1 decline between 2 groups, augmented group FEV_1=10·61± 21·4 mL/yr. non-augmented group FEV_1 -36·96 ± 12·1 mL/yr. Survival - No differences were observed in the 5-year mortality rate.

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
Vidal 201022 Uncontrolled Observational	AATD with pulmonary emphysema; recipient or planned recipient of AAT augmentation	N= 23 9 Hospital sites across Spain. Median Age (yrs.) (IQR): Int: 49(43-61) Sex (male) n (%): Int: 11(47·8) Median FEV_1 % predicted (IQR): Int: 46·3(39·0-58·0)	AAT Augmentation (n=23) Trypsone: Infusions of 60mg/kg 5 Subjects – 60mg/Kg once a week 18 subjects – 180mg/kg every three weeks		Adverse events – Safe and well tolerated Vital Signs - No Clinically significant changes in vital signs.
Barros-Tizón 2012 Observational Controlled study	>18 years; diagnosis of severe AATD (i.e. PI*ZZ genotypes and combinations of Z, rare and null alleles expressing AAT serum concentrations <11 µmol or 50 mg/dl); recipient of continuous augmentation therapy with Trypsone or Prolastin ≥18	N=127 Multicentre study across Spain Mean Age (yrs.) (SD): Int: 51·7(9·1) Sex (male) n (%): Int: 81(63·8) Mean FEV_1 (L) (SD): Int: 1·25(0·5)	AAT Augmentation (n=127) Differing treatments and dosing regimes Prolastin: 68 patients (53·5%) Trypsone: 59 patients (46·5%). Weekly Therapy: 8 patients (6·3%) Bi-Weekly Therapy: 22 patients (17·3%) Every 3 weeks: 97 patients (76·4%) The average AAT concentrate dose administered was 60·7 ± 3·8 mg/kg/week		Exacerbation rate - Reductions in administration of systemic antibiotics prior to and following commencement of augmentation therapy was observed, $p<0·05$. Reductions in exacerbations per patient ($p<0·01$). Lung Function - Statistically significant decline FEV_1 (L) for the total patient population $p < 0·05$ were observed however this is within normal decline. Health care cost (Hospitalisation only) – Saving of €416·76 per patient Adverse Events – Safe and well tolerated.

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
	months prior to inclusion; available medical records of 18 months before starting augmentation therapy.				
Subramanian 2012 Uncontrolled Observational	≥18 years old; FEV_1/FVC < 0·7; AAT serum level < 11 μM or < 80 mg/dL and PiZ phenotype.	N=29 Single centre open label UK study. 3 groups; healthy control, non AAT related COPD, and AATD related COPD. Only data for AATD patients used. Of the 10 AATD patients: Mean Age (yrs.) (SE): Int: 57·2(2·9) Sex (male) n (%): Int: 9(90) Mean FEV_1 % predicted (SE): Int: 51·5(5·7)	AAT Augmentation (n=10) Prolastin: 12 Weekly intravenous infusions of 60 mg/kg body weight.		Change in Neutrophilic inflammation measured by PET scanning – No Changes pre and post treatment.

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Endpoints and Outcomes
Campos 2018 Observational controlled study	This retrospective study included commercial and Medicare Advantage health insurance plan members with ≥1 claim with diagnosis codes for COPD and ≥1 medical or pharmacy claim including A1PI.	N= 445 patients Mean (SD) age 55.5 (10.1) Male 50.8% Presence of emphysema 78.7% A1PI use 65.2%	Prolastin health management program patients (n = 213), receiving Prolastin or Prolastin-C	Comparator cohort consisting of patients on any other brand of A1PI (Aralast, Aralast-NP, Glassia, or Respreeza) (n = 232)	Exacerbations – no significant difference in mean number of episodes or non-severe episodes, but significantly fewer severe episodes in patients under the Prolastin health management programme vs any other A1PI All-cause hospital resource utilisation – significantly fewer inpatients stays (p=0.012) and shorter lengths of stay (p=0.009). No differences in ambulatory care of ER visits.
Wewers 2017 Observational controlled study	PIZZ patients with alpha 1-antitrypsin deficiency (O'Brien et al. Cleveland Clinic Foundation), with 4 or more post-bronchodilator FEV_1 measurements, no lung transplantation or lung volume reduction surgery.	N=732 Study only published in abstract form so no further details on the participants were available.	Augmentation therapy, n=unknown Study only published in abstract form, so no further details were available.	Patients not treated with augmentation therapy, n=unknown Study only published in abstract form, so no further details were available.	There was no statistically significant effect of augmentation therapy on FEV_1 decline from all subjects (48±5 vs 55±3 ml/y, p = 0.19, untreated vs treated respectively) or from subjects classified by COPD severity: (FEV_1 80% predicted: 44±22 vs 50±6 p=0.81); (FEV_1 55-79% predicted: 92±13 vs 85±7, p=0.61); (FEV_1 35-49% predicted: 56±8 vs 66±8, p=0.24); or (FEV_1 <35% predicted: 30±5 vs 37±4, p=0.32) (mean±SEM ml/y, untreated vs treated respectively).

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

See Section 9.3.1 for details on studies not included.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

Evidence for the safety and efficacy of Respreeza is primarily taken from the RAPID study and its extension. The evidence detailed here is taken from the primary study publication from RAPID and the OLE (Chapman et al., 2015, McElvaney et al., 2017), with supplementary detail from the clinical study report (CSR - CE1226_4001_Zemaira_CSR_Final_(30 Oct 2013)).

The other RCT for Respreeza, Study 2002, was a biochemical efficacy study compared to Prolastin which is not relevant to the decision problem. Therefore, this study is not considered to be a relevant study and is not described in further detail.

In addition to the evidence for Respreeza, supportive evidence of the efficacy of other A1PI brands is presented here as relevant RCTs. These were not conducted by the study sponsor and so the information presented is obtained from the peer-reviewed literature.

RAPID and RAPID extension

Study 4001 (RAPID) and Study 3001 (McElvaney et al.) provide the main evidence base for this submission and therefore have been described in detail below. The RAPID study was a randomised, double-blind, placebo-controlled, multi-centre study primarily investigating the clinical efficacy of Respreeza. The RAPID extension was an open-label extension of the RAPID study. Both studies investigated doses of 60 mg/kg/week for a two-year period.

Relevance of the outcome measures used

To generate evidence on the effect of Respreeza on emphysema due to A1PI deficiency, CSL Behring conducted a randomised clinical trial for Respreeza in A1PI deficiency with CT lung density as the primary end point.

Demonstrating clinical efficacy in A1PI deficiency is challenging, as it requires quantitative documentation of lung function changes in a slowly progressive disease process that can take decades to manifest as a clinically significant detriment to the patient (Wewers and Crystal, 2013). Expert guidelines state that densitometric parameters derived from repeated CT scans are sensitive and specific markers of the extent of emphysema, and that the progression of emphysema is assessed more accurately by repeated quantitative CT than by measuring FEV_1 (Dirksen et al., 1999, Dirksen et al., 2009, Stockley et al., 2010, American Thoracic Society/European Respiratory Society, 2003).

There is consistent evidence demonstrating that CT-measured lung density decline is the optimum and most sensitive indicator of disease progression in A1PI deficiency (Chapman et al., 2015, Dirksen et al., 1999, Dowson et al., 2001a, Bakker et al., 2005, Dirksen et al., 2009, Stockley et al., 2010)

In addition, regulators have also consistently agreed that CT-measured lung density decline is the best indicator of disease progression in A1PI deficiency:

- The FDA found that CT lung density measurement is an appropriate clinically meaningful endpoint to assess the efficacy of human A1PI products on emphysema disease progression (US Food and Drug Administration, 2009)
- The joint statement of the American Thoracic Society/European Respiratory Society also states that use of CT scans to measure lung density provides a practical, quantitative way to assess the efficacy of augmentation therapy in future studies (American Thoracic Society/European Respiratory Society, 2003). Specifically, they state that the progression of emphysema may be assessed more accurately by repeated quantitative CT scans than by measuring the FEV_1.
- Further acceptance of the suitability of measurement by CT scan was confirmed in January 2015, when the CHMP convened a Scientific Advisory Group to review aspects of the Respreeza dossier.
- The CTS 2012 guidelines, ERS 2017 guidelines and a recent publication of US based pulmonologists/AATD experts all accept the clinical relevance of CT lung density outcomes (American Thoracic Society/European Respiratory Society, 2003, Miravitlles et al., 2017)

In rare long-term diseases such as A1PI deficiency, surrogate endpoints have become an acceptable measure of treatment effect. Recent data from the ADAPT UK registry has clearly demonstrated that CT lung density is predictive of both mortality and quality of life (Green et al., 2014a, Green et al., 2016) (see Section 6.3 and 9.9.3), and therefore translates to a clinically relevant effect. By the nature of a CT scan, it is also clearly a measure of disease progression.

A meta-analysis of 1509 patients from 5 clinical trials found that A1PI was associated with a 26% reduction in the rate of FEV_1 decline in patients with FEV_1 30-65% predicted (Chapman et al., 2009). Therefore, it is expected that administration of A1PI will have a significant effect of on FEV_1, but this can only be observed over long periods of time or in very large patient numbers. It is challenging to use FEV_1 as an outcome in clinical trials because it measures the obstruction of airways and not parenchymal tissue loss which is the first to be affected by neutrophil elastase, and the large sample sizes required to observe statistically meaningful improvement in treated versus untreated patients are prohibitive in this rare disorder (Stockley et al., 2010). Stolk et al demonstrated that lung density declines in the first year were correlated to annual FEV_1 declines over the subsequent 8 years ($r=0.41$, $p=0.003$, $n=51$ AATD patients) (Stolk et al., 2015).

Similarly, although a favourable and statistically significant reduction in the mortality rate was established in the NHBLI registry, it is challenging to detect reduction in mortality in controlled clinical trials. The NHLBI registry data is currently being

investigated for further signals of treatment benefit. Resulting data will be made available to NICE.

Study methodology

RAPID was a randomised, placebo-controlled, double-blind, multi-centre Phase III/IV study to compare the efficacy and safety of 60 mg/kg body weight of Respreeza weekly IV with placebo weekly IV administration in patients with emphysema due to A1PI deficiency. The primary objective for the trial was to investigate the effect of Respreeza on the progression of emphysema, assessed by the decline of lung density, measured by CT. This was the only endpoint which was appropriately powered at 180 patients.

The comparator, placebo, is representative of best supportive care in England. No restriction was placed on concomitant medications such as symptomatic treatments included as part of best supportive care. Patients were not allowed to receive any A1PI replacement therapy other than Respreeza during the study period.

Table 9 shows the design of the RAPID study and extension. An overview of the study methodology is shown in Figure 9. Further details of assessments are given below the table.

Upon entry to the extension study, any patients that were randomised to placebo in the RAPID study were switched to Respreeza ("Delayed Starters") while all patients randomised to Respreeza in RAPID continued to receive Respreeza for another 2 years in the extension ("Early Starters").

Figure 9. Design of Phase IV Respreeza RAPID and Extension Studies

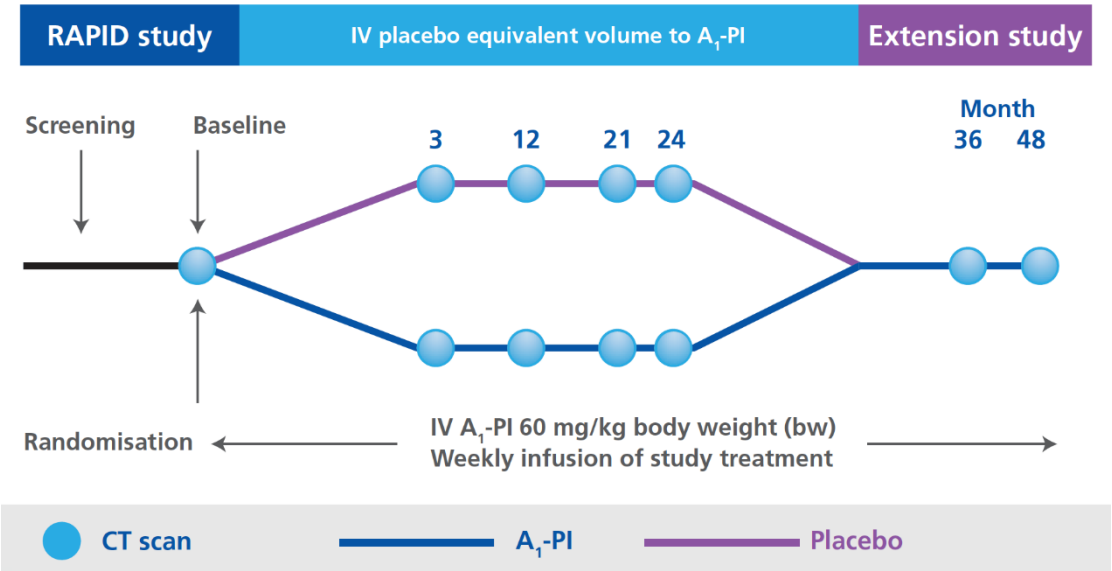


Table 9. Summary of methodology of the RAPID trial and extension

METHODS	**Location**	28 centres in Australia (11.1%), Canada (16.1%), Czech Republic (1.1%), Denmark (20.6%), Estonia (1.1%), Finland (2.2%), Germany (10.6%), Ireland (12.2%), Poland (3.9%), Romania (0.6%), Russia (0.6%), Sweden (10.6%), United States (9.4%)
	Study duration	2 years with 2 years extension
	Entry criteria	Key inclusion: • 18-65 years of age • Diagnosis of A1-PI deficiency (serum A1-PI levels < 11 µM, or < 50 mg/dL [as determined by nephelometry]). This included newly diagnosed subjects, previously untreated subjects, currently treated subjects, and subjects currently not on treatment therapy but on treatment in the past. Genotypes were not restricted, >90% were PiZZ. • Diagnosed with emphysema resulting from A1PI deficiency and have a FEV_1 of ≥35% and ≤70% predicted. Key exclusion: • Smoked tobacco within six months prior to recruitment • Undergone or were on a waiting list for lung transplantation, lobectomy or lung volume reduction surgery • A history of transfusion reactions
	Method of randomisation	Subjects were randomised evenly, at a ratio of 1:1. The randomisation was stratified by centre. A randomisation list containing the assignment of subject numbers to treatment groups was reproducibly generated by a computerised pseudo-random number generator. A copy of the randomisation list was transferred to the drug supply and logistics group of the Clinical Operations Department at CSL Behring. Standard operating procedures were followed to ensure confidentiality of the randomisation list.
	Method of blinding	This was a double-blind study. Respreeza and placebo were packaged identically. Individual packages were identified only by the subject number. The treatment groups randomised to the subject numbers were only known to the randomisation code administrator, and to the drug supply and logistics group of the Clinical Operations Department at CSL Behring.
	Treatments, allocation and retention	After a screening period of 1 week to 1 month, each subject received, according to his or her subject number, weekly infusions of Respreeza at a dose of 60 mg/kg or an equivalent volume of placebo over 24 months. Respreeza and placebo were administered intravenously at a rate of 0.08 mL/kg/min, as determined by the response and comfort of the subject. The first dose and the doses given during the following quarterly visits at the study centre were administered by the investigator or designate. All other weekly doses could be given by the nurses of a home care service or by the family doctor. Where possible, all doses were given at the study centre. In exceptional cases (e.g. holidays) a single weekly dose of 120 mg/kg bi-weekly was allowed to cover a 2-week time period.

OUTCOMES	**Primary outcome objective**	To investigate the effect of Respreeza on the progression of emphysema, assessed by the decline of lung density, measured by computed tomography (CT).
	Secondary outcome objectives	To assess the effect of treatment with Respreeza on the following clinical assessments: • Change in exercise capacity assessed by incremental shuttle walk test (ISWT) • Change in symptoms assessed by the St George's Respiratory Questionnaire (SGRQ) • Rate of pulmonary exacerbations (according to (Anthonisen et al., 1987)
	Additional outcome objectives	• A1PI levels • Pulmonary function test parameters • Other domains of the SGRQ
	Safety outcomes	The incidence and nature of adverse events, viral serology, serum A1PI antibodies, laboratory parameter levels, and vital signs.
	Duration of follow up	24 months followed by a further 24 month period in which all patients switched to Respreeza

Abbreviations: FEV, forced expiratory volume

Assessments

CT scans were performed at randomisation and months 3, 12, 21, and 24 after the start of treatment. All CT scans were evaluated and analysed at a single core CT laboratory. The secondary and other outcomes were assessed at quarterly intervals apart from: PFTs, ISWT, exacerbations (for which time of onset, duration, and number of days of hospitalisation were recorded) and the SGRQ (completed prior to treatment and after 12 and 24 months of treatment).

Lung density was assessed by serial spiral computed tomography (CT) scan (HRCT scans were not used as they require a higher degree of radiational exposure and do not improve upon the lung density assessments acquired from serial spiral CT scans) at two different lung volumes: total lung capacity (TLC) and functional residual capacity (FRC). At the time of protocol design for the RAPID trial, CT scanning at two levels of inspiration was thought to be optimal for detecting changes in lung density over time. TLC refers to the volume of gas in the lungs after maximal inspiration. The FRC is the volume of gas present in the lung at end-expiration during tidal breathing (Wanger et al., 2005). The generally accepted 15th percentile (PD15) of the frequency histogram of density values in the lung voxels was used to measure changes in lung density (Stolk et al., 2003b).

The primary endpoint of RAPID was therefore the lung volume-adjusted lung density (Adjusted PD15) estimated by the 15th percentile of the frequency histogram of the lung voxels.

This led to the composite primary statistical endpoint for the RAPID trial being defined as lung density decline at combined TLC/FRC.

However, it has since become apparent that CT scans performed at TLC provide optimal data for making longitudinal observations of lung density (Parr et al., 2008). FRC is the better inhalation state to assess changes in air trapping phenomena, while TLC has demonstrated lower variability as patients find it easier to replicate this inhalation state over the course of long-term studies. Further, TLC is the standard measure currently approved by the CHMP as the optimal method of monitoring disease progression. At the moment, the RAPID trial has been the only study that has used FRC, with all other trials employing TLC only. CT scans were evaluated as explained below.

It has been suggested that the most important source of variability in lung density measurements is the lung volume, and it is essential subsequently to adjust lung density measurements for variation in the measured total lung volume (mTLV) (Dirksen, 2008). Therefore, for this study, the mTLV was used for adjustment of lung density.

The lung density was measured in Hounsfield units. These units were transformed to g/L by adding the constant 1000 to the original measurement (Chapman et al., 2015). CT scans with negative density after this transformation were set to missing. One method used to standardise percentile densities for variations in mTLV measured from CT is the physiological adjustment method (Shaker et al., 2004). This adjustment has the advantage of being intuitively meaningful (the lung behaves like a sponge), and each measured density value can be adjusted for simultaneously measured lung volume independent of density measurements from other scans (Dirksen, 2008). Therefore, the primary efficacy variable of the study, Adjusted PD15, was based on the physiological adjustment for the primary efficacy analysis.

Adjusted PD15 = observed PD15 x (observed mTLV / predicted TLC).

Predicted TLC was derived as:

7.99 x [height in m] - 7.08 for males, and 6.60 x [height in m] - 5.79 for females.

Statistical methods

It was estimated that 180 subjects would enable the study to achieve 92% power at a 1-sided level of significance of 0.025 to detect an effect size of 1 g/L/year on the decline in lung density, with a standard deviation (SD) of approximately 2.5 g/L/year.

The primary analysis population consisted of all randomised patients who had at least one scan (the modified ITT population). The safety population consisted of all patients who received at least 1 administration of study drug. A random regression model which makes use of all data contributed from all patients at each time point was used in the primary analysis. In this model, the assumption was made that the data were missing at random. Based on EMA guidelines, a set of analyses where the missing data were

handled in different ways were used as sensitivity analyses to verify the results from the primary analysis (European Medicines Agency, 2010).

The following sensitivity analyses were conducted to support the primary analysis using the subject populations.

- Complete-case analysis (baseline and Month 24): all subjects with valid CT scans at baseline and Month 24 were included in this analysis. Missing CT scans at Months 3, 12, or 21 were not imputed. The missing values were assumed to be missing completely at random. This analysis was considered to have more bias in favour of Respreeza, as completers are expected to have a better treatment outcome.
- Pattern-mixture model with placebo-based pattern imputation: the ITT population was used for this imputation including randomised subjects without any valid CT scans. All missing data were replaced by multiple imputation based on the subjects randomised to placebo. The missing values were assumed to be missing not at random. Since the imputations were sampled from the subjects randomised to placebo, this analysis was considered to be conservative in favour of placebo.
- Worst-case approach: the ITT population was used for this imputation including randomised subjects without any valid CT scans. All subjects with a valid CT scan at baseline and a scan at any given time point were used for worst-case estimation for the given time point. The missing scans were replaced by multiple imputations. This analysis was considered to be the most conservative approach in favour of placebo.

Analysis of secondary end points:

Exercise capacity test – distance walked

The change from baseline to Month 24 in the distance walked was analysed. For the ITT population, analyses based on observed and imputed values are presented. As a sensitivity analysis, an analysis of the PP population using only subjects with baseline and Month 24 values available was carried out. An analysis of covariance (ANCOVA) with country, treatment, and the baseline value of the distance walked as fixed covariates was carried out. The estimated treatment difference derived from the ANCOVA along with 2-sided 95% CIs and the 2-sided p-values are presented for imputed and observed values in the ITT population and for observed values in the PP population. The p-values were considered to be exploratory.

SGRQ symptoms score

The change from baseline to Month 24 in the SGRQ symptoms score was analysed using the same methodology as described for the exercise capacity test above using the baseline value of the SGRQ symptoms score as fixed covariate.

Number and annual rate of exacerbations

Pulmonary exacerbations were described by the number of subjects with exacerbations, and by calculating the annual rates of events that met the definition of an exacerbation, for the ITT and PP populations. Treatments were compared for the number of exacerbations adjusting for the treatment duration in years. A negative binomial regression was applied with country and treatment as fixed effects. Adjustment was made for the subject's study duration by including log study duration as an offset variable in the model.

Change from baseline to Month 24 for Adjusted PD15

The absolute change from baseline to Month 24 in Adjusted PD15 was analysed for the TLC and FRC states combined and separately. Missing values at 24 months were imputed based on the single imputation method. A mixed effects model with treatment, country, baseline value of Adjusted PD15 as fixed covariates, and the inspiration level as a repeated measures was applied for observed change and imputed change in the ITT population and for observed change in the PP population.

The estimated treatment difference derived from the mixed effects model along with 2-sided 95% CIs and the 2-sided p-values for imputed and observed values in the ITT population and observed values in the PP population are presented. The p-values were considered to be exploratory.

The change from baseline to Month 24 in Adjusted PD15 was analysed post-hoc in the ITT population using statistically adjusted lung density values and an ANCOVA model. For the analysis at TLC and FRC states separately, the change from baseline to Month 24 in PD15 was used as the dependent variable, and the baseline value of PD15, the change between the log of mTLV at Month 24 and the log of mTLV at baseline, treatment, country, and treatment-by- time interaction as fixed effects. For the analysis at TLC and FRC states combined, inspiration state was also used as a repeated measure in addition to the covariates described above.

Key spirometry variables: FEV_1, FEV_1 % predicted, DL_{CO}, FEV_1/FVC ratio

Descriptive statistics are provided for measured values and % change from baseline by quarterly visit for the observed values and at Month 24 for imputed values in the ITT population. For the PP population, the same data were analysed based on observed values. Analyses were also performed for subgroups of data according to the categorized baseline parameters. In addition, descriptive statistics were performed by country.

The % change from baseline to Month 24 (imputed and observed for ITT and observed for PP) for each of the key spirometry variables was analysed by an ANCOVA with country, treatment, and the baseline value of the dependent variable as fixed covariates in the model.

For the key spirometry variables, the difference of slopes in subjects treated with CE1226 versus placebo was examined using a linear random regression model with country, time, treatment and treatment-by-time interaction (a regression of time within

treatment) as fixed effects and subject and subject-by-time interaction as random coefficients.

Time to first exacerbation

A time-to-event analysis was carried out for time to first exacerbation in years using both ITT and PP populations. Kaplan-Meier estimates of the survivor function were calculated for both treatment groups.

Differences in time to first exacerbation between the treatments were analysed using a Cox proportional hazards model with country, treatment, and duration of disease at inclusion (years) as explanatory variables.

Duration and severity of exacerbations

Descriptive statistics are provided for the duration and relative duration of exacerbations, the number and annual rates of hospitalisations due to exacerbations, the duration and relative duration of hospitalisations due to exacerbations, and the duration and relative duration of antibiotic treatment for exacerbations. In addition, the numbers of subjects requiring hospitalisation due to exacerbations, as well as, the number of subjects requiring antibiotic treatment by quarterly visit interval are provided. Analyses were performed for the ITT and PP populations.

A Randomised Clinical Trial of Alpha1-Antitrypsin Augmentation Therapy (Dirksen et al., 1999)

The study conducted by Dirksen et al was to investigate the rate of change in FEV_1 in PiZZ along with comparing other pulmonary function of emphysema by computerised tomography (CT) of patients receiving augmentation therapy compared to placebo (Dirksen et al., 1999).

Methodology

From the Danish Alpha1-Antitrypsin Deficiency Registry (1991 to 1995), 26 patients and 32 patients from a similar Dutch registry (1993 to 1997) took part in the RCT. All patients had A1PI Deficiency of the phenotype, Pi*ZZ and moderate to severe emphysema with an FEV_1 between 30% and 80% of predicted. For at least 6 months prior to entering the trial, all patients refrained from smoking. Every 4 weeks during the trial urinary cotinine was examined. During the two years of the trial, data was omitted as two Dutch patients who dropped out as they resumed smoking. All participants on the trial gave informed consent and was approved by the ethics committee of both participating hospitals,

Two centres in Denmark and the Netherlands were used to undertake the randomised, parallel, double-blind and placebo-controlled trial. Statistical calculations of lung function data from Pi*ZZ subjects in the UK (Hutchison, 1988) and Denmark (Evald et al., 1990) were used to identify that 50 patients were needed in order to indicate that a significant effect of intravenous A1PI augmentation on FEV_1 could be met. Providing a daily measurement of FEV_1 over three years and a treatment effect of at least 50% (Dirksen et al., 1991)..

Stratification was undertaken by age, level of FEV_1 and nationality with the minimisation method being used for randomisation (Pocock, 1983) to receive either alpha1-antitrypsin (250 mg/kg body weight) or placebo (human albumin, 625mg/kg body weight. The dose of A1PI used in the study in not similar to the licensed dose of Respreeza, but it was designed to raise the serum concentrations above 11 μM for a month. All participants were treated for at least 3 years with termination of the study after 5 years.

EXACTLE trial (Dirksen et al., 2009)

The EXACTLE trial (the EXAcerbation and CT scan as Lung End-points) conducted by Dirksen and colleagues was to investigate various outcome measures for the progression of emphysema, with focus on CT lung densitometry

Three A1PI registries in Denmark (Copenhagen), UK (Birmingham) and Sweden (Malmo) were used to undertake the randomised, parallel, double-blind and placebo-controlled trial.

Patients with severe congenital A1PI deficiency, with an A1PI serum concentration <11μM were assigned randomly to either weekly infusions of A1PI (60 mg/kg^{-1} body weight Prolastin1, Talecris Biotherapeutics, Inc) or placebo (2% albumin), in permuted blocks of four with stratification according to country, for 24 months, with an optional extension to 30 months in subjects who agreed to continue in the study. Patients received either Alpha1-Antitrypsin or placebo every week after randomisation along with their diary card checked, record any unscheduled visits to a healthcare provider, and note the occurrence of any adverse events (AEs). CT scans were performed at baseline and at 12 and 24 months, with an option for additional scans at 3 and 30 months. Post-bronchodilator lung function and health status were assessed at baseline and at 6, 12, 18, 24 and 30 months.

Statistical Methods

Analysis of the study population included intent-to-treat (ITT) and modified intent-to-treat (mITT) populations. The ITT population included all randomised subjects. The mITT population comprised the ITT population excluding patients with fewer than two valid CT scans (baseline and 12 months or after). Prior to unblinding, a review panel assessed CT scan data to identify invalid scans due to technical issues. These values were excluded from further statistical analyses. All CT scan analyses were based on the mITT population, whereas analyses on other end-points used the ITT population.

In Methods 1 and 2 for the densitometric analysis (Figure 10), treatment differences (Prolastin vs Placebo) were tested by linear regression on time of PD15 measurement in a random coefficient regression model as follows (Table 10).

The rate of lung density change with respect to time was represented by the estimated mean slope for each treatment group. The tested treatment difference was the estimated difference in slope between the two groups, considered to be equivalent to the difference in the rates of emphysema progression.

The first and last available CT scans were used in an end-point analysis (main effect ANCOVA model), with method 3 using the physiological adjustment or the inclusion of the logarithm of TVL as a covariate in the model for method 4 (Table 10).

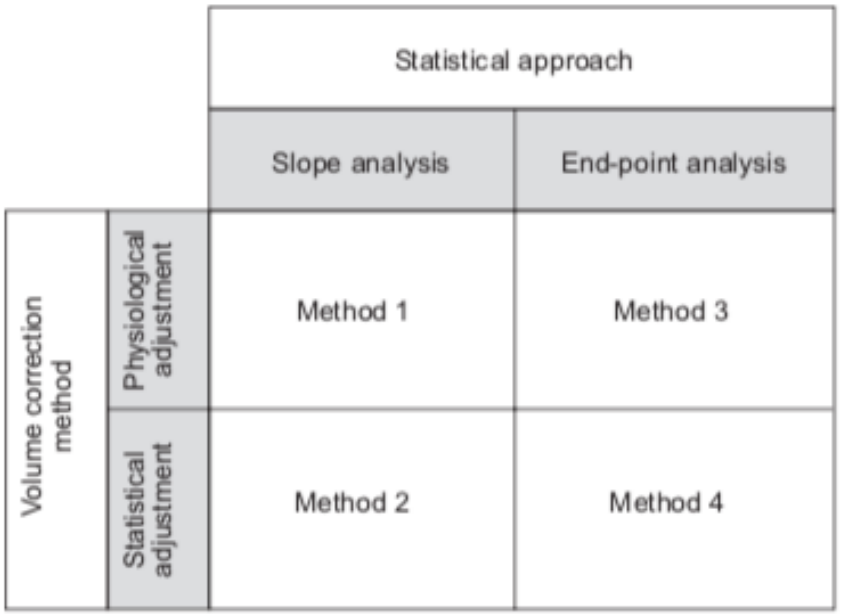
The primary endpoint was for Method 1, with Methods 2,3 and 4 as secondary outcomes, before unblinding. The random effects model or the Cochran-Mantel-Haenszel test were undertaken for other efficacy variables. The study was exploratory

and the trial was not powered a definitive study for illustrating a beneficial effect of augmentation therapy for any of the efficacy endpoints. Statistical analyses was performed using PROC MIXED procedure in SAS

Table 10. Statistical methods used in (Dirksen et al., 2009)

	Method 1	**Method 2**	**Method 3**	**Method 4**
Dependent Variable	TLC- adjusted PD15 from CT scan	PD15 from CT scan	change from baseline to the last CT scan measurement in TLC-adjusted PD15	change from baseline to the last CT scan measurement in PD15
Fixed Effects	treatment, centre and treatment by time interaction	treatment, centre and treatment by time interaction	treatment and centre	treatment and centre
Random Effects	intercept and time	intercept and time	-	-
Covariate		Time dependent covariat: logarithm of TLV	baseline measurement	change in logarithm of CT-measured TLV and baseline measurement

Figure 10. The four methods that were used for densitometric analysis (Dirksen et al., 2009)



9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Study	Primary Publication	Additional data sources
RAPID	Chapman, K. R., Burdon, J. G., Piitulainen, E et al. 2015. Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet,* 386**,** 360-8.	Study 4001 CSR
RAPID extension (OLE)	McElvaney, N. G., Burdon, J., Holmes, M. et al; RAPID Extension Trial Group. 2017. Long-term efficacy and safety of α1 proteinase inhibitor treatment for emphysema caused by severe α1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE). *Lancet Respir Med,* 5(1): 51-60	(Chapman et al., 2015) (RAPID)

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

There were no significant imbalances in clinically relevant baseline characteristics between the two study groups in RAPID. Baseline characteristics are summarised in Table 11.

At baseline, all subjects (mean age 53.1 years) had A1PI deficiency with serum concentrations of antigenic A1PI <0.5 mg/mL (11 μM), reduced lung function as assessed by spirometry and gas diffusion, reduced lung density as measured by CT, and impaired functionality indicated by shortened walk test distances and high disease-specific quality of life scores (meaning poorer QoL). The majority of subjects (92.2%) presented with the PiZZ phenotype of A1PI deficiency.

Table 11: RAPID Study baseline demographics and disease characteristics (ITT Population)

	Respreeza	Placebo
N	93	87
Mean age, years (SD)	53.8 (6.9)	52.4 (7.8)
Gender [M/F], %	52/48	57/43
Race [Caucasian/Other], %	100/0	100/0
Patients by region, %		
Australia	9.7	12.6
Europe	32.3	27.6
North America	25.8	25.3
Nordic	32.3	34.5
CT lung density, adjusted PD15 g/L, mean (SD)*		
TLC	45.5 (15.8)	48.8 (15.5)
FRC	47.6 (15.7)	50.7 (15.0)
Total	46.6 (15.6)	49.8 (15.0)
FEV_1, % predicted, mean(SD)	47.5 (12.1)	47.2 (11.1)
FEV_1/FVC ratio, mean (SD)	45.2 (11.4)	43.2 (10.4)
DLco, mL/mmHg/min, mean (SD)	13.6 (5.3)	15.0 (5.6)
Antigenic A1PI level, mg/mL, mean (SD)	0.29 (0.21)	0.27 (0.11)
Distance walked, m, mean (SD)	424.5 (183.0)	435.1 (199.7)
SGRQ, symptoms score, mean (SD)	46.5 (22.7)	44.1 (24.8)
A1PI phenotype, n (%)		
ZZ	83 (89.2)	83 (95.4)
SZ	2 (2.2)	0 (0.0)
Z	2 (2.2)	1 (1.1)
Other	6 (6.5)	3 (3.4)
Prior medications (total frequency >3), n		
Vaccine (e.g. hepatitis / influenza)	7	11
Beta-2 agonist / corticosteroids	12	6
Nonsteroidal anti-inflammatory drugs	2	5
Antibiotics	10	11
Human A1PI (Prolastin)	3	1

Abbreviations: CT, computed tomography; DLco, diffusing capacity of the lung for carbon monoxide; F, female; FEV, forced expiratory volume; FRC, functional residual capacity; M, male; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

For the RAPID trial, subgroup analyses were conducted to investigate the impact of some or all of the following baseline parameters on the analyses of the primary and secondary efficacy variables. Regarding the the two reported Dirksen RCTs (Dirksen et al., 1999, Dirksen et al., 2009), there does not seem to be a reasonable subgroup analysis.

Table 12. Baseline parameters of subgroup from RAPID trial

Baseline Parameters	**Stratification**
Region	Australia, North America [Canada and United States], Nordic [Denmark, Finland, Sweden], Europe [Czech Republic, Estonia, Germany, Ireland, Poland, Romania, and Russia
Age	< 54 years (Male), ≥ 54 years (Female)
Sex	Male, Female
Adjusted PD15 at baseline	< 25 percentile, 25 to 50 percentile, > 50 to 75 percentile, and > 75 percentile
BMI	< 30 kg/m^2, ≥ 30 kg/m^2
FEV_1 % predicted	< 50%, ≥ 50%
FEV_1/FVC ratio	≤ median at baseline, > median at baseline
DL_{CO}	≤ median at baseline, > median at baseline
Exercise Capacity – Distance walked	≤ 400 m, > 400 m
SGRQ symptoms score	≤ median at baseline, > median at baseline
SGRQ activity score	≤ median at baseline, > median at baseline
SGRQ impacts score	≤ median at baseline, > median at baseline

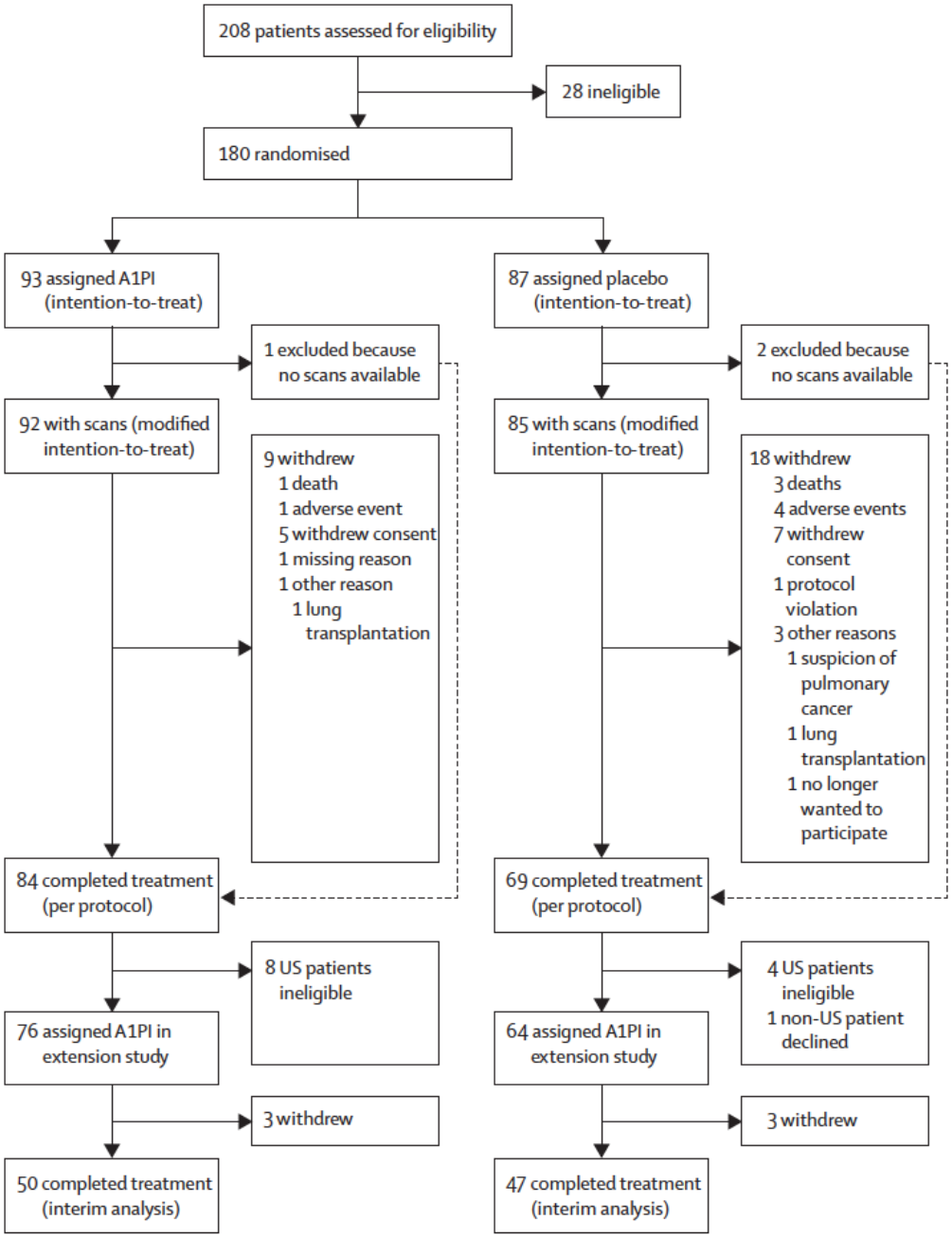
Duration of disease	≤ median at baseline, > median at baseline
Functional A_1-PI levels	< 33 percentile, 33 to 66 percentile, and > 66 percentile
Antigenic A_1-PI levels	< 33 percentile, 33 to 66 percentile, and > 66 percentile

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

RAPID and RAPID extension

In total, 180 patients with A1PI deficiency were randomised and treated at 28 study sites (Figure 11) The intention to treat (ITT) and safety populations comprised 93 subjects who received Respreeza and 87 subjects who received placebo. Of these 180 subjects, 159 were treated as per-protocol: 83 received Respreeza and 76 received placebo. At the end of the two-year study period, all non-US subjects were invited to enrol in the extension study; 99% of non-US patients who completed the RAPID study enrolled into the extension study and received Respreeza.

Figure 11. RAPID and Extension Study Subject Disposition



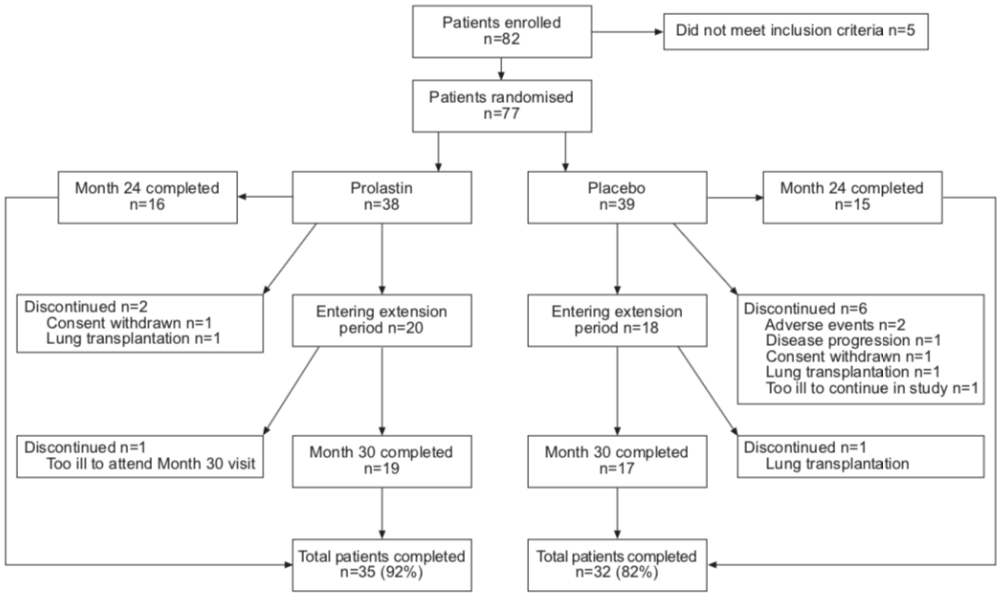
A Randomised Clinical Trial of Alpha1-Antitrypsin Augmentation Therapy, Dirksen et al 1999

As detailed in section 9.4.1, 58 patients were randomised and treated, and two patients withdraw during the study. No further details regarding patient disposition were detailed in the publication.

EXACTLE trial

Patient disposition is illustrated in Figure 12. Of the 82 patients enrolled into the study from the three centres, 77 patients were randomised to Prolastin or placebo, and 71 patients were included in the mITT population. The ITT population who completed the study (either 24 or 30 months) comprised of 67 patients, with 10 patients (three in the Prolastin group and seven in the placebo group) who discontinued prematurely, resulting in a median of 127 weeks of exposure to Prolastin and 108 weeks to placebo. the trial was completed by 34 patients (94%) in the Prolastin group and 31 patients (89%) patients in placebo group, in rewards to the mITT population.

Figure 12. EXACTLE trial subject disposition



9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

RAPID and RAPID extension

Reasons for withdrawal are shown in Figure 11. Fewer patients withdrew from the Respreeza group; the implications of this for study quality are negligible (see discussion of withdrawals in Table 13).

A Randomised Clinical Trial of Alpha1-Antitrypsin Augmentation Therapy (Dirksen et al., 1999)

Reason for withdrawal are shown in Section 9.4.5

A randomised study of augmentation therapy in a1-antitrypsin deficiency - EXACTLE trial (Dirksen et al., 2009)

Reasons for withdrawal are shown in Figure 12

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

A critical appraisal of the RAPID study (Study 4001) and the corresponding open-label extension (Study 3001) is presented in Table 13.

Table 13. Critical Appraisal of RAPID study (Chapman et al., 2015)

Study name	**RAPID**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Subjects were randomised evenly, at a ratio of 1:1. A randomisation list containing the assignment of subject numbers to treatment groups was reproducibly generated by a computerised pseudo-random number generator. A copy of the randomisation list was transferred to the drug supply and logistics group of the Clinical Operations Department at CSL Behring. The randomisation was stratified by centre. Standard operating procedures were followed to ensure confidentiality of the randomisation list.
Was the concealment of treatment allocation adequate?	Yes	This was a double-blind study. Respreeza and placebo were packaged identically. Individual packages were identified only by the subject number. The treatment groups randomised to the subject numbers were only known to the randomisation code administrator, and to the drug supply and logistics group of the Clinical Operations Department at CSL Behring.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	There were no significant imbalances in clinically relevant baseline characteristics between the two study groups in RAPID.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The study was double blinded so patients, caregivers, clinic staff, and other study personnel were blind to efficacy and safety data.

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes	A post-hoc Kaplan-Meier analysis and log rank test revealed a statistically significantly (p = 0.04) lower probability for withdrawal of subjects in the Respreeza group, although the pattern of withdrawals over time was similar for each treatment group. The timings of the withdrawals across the time period of the study suggest that differences present throughout the study influenced the probability of withdrawal rather than events at certain points in time that would be related to specific study design issues. The lower number of subjects who withdrew in the Respreeza arm is attributed to a lower number of subjects withdrawing due to an AE, fewer withdrawals of consent, fewer deaths and fewer "other reasons" (suspicion of pulmonary cancer and disinterest in spending time as a participant).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The study protocol is available and all outcomes have been reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The pre-specified intent-to-treat (ITT) population included all randomised subjects with A1PI deficiency included in the study. In the ITT analysis, subjects were assigned to the treatment to which they were randomised. The number of subjects with major protocol deviations was comparable between the two treatment arms, including the number of subjects who were non-compliant with the investigational medicinal product regimen. The ITT population was the primary population for the analysis of the primary efficacy variable. ITT analyses were performed with and without (observed cases) imputation; some subjects were missing valid CT scans. In the primary analysis, the assumption was made that data were missing at random. Sensitivity analyses were conducted to verify the results of the primary analysis using multiple imputations to replace the missing data. The three sensitivity analyses indicated that the results of the primary analysis are robust with respect to the presence of missing CT data (Section 3.2.1). For endpoint analyses, observed cases were subjects with a baseline and at least 1 endpoint assessment available.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Abbreviations: AE, adverse event; CT, computed tomography

A critical appraisal of the RAPID-OLE study is presented in Table 14.

Table 14. Critical Appraisal of the RAPID-OLE study (McElvaney et al., 2017)

Study name	**RAPID-OLE**

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	RAPID-OLE is an extension trial of RAPID-RCT study. This extension trial was designed as an open-label extension. To ensure that appropriate subjects were selected, eligibility requirements for RAPID-OLE were: patients recruited from RAPID-RCT, and who had either completed 2 years of A1PI treatment at a dose of 60 mg/kg weekly, or had received placebo for 2 years during RAPID-RCT. Further to this, inclusion criteria for RAPID-OLE included: serum A1PI concentrations of less than 11 μM and FEV_1 of 35-70% predicted at randomisation in RAPID-RCT. The entry criteria for both groups (early-start treatment group and delayed-start treatment group) were identical to allow for valid comparisons between the early-start treatment group, and delayed-start treatment group. The study was conducted in 11 countries in 22 hospitals outside of the USA, with the principle investigators considered specialists in the field of study.
Was the concealment of treatment allocation adequate?	No	This is an open-label study, and therefore patients and investigators are aware of the patient's treatment.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	N/A	The main difference between the enrolled groups was that the early-start treatment group had higher antigenic and functional serum concentrations, as compared with the delayed-start treatment group. There were some differences in the AATD genotypes between the early-start treatment group and delayed-start treatment groups, where SZ genotype and Z/null genotypes were present in the early-start treatment group and absent in the delayed-start treatment group.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	As this is an open-label study, patients and investigators are aware of the patient's treatment.
Were there any unexpected imbalances in drop-outs between groups? If so, were	Yes	131 of the planned 140 patients recruited from the RAPID-RCT trial were enrolled. Of those that withdrew from the RAPID-OLE; 6 were from the early-start treatment cohort (1 death, 3 withdrew consent, 1 adverse event –

they explained or adjusted for?		drug abuse, 1 lung transplantation), and 3 were from the delayed-start treatment cohort (1 adverse event, 1 withdrew consent, 1 prolonged vacation).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	All outcomes were reported a priori either in the article or in the appendices.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Since the duration of treatment received was different for patients in the delayed-treatment group who received placebo during RAPID-RCT, compared with the early-start treatment group who had received 60 mg/kg during RAPID-RCT, analyses were conducted accounting for the treatment duration for the full population. An ITT was included to assess the primary outcome on change in lung density (adjusted PD15) at different inspiration states. The RAPID-OLE intention-to-treat (ITT) population comprised all patients enrolled in RAPID-OLE. An analysis was also conducted in the completer population; a subset of the ITT population, comprised patients who had valid lung density values at day 1 in RAPID-RCT and at month 48 in RAPID-OLE.
Was the exposure accurately measured to minimise bias?	Yes	RAPID-OLE was a prospective, interventional study with a planned treatment duration of 24 months. All patients received treatment for 24 months in this period. As this is an extension to RAPID-RCT, the early-start treatment group received A1PI for 48 months (the time point for analysis), and the delay-start treatment group received A1PI for 24 months.
Was the outcome accurately measured to minimise bias?		A statistical analysis plan was created to test for disease modifying characteristics in RAPID-OLE. is an open-label, extension trial assessing sustained efficacy and longer-term safety and tolerability. The primary efficacy outcome was the annual rate of lung density loss assessed by adjusted PD15, which was the primary outcome in RAPID-RCT. Secondary outcomes included spirometric pulmonary function, health-related quality of life using the St George's Respiratory Questionnaire, serum antigenic and functional Q1PI concentrations, and safety (treatment-emergent adverse events, laboratory values, vital signs, and physical findings).
Have the authors taken account of the confounding factors	N/A	

in the design and/or analysis?		
Was the follow-up of patients complete?	N/A	

A critical appraisal of the A Randomised Clinical Trial of Alpha1-Antitrypsin Augmentation Therapy trial (Dirksen et al., 1999) is presented in Table 15.

Table 15. Critical appraisal of A Randomised Clinical Trial of Alpha1-Antitrypsin Augmentation Therapy (Dirksen et al., 1999)

Study name	**A Randomised Clinical Trial of Alpha1-Antitrypsin Augmentation Therapy**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Subjects were randomised evenly by the minimisation method. No further information was provided in the publication.
Was the concealment of treatment allocation adequate?	Not clear	This was a double-blind study with no further information provided in the publication.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	There were no significant imbalances in clinically relevant baseline characteristics between the two study groups as stated in the publication. However, the female/male ratio differed between the centres and the Danes were on average 5 years older.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not clear	The study is stated as double blinded. Any deficiencies in maintaining the blind could impact effort based pulmonary measuments such as FVC and FEV_1, but not measurements such as CT scans and K_{CO}.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes	Two Dutch subjects dropped out of the study during the first 2 years as they resumed smoking. Their data were omitted from further analyses.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	It appears that all outcomes have been reported. As the publication may not provide details on the complete clinical study report we cannot be certain.

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	As two Dutch subjects dropped out of the study during the first 2 years because they resumed smoking and their data were omitted from further analyses.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

A critical appraisal of the EXACTLE trial (Dirksen et al., 2009) is presented in Table 16.

Table 16. Critical Appraisal of EXACTLE trial (Dirksen et al., 2009)

Study name	**EXACTLE Trial**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Subjects were randomly assigned to the treatment or placebo group. When all appropriate study entrance criteria had been met, subjects were randomised in a 1:1 ratio to receive treatment or placebo. A computer-generated random code was used to produce randomisation envelopes that were issued to the unblinded pharmacist or designee at each study centre and which were to be kept confidential. The randomisation envelopes were sent to the pharmacist with the study medication. The randomisation numbers were assigned to subjects in ascending order at the baseline visit, when the subject's eligibility had been confirmed.
Was the concealment of treatment allocation adequate?	Yes	This was a double-blind study .Several measures were taken to ensure blinding, both with regard to the study drug and to the assessment of efficacy results. Blinding of different study groups was guaranteed by ensuring that all subjects received the same total volume per kg body weight of study medication with no visible difference in the external aspect between treatment and placebo (variation in colour by lot was masked by using opaque sleeves).
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Overall, demographics and disease severity for patients at baseline were well distributed between the groups. There were some sex differences between the treatment groups, with more males in the treatment group and more females in the placebo group ($p = 0.021$). There were also sex differences between participating centres: in the UK there were more males enrolled into the study, and in Sweden there were more females. In Denmark, conversely, males and females were equally distributed. All patients

		fulfilled the physiological inclusion criteria, except for two patients with FEV_1 baseline values slightly below 25% predicted.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Throughout the course of the study, individual treatment assignments were unknown to the treating investigators and nurses, the subjects, the clinical management and monitoring team, the central computed tomography (CT) scan facility, and the sponsor's data management, clinical and biostatistical teams. Every effort was made to maintain the integrity of the blinding through locking of the database. The randomisation block size was not disclosed to the study sites. During the course of the study, the randomisation code was maintained in a secure fashion and was made available only to designated unblinded team members, which included the clinical site pharmacy personnel who prepared the study medication and the BeroSearch monitor responsible for monitoring the pharmacy. It is possible that the lack of blinding of participants may impact the lung function tests and SGRQ, but not measurements such as CT parameters.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Not clear	The number of patients in the ITT population who completed the study was 67/77, as 10 patients (three in the Prolastin1 group and seven in the placebo group) discontinued prematurely. In terms of the mITT population, the study was completed by 34 (94%) and 31 (89%) patients in the Prolastin1 and placebo groups, respectively of a total 77 patient.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	It appears that all outcomes have been reported. As the publication may not provide details on the complete clinical study report we cannot be certain.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The pre-specified intent-to-treat (ITT) population included all randomised subjects with A1PI deficiency included in the study. In the ITT analysis, subjects were assigned to the treatment to which they were randomised.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

An overview of the results for RAPID trial are shown in Table 17

Table 17. Outcomes from RAPID trial (Chapman et al., 2015)

Study name		**RAPID trial**
Size of study groups	**Treatment**	93
	Control	87
Study duration	**Time unit**	2 years with 2 years extension
Type of analysis	**Intention-to - treat/per protocol**	Modified Intention to Treat
Primary Outcome	**Name**	Annual rate of decrease in lung density calculated from the shift of the 15th percentile of lung density measured by CT at baseline, 3, 12, 21 and 24 months with TLC and FRC combined
	Unit	g/L
Effect size	**Value**	-1.50 g/L (Treatment group) -2.12 g/L (Placebo group) Absolute difference in lung density between the augmentation treatment group and placebo group: 0.62 g/L per year
	95% CI	-0.02 g/L to 1.26 g/L
Statistical test	**Type**	SAS PROC MIXED
	p value	p=0.06
Primary outcome	**Name**	Separate measurements of PD15 density measures at FRC and TLC alone
	Unit	g/L
Effect size	**Value**	**TLC:** -1.45g/L per year (Treatment group) -2.19g/L per year (Placebo group) **FRC:** 0.48g/L per year (Treatment group) -2.02g/L per year (Placebo group)
	95% CI	**TLC** 0.059 - 1.420 **FRC** -0.22 to 1.18
Statistical test	**Type**	Not stated
	p value	**TLC:** p=0.03 **FRC:** p=0.18

Other outcome	**Name**	Number of exacerbations (severity) *(defined by the Anthonisen criteria)*
	Unit	Annual number of exacerbations occurring in the first 2 years
Effect size	**Value**	**24 months** 1.70 (Treatment group) 1.42 (Control group) **Treatment vs Placebo:** 1.26
	95% CI	**24 months** 1.51 – 1.89 (Treatment group) 1.23 – 1.61 (Control group) **Treatment vs Placebo:** 0.92 – 1.74
Statistical test	**Type**	Not stated
	p value	Not stated
Other outcome	**Name**	Exacerbation relative duration
	Unit	Days
Effect size	**Value**	**24 months** 13.8 (Treatment group) 10.8 (Control group) **Treatment vs Placebo:** 0.56
	95% CI	Not stated
Statistical test	**Type**	Not stated
	p value	**24 months** p=15.0 (Treatment group) p=11.6 (Control group) **Treatment vs Placebo:** p=0.18
Other outcome	**Name**	FEV_1
	Unit	%
Effect size	**Value**	**Baseline** 47.4% (Treatment group) 47.2% (Control group) **24 months** -3.1% (Treatment group) -2.3% (Control group)
	95% CI	Not stated
Statistical test	**Type**	Not stated
	p value	**Treatment vs Placebo:** p=0.21
Other outcome	**Name**	Single-breath diffusion capacity (DL_{CO})
	Unit	mL/mm Hg per min, %
Effect size	**Value**	**Baseline** 13.6% (Treatment group) 15.0% (Control group) **24 months** -2.2% (Treatment group) -1.5% (Control group)
	95% CI	Not stated
Statistical test	**Type**	Not stated

	p value	**Treatment vs Placebo:** p=0.64
Other outcome	**Name**	Baseline and achieved A1PI concentrations (functional and antigenic assays)
	Unit	μM
Effect size	**Value**	**Antigenic** Baseline: 6.38μM (Treatment group), 5.94μM (Control group) 24 months: 10.12μM (Treatment group), -0.07μM (Control group) **Functional** Baseline: 2.88μM (Treatment group), 2.30μM (Control group) 24 months: 7.30μM (Treatment group), 0.12μM (Control group)
	95% CI	Not stated
Statistical test	**Type**	Not stated
	p value	**Treatment vs Placebo** Antigenic: p=0.02 Functional: p=0.02
Other outcome	**Name**	Incremental shuttle walk test
	Unit	Meters (m)
Effect size	**Value**	**Baseline** 424.5m (Treatment group) 435.1m (Control group) **24 months** 10.8m (Treatment group) 16.1m (Control group) **Treatment vs Control:** -13.09m
	95% CI	-49.32 - 23.14
Statistical test	**Type**	Not stated
	p value	**Treatment vs Control:** p=0.48
Other outcome	**Name**	Health Status
	Unit	St George's Respiratory Questionnaire (SGRQ)
Effect size	**Value**	**Baseline** Total: 44.3 (Treatment) / 42.4 (Control) Symptoms: 46.5 (Treatment) / 44.1 (Control) Activity: 62.1 (Treatment) / 60.1 (Control) Impact: 33.6 (Treatment) / 31.4 (Control) **24 months** Total: 1.4 (Treatment) / 2.2 (Control) Symptoms: -1.4 (Treatment) / 2.0 (Control) Activity: 1.7 (Treatment) / 2.6 (Control) Impact: 2.1 (Treatment) / 1.8 (Control) **Treatment vs Control** Total: -0.19 Symptoms: -1.11 Activity: -0.16

		Impact: 0.74
	95% CI	Not stated
Statistical test	**Type**	Not stated
	p value	**Treatment vs Control** Total: p=0.91 Symptoms: p=0.67 Activity: p=0.94 Impact: p=0.72
Comments		The cross-study comparison was conducted to eliminate the risk that the CT lung density outcomes were spurious in nature. The outcomes of this analysis is reported in McElvaney 2017 and strongly support CT lung density as a consistent reliable measure to monitor disease progression. The Early Start group maintained a lower annual lung density decline rate over the Delayed Start group. The 2-year treatment effect was confirmed in the smaller RAPID OLE ITT. The Delayed Start group demonstrated a statistically significant reduction in the annual lung density decline rate temporal to the switch from placebo to active therapy supporting the observation that lung density decline rates are consistently reduced irrespective of the time at which augmentation therapy is introduced. Furthermore given the 4-year treatment duration long term correlations between CT lung density decline and declines in FEV_1, FEV_1 % predicted and FVC were established.

An overview of the results for RAPID-OLE are shown in Table 18, alongside results from RAPID RCT. RAPID-OLE investigated early-start treatment and delayed-start treatment.

Table 18. Outcomes from RAPID-OLE

Study name		**RAPID-OLE**
Size of study groups	**Early-start treatment group**	76
	Delayed-start treatment group	64
Study duration	**Time unit**	24 months
Type of analysis	**Intention-to - treat/per protocol**	Intention to treat using mixed-effects regression model
Primary Outcome	**Name**	Change in lung density (adjusted PD15) at TLC different inspiration states in RAPID-RCT and RAPID-OLE (early-start treatment group and delayed-start treatment group) – ITT population
	Unit	g/L per year
Effect size	**Value**	**TLC:** -0.75 g/L per year (RAPID-RCT, day 1 to month 24) -0.37 g/L per year (RAPID-OLE, month 24 to month 48) **FRC:**

		0.45 g/L per year (RAPID-RCT, day 1 to month 24) -0.18 g/L per year (RAPID-OLE, month 24 to month 48) **TLC+FRC:** 0.60 g/L per year (RAPID-RCT, day 1 to month 24) -0.28 g/L per year (RAPID-OLE, month 24 to month 48)
	95% CI	**TLC:** 0.02 to 1.47 (RAPID-RCT, day 1 to month 24) -1.16 to 0.42 (RAPID-OLE, month 24 to month 48) **FRC:** -0.31 to 1.21 (RAPID-RCT, day 1 to month 24) -1.09 to 0.74 (RAPID-OLE, month 24 to month 48) **TLC+FRC:** -0.09 to 1.30 (RAPID-RCT, day 1 to month 24) -1.09 to 0.53 (RAPID-OLE, month 24 to month 48)
Statistical test	**Type**	One-sided
	p value	**TLC:** P= 0.0210 (RAPID-RCT, day 1 to month 24) P=0.8233 (RAPID-OLE, month 24 to month 48) **FRC:** P=0.1235 (RAPID-RCT, day 1 to month 24) P=0.6482 (RAPID-OLE, month 24 to month 48) **TLC+FRC:** P=0.0447 (RAPID-RCT, day 1 to month 24) P=0.7519 (RAPID-OLE, month 24 to month 48)
Primary Outcome	**Name**	Change in lung density (adjusted PD15) at different inspiration states in RAPID-RCT and RAPID-OLE (early-start treatment group and delayed-start treatment group) – Completer population
	Unit	g/L per year
Effect size	**Value**	**TLC:** -0.75 g/L per year (RAPID-RCT, day 1 to month 24) -0.17 g/L per year (RAPID-OLE, month 24 to month 48) **FRC:** 0.29 g/L per year (RAPID-RCT, day 1 to month 24) -0.01 g/L per year (RAPID-OLE, month 24 to month 48) **TLC+FRC:** 0.52 g/L per year (RAPID-RCT, day 1 to month 24) -0.11 g/L per year (RAPID-OLE, month 24 to month 48)
	95% CI	**TLC:** -0.03 to 1.53 (RAPID-RCT, day 1 to month 24) -0.93 to 0.59 (RAPID-OLE, month 24 to month 48) **FRC:** -0.53 to 1.12 (RAPID-RCT, day 1 to month 24) -0.87 to 0.85 (RAPID-OLE, month 24 to month 48) **TLC+FRC:** -0.23 to 1.28 (RAPID-RCT, day 1 to month 24) -0.88 to 0.66 (RAPID-OLE, month 24 to month 48)
	Type	One-sided

Statistical test	**p value**	**TLC:** P= 0.0291 (RAPID-RCT, day 1 to month 24) P=0.6715 (RAPID-OLE, month 24 to month 48) **FRC:** P=0.2412 (RAPID-RCT, day 1 to month 24) P=0.5114 (RAPID-OLE, month 24 to month 48) **TLC+FRC:** P=0.0870 (RAPID-RCT, day 1 to month 24) P=0.6094 (RAPID-OLE, month 24 to month 48)
Primary Outcome	**Name**	Annual rate of adjusted 15th percentile lung density loss measured by CT at baseline – mean difference (early-start treatment group and delayed-start treatment group) - day 1 to month 24
	Unit	g/L per year
Effect size	**Value**	0.75
	95% CI	0.03 to 1.47
Statistical test	**Type**	One-sided
	p value	0.0210
Primary outcome	**Name**	Annual rate of adjusted 15th percentile lung density loss – mean difference (early-start treatment group and delayed-start treatment group) - month 24 to month 48
	Unit	g/L per year
Effect size	**Value**	-0.37
	95% CI	-1.16 to 0.42
Statistical test	**Type**	One-sided
	p value	0.822
Other outcome	**Name**	Absolute change of adjusted 15th percentile lung density loss – mean difference (early-start treatment group and delayed-start treatment group) - day 1 to month 48
	Unit	g/L per year
Effect size	**Value**	0.67
	95% CI	-1.09 to 2.42
Statistical test	**Type**	Two-sided
	p value	0.4530
Other outcome	**Name**	Percentage change of adjusted 15th percentile lung density loss – mean difference (early-start treatment group and delayed-start treatment group) - day 1 to month 48
	Unit	g/L per year
Effect size	**Value**	2.77
	95% CI	-1.37 to 6.92
Statistical test	**Type**	Two-sided
	p value	0.1879
Other outcome	**Name**	Rate of change in lung density decline rate at total lung capacity – RAPID OLE month 24 to month 48 (A1PI early-start group vs A1PI delayed-start group)
	Unit	g/L per year
Effect size	**Value**	0.17

	95% CI	SE 0.23 (95% CI -0.28 to 0.62)
Statistical test	**Type**	Two-sided
	p value	0.4581
Other outcome	**Name**	Rate of change in lung density decline rate at total lung capacity – RAPID-RCT day 1 to month 24 A1PI versus RAPID-OLE month 24 to month 48 early-start treatment group
	Unit	g/L per year
Effect size	**Value**	-0.04
	95% CI	SE 0.15 (95% CI -0.32 to 0.25)
Statistical test	**Type**	Two-sided
	p value	0.8036
Other outcome	**Name**	Rate of change in lung density decline rate at total lung capacity – RAPID-RCT day 1 to month 24 A1PI versus RAPID-OLE month 24 to month 48 delayed-start treatment group
	Unit	g/L per year
Effect size	**Value**	0.52
	95% CI	SE 0.16 (95% CI 0.22 to 0.83)
Statistical test	**Type**	Two-sided
	p value	0.0008
Comments		

TC=Total Lung Capacity; FRC=Functional Residual Capacity; ITT=Intention to treat; Adjusted PD15=lung volume adjusted 15th percentile of the lung density

An overview of the results from the Randomised Clinical Trial of alpha1-Antityrpsin Augmentation Therapy are shown in Table 19.

Table 19. Outcomes from A Randomised Clinical Trial of alpha1-Antityrpsin Augmentation Therapy (Dirksen et al., 1999)

Study name		A Randomized Clinical Trial of alpha1-Antitrypsin Augmentation Therapy
Size of study groups	**Treatment**	28 (13 Danish and 15 Dutch)
	Control	28 (13 Danish and 15 Dutch)
Study duration	**Time unit**	The study was terminated after five years and all subjects were treated for three years
Type of analysis	**Intention-to - treat/per protocol**	Modified intention to treat (Two Dutch subjects dropped out of the study during the first 2 yr because they resumed smoking. Their data were omitted from further analyses)
Primary Outcome	**Name**	Patient-administered Serial Spiromentry (PASS) FEV_1 (measured at home)
	Unit	mL
Effect size	**Value**	**Treatment vs Placebo (annual change)** 26.5 (± 15.1) vs 25.2 (± 22)
	95% CI	Not stated
Statistical test	**Type**	Not Stated in Publication
	p value	No significant difference (p=0.96)
Other outcome	**Name**	15^{th} percentile point of the lung density distribution of the whole lung measured by CT scanning
	Unit	g/L
Effect size	**Value**	**Treatment vs Placebo (annual change)** 1.50 (± 0.41) vs 2.57 (± 0.41)
	95% CI	0.7 to 2.3 g/L
Statistical test	**Type**	Not stated
	p value	p=0.07
Other outcome	**Name**	15^{th} percentile point of the lung density distribution of a sice 5 cm below the carina measured by CT scanning
	Unit	g/L
Effect size	**Value**	**Treatment vs Placebo (annual change)** 1.90 (± 0.47) vs 2.74 (± 0.46)
	95% CI	Not stated
Statistical test	**Type**	Not stated
	p value	p=0.21
Other outcome	**Name**	FVC maneuver FEV_1
	Unit	mL
Effect size	**Value**	**Treatment vs Placebo (annual change)** 78.9 (± 12.0) vs 59.1 (± 11.9)
	95% CI	Not stated
Statistical test	**Type**	Not stated
	p value	p=0.25
Other outcome	**Name**	FVC maneuver FVC
	Unit	mL
Effect size	**Value**	**Treatment vs Placebo (annual change)** 33.1 (± 27.1) vs 8.1 (± 27.0)
	95% CI	Not stated
Statistical test	**Type**	Not stated

	p value	p=0.52
Other outcome	**Name**	Slow vital capacity maneuver VC
	Unit	mL
Effect size	**Value**	**Treatment vs Placebo (annual change)** 77.4 (± 23.3) vs 49.9 (± 23.2)
	95% CI	Not stated
Statistical test	**Type**	Not stated
	p value	p=0.41
Other outcome	**Name**	Diffusion Capacity (DL_{CO})
	Unit	mmol/min/kPa
Effect size	**Value**	**Treatment vs Placebo (annual change)** 0.19 (± 0.04) vs 0.16 (± 0.04)
	95% CI	Not stated
Statistical test	**Type**	Not stated
	p value	p=0.6
Other outcome	**Name**	K_{LCO}
	Unit	mmol/min/kPa
Effect size	**Value**	**Treatment vs Placebo (annual change)** 0.0168 (± 0.004) vs 0.0162 (± 0.004)
	95% CI	Not stated
Statistical test	**Type**	Not stated
	p value	p=0.92
Comments		250 mg/kg monthly administrations were not successful in maintaining AAT serum concentrations above 11 uM for the full 28 days. However this was the first trial to establish a trend towards reduced annual lung density decline rates in favour of augmentation therapy.

An overview of the results from the Randomised Clinical Trial of alpha1-Antityrpsin Augmentation Therapy are shown in Table 20

Table 20. Outcomes from EXACTLE trial (Dirksen et al., 2009)

Study name		EXACTLE trial
Size of study groups	**Treatment**	35 (Prolastin)
	Control	32 (Placebo)
Study duration	**Time unit**	30 months
Type of analysis	**Intention-to - treat/per protocol**	Intention to treat (ITT) and modified intention to treat (MITT)
Primary Outcome	**Name**	Change in the 15th percentile lung density (PD15) derived from the CT voxel distribution histogram of the whole lung
	Unit	**Total Lung Capacity (TLC) adjusted 15th percentile lung density (PD15)** TLC-adjusted PD15 (Method 1): g.L^{-1}.yr^{-1} Statistically adjusted PD15 (Method 2): g.L^{-1}.yr^{-1} TLC-adjusted PD15 (Method 3): g.L^{-1} Statistically adjusted PD15 (Method 4): g.L^{-1}
Effect size	**Value**	**Mean Change** TLC-adjusted PD15 (Method 1): -2.24 Statistically adjusted PD15 (Method 2): -1.81 TLC-adjusted PD15 (Method 3): -4.80 Statistically adjusted PD15 (Method 4): -4.12
	95% CI	Not stated
Statistical test	**Type**	F-test
	p value	TLC-adjusted PD15 (Method 1): p=not significant Statistically adjusted PD15 (Method 2): p=not significant TLC-adjusted PD15 (Method 3): p=not significant Statistically adjusted PD15 (Method 4): not stated
Other outcome	**Name**	Lung function
	Unit	FEV_1: mL.yr^{-1} DL_{CO}: mmol.min^{-1}.kPa^{-1}.yr^{-1} Kco: mmol.min^{-1}.kPa^{-1}. L^{-1}.yr^{-1}
Effect size	**Value**	FEV_1: -23 DL_{CO}: -0.37 Kco: -0.036
	95% CI	Not stated
Statistical test	**Type**	F-test
	p value	FEV_1: p=<0.01 DL_{CO}: p=not significant Kco: p=<0.05
Other outcome	**Name**	Health-related quality of life
	Unit	St. Georges Respiratory Questionnaire (SGRQ)
Effect size	**Value**	**Mean change** Overall: 0.81 Symptom domain: -0.09 Activity domain: 2.58 Impacts domain: -0.15
	95% CI	Not stated

Statistical test	**Type**	F-test
	p value	Overall: p=<0.01 Symptom domain: p=<0.01 Activity domain: p=<0.05 Impacts domain: p=<0.01
Comments		This was the first RCT to establish a trend towards reducing lung density decline rates as assessed by CT scans at TLC with weekly administration of 60 mg/kg. A correlation between annual lung density decline rates and the annual rate of FEV_1 loss was established.

Summary of efficacy for Respreeza vs placebo, RAPID study

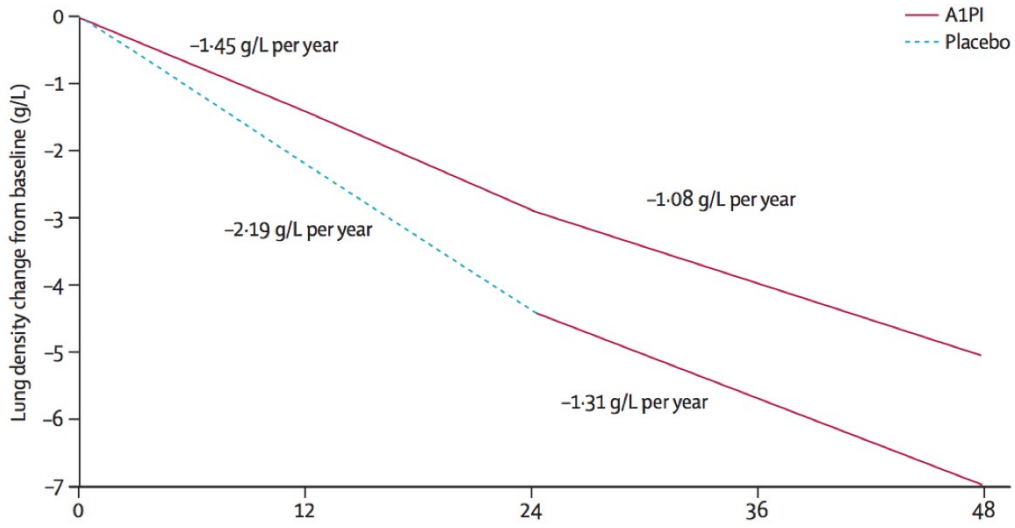
- Registry data from the UK have shown that lung density as measured by CT is predictive of both mortality and quality of life in persons with emphysema due to A1PI deficiency (Stockley, 2015).
- Respreeza slowed the annual rate of lung density decline by 34% over 2 years: the rate of decline was -1.45 g/L/y with Respreeza versus -2.19 g/L/y with placebo (difference 0.74 g/L/y, p = 0.03).
- Patients treated with Respreeza in the initial study and also the extension study maintained a reduced annual decline rate across all four years (1.51 g/L/y RAPID vs -1.63 g/L/y RAPID OLE).
- Patients switching from placebo to Respreeza in the extension study demonstrated a statistically significant reduction in the annual lung density decline rate temporal to the introduction of active therapy (0.52, p=0.001).
- Patients treated with Respreeza maintained trough levels of serum antigenic A1PI above the protective 11 μM threshold throughout the RAPID trial and extension.
- RAPID was not powered to detect significant between-group differences in other end points. However, patients treated with Respreeza had improvements in the SGRQ symptoms score at 24 months compared with baseline, whereas scores for placebo patients worsened (change from baseline of -1.4 and -2.0, respectively, difference did not reach statistical significance).

Primary outcome measure: reduction in rates of lung density decline

Respreeza, administered weekly at a dose of 60 mg/kg body weight, reduced the rate of lung density decline in patients with A1PI deficiency when compared with placebo in the RAPID trial Figure 13.

Respreeza demonstrated a consistent effect in slowing the annual rate of lung density decline compared to placebo. The annual rate of lung density decline, as measured by CT scan at total lung capacity (TLC) over 2 years was lower with Respreeza (-1.45 g/L/y) than with placebo (-2.19 g/L/y), reflecting a 34% reduction (difference 0.74 g/L/y, p = 0.03, n=180).

Figure 13. Rates of lung density decrease at TLC during 24-month RAPID study



The efficacy of Respreeza was further confirmed in the extension study. Upon entry to the extension study, any patients that were randomised to placebo in the RAPID study were switched to Respreeza ("Delayed Starters") while all patients randomised to Respreeza in RAPID continued to receive Respreeza for another 2 years in the extension ("Early Starters").

An analysis of the RAPID extension subjects (n=130) in the first 24 months of therapy in the RAPID OLE trial demonstrated that the annual rate of lung density decline as measured by TLC was also reduced by 0.750 g/L/y (p=0.021) Figure 15. This represents a consistent, statistically significant effect in a sample size which was 27% smaller than the RAPID trial ITT (McElvaney et al., 2017).

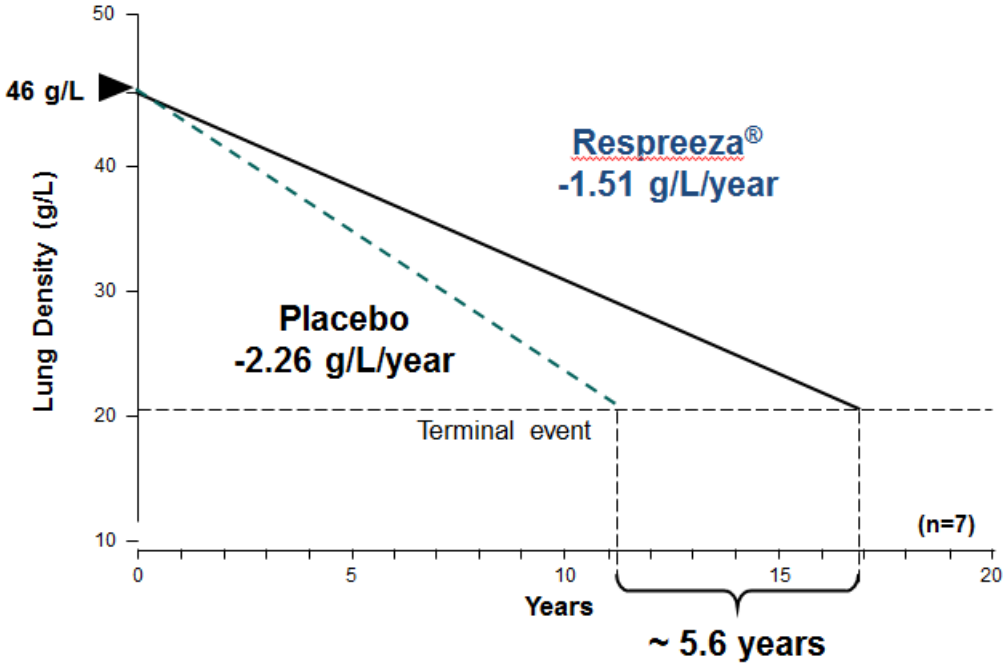
Furthermore, the annual lung density decline rate for the Delayed Start group was reduced from -2.26 g/L/y while administered placebo in the RAPID trial to -1.26 g/L/y while receiving Respreeza in the RAPID extension trial. In a mixed model which assessed lung density decline across trials, the lung density decline rate was reduced

by 0.52 g/L/y (p=0.001) temporal to the switch from placebo to active therapy in the Delayed Start group.

The Early Start group maintained a reduced annual decline rate across all four years. In terms of annual lung density decline rates, the subjects in the Delayed Start group failed to “catch-up” with the Early Start group.

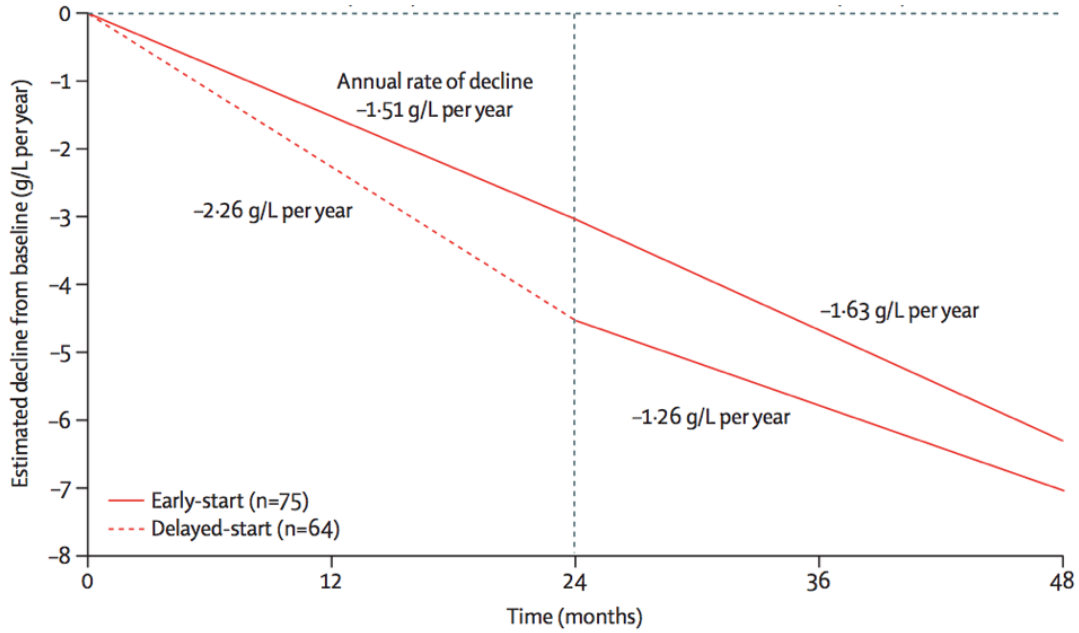
Lastly an analysis was conducted assessing the time to respiratory crisis which favoured active therapy by 5.6 years (CSLB Data on File). The respiratory crisis threshold was determined to be 19.5 g/L based on the average last recorded lung density assessments in patients who either died, underwent lung transplantation or withdrew due to severe respiratory complaint. The mean baseline lung density for all RAPID patients was 46 g/L and the 5.6 years was the result of extrapolation from 46 g/L to 19.5 g/L with either a rate of -1.51 g/L/y with active therapy or -2.26 for placebo administration.

Figure 14. Extrapolated prolongation of time to respiratory crisis



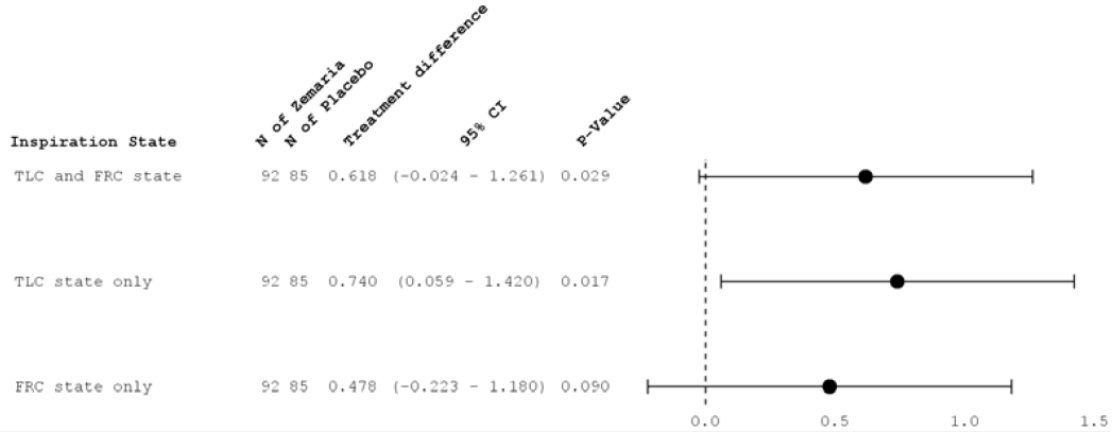
Taken together these results confirm that treatment with Respreeza effectively reduces the rate of annual lung density decline to preserve lung tissue which can never be regained irrespective of when treatment commences.

Figure 15. Rates of lung density decrease at TLC during the double-blind and open-label portions of the trial in patients completing the open-label study (ITT)



Given that a combined TLC/FRC was thought to be optimal for detecting changes in lung density over time at the time of protocol design for the RAPID trial, results of lung density decline at combined TLC/FRC are presented in Figure 16.

Figure 16. Comparison of RAPID results of lung density decline at combined TLC/FRC and FRC only, and the optimal measure of TLC only



Sensitivity analyses

Three sensitivity analyses were conducted to assess how missing CT data may have affected the validity of the conclusion drawn from the primary analysis. The analyses were performed using the lung density decline at TLC and FRC combined.

The complete-case analysis with a potential bias in favour of Respreeza revealed a treatment difference in the annual rate of lung density decline of 0.59 g/L in favour of Respreeza. The pattern-mixture model with a potential bias in favour of placebo revealed a treatment difference of 0.54 g/L in favour of Respreeza, and the most

conservative worst-case approach revealed a treatment difference of 0.71 g/L in favour of Respreeza. Taken together, these sensitivity analyses revealed consistent trends of reductions in the annual rates of decline in CT lung density in favour of Respreeza, as compared with placebo, indicating that the results of the primary analysis are robust with respect to the presence of missing CT data Table 21.

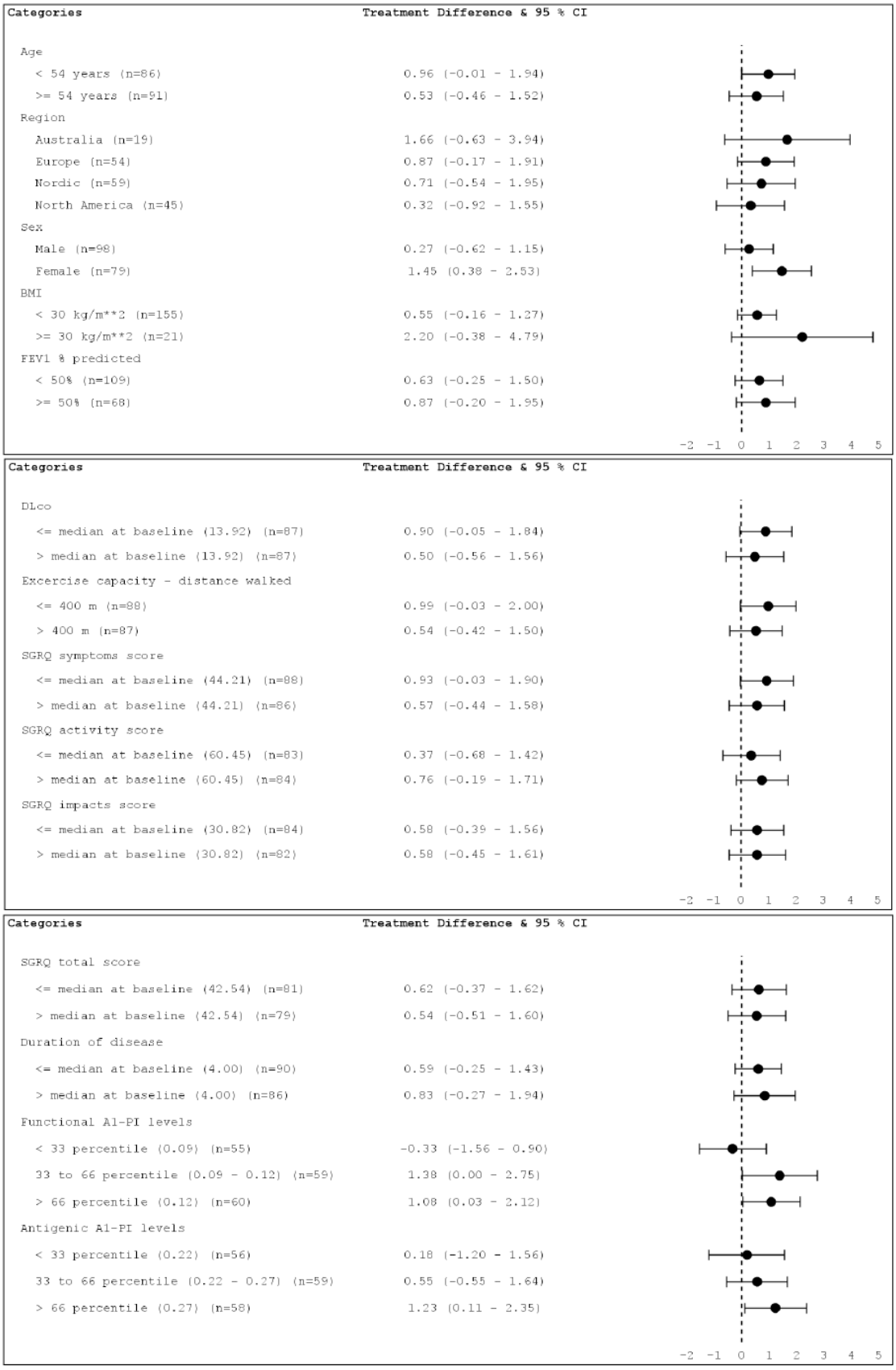
Table 21. Sensitivity analysis to assess impact of missing data at the combined FRC and TLC state in RAPID study

Analysis	Respreeza		Placebo		Difference (95% CI)	1-sided p-value
	Number	Mean (SE)	Number	Mean (SE)		
Complete-case analysis	80	-1.49 (0.22)	67	-2.08 (0.25)	0.59 (-0.07; 1.25)	0.040
Pattern-mixture model	93	-1.58 (0.22)	87	-2.13 (0.24)	0.54 (-0.09; 1.17)	0.047
Worst-case approach	93	-1.55 (0.33)	87	-2.26 (0.34)	0.71 (-0.23; 1.64)	0.068

Abbreviations: CI, confidence interval; SE, standard error

The only pre-defined subgroup analyses that resulted in statistically significant differences between arms were gender and A1PI levels (Figure 17). A greater treatment benefit was observed in females (1.45 g/L/y) (1-sided p-value = 0.004) compared to males (0.27 g/L/y). Patients with either functional or antigenic A1PI levels below the 33rd percentile at baseline experienced less treatment benefit than those with higher levels.

Figure 17. Treatment differences in rate of decline in lung density (g/L) by various baseline parameters at the TLC state in RAPID study



Non-primary endpoints

Results of non-primary endpoint investigations are summarised in Table 22, which gives an overview of results of A1PI blood levels, the SGRQ, the ISWT and the rates of pulmonary exacerbations in patients treated with Respreeza and patients treated a placebo over the 2-year period.

The RAPID study was not powered to detect the treatment effect on changes in pulmonary function tests, DLco, ISWT or SGRQ scores. Powering to show an effect on FEV_1 would require 1,100 subjects (Miravitlles et al., 2017). For these reasons, and as expected, there were no significant differences between Respreeza and placebo in non-primary endpoints other than A1PI concentrations.

Table 22. Non-primary endpoint results for Respreeza and placebo in the RAPID study

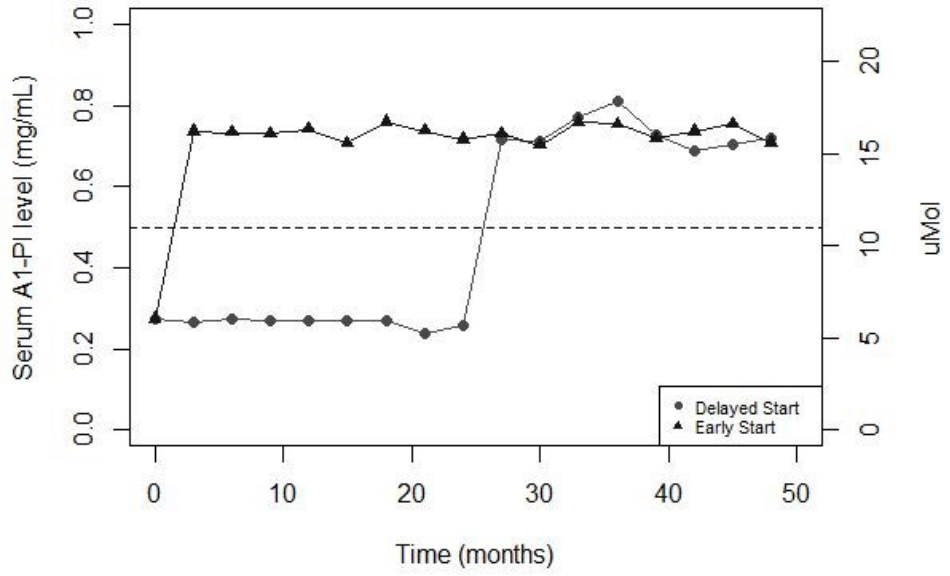
	Respreeza (n=93)		**Placebo (n=87)**		**Respreeza vs. placebo**
	Baseline	24 months	Baseline	24 months	Least-square mean difference
FEV_1 % Predicted	47.4% (12.1)	−3.1% (10.7)	47.2% (11.1)	−2.3% (13.1)	−2.26%* (p=0.21)
DLco (mL/mm Hg per min; %)	13.6% (5.3)	−2.2% (18.2)	15.0% (5.6)	−1.5% (19.5)	−1.31%* (p=0.64)
SGRQ score					
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)
Shuttle walk distance (m)	424.5 (183.0)	10.8 (139.8)	435.1 (199.7)	16.1 (101.6)	−13.09* (p=0.48)
A1PI concentration (μM)					
Antigenic	6.38 (4.62)	10.12 (3.52)	5·94 (2·42)	−0.07 (1.32)	10.05† (p=0.02)
Functional	2.88 (3.65)	7.30 (2.50)	2·30 (1·34)	0.12 (0.96)	7.18† (p=0.02)
Exacerbations					
Annual number	1.70 (1.51–1.89)		1.42 (1.23–1.61)		1.26§ (0.92–1.74)
Relative duration (days)	13.8 (15.0)		10.8 (11.6)		0.56 (p=0.18)

Data are mean (SD) or n (95% CI), unless otherwise stated.
FEV_1=forced expiratory volume in 1 s; DLco=diffusion capacity; SGRQ=St George's Respiratory Questionnaire.
**Adjusted for country, treatment group, and baseline values.*
†Based on a post-hoc analysis and are the results from t tests.
§Presented as an adjusted risk ratio from a negative binomial regression model in which country and treatment were fixed effects, and adjustment was made for treatment duration.

Changes in A1PI Blood Serum Levels

An important goal of treatment is to raise the serum levels of A1PI above 11 µM. Figure 18 clearly shows that Respreeza maintained through level above the protective 11 µM threshold in the RAPID trial.

Figure 18. Mean trough serum antigenic A1PI concentrations in the RAPID study and extension



The simultaneous goals of treatment for A1PI deficiency are to preserve lung tissue and slow the decline in lung density.

SGRQ

Higher scores in the SGRQ indicate more limitations in terms of overall health, daily life, and perceived well-being in subjects with obstructive airways disease (Nagai et al., 2015). In the secondary endpoint analysis, patients treated with Respreeza had improvements in the SGRQ symptoms score at 24 months compared with baseline, whereas the score of placebo patients worsened (change from baseline of -1.4 and 2.0, respectively). In the additional exploratory analyses, patients treated with Respreeza also had less worsening in the activity domain (1.7 versus 2.6) and less worsening in the total SGRQ score (1.4 versus 2.2) than placebo patients. However, none of these treatment differences were statistically significant.

A Randomized Clinical Trial of alpha1-Antitrypsin Augmentation Therapy

Results from the study illustrated similar results of the pulmonary function tests and CT lung densities. No adverse events were observed in the treatment or placebo group.

Primary outcome measure: Daily FEV_1 measured at home

No significant difference (p = 0.96) was observed between the annual decline in the treatment (26.5ml +/-15.1ml) and placebo group (25.2 +/- 22.0ml)

15th percentile point of the lung density distribution of the whole lung measured by CT scanning

Results suggested that compared with placebo, treatment inhibited the annual loss of lung tissue by 1.07g/L (p = 0.07)

Secondary outcomes

Results of the secondary outcomes of the study is discussed in Table 19.

Table 19.

EXACTLE trial

Primary outcome measure: Change in the PD15 derived from the CT voxel distribution histogram of the whole lung

In the treatment (Prolastin) and placebo group a significant difference in lung density decline was observed with all four analytical methods (Section 9.4.1, Table 10 and Figure 10), suggesting a trend towards a beneficial treatment effect with Prolastin (range: p = 0.049 – 0.084).

Using Method 1, the change in TLC-adjusted PD15 from baseline over the course of the study illustrated an increase in the difference in lung density increased with time between the treatment and placebo group (Figure 19). Measured decline in lung density showed a significant difference (p<0.001) between the centres, however between centre and treatment no significant interation was identified. Thus, variation between centres did not have an impact on the differences in the treatment effect observed between the two groups.

Throughout the study mean values of lung volume by CT remained unaltered. However, individual patients showed wide variation in lung volume between scans. For both treatment groups, when there was no change in lung volume a significant (p<0.001) decrease in lung density was observed. Indicating a proportion of the loss of lung density was consistant with an absolute loss of lung mass, which was greater

in the placebo group and not secondary to progressive hyperinflation. This was further supported from the mean values of CT-measured lung weight, which observed a decrease in both treatment groups. A greater decrease in lung weights was observed in the placebo group, however the treatment difference was not statistically different.

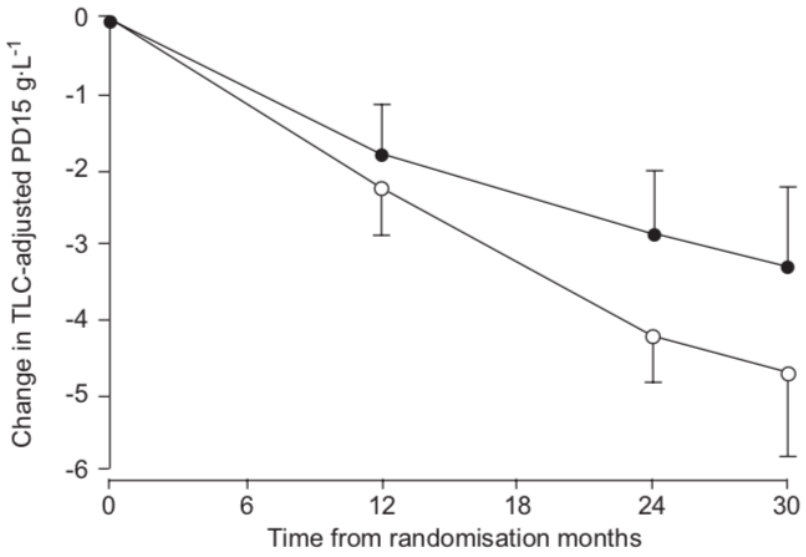
Secondary outcomes

A slight decrease was seen in both treatment groups for FEV_1, DL_{CO}, and K_{CO}, however no significant differences were observed between the treatment and placebo group as these measures were less sensitive than CT

Detailed results of the secondary outcomes of the study is discussed in An overview of the results from the Randomised Clinical Trial of alpha1-Antityrpsin Augmentation Therapy are shown in Table 20

Table 20

Figure 19. Change from baseline in total lung capacity (TLC)-adjusted 15th percentile lung density (PD15) over the course of the study using Method 1 for densitometric analysis on the modified intent-to-treat population.



9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

An mITT population was considered in the RAPID study as one patient assigned to A1PI treatment and two patients assigned to placebo were excluded due to no CT scans available (patients needed at least one evaluable lung density measurement).

9.7 Adverse events

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The identification of studies reporting safety data for Respreeza is described in sections 9.1 to 9.5. Detailed safety data from the RAPID and OLE studies are also provided.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.

The overall adverse event (AE) profile observed with Respreeza during five clinical studies was similar to that of placebo, and the types of AE reported in the clinical trials are very similar to those that arise due to the underlying disease. Respreeza was well tolerated in patients with A1PI deficiency and most adverse events were mild or moderate in intensity (Chapman et al., 2009). No subjects developed A1PI antibodies and there was no indication of viral transmission during any of the clinical studies with Respreeza.

Overall, the proportion of subjects with a treatment-emergent adverse event (TEAE) were similar between the Respreeza and placebo groups in the RAPID and OLE study Table 23 (Chapman et al., 2015)and Table 24Table 24. Summary of TEAEs in the RAPID-OLE study (McElvaney et al., 2017). Four patients died during the RAPID study (1 in the Respreeza group, 3 in the placebo group). Nine subjects receiving Respreeza withdrew from the trial prematurely compared to 18 from the placebo group (p=0.04). In the Respreeza group, one subject had a related TEAE (back pain), which led to withdrawal. Comparatively, in the placebo group there were five subjects who experienced a total of 11 TEAEs that led to withdrawal from the study. In RAPID-OLE, one patient died during the study.

Table 23. Summary of TEAEs in the RAPID study (Chapman et al., 2015)

	Respreeza (N=93)		Placebo (N=87)	
	Number of subjects	Number of events	Number of subjects	Number of events
Any TEAE	92 (99%)	1298 (7.58)	86 (99%)	1068
Mild Moderate Severe	13 (14%) 54 (58%) 25 (27%)	- - -	16 (18%) 43 (49%) 27 (31%)	- - -
Any related TEAE	21 (23%)	91 (0.53)	21 (24%)	50
Any serious TEAE	28 (30%)	57 (0.33)	28 (32%)	45
Any related serious TEAE	1 (1%)	1 (0.01)	1 (1%)	1
Any TEAE leading to withdrawal from study	1 (1%)	1 (0.01)	4 (5%)	10
Any related TEAE leading to withdrawal from study	1 (1%)	1 (0.01)	1 (1%)	4
Death due to TEAE	1 (1%)	1 (0.01)	3 (3%)	3

Abbreviations: TEAE, treatment-emergent adverse event

Table 24. Summary of TEAEs in the RAPID-OLE study (McElvaney et al., 2017)

	Early-start (N=76)		Delayed-start (N=87)	
	Number of subjects	Number of events	Number of subjects	Number of events
Any TEAE	76 (100%)	773 (5.28)	62 (96.9%)	620 (4.97%)
Mild Moderate Severe	15 (19.7%) 38 (50%) 23 (30.3%)	- - -	10 (15.6%) 33 (51.6%) 19 (29.7%)	- - -
Any related TEAE	11 (14.5%)	21 (0.14)	7 (10.9%)	7 (0.06%)
Any serious TEAE	28 (36.8%)	57 (0.39)	23 (35.9%)	56 (0.45%)
Any related serious TEAE	1 (1.3%)	1 (0.01)	3 (4.7%)	3 (0.02%)
Death due to TEAE	1 (1.3%)	1 (0.01)	0	0
Death due to related TEAE	0	0	0	0

Table 25 shows the summary of TEAEs by preferred term. Headache was the most common TEAE, affecting 37 Respreeza patients and 33 placebo patients, respectively, but with a lower number of events in the Respreeza arm (98 and 105, respectively). There were more (≥10) bronchitis, respiratory disorders, nausea and condition aggravated events in the Respreeza group than the placebo group but more cases of pneumonia in the placebo group.

Table 25. Reported TEAEs and exposure-adjusted incidence rates organised by selected system organ classifications and preferred terms experienced by ≥10% of patients in either treatment group (Chapman et al., 2015)

	Respreeza (N=93)		Placebo (N=87)	
	Number (%) of subjects	Number of events	Number (%) of subjects	Number of events
Any event	92 (98.9)	1298	86 (98.9)	1068 (7.23)
Infections and infestations	**77 (83%)**	**334 (1.95)**	**76 (87%)**	**369 (2.50)**
Bronchitis	12 (13%)	26 (0.15)	11 (13%)	16 (0.11)
Influenza	14 (15%)	14 (0.08)	10 (11%)	12 (0.08)
Nasopharyngitis	30 (32%)	53 (0.31)	26 (30%)	58 (0.39)
Pneumonia	11 (12%)	15 (0.09)	12 (14%)	25 (0.17)
Sinusitis	12 (13%)	17 (0.10)	10 (11%)	18 (0.12)
Upper respiratory	14 (15%)	26 (0.15)	14 (16%)	25 (0.17)
Lower respiratory	18 (19%)	88 (0.51)	17 (20%)	72 (0.49)
Viral*	3 (3%)	5 (0.03)	4 (5%)	6 (0.04)
Respiratory disorders	**63 (68%)**	**249 (1.45)**	**49 (56%)**	**127 (0.86)**
Chronic obstructive pulmonary disease	30 (32%)	107 (0.63)	20 (23%)	53 (0.36)
Cough	20 (22%)	31 (0.18)	7 (8%)	7 (0.05)
Dyspnoea	17 (18%)	29 (0.17)	10 (11%)	11 (0.07)
Oropharyngeal pain	22 (24%)	36 (0.21)	10 (11%)	13 (0.09)
Gastrointestinal disorders	**46 (49%)**	**104 (0.61)**	**47 (54%)**	**92 (0.62)**
Nausea	15 (16%)	23 (0.13)	8 (9%)	11 (0.07)
General and administration site disorders	**48 (52%)**	**144 (0.84)**	**42 (48%)**	**101 (0.68)**
Condition aggravated	20 (22%)	62 (0.36)	14 (16%)	41 (0.28)
Fatigue	8 (9%)	14 (0.08)	10 (11%)	12 (0.08)
Pyrexia	13 (14%)	15 (0.09)	6 (7%)	8 (0.05)
Nervous system	**46 (49%)**	**194 (1.13)**	**43 (49%)**	**134 (0.91)**
Headache	37 (40%)	98 (0.57)	33 (38%)	105 (0.71)
Musculoskeletal and connective tissue disorders	**35 (38%)**	**68 (0.40)**	**37 (43%)**	**75 (0.51)**
Back pain	12 (13%)	12 (0.07)	10 (11%)	12 (0.08)

Table 26. TEAEs reported ≥10%of patients and exposure-adjusted incidence rates by MedDRA preferred term (safety population) (McElvaney et al., 2017)

	Early-start (N=76)		Delayed-start (N=87)	
	Number (%) of subjects	Number of events	Number (%) of subjects	Number of events
Any event	76 (100%)	773 (5.28%)	62 (96.9%)	620 (4.97%)
Bronchitis	8 (10.5%)	15 (0.15)	4 (6.3%)	7 (0.06)
Influenza	6 (7.9%)	7 (0.05)	10 (15.6%)	11 (0.09)
Nasopharyngitis	24 (31.6%)	34 (0.23)	16 (25%)	38 (0.30)
Pneumonia	8 (10.5%)	13 (0.09)	7 (10.9%)	10 (0.08)
Oral Candidiasis	5 (6.6%)	16 (0.11)	8 (12.5%)	21 (0.17)
Upper respiratory	11 (14.5%)	23 (0.16)	6 (9.4%)	15 (0.12)
Lower respiratory	11 (14.5%)	66 (0.45)	6 (14.1%)	48 (0.38)
Chronic obstructive pulmonary disease	35 (46.1%)	105 (0.72)	21 (32.8%)	75 (0.60)
Cough	8 (10.5%)	16 (0.11)	7 (10.9%)	11 (0.09)
Dyspnoea	13 (17.1%)	36 (0.25)	5 (7.8%)	5 (0.04)
Oropharyngeal pain	12 (15.8%)	13 (0.09)	7 (10.9%)	8 (0.06)
Nausea	8 (10.5%)	9 (0.06)	3 (4.7%)	3 (0.02)
Diarrhoea	9 (11.8%)	9 (0.06)	3 (4.7%)	3 (0.02)
Oedema peripheral	5 (6.6%)	6 (0.04)	7 (10.9%)	7 (0.06)
Condition aggravated	16 (21.1.%)	38 (0.26)	11 (17.2%)	37 (0.30)
Headache	15 (19.7%)	25 (0.17)	13 (20.3%)	33 (0.26)
Back pain	9 (11.8%)	12 (0.07)	10 (11%)	13 (0.08)

The safety profile of Respreeza is consistent with long-term studies of other human A1PI therapies (Wencker et al., 1998).

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Please refer to 9.7.2.

9.8 Evidence synthesis and meta-analysis

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

A meta-analysis has been undertaken with three international multisite placebo-controlled RCTs (Edgar et al., 2017). All three RCTs used change in CT density as an outcome with the Dirksen et al. studies employing CT density change as an experimental measure and as the primary outcome for the RAPID trial. QoL, gas transfer, spirometry and COPD exacerbation were examples of other outcome measures.

A standard weekly intravenous infusion dose of 60 mg/kg body weight was used in the EXACTLE and RAPID trials, whereas the 1999 Dirksen et al. trial used a dose of 250 mg/kg infusion every four weeks. Adverse events, treatment related or not were similarly reported in EXACTLE and RAPID, however no adverse events were reported in the 1999 study.

The preferred and most validated method of volume-corrected CT scans at total lung capacity were undertaken in all three studies, with three scanning methods reported in RAPID. In the 1999 trial and RAPID, regression analysis was undertaken to analyse lung density, with four analysis methods being utilised in EXACTLE. More detail of the four analysis methods are discussed in 9.4.1. The first method of the EXACTLE was undertaken in the meta-analysis with the same regression technique as Dirksen et al., 1999 and RAPID. However, sensitivity analysis did not vary the outcome or significance from the other three methods of EXACTLE.

With augmentation therapy there was a significant difference in the annual deterioration in lung density of 0.79 g/L/year compared with the placebo (Figure 20). In annual FEV_1 and DL_{CO}, no significant difference was observed with treatment (Figure 21 and Figure 22).

Statistically significant increases occurred in annual exacerbations in the EXACTLE and RAPID trial, however, no such annual exacerbations were reported in the 1999 study. These episodes are associated with greater neutrophilic inflammation and more free elastase activity in A1PI deficiency compared with usual COPD. It is therefore likely that the episodes in patients who received A1PI augmentation therapy may be associated with less inflammation (Dirksen et al., 2009).

For health status, both groups showed small and nonsignificant changes, illustrating a greater worsening in SGRQ on placebo (Figure 23 and Figure 24).

Figure 20. forest plots of mean annual change in lung density from the meta-analysis of the three augmentation trials (Edgar et al., 2017)

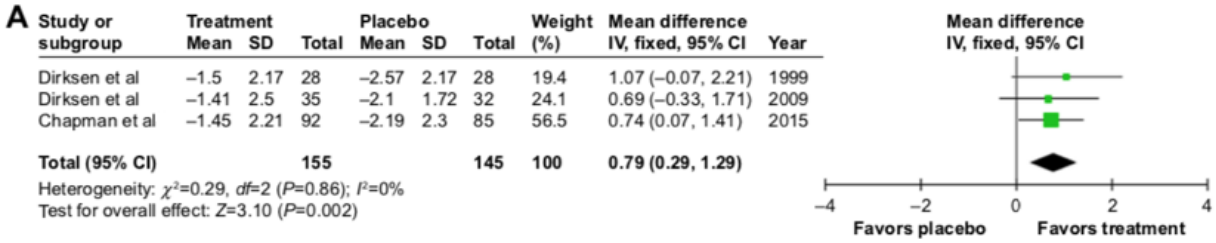


Figure 21. Forest plots of predicted mean FEV_1 % from the meta-analysis of the three augmentation trials (Edgar et al., 2017)

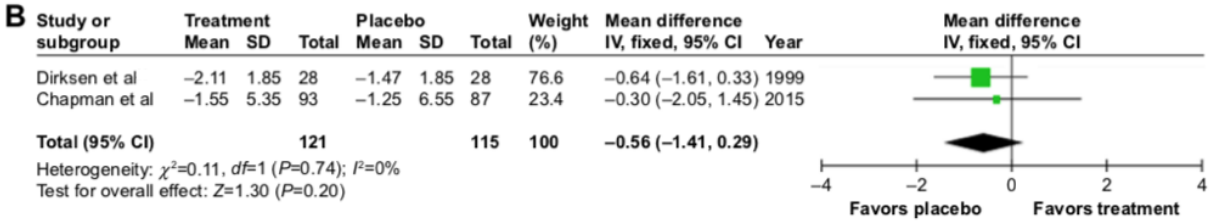


Figure 22 Forest plots of standardised mean difference in DL_{CO} from the meta-analysis of the three augmentation trials (Edgar et al., 2017).

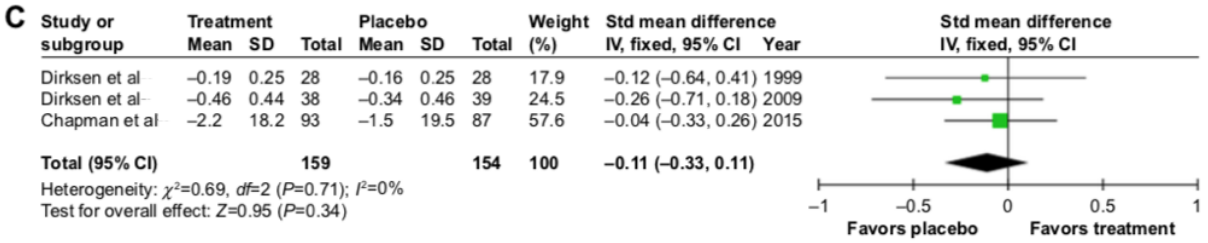


Figure 23. Forrest plots for annual patient-reported exacerbation episodes (Edgar et al., 2017)

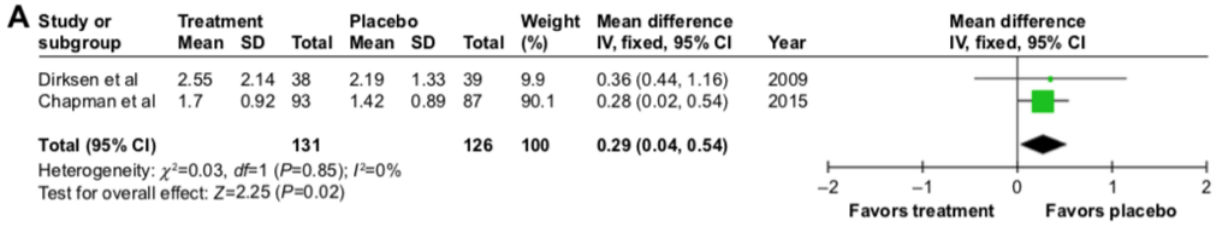
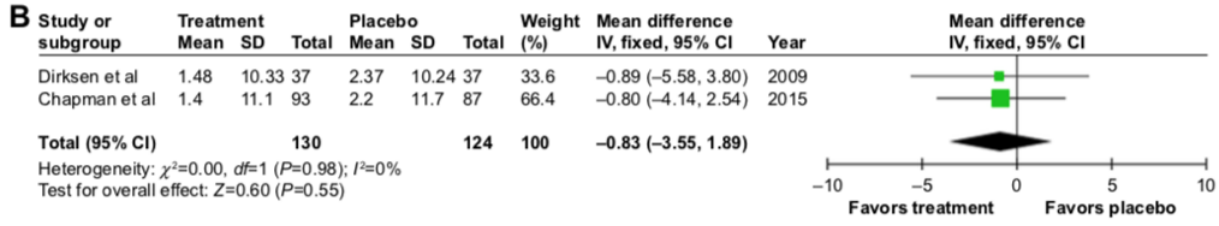


Figure 24. Forrest plots for health status (SGRQ), changes from baseline (Edgar et al., 2017)



It is important to consider the review of the Cochrane group published in 2010 (Gøtzsche and Johansen, 2016) to illustrate what happens when the validity and utility of CT lung density measurements are not correctly taken into consideration, in the context of A1PI therapy to preserve lung tissue in subjects with advanced COPD lung disease due to A1PI congenital deficiency. Gøtzsche's evaluation, using a well-established methodology, comes to a negative conclusion regarding the utility of A_1-PI augmentation therapy. In the view of CSL Behring (CSLB), this conclusion is based on a number of fundamental misunderstandings, which seem quite common in discussions of A_1-PI therapy outside of the specialist canon.

Only 2 randomised exploratory studies (Dirksen et al., 1999, Dirksen et al., 2009) are considered in the Cochrane review, with a total of 140 subjects across treatment groups assessed at 2 and 3 centers, respectively. The main error is to discount the most positive endpoints assessed in these studies in favor of those better known endpoints, with no consideration of the relative sensitivity and utility of each endpoint. The approach taken is typical for "smoking-COPD" studies and ignores any considerations for the rare disease of A1PI deficiency related emphysema and the known mechanism of action and expected effects of A1PI augmentation. According to the peer-reviewed literature, CT lung densitometry is the most sensitive endpoint in this disease, and the only one that might be expected to show some difference in a study of the size of the 2 considered in the review. However, the Cochrane authors rank this 9th amongst the endpoints evaluated, after 3 primary (mortality, FEV_1, safety) and 5 other secondary outcome measures (exacerbations, lung infections, hospitalisations, quality of life, DL_{CO}).

As acknowledged elsewhere, meaningful differences in outcome measures that are far more familiar is desirable; nevertheless, these endpoints are mostly unsuitable in the context of A1PI deficiency related emphysema:

- Mortality requires many subjects studied over a long duration in order to detect the effect of A1PI augmentation therapy. As demonstrated in the National Heart, Lung and Blood Institute (NHLBI) alpha-1 registry [NHLBI registry 1998], A1PI therapy has a profound effect on mortality, but conducting a randomised, controlled study is deemed unfeasible (The Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998).
- FEV_1 (and spirometry in general) was developed as a physiological surrogate, meant to reflect differences among anatomically defined conditions of the lung, at a time when suitable imaging modalities were not available. FEV_1 has subsequently become a familiar surrogate, and is used as a tool in COPD clinical practice and clinical studies to evaluate the effects of treatments that aid in improving symptoms and decreasing the risk of exacerbations (eg, bronchodilators). However, the limitations of FEV_1, particularly in assessing emphysema, have recently been discussed, suggesting that other, more sensitive imaging endpoints are to be preferred (Coxson et al., 2014, Brebner and Turner, 2013, Holme and Stockley, 2007). Patients with A1-PI deficiency

would not be expected to show improvements based on FEV_1 because FEV_1 is too insensitive to capture short-term differences in rates of decline in the small, mixed-severity cohorts in the studies that make up the Cochrane review.

- Exacerbations and lung infections: In severe COPD (as in the studies included in the Cochrane review) it is inevitable that many patients will experience exacerbations and infections. While A1-PI therapy may direct anti-inflammatory effects (Bergin et al., 2010), CSLB believes that it is highly improbable to see a meaningful impact on the rate of exacerbations or frequency of lung infections in the studies reviewed by Cochrane. The main reasons for this are the limited sample size focused on CT lung density measures, the broad spectrum of disease severity and the short duration of the studies.
- Hospitalisations: As A1PI deficiency related emphysema is a progressive disease and patients are therefore not expected to improve from their pre-existing disease state, it is again highly unlikely to see an impact on the rate or duration of hospitalisation due to A1-PI augmentation therapy (see explanation for exacerbations above).
- Quality of Life: The impact on quality of life is again expected to be negligible in the timescale of these studies. Slowing deterioration of the lungs over a longer duration would be expected to have a measurable effect (versus untreated patients) on functionality and quality, but not within the timeframe of these studies and given the pre-existing burden of disease.
- DL_{CO}: It has been proposed that gas diffusion testing might be the next most-relevant outcome measure for assessing the effects of preservation of lung tissue with A1-PI therapy assessed by CT densitometry. However, diffusing capacity measurements have a high variability, even in tightly standardized studies conducted in very small numbers of highly specialized centers. Therefore, it is estimated that a doubling of exposure, either in time or in the number of subjects, would be required to demonstrate beneficial effects based on this endpoint.

Conclusions drawn from commentary on Cochrane review

The limited suitability of the approach taken by the Cochrane authors recurs in different manifestations throughout their review in both the 2010 and 2016 papers, and the peer review process is limited when compared to published journals. The tools and therapeutic goals, familiar from smoking-related COPD, are not suitable for evaluating A1PI augmentation therapy. A1PI augmentation is not a treatment to improve symptoms or directly prevent exacerbations, thus the selection and hierarchy of endpoints adopted for the Cochrane review is flawed. There is a failure throughout the review to recognize the difference in the nature of A1PI augmentation therapy to those more commonly studied in smoking-related COPD and therefore the lack of validation for these common endpoints in A1PI augmentation therapy is overlooked.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

The safety and efficacy of Respreeza was evaluated in a pivotal randomised, double-blind, placebo-controlled, multi-centre study (RAPID), followed by a 2-year open-label extension study (RAPID extension study). The aim of the RAPID study was to compare the efficacy and safety of 60 mg/kg body weight of Respreeza weekly intravenous (Teschler et al.) administration with placebo over 2 years in subjects with emphysema due to A1PI deficiency. The marketing authorisation was granted based on the results of the RAPID study and extension.

Between 2006 and 2010, 93 and 87 patients were randomly allocated to Respreeza and placebo, respectively, analysing 92 in the Respreeza group and 85 in the placebo group. The annual rate of lung density loss at TLC was significantly less in patients in the Respreeza group (–1.45 g/L per year [SE 0.23]) than in the placebo group (–2.19 g/L per year [0.25]; difference 0.74 g/L per year [95% CI 0.06–1.42], p=0.03).

Hence, CT lung density measurement at TLC showed a significant difference between the rate of parenchymal tissue loss in patients with emphysema due to A1PI deficiency who received Respreeza infusions and those who did not, about a third slower in actively treated patients.

Two prior randomised controlled trials of other A1PI augmentation therapies (not licensed in the UK) have demonstrated a reduction in the decline in lung density. In one study with 56 patients with A1PI deficiency, the decline in lung density measured by CT was 2.6 g/L/y with placebo as compared with 1.5 g/L/y for A1PI replacement therapy (p = 0.07) (Dirksen et al., 1999). In a second study ('EXACTLE'), 77 patients with A1PI deficiency were followed for 2-2.5 years and were found to benefit from A1PI replacement therapy in terms of CT densitometry but no benefit in FEV_1 was seen (Dirksen et al., 2009). A pooled analysis of the two studies showed that, during approximately 2.5 years of follow-up, the mean change in lung density from baseline

was −4.082 g/L with A1PI replacement therapy and −6.379 g/L for placebo, with a treatment difference of 2.297 (n=125 patients, 95% CI 0.669 to 3.926; P=0.006). The corresponding annual declines were -1.73 and -2.74 g/L/y, respectively (Dirksen et al., 1999). This combined analysis of two controlled clinical trials confirmed that A1PI replacement therapy significantly reduces the decline in lung density, and may thus reduce the future risk of mortality as well as the deterioration in health status (Stockley et al., 2010).

In the past there was a debate regarding clinically meaningful endpoints in assessing the response to therapies for A1PI deficiency (Marciniuk et al., 2012). Historically, several studies have attempted to demonstrate efficacy using FEV_1, but this can only be observed over long periods of time or in very large patient numbers. It is challenging to use FEV_1 as an outcome in clinical trials because it measures the obstruction of airways and not parenchymal tissue loss which is the first to be affected by neutrophil elastase, and the large sample sizes required to observe statistically meaningful improvement in treated versus untreated patients are prohibitive in this rare disorder (Stockley et al., 2010).

Some of these challenges can be overcome by measurement of lung density using CT, which is a more direct and more sensitive measure of pathological emphysema that relates well to physiological and clinical features of the disease (Dirksen et al., 2009, Stockley et al., 2010). It has been shown to be the best independent predictor of mortality in patients with severe A1PI deficiency (Stockley et al., 2010). To date there is no established minimum clinically relevant threshold for a change in lung density measured by CT scan. The lung density of health human lung tissue was determined to be 120 g/L, whereas average last known lung density those RAPID patients which either died, underwent lung transplantation or withdrew for severe respiratory complaint was 19.5 g/L (Stolk et al., 2007) (McElvaney et al., 2017). The mean lung density for all RAPID patients at baseline was 46 g/L which is 60% less than health lung tissue (Chapman et al., 2015)). It is assumed that any effect in preserving parenchymal lung tissue is clinically relevant, as this tissue is never regained once destroyed.

In 2009, an FDA advisory group agreed that lung density was a sensitive and clinically meaningful endpoint to evaluate the efficacy of therapeutic products for emphysema due to severe A1PI deficiency (US Food and Drug Administration, 2009). Specifically, it stated that the density corresponding to the 15th percentile of lung voxels (three-dimensional pixels) could be used as the primary endpoint for high-resolution computed tomography (HRCT) clinical trials in emphysema (US Food and Drug Administration, 2009). The joint statement of the American Thoracic Society/European Respiratory Society also states that use of HRCT scans to measure lung tissue density provides a practical, quantitative way to assess the efficacy of A1PI replacement therapy in future studies (American Thoracic Society/European Respiratory Society, 2003). Specifically, they mention that densitometric parameters derived from repeated CT scans could be sensitive and specific markers of the emphysema, and the progression of emphysema may be assessed more accurately by repeated quantitative

CT than by measuring the FEV_1. HRCT scans require a higher degree of radiational exposure and do not improve upon the lung density assessments acquired from serial spiral CT scans. The European Respiratory Society, Canadian Thoracic Society and select US pulmonologists/A1PI experts recognize CT lung density as a clinically meaningful outcome to assess disease progression in A1PI patients. Overall, CT density is the best available predictor for mortality in patients with severe A1PI deficiency (Miravitlles et al., 2017).

Further acceptance of the suitability of measurement by CT scan and scanning at total lung capacity (TLC) was confirmed in January 2015, when the CHMP convened a Scientific Advisory Group (Prepared by the PSSAG Secretariat) to review aspects of the Respreeza dossier. Among other assessments the SAG concluded (European Medicines Agency, 2018):

- Lung density measurement by CT scan has been used since the 1980s and is the most sensitive-to-change endpoint in emphysema; it is uniquely suitable as a clinical study endpoint due to its direct and validated representation and quantification of the anatomical changes underlying this condition.
- CT density measurements performed at TLC are valid since they ensure a much lower variability than the scans taken at FRC.

Clinically relevant effects of A1PI replacement therapy are demonstrable by an elevation of the mean trough serum A1PI level in subjects to above 11 μM and a reduction of the rate of lung density decline as measured by CT scan.

The overall adverse event (AE) profile observed with Respreeza during five clinical studies is similar to that of placebo and the types of AE reported in the clinical trials are very similar to those that arise due to the underlying disease. Respreeza is well tolerated in patients with A1PI deficiency and most adverse events were mild or moderate in intensity. No subjects developed A1PI antibodies and there was no indication of viral transmission during any of the clinical studies with Respreeza.

Overall, the proportion of subjects with a treatment-emergent adverse event (TEAE) were similar between the Respreeza and placebo groups in the RAPID study. See section 9.7.2. Four patients died during the RAPID study (1 in the Respreeza group, 3 in the placebo group). Nine subjects receiving Respreeza withdrew from the trial prematurely compared to 18 from the placebo group (p=0.04). In the Respreeza group, one subject had a related TEAE (back pain), which led to withdrawal. Comparatively, in the placebo group there were five subjects who experienced a total of 11 TEAEs that led to withdrawal from the study.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The evidence base for A1PI replacement therapy is as strong as could reasonably be expected given the rarity of the condition and its long clinical course.

Strengths and limitations of the RAPID study

RAPID was appropriately powered to detect changes in the annual lung density decline rates as measured by CT scans, the most sensitive and appropriate technique to assess disease progression in emphysema. Although pulmonary function, exercise capacity, Quality of Life, and exacerbation data was collected the trial was underpowered to demonstrate a treatment benefit in these parameters.

For the primary endpoint of the RAPID trial marginally missed statistical significance at TLC/FRC in the difference in lung density decline rates between Respreeza and placebo. For the majority of the secondary and other exploratory endpoint measures in the RAPID study, there were no consistent differences between Respreeza and placebo, with the exception of A1PI concentration Table 22. It appears that the other parameters are insufficiently sensitive to detect changes in relatively small populations of patients with A1PI deficiency over short durations.

The sample size and trial duration of RAPID reflect those necessary to demonstrate an effect on slowing the annual rate of decline in lung density; significantly more subjects followed for periods longer than 2 years would be required to investigate benefits of A1PI replacement therapy in the secondary endpoints. At least 1,100 patients would be required in a 3-year placebo-cotrolled study to use FEV_1 as an outcome according to the recent ERS statement (Miravitlles et al., 2017). Given the mortality associated with A1PI deficiency, it would be unethical to randomise patients to placebo for more than 2 years.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The evidence base is aligned with the scope. The population tested for safety and efficacy in the RAPID study and its OLE extension includes patients aged 18-65 with emphysema secondary to A1PI deficiency (with a serum A1PI concentration of ≤11 μM) and an FEV_1 of 35–70% of the predicted normal value (Chapman et al., 2015, McElvaney et al., 2017). UK clinicians have confirmed that patients in the RAPID study received care that is representative of best supportive care in the UK.

Lung densitometry by CT was the primary endpoint for the clinical studies because it is the best measure to determine a treatment effect for the purposes of a clinical trial,

but CT scans are not required in clinical practice, either to select eligible patients or monitor them whilst under treatment with Respreeza.

CT scans are not regularly conducted in patients with A1PI deficiency in clinical practice due to radiological considerations, and are not used at all centres. However, the proposed treatment initiation criteria for Respreeza are in patients who either have a declining lung density measured by CT (if measured at centres), or declining lung function which is measured using more common tests such as FEV_1 and DLco. The effects of Respreeza on these parameters would be evident over the long term.

As A1PI deficiency has low prevalence and a slow progression, lung densitometry by CT scan is the only feasible measure to assess the disease in placebo-controlled clinical trials (CSL Behring Canada Inc, 2016). The use of tests such as FEV_1, are insensitive to the incremental changes that would occur during the 2-year trial period and would require an infeasibly large sample population to be followed over a long period to adequately evaluate the rate of decline in lung function (CSL Behring Canada Inc, 2016). This is due to the fact that:

- FEV_1 measures the loss of lung function which would be associated with a significant loss of lung structure, however the time period over which these incremental changes manifest into a detectable signal is necessarily long;
- The variability of FEV_1 measurements is high, and further complicated by the introduction of multiple clinical sites where machinery, staff and methods may differ.

Patients with severe airflow obstruction (FEV_1 ≤35% predicted) are at very high risk of respiratory failure. For this reason, these severe patients were excluded from the RAPID study. Given the high risk of respiratory failure at FEV_1 <30% predicted, it is not recommended that these patients in England are started on treatment. Since lung damage from emphysema is irreversible, patients with FEV_1 <30% predicted have very little lung function left to preserve through the use of Respreeza. It is thus unlikely that the patient would substantially benefit by starting therapy so late in the disease progression.

Demonstrating clinical efficacy in emphysema is challenging. It requires quantitative documentation of lung function changes in a slowly progressive process that takes decades to manifest as a clinically significant phenotype (Wewers and Crystal, 2013).

The clinical efficacy of unlicensed A1PI products has been tested in clinical and observational studies, as described above. These studies showed:

- a slowed rate of lung function decline,
- slowed progression of emphysema based on CT densitometric analysis of chest CT scans,
- enhanced survival,
- decreased exacerbation frequency

- improved functional status (Mohanka et al., 2012).

The conclusions from these studies in terms of CT lung density decline being correlated with increased quality of life and survival can be equally applied to Respreeza. Thus, it is expected that Respreeza will maintain lung function by slowing the rate of lung density decline, thereby reducing shortness of breath (dyspnoea). This reduced dyspnoea will provide an improved quality of life and increased survival.

Given the rarity of the condition, it is not possible to detect changes with sufficient statistical power in patient outcomes such as quality of life, exacerbations, and mortality, all of which would require infeasible sample sizes and unacceptable prolonged placebo exposure. These challenges are largely overcome by measuring changes in lung density using CT, due to its direct quantification of the underlying pathology and greater sensitivity than classical functional measurements to detect the loss of lung tissue and disease progression in A1-PI deficiency (CSL Behring Canada Inc, 2016).

The validity of CT lung density changes as a clinically relevant measure is also based on evidence that it appears to be an independent predictor of mortality and has been shown to correlate with other clinical outcomes of disease progression such as changes in lung function (as measured by a decline in FEV_1) and changes in health status (as measured by SGRQ total score) in A1PI deficient patients (CSL Behring Canada Inc, 2016). Hence, changes in lung density, as quantified by CT, was chosen as the primary measure of the extent of emphysema in the two studies.

Further analysis of the endpoints in the RAPID study showed that higher CT lung density measurements correlated with FEV_1 (Pearson correlation coefficient [PCC] 0.31, $p < 0.001$), higher DLco (PCC = 0.46, $p < 0.001$), higher exercise capacity (PCC = 0.26, $p = 0.002$), and lower SGRQ activity score (PCC = -0.26, $p = 0.002$) throughout the study Table 27. This implies that the lung density is a suitable outcome variable to demonstrate clinical efficacy and patient-relevant benefits.

Table 27: Correlations between lung density (Adjusted PD15) at the TLC state and clinical parameters in RAPID (per-protocol population) at baseline

Clinical parameter	Pearson correlation coefficient	
	Baseline (p-value) (N=159)	Month 24 (p-value) (N=140)
DL_{CO}	0.48 (<0.001)	0.46 (<0.001)
FEV_1 % predicted	0.24 (0.003)	0.31 (<0.001)
Exercise capacity test (ISWT)	0.15 (0.063)	0.26 (0.002)
SGRQ Activity Score	-0.24 (0.004)	-0.26 (0.002)

In addition, 4-year longitudinal correlation analyses between adjusted CT-measured lung density with functional parameters over the combined treatment period of both studies showed a statistically significant correlation between loss of lung density and lung functioning (FEV_1: r=0.286, p=0.002; FEV_1 % predicted: r=0.338, p<0.001; FVC: r=0.296, p=0.001). DLco was not measured in the extension study.

The long term correlations between CT lung density measurements and FEV_1, FEV_1 % predicted, FVC and SGRQ have been published on numerous occasions and are summarized beneath in Table 28. The moderate, statistically significant correlation between CT lung density decline over 1-year and the FEV_1 annual decline rate over 8-years represent the longest investigation of the relationship where the variability introduced by differences in machinery and technicians across multiple sites was minimized (Stolk et al., 2015).

Table 28. Longitudinal Correlations Between CT Lung Density and FEV_1, FEV_1 % predicted, FVC and SGRQ

Parameter	**Correlation (p-value) Study duration**	**Reference**
FEV_1	0.52 (p=0.001) (n=34) 3 years, 1 center	(Parr et al., 2006)
	0.32 (p=0.007) (n=77) 2-2.5 years, 3 centers	(Dirksen et al., 2009)
	0.41 (p=0.003) (n=51) 8 years, 3 centers	(Stolk et al., 2015)
	0.286 (p=0.002) (n=118) 4 years, 22 centers	(McElvaney et al., 2017)
FEV1 % predicted	0.338 (p<0.001) (n=118) 4 years, 22 centers	(McElvaney et al., 2017)

FVC	0.296 (p=0.001) (n=118) 4 years, 22 centers	(McElvaney et al., 2017)
SGRQ	0.56 (p=0.007) (n=22) 2.5 years, 1 center	(Stolk et al., 2003a)

Supporting real-world data

The ADAPT registry

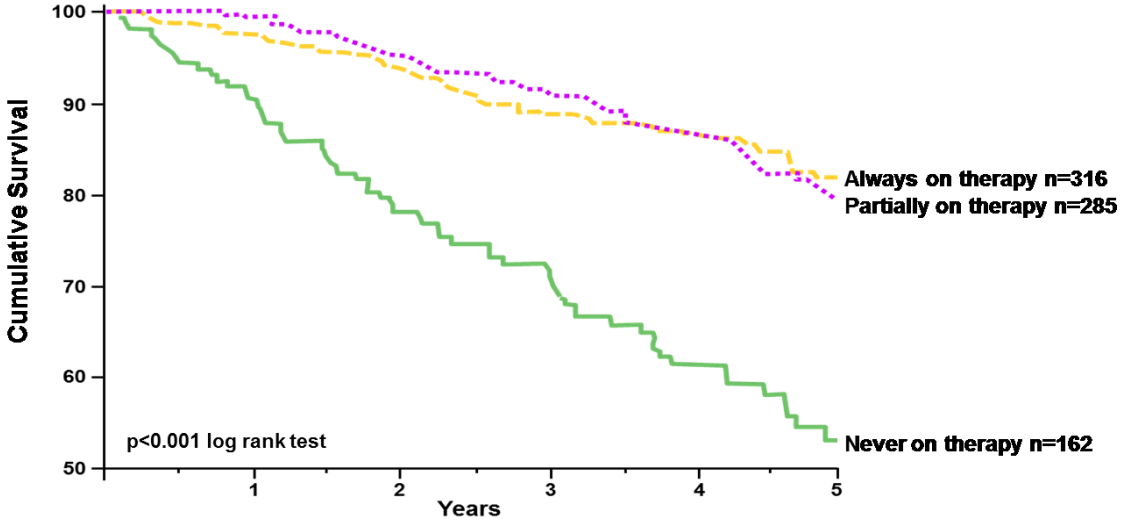
Established in 1996, the ADAPT registry is the UK registry for A1PI deficiency patients. People with A1PI deficiency are referred to the registry by their GP or hospital consultant, or are identified by screening (Holme, 2011). Patients attend a single national centre in Birmingham to undergo an annual assessment of clinical health, lung function, health status, comorbid disease, and exacerbations. This uses a range of validated questionnaires combined with nursing and medical reviews (Pillai et al., 2014). There are no licensed treatments for A1PI deficiency in the UK so patients receive only supportive care.

The RAPID study alone was not able to detect significant differences in mortality despite there being numerically fewer deaths in the Respreeza arm compared to the placebo arm (1:3). CT lung density was identified as a surrogate measure for mortality risk (Green et al., 2014a). An analysis of data collected from the ADAPT registry has shown that there is a statistically significant difference in survival of patients depending on their rate of CT-measured lung density decline (Stockley, 2015). Please see section 6.3 for the analysis of the results.

NHLBI registry

In addition, evidence from the largest longitudinal study to date in A1PI deficiency suggests that A1PI replacement therapy reduces overall mortality in treated A1PI patients with an FEV_1 <50% predicted. In the National Heart, Lung and Blood Institute (NHLBI) registry of 37 American centres studying 1,129 patients with A1PI deficiency (A1PI< 11μM or PiZZ phenotype) between 1989 and 1992, 5-year mortality was 19% (95% CI: 16 to 21%). In multivariate analyses of 1,048 subjects with at least 6 months follow-up, patients receiving A1PI replacement therapy had decreased mortality (risk ratio [RR] = 0.64, 95% CI: 0.43 to 0.94, p = 0.02) (The Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998) (Figure 22).

Figure 25. Cumulative survival with A1PI augmentation therapy in A1PI patients FEV_1 <50% predicted (The Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998)



Guidelines

The joint statement of the American Thoracic Society / European Respiratory Society also cites available studies indicating a lowered overall mortality in patients receiving A1PI replacement therapy (American Thoracic Society/European Respiratory Society, 2003). Although the ATS guidelines have not been updated since 2003 and do not incorporate the results of the EXACTLE and RAPID trials, guidance for US physicians was recently published (Sandhaus 2016). This group acknowledged that FEV_1 measurements "may not accurately reflect the degree of parenchymal destruction associated with A1PI-related pulmonary emphysema". The guidance document strongly recommends the administration of augmentation therapy to non-smoking A1PI patients with an FEV_1 30-65% predicted based on the ability of active therapy to lower levels of elastin degradation products and reduce annual lung density declines as measured by CT scan established in placebo-controlled trials.

In 2009 the US Food and Drug Administration (FDA) convened a Blood Products Advisory Committee (BPAC) which concluded:

"FDA accepts serial lung density measurements by high-resolution computed tomography (HRCT) as an appropriate clinically meaningful endpoint to assess the efficacy of augmentation therapy with IV A_1-PI products on emphysema disease progression and has permitted its use as a primary endpoint in Phase 4 studies. This is based on studies that show that lung density as measured by HRCT correlates with anatomic pathology, PFTs and mortality in patients with emphysema."

In 2015, the EU Committee for Medicinal Products for Human Use (CHMP) convened a Scientific Advisory Group (Prepared by the PSSAG Secretariat) which concluded that although there is uncertainty in terms of how lung density decline rates translate into clinically relevant effects, this uncertainty cannot be resolved via feasible clinical

trials and that the efficacy of the treatment has been demonstrated as far as it possibly can be achieved (CSL Behring Canada Inc, 2016).

The most recently updated treatment guidelines (ERS guidelines) confirm that CT densitometry has been established as the most specific and sensitive surrogate end-point for the evaluation of therapeutic benefit of augmentation therapy. Implementation of CT lung density as the primary endpoint has facilitated the collection of relevant research data in less time than trials which would necessarily attempt to recruit more than 1,100 patients into a 3-year placebo-controlled study where these trials powered to detect an FEV_1 signal. The ERS guidelines specifically cite the BPAC 2009 outcomes to establish CT lung density as a clinically meaningful endpoint and promote its use as a primary end-point in phase 4 studies (Miravitlles et al., 2017).

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

No factors have been identified that may influence the external validity of study results to patients in routine clinical practice. This has been discussed and confirmed with clinical experts in the UK and Ireland in a series of meetings as described in section 10.1.10 and is explored below.

The results of the RAPID study, which is the largest randomised controlled trial in A1PI deficiency to date, have shown that therapy with Respreeza appears to be effective in a slightly wider FEV_1 range as highlighted in (Ficker et al., 2017). This analysis shows that there is no subgroup across the entire range of FEV_1 % predicted at baseline that may indicate patients are more or less appropriate for augmentation therapy. Figure 17 and Figure 19 and show results of the assessments completed to identify subgroups of patients based on baseline FEV_1 % predicted and lung density. This is unlikely to be due to differences in clinical efficacy of Respreeza compared to other unlicensed A1PI replacement therapies but rather that RAPID was a much larger study that those previously conducted and was better powered to detect treatment effects.

A meta-analysis of FEV_1 data from five trials assessing other experimental A1PI augmentation therapies in a total of 1509 patients showed that the decline in FEV_1 was slower by 13.4 ml/year among all patients receiving treatment. This overall protective effect reflected predominantly the results in the subset of patients with baseline FEV_1 30–65% of predicted. In that subset, A1PI augmentation therapy was associated with a reduction in rate of FEV_1 decline by 17.9 ml/year (Chapman et al., 2009).

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Respreeza is indicated for all patients with emphysema due to severe A1PI deficiency (<11μM) who are showing signs of ongoing progressive lung disease. The treatment is to be used in patients with a FEV_1 30-70% predicted and FEV_1/FVC <0.7 or a CT scan indicating emphysema. Repreeza is to be administered in conjunction with current symptomatic treatment (e.g. inhaled bronchodilators) where there is clear evidence of lung density decline. See section 8.4 for details.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

As described in section 7, emphysema due to severe A1PI deficiency is a serious and chronic respiratory disorder, and profoundly impacts an affected individuals quality of life and their ability to work and function (Kaplan and Ries, 2008). This significantly reduces patient life expectancy with studies estimating a life expectancy of 54 to 59 years (Lara and Miravitlles, 2015, National Institute for Health Research, 2014). In addition to a shorter life expectancy, this patient population experience a lower quality of life and experience significant limitations in daily activities than patients without A1PI deficiency (Manca et al., 2013, Kaplan and Ries, 2008).

Emphysema due to severe A1PI deficiency presents itself most commonly with shortness of breath. Emphysema causes a progressive difficulty in breathing and a hacking cough (short, dry, frequent cough). The delay between onset of first symptoms of A1PI deficiency and receiving a correct diagnosis can be between 6 - 7 years, contributing to irreversible lung damage (McElvaney et al., 1997, Rahaghi et al., 2012). The progression of lung disease in individuals with A1PI deficiency is slow and symptoms such as cough or wheezing often appear only within the third to fourth decade of life.

Patients experience a suffocating effect of breathlessness in the last years of life causing a tremendous burden of disease (Tanash et al., 2010a, Seersholm et al., 1994, Lara and Miravitlles, 2015). Patients usually receive largely inhaled therapy with combinations of bronchodilators and corticosteroids to treat the symptoms of A1PI deficiency. These have limited short-term benefits but do not treat the underlying cause of the disease. In the later stages of the condition home oxygen therapy may be needed or lung transplantation, but availability of lungs is limited and outcomes are variable (Stoller and Aboussouan, 2012, American Thoracic Society/European Respiratory Society, 2003). These patients suffer from several exacerbations per year despite treatment with optimised therapy, and such exacerbations are associated with poor prognosis and quality of life; and increased mortality risk.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

The simultaneous goals of treatment for A1PI deficiency are to preserve lung tissue and slow the decline in lung density. The burden that the disease imposes on patients with emphysema has been established in studies where patients experience significant limitations in daily activities and reduced quality of life (QoL) (Kaplan and Ries, 2008). The positive impact of A1PI deficiency treatment is shown from the correlation between disease severity and lung density decline and HRQL (Stolk et al., 2003a). Additionally, an observational, cross-sectional study was conducted in patients with emphysema due to severe A1PI deficiency (phenotype PiZZ, n=35) and a control group of COPD (n=61) emphasised this increase in the HRQL increased from treatment, as the relationship between severity of lung disease and QoL, both generic and specific, is stronger in emphysema associated with A1PI deficiency compared with COPD (Manca et al., 2013).

A decrease in the rate of respiratory decline and delay in the need for lung transplantation is likely to have a positive impact on the psychological distress and reduce the health burden placed on patients, family members and caregivers.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The HRQL data captured in clinical trials does not meet the reference case for cost-effectiveness analysis as no generic measures of HRQL were captured. In the RAPID trial, HRQL was measured by the SGRQ instrument. It is possible to generate utilities from SGRQ by mapping to the EQ-5D using an algorithm reported in (Starkie et al., 2011). However, the findings of this mapping exercise recommended that a more precise and accurate approach to obtaining utility values such as being measured

directly from trial should be taken rather than mapping when used in health technology appraisals.

Further to this, the data required to classify the trial patients into health states for the chosen model structure was not collected in the studies e.g. EQ-5D (Section 12.1.3). Therefore, it is not possible to generate health-state utility data from the clinical trial that exactly matches the health state definitions used by Starkie and colleagues (Starkie et al., 2011).

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was conducted to transform the HRQL data collected in the clinical trials.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

The systematic literature review reported for the cost-effectiveness included searches for HRQL studies that would be applicable to the economic analysis in section 11. The systematic literature search was conducted in April 2018 by two independent health economists.

Pre-specified inclusion and exclusion search criteria as described in Section 11.1.2 were used to screen and identify relevant studies in MEDLINE and EMBASE. A combination of MESH terms and free-text were used (Appendix 17.3.4). Additional hand searches of the Centre for Reviews and Dissemination, Cochrane library, conference websites and clinical trials registries were conducted (Appendix 17.3.5) for full search strategy). The included articles were assessed in full text (Section 11.1.2

for inclusion/exclusion criteria). Data was extracted from the final selection of articles and the most relevant studies are summarised in Section 11.2.

The search strategy identified 460 studies from the literature, of which eight quality of life studies were included in the narrative synthesis. The update search identified 95 studies from the literature of which five UK quality of life studies were included (see section 11.1.3, Figure 27 for PRISMA diagram).

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

An overview of the following studies below was included in the review but did not provide adequate data that could be used to inform the economic model either because utilities were not presented, could not be calculated, or the data was not published by lung density decline rate or because data was reported for the total population rather than by health state:

1. Crossley and colleagues measured St George Respiratory Questionnaire (SGRQ) and (Coronary Obstructive Pulmonary Disease Assessment Test (CAT) scores in 84 UK PiZZ A1PI patients. No utility scores according to disease severity or health state were reported (Crossley et al., 2016)

2. A longitudinal prospective study by Dowson et al. measured SGRQ and SF-36 in 43 PiZ A1PI US patients. No data were collected according to disease severity or health state (Dowson et al., 2001b).
3. A cross-sectional study by Dowson et al. assessed HRQL using SGRQ and SF-36 in 111 US PiZ A1PI patients. Mean total and domain scores were reported. No estimates of utilities by health state or disease severity were reported (Dowson. et al., 2001).
4. A cross-sectional study by Dowson et al. assessed quality of life of UK patients using the SGRQ and Short Form-36 (SF-36) in 117 patients with PiZ A1PI and chronic sputum expectoration status. HRQL using SF-36 was also compared between PiZ A1PI patients and the general UK population. Results were reported by total and domain scores, however results were not reported by health state (Dowson et al., 2002).
5. A longitudinal prospective study by Gauvain et al. measured base line health-related quality of life using SGRQ, and factors associated with health-related quality of life in 273 French patients. No estimates of utilities by health state were reported (Gauvain et al., 2015).
6. A cross-sectional study by Holme et al. measured SGRQ in 45 UK PiZ A1PI patients, but results were not reported by health state, only mean total scores were reported across disease severity (Holme and Stockley, 2007).
7. A cross-sectional study with two year follow up by Knebel et al. measured Chronic Respiratory Questionnaire (CRQ) in 45 Dutch A1PI patients. Utilities were reported on a domain scale. No estimates of utilities were reported by health state or disease severity (Knebel et al., 1999)
8. A cross-sectional Spanish study by Manca et al. measured EQ-5D, LCOPD, and CAT in 35 patients with A1PI and 61 patients with non-A1PI COPD. Utilities were reported by total scores, from which no estimates of utilities by health state or severity were reported (Manca et al., 2014).
9. Tejwani et al. measured SGRQ and CAT in 38 newly diagnosed patients with severe A1PI. No estimates of utilities by health state or severity were reported (Tejwani et al., 2017).
10. Stockley et al. measured SGRQ in 196 UK PiZZ A1PI patients who had never smoked. No estimates of utilities by health state were reported (Stockley et al., 2017).
11. Stone et al. reported SGRQ in 30 UK patients with PiZ A1PI. No estimates of utilities by health states were reported (Stone et al., 2016).
12. Teschler et al. measured SGRQ in 140 A1PI patients randomised to receive placebo (n=85) or A1PI Zemaira/Respreeza therapy (n=93). No estimates of utilities were reported (Teschler et al., 2016).

13. A cross-sectional study by Ward et al. measured SGRQ in 530 UK PiZZ A1PI patients. 255 patients had a 3 year follow up for longitudinal analysis. No estimates of utilities by disease severity or health state were reported (Ward et al., 2014).

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Utilities were not generated from the quality of life data collected in the clinical trials.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

As discussed in section 9.7.3, Respreeza was well tolerated in patients with A1PI deficiency and the profile and types of adverse events reported in the six clinical trials were similar in the placebo and Respreeza arms of the study. Of the small number of adverse events that occurred more frequently in the Respreeza arm of the RAPID study than the placebo arm, none were expected to have a significant impact on quality of life.

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

No generic measures of health-related quality of life were captured in the Phase III study (RAPID). Therefore, EQ-5D values, stratified by FEV_1 % of predicted, were obtained from the UK registry that provided the natural history mortality and FEV_1 % of predicted decline data (see Section 6.3 and 12.2.1 (Ejiofor and Stockley, 2015). In the absence of any direct HRQL data for people with A1P1 deficiency who had undergone lung transplant, utilities reported for another economic study, (Groen et al., 2004), were used to inform the HRQL associated with the lung transplant states. These values were derived from a Dutch cohort using the EQ-5D, however the exact method of health valuation was not reported in full. Further details are provided in Section 12.2.1.7

The utility values used for the base case cost-effectiveness analysis are shown in Table 29 below.

Table 29. Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value (utility decrement calculated from reference state)	Confidence interval	Reference in submission	Justification
FEV_1 ≥50% predicted (all rates of lung density decline)	0.79 (0.12)	0.76 to 0.82 SE = 0.01	12.2.1.7: Health-related quality of life estimates.	Use of EQ-5D to estimate as per NICE reference case
FEV_1 <50% predicted (all rates of lung density decline)	0.59 (0.32)	0.55 to 0.63 SE = 0.02	12.2.1.7: Health-related quality of life estimates.	Use of EQ-5D to estimate as per NICE reference case
First year of lung transplant	0.82 (0.09)	0.40 to 1 SE = 0.16	12.2.1.7: Health-related quality of life estimates.	Use of EQ-5D to estimate as per NICE reference case
Subsequent years following lung transplant (reference state)	0.91 (0.00)	0.30 to 1 SE = 0.18	12.2.1.7: Health-related quality of life estimates.	Use of EQ-5D to estimate as per NICE reference case

Please note that the cost-effectiveness model includes a scenario analysis in which a further (assumed) utility decrement is applied to account for potential decreases in carer utility as the patient's disease progresses. Please see Section 12.2.1.7 for further details.

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts were selected based on two criteria:

1. involvement in the Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT), which is the UK registry for A1PI deficiency patients, established in 1996. The ADAPT registry is described in more detail in section 6.3
2. interest in A1PI deficiency, based on being based in an NHS centre that manages patients

Nine UK and Ireland clinical experts were approached from 2014 to 2018. All were interested to some extent but some were unable to engage in detailed discussion due to a conflict of interest with their national role on the Adult Respiratory Clinical Reference Group.

Four of the clinical experts were engaged to provide insights based on their experience of A1PI deficiency patients, which informed the development of the proposed treatment initiation criteria for Respreeza as well as validated the clinical and health economic approach taken in this submission.

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Questions asked of clinical experts

- What is the standard of care for A1PI deficiency?
- What is the incidence of A1PI deficiency?
- What is the prevalence of A1PI deficiency?
- Which patient sub-groups do advisors consider will be most clinically plausible?
- What relationships and trends might exist amongst surrogate endpoints?
- Which categories or thresholds should be used for FEV_1 and lung density?
- Does this data influence who to treat or when to treat?
- Are there any factors that may influence the external validity of study results to patients in routine clinical practice?
- How might the provision of care change with the introduction of licensed treatment for A1PI deficiency?

Questions were asked in personal interviews and in a group discussion held at a European Respiratory Society conference, notes were collated by a market access consultant and then used to guide the development of the submissions to UK and Ireland HTA organisations.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

No difference in quality of life between patients in different lung density decline health states were applied; quality of life was assumed to be only driven by status in predicted FEV_1 % in the health states. Although there is a correlation between lung density decline and quality of life (Stolk et al., 2003a), no specific published data on quality of life by lung density decline rate is published so we cannot factor this in to the analysis.

[redacted]

Given this evidence and the intuitive clinical expectation that a decline in lung density would lead to patients being less able to breathe and therefore having a lower quality, it is highly likely that by not capturing the effect of reducing lung density decline on quality of life, the effect of Respreeza is being underestimated.

Figure 26.Cox regression analysis of the combined group of patients seeking association with minimal clinically important difference of at least 4 in the SGRQ score

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Lung density, which is a globally accepted surrogate measure was used for predicting survival and quality of life. Although EQ-5D has shown a significant correlation with FEV_1% predicted, at best FEV_1% predicted explains about 43% of the variation in health status so factors other than FEV_1% predicted have an important impact on health status (Ejiofor and Stockley, 2015). Thus, only applying different utilities by FEV_1% predicted is unlikely to capture the full health status of A1PI deficiency patients and the benefit of Respreeza, but it is the best available data to date.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Baseline quality of life was informed by population estimates for a UK population. The population estimates were derived from values reported by (Kind et al., 1999a) which

were stratified by age and gender. The values used in the model were a weighted average according to the ratio of male to females within the model and a linear decline between utilities reported for each age category was assumed. The model assumes that HRQL of the modelled cohort cannot exceed the population estimate for any respective age. The model assumes that HRQL two years subsequent to lung transplant is the same as the population norm for a given age. Utility decrements were applied to the population norm to estimate the utility applied to all other health states. Further information is detailed in Section 12.2.1.7.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The utility values assigned to health states in the de novo economic model, expressed as utility decrements, are assumed constant over time. However, the utility decrements for a given health state were applied to population HRQL estimates, whereby utility decreases as the population ages over time. Further information is detailed in Section 12.2.1.7. In addition, a discount rate of 3.5% was applied in the base case of the cost-effectiveness analysis in line with the NICE reference case, with a scenario analysis undertaken with a discount rate of 1.5% (please see Section 12.1).

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

EQ-5D values, stratified by FEV_1 % predicted, were obtained from the UK registry (see Section 6.3) to inform the HRQL of the clinical health states prior to lung transplantation. Ejiofar et al., and Stockley et al., presented utility values derived from the registry by predicted FEV_1 category >50% and various categories <50% (Ejiofor and Stockley, 2015, Stockley, 2015). A weighted average of the utilities of patients with a FEV_1 <30%, 30-35%, 35-40%, 40-45% and 45-50% was taken to derive the utility for the FEV_1 <50% predicted in the model. No other amendments to the reported absolute values were undertaken (see Section 12.2.1.7.)

To model HRQL by health state, the model uses utility decrements, applied to population norms, rather than the absolute utility derived from the registry or reported by the literature. This method was undertaken as the unadjusted utility reported for the lung transplant state would have been higher than the utility expected for a population of similar age to the modelled cohort. Utilising absolute values rather than adjusting for population norms may have overestimated the ICER for Respreeza, given that Respreeza may act to prolong the time to or obviate the need for lung transplant. Further detail regarding the adjustment of utility values is given in Section 12.2.1.7

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Respreeza will be considered as a treatment within the licensed indication in the patients with the following characteristics:

- diagnosis of severe A1PI deficiency (<11μM)
- FEV_1/FVC<0.7 (indicating moderate airways obstruction) or emphysema demonstrated by CT scan via multi-disciplinary team consensus
- FEV_1 30-70% predicted
- rapidly declining lung function (FEV_1/DL_{CO}) or lung density decline.

In this submission the following continuation rule (stopping criteria) is proposed:

When a patient receives a lung transplant, the patient's physician should consider stopping Respreeza treatment. Treatment should not be stopped if the patient is lung transplant-naïve. Clinical experts have advised that Respreeza will only be initiated in patients that want, and are committed to, lifelong treatment so it is expected that patients will fully adhere to treatment. Discontinuation is expected only to occur when a patient receives a lung transplant or until death.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in Section 17.3.

A systematic literature review of economic studies and quality of life in A1PI deficiency related emphysema was conducted. The study question was defined according to the population, intervention, comparator, outcome and study (PICOS) framework (Table 30). The systematic search, which was based on a combination of MESH terms and free-text, was conducted on MEDLINE and EMBASE on 11th April 2016, and an updated search was conducted for 12th April 2016 to 9th April 2018 (Appendix 17.3.4). Additional hand searches of the Centre for Reviews and Dissemination, Cochrane library, conference websites and clinical trials registries were conducted (Appendix 17.3.5) for full search strategy). Titles and abstracts of identified citations were reviewed according to a pre-specified inclusion and exclusion criteria by two health economists acting as independent reviewers and the included articles were assessed in full text (see (Table 30) for inclusion/exclusion criteria). Inclusion and exclusion criteria were specific to the topic of the review. Data was extracted from the final selection of articles and the most relevant studies are summarised below.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in Table 30 below. Other headings should be used if necessary.

Table 30. Selection criteria used for health economic studies

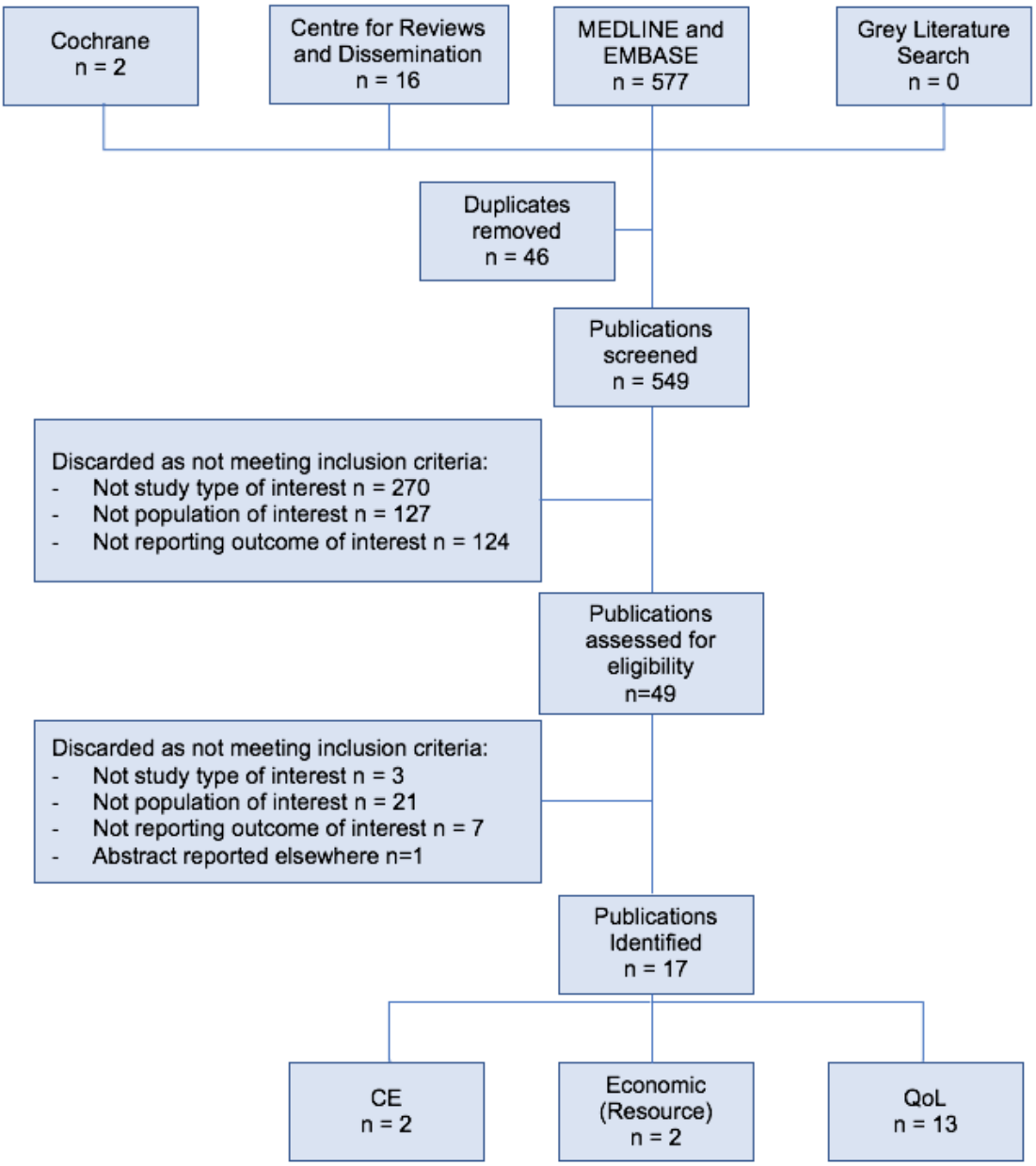
Inclusion criteria to identify relevant economic studies	
Population	Emphysema due to A1PI deficiency in the UK
Interventions	Augmentation therapy compared with any other intervention
Outcomes	Costs, resource use, cost-effectiveness, cost of illness, cost-utility, quality of life scores
Study design	Observational (registries) Cohort studies
Language restrictions	None
Search dates	1st search: until 11 April 2016 2nd search: 12 April 2016 to 09 April 2018
General exclusion criteria to identify relevant economic studies	
Population	• Liver Disease • Panniculitis • Children
Interventions	Screening
Outcomes	• Clinical outcomes • Validation studies
Study design	• Animal • Individual case study reports • Letters • Comment articles • Abstracts • Reviews • Epidemiology
Language restrictions	None
Search dates	1st search: until 11 April 2016 2nd search: 12 April 2016 to 09 April 2018

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Initial searches identified a total of 595 studies. After removing duplicates and screening, 49 articles were full text reviewed. Two cost-effectiveness studies, two economic studies regarding resource use and cost, and 13 quality of life studies were identified (Figure 27). The two cost effectiveness studies were excluded because they

did not compare against Respreeza specifically as an intervention. The four economic non-comparative economic studies regarding resource use and cost were excluded as they were not applicable to the UK context. Further detail regarding the quality of life review is reported in Section 10.

Figure 27. PRISMA for economic systematic review



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

The review identified 17 studies of potential interest in total, however, no economic study compared against Respreeza specifically or were undertaken from a context applicable to the UK. Two studies were included in the economic systematic review.

Gildea et al. (2003) (Gildea et al., 2003) conducted a cost-utility analysis assessing the cost-effectiveness of different strategies for treating severe A1PI deficiency from a US healthcare perspective. The three strategies compared were: no treatment, treating A1PI deficiency patients with human A1PI for life, and treating patients until FEV_1 is below 35% predicted. A hypothetical cohort of 46 year-old patients (50% male) with FEV_1 49% predicted was followed over a lifetime horizon at yearly cycles using a Monte Carlo simulation (30,000 simulations). The five health states included were: FEV_1 50 to 79% predicted, FEV_1 35 to 49% predicted, FEV_1 below 35% predicted, post-lung transplantation, and dead. An annual discount rate of 3% was applied to costs and outcomes, and effectiveness was measured in QALYs. The ICER for lifetime treatment with human A1PI was $312,511. The ICER for lifetime treatment with human A1PI only until patients had an FEV_1<35% predicted was associated with an ICER of $207,841. In all sensitivity analyses, the ICER for lifetime treatment exceeded $100,000.

Sclar et al. (2012) (Sclar et al., 2012) also performed a cost-effectiveness analysis to ascertain the number of life-years gained, and the expense per life-year gained, associated with the use of human A1PI (Aralast®, Baxter Bioscience), relative to no therapy in patients with hereditary emphysema secondary to A1PI deficiency from a US payer's perspective. A Monte Carlo simulation estimated the total number of life-years gained and costs of each intervention. Regression models were used to estimate FEV_1 % predicted values based on individual's age, sex and height. A survival function stochastically determined mortality, but death occurred on a deterministic basis when the percent predicted FEV_1 was <15%. Use of human A1PI was associated with an increase in life-years gained at a cost per life-year gained of $59,234 to $248,361, depending on geneder and smoking history.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Table 31. Quality assessment of (Gildea et al., 2003) health economic study

(Gildea et al., 2003)		
Study design		
Study question	**Response**	**Comments**
1. Was the research question stated?	Yes	To assess the cost-effectiveness of augmentation therapy for severe alpha anti-trypsin deficiency
2. Was the economic importance of the research question stated?	Yes	Two previous cost-effectiveness analyses had been conducted but the authors wanted to investigate this further using different inputs
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Direct healthcare perspective was used in the analysis
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes	Three strategies were compared based on whether or not patients were being treated and if the FEV_1 score was below 35% predicted
5. Were the alternatives being compared clearly described?	Yes	There are clear descriptions of the alternatives given
6. Was the form of economic evaluation stated?	Yes	Cost utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost-effectiveness used the cost per QALY
12. Were the methods used to value health states and other benefits stated?		Estimates of utility weights were obtained through a prospective survey of pulmonologists experienced in treating AAT deficiency using the health utilities index (MarkIII)

13. Were the details of the subjects from whom valuations were obtained given?	Yes	The analysis used a hypothetical cohort of population who was 46 years old, 50% male and had an FEV_1 of 49% predicted
14. Were productivity changes (if included) reported separately?	N/A	Only direct costs were considered
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	No quantities are given
17. Were the methods for the estimation of quantities and unit costs described?	Partly	Only the methods used for the costs of augmentation therapy and COPD treatment are described
18. Were currency and price data recorded?	Partly	Only the costs for augmentation therapy and COPD treatment are given
19. Were details of price adjustments for inflation or currency conversion given?	Yes	All costs were in US dollars and were adjusted to 2001 using the medical care services component of the consumer price index
20. Were details of any model used given?	Yes	Three-state Markov-based decision analytic model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	There was no justification given for the choice of model
22. Was the time horizon of cost and benefits stated?	No	Patients were modelled until death
23. Was the discount rate stated?	Yes	A 3% discount rate was used
24. Was the choice of rate justified?	Yes	This was also varied in the sensitivity analysis
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Monte Carlo was run with only the overall range given
27. Was the approach to sensitivity analysis described?	Yes	A clear description of sensitivity analysis conducted is given
28. Was the choice of variables for sensitivity analysis justified?	Partly	Only some of the sensitivity analyses conducted were justified e.g. the threshold analysis
29. Were the ranges over which the parameters were varied stated?	Yes	This is clearly given in the text with an additional table giving low and high ranges
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	All comparisons were made against no treatment

31. Was an incremental analysis reported?	Yes	ICERs are presented in a table
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Only overall aggregated values are given
33. Was the answer to the study question given?	Yes	The ICER (cost per QALY) is presented for the comparisons made
34. Did conclusions follow from the data reported?	Yes	The augmentation therapy is not cost-effective
35. Were conclusions accompanied by the appropriate caveats?	No	There is a clear statement of the lack of cost-effectiveness of the considered comparators but no caveats to the conclusion is given
36. Were generalisability issues addressed?	Yes	There is a clear discussion which discusses issues such as assumptions made with regards the patients e.g. their phenotypes

Table 32. Quality assessment of (Sclar et al., 2012) health economic study

(Sclar et al., 2012)		
Study design		
Study question	**Response**	**Comments**
1. Was the research question stated?	Yes	The stated objective of the papers was to estimate the number of years of life gained and the expense per year of life gained associated with the use of A1PI.
2. Was the economic importance of the research question stated?	No	A description of the of A1PI was discussed however discussions of the economic importance of the research question was not.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Partly	The viewpoint from a payer perspective in US dollars at 2010 costs.
4. Was a rationale reported for the choice of the alternative interventions compared?	N/A	A1PI augmentation therapy is compared with no therapeutic intervervention.
5. Were the alternatives being compared clearly described?	No	
6. Was the form of economic evaluation stated?	Yes	The stated analysis was a cost effectiveness analysis, investigating the number are costs of life years gained.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	
9. Were details of the design and results of the effectiveness study	Yes	Stochastic components used age specific body weight and height, age-specific

given (if based on a single study)?		mortality and probability distribution for receipt of a lung transplant, as a function of FEV_1. Deterministic components used age in years for the stimulated cohort, outlays for A1PI augmentation therapy, health service expenditures associated with recept of a lung transplant, annual decline in FEV_1, initiation of A1PI augmentation therapy as a function of percent predicted FEV_1, need for a lung transplant as a function of percent predicted FEV_1, annual rate of lung infection and mortality as a function of percent predicted FEV_1.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	No meta-analysis was conducted
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost effectiveness measured in terms of the number and costs of life years gained
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	No subjects were used per se but a hypothetical cohort was run. Random numbers were generated. Each of these numbers was then assigned to each of eight possible combinations of sex, smoking status and receipt of A1PI augmentation therapy.
14. Were productivity changes (if included) reported separately?	N/A	Productivity losses were not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	Productivity losses were not included
16. Were quantities of resources reported separately from their unit cost?	No	Costs were only presented as mean expense per life year gained
17. Were the methods for the estimation of quantities and unit costs described?	No	All costs were obtained from the literature
18. Were currency and price data recorded?	Yes	Costs were expressed in US Dollars ($) in 2010 prices
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	A stochastic hypothetical simulation model estimated the total number of life-years gained and costs of each intervention
21. Was there a justification for the choice of model used and the	No	There was no justification given for the choice of model

key parameters on which it was based?		
22. Was the time horizon of cost and benefits stated?	No	
23. Was the discount rate stated?	No	No discount rate was stated
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	A Monte Carlo simulation estimated the total number of life-years gained and costs of each intervention
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis was conducted
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	Yes	This is clearly given in the text with an additional data giving low and high ranges
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	All comparisons were made against no treatment
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	Use of human A1PI was associated with an increase in life-years gained at a cost per life-year gained of $59,234 to $248,361, depending on geneder and smoking history
34. Did conclusions follow from the data reported?	Yes	The conclusion stated that A1PI augmentation therapy was associated with increase in life years gained as well as a cost per year of life gained comparable to other evidence-based interventions (e.g. Statins, Mammography)
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations with the use of decision analytic models were stated. Specifically, the inegrity and utility of the results is predicated on the certainty ascribed to the model imputs and the assumption that the requisite inputs are known and/or available.
36. Were generalisability issues addressed?	No	

12 Economic analysis

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The cost-utility analysis of Respreeza is conducted within its licensed indication for the treatment of patients with emphysema, as outlined in Section 3.1 (Medicines.org.uk, 2018b). In line with the scope defined by NICE, the cost-effectiveness analysis considers adults with severe alpha 1-proteinase inhibitor deficiency who have progressive lung disease. In clinical practice, the population is defined as patients with a serum A1PI level <11µmol/L. Evidence of progressive lung disease can be a lower forced expiratory volume per second (FEV_1) % predicted, impaired walking capacity, or increased number of exacerbations as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency (Medicines.org.uk, 2018b).

No subgroup of interest were identified within the scope. Subgroup analysis of patients in the pivotal study (RAPID) using primary and key secondary outcomes has not suggested that there is a group of patients in which the treatment provides greater clinical benefits.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

Respreeza is the first licensed disease-modifying therapy for A1PI deficiency. Current best supportive care, as defined in the comparator Section of the scope aims to alleviate disease symptoms and does not address the underlying cause of disease. Hence, established clinical management as listed in the scope is clinically equivalent to “best supportive care” (BSC) since most patients with A1PI deficiency will receive a combination of these options to treat the symptoms, which have short-term benefits but do not address the underlying problem of the deficient protein.

End-stage disease may be treated by lung transplantation and/or lung volume reduction surgery. In patients with this condition, Respreeza may act to prolong the time to or obviate the need for lung transplant. Therefore, lung transplant and/or reduction surgery are considered as components of downstream options within the treatment pathway as opposed to a standalone frontline comparator.

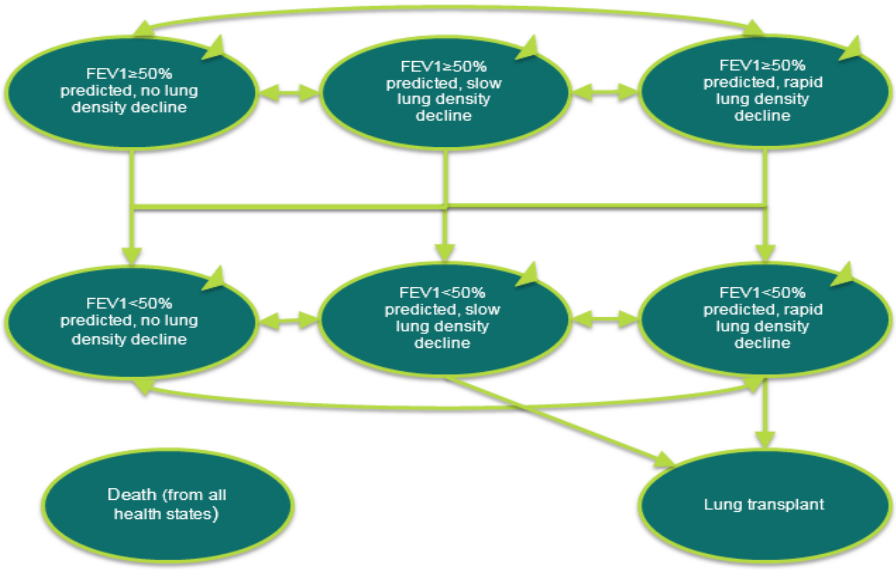
The definition of the treatment arm in the economic evaluation is therefore Respreeza in addition to BSC and the definition of the comparator arm is BSC alone. The placebo arm of the pivotal study (RAPID) which underpins the economic study is representative of patients receiving BSC.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

A Markov model structure with a cycle length of 1 year was used to track the progression of patients through a series of eight health states. This is depicted in Figure 28. An overview of model properties is provided in Table 34.

Figure 28. Model Structure



12.1.4 Justify the chosen structure in line with the clinical pathway of care.

A1PI deficiency is a rare, genetic disorder that causes low serum levels of the A1PI protein and is the only known hereditary cause for emphysema.

In people with emphysema, the lung tissue involved in exchange of gases (oxygen and carbon dioxide) is impaired or destroyed. Established clinical markers to understand disease progression in emphysema include FEV_1 % predicted and CT-measured lung density decline status. Natural history studies of severe A1PI deficiency leads to a reduced life expectancy, and that emphysema and liver disease are the most common causes of death (Larsson, 1978, Tanash et al., 2010b). Lung transplantation may be considered for people with end stage disease (Mal et al., 1989). For more information regarding the clinical nature of the condition, please see Section 6.

Due to the ultra-orphan nature of A1PI deficiency, there are limited published data on the natural history of the disease in terms of survival and health-related quality of life, which is challenging for modelling the consequences and outcomes associated with the long term natural history of the disease.

The 2-year Phase III RAPID clinical trial results showed a statistically significant reduction in the annual rate of decline in CT-measured lung density at total lung capacity versus placebo (34% reduction; p=0.03) (Chapman et al., 2015), which continued in the 2-year extension study. RAPID was powered to measure treatment effects on lung density, which is a clinically plausible and globally accepted indicator for disease progression in A1P1 deficiency patients (Dirksen et al., 1999, Dowson et al., 2001b, Bakker et al., 2005, Dirksen et al., 2009, Stockley et al., 2010, Chapman et al., 2015) (please also see Section 9.4.1) and predictor of survival and health-related quality of life (Green et al., 2014b, Green et al., 2016) (see Section 9.9.3).

Although FEV_1 % predicted is a clinically accepted and commonly used marker of lung function and disease progression, quantifying a statistically or clinically significant treatment effect on FEV_1 % predicted in a cohort with A1PI deficiency would require a very large study conducted over many years due to the slow nature of progression of the underlying condition. The RAPID study (Chapman et al., 2015) had insufficient sample size and was not long enough to observe any significant treatment effect on FEV_1 % predicted. However, analysis of data collected from a UK registry of patients with A1PI deficiency (Stockley, 2015) has shown that there is a statistically significant difference in survival of patients with rapid, slow or no decline in CT-measured lung density in patients with A1PI deficiency (see 6.3).

The overall model design intends to capture both the long-term costs and outcomes of A1PI deficiency and the treatment effect of Respreeza compared to BSC alone. In line with the chronic and progressive nature of disease, a state transition (Markov) model approach was chosen. Given the available data within RAPID and the UK A1PI registry, health states are based on both a combination of lung density decline (none, slow or rapid) and FEV_1 % predicted to capture the clinical status and disease progression in the patient group.

In line with the analysis of patients in the UK registry (Stockley, 2015, Green et al., 2014b) the lung density decline health states are:

- No lung density decline health state: defined as <0 g/l/year.
- Slow lung density decline health state: defined as 0-2 g/l/year.
- Rapid lung density decline health state: defined as >2 g/l/year.

The threshold at 2 g/L/year was defined by the clinical experts contributing to the UK registry as the most appropriate level by which to define slow and rapid decliners based on a stratified analysis of all available patient data. A greater selection of thresholds were assessed by the experts but were no more informative.

Patients may progress or regress through the no decline, slow decline and rapid decline health states. Patients can progress from FEV_1 ≥50% predicted health states to FEV_1<50% predicted health states but not regress. The risk of mortality is increased as lung density declines and when FEV_1 % predicted decreases. It is assumed that only patients with an FEV_1<50% predicted with a slow or rapid decline in lung density would be eligible to receive a lung transplant. At baseline, patients were distributed across the health states according to the distribution of patients experiencing a rate of decline in the first year from the placebo cohort of the RAPID study (see Section 12.2.1.3).

Respreeza also may act to prolong the time to or obviate the need for lung transplant, and therefore transition to lung transplant was considered. Due to the evidence suggesting a differential in health-related quality of life and cost between first and subsequent years, the population entering this state had different utilities and costs applied to the cycle when new to state and years that followed subsequently. Death is possible from any of the health transition states.

The model structure allows results to be driven where possible from the pivotal phase III study (RAPID). Transitions between health states with varying rates of lung density decline were based on observations of the RAPID study and extension. Transitions between FEV_1 % predicted states were based on observational UK registry data and a meta-analysis of A1P1 studies since FEV_1 % predicted changes slowly thus could not be observed in the 2-year clinical study. The structure of the model, and number of health states, was designed with data limitations in consideration. In particular, the advantage of fewer health states is that the data used to generate the transition probabilities is not reduced to small numbers. This is particularly important given the rarity of the disease and the relatively small number of patients in the RAPID trial.

Mortality data for BSC and Respreeza were taken from the RAPID study and extension study and informed the first two and four annual cycles, respectively. Distributions of patient counts at the end of each year were derived by linear regression to account for small differences in baseline characteristics between the RAPID and extension study populations. These were used to estimate annual transition probabilities which were applied to the first two and four year cycles in the respective arms of the model. Mortality data for the remainder of the model lifelong time horizon were based on observations from the UK registry (Stockley, 2015), stratified by rate of decline (please see Section 9.9.3 and 6.3.

The treatment effect associated with Respreeza was also incorporated into the model via a change in the transition probabilities between rates of CT lung density decline. This leads to an indirect treatment effect on mortality since patients with higher rates of lung density decline had a greater risk of death (Section 12.1.5). Clinical opinion is that that Respreeza would reduce rate of decline in FEV_1 % predicted over the long term. A treatment effect was applied to the baseline probability of transition from FEV_1 >50% predictedto FEV_1 <50% predicted using data from a meta-analysis that reported

the decline in FEV_1 % predicted was slower by 13.4 mL/year among all patients receiving A1P1 treatment (Chapman et al., 2009) (also see Section 9.9.4).

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

A summary of the assumptions made in the model and corresponding justifications are given in Table 33. The majority of assumptions were made due to lack of published evidence; A1PI deficiency is a rare disease and the A1PI deficiency community is still continuing to understand and quantify the many aspects of the condition.

Table 33. Summary of assumptions applied in the cost-effectiveness analysis

Category	Assumption	Justification / impact
Time horizon	Lifetime	A lifelong time horizon is used to capture all differences in costs and outcomes for all patients.
Lung transplant	Patients are only eligible to receive a lung when they have an FEV_1 ≤50% predicted and either a slow or rapid decline.	Guidelines recommend lung transplantation in patients with an FEV_1<30% predicted (American Thoracic and European Respiratory, 2003, Stoller and Aboussouan, 2004) but this specific health state was not included in the analysis, so it was assumed only patients with a decline in lung density and an FEV_1 <50% predicted would be eligible. Also see Section 12.2.1.5
Mortality	Risk factors are a higher rate of lung density decline or FEV_1 ≤50% predicted.	Based on evidence provided from the UK registry of patients with A1PI deficiency (Stockley, 2015) (see Section 6.3).
	All patients with FEV_1>50% were assumed to have the same rate of death, regardless of the rate of lung density decline.	Data for patients with FEV_1>50% predicted and no decline in lung density appeared to have much greater mortality than patients with FEV_1>50% predicted and slow or rapid decline in lung density (Chapman et al., 2015, Stockley, 2015). However only 3 patients with FEV_1>50% predicted and no decline in lung density were included in the analysis. The resulting survival curve for the FEV_1>50% predicted and no decline in lung density group was counter-intuitive and omitted from the model.
	It is assumed that death will occur due to A1P1 deficiency and hence mortality due to other causes is not included within the model.	Life expectancy is dependent on disease progression rather than age.
Transition probabilities	It is assumed that treatment effect remains constant over time.	There is insufficient long term data on Respreeza specifically to evidence that the mechanism of action could deteriorate over time. Please see Sections 0 and 12.2.1.3
	Rate of FEV_1 % predicted decline is independent from rate of lung density decline	It is clinical opinion that as rate of CT density decline increases, it is likely that rate of FEV_1 % predicted decline also increases. However, there was no data to parametrise this correlation in the model. As Respreeza reduces rate of lung density decline, this may mean that overall benefit of Respreeza is underestimated. Please see Sections 0 and 12.2.1.3
Costs and resource use	Disease monitoring costs from COPD patients are representative for patients with A1PI deficiency.	Emphysema is one of several diseases known collectively as COPD thus this is an appropriate assumption. No specific disease monitoring costs of patients with A1PI deficiency stratified by disease status are available. Please see Section 12.3.7

Category	Assumption	Justification / impact
	100% adherence and continuation is assumed.	The mean dosing compliance in the RAPID study was 99.9%. Clinical experts have advised that Respreeza will only be initiated in patients that want, and are committed to, lifelong treatment. Given this commitment and the severity of the disease, it is expected that patients will fully adhere to treatment.
	Disease monitoring costs depend on the FEV_1 % predicted state, and do not vary by the rate of lung density decline.	Although it is expected that patients with no decline in lung density would incur fewer disease monitoring costs, no specific evidence on the cost by lung density decline rate is published to include in the model. This is likely to overestimate the ICER for Respreeza. Please see Section 12.3.7
	Costs of any serious treatment related adverse events are not included.	One percent of the study population In the Respreeza arm and one percent of the study population in the placebo arm of the RAPID study had a serious treatment related adverse event. Therefore, it was assumed that no additional cost due to adverse events in the model (see Section9.7).
Health-related quality of life (HRQoL)	Utility depend solely on FEV_1 % predicted and does not vary by the rate of lung density decline.	Although there is a correlation between lung density decline and HRQoL (Stolk et al., 2003a), no specific published data on and HRQoL by lung density decline rate is published to inform the analysis. This assumption is likely to overestimate the ICER for Respreeza.
	Dis-utilities of adverse events are not included.	Of the small number of adverse events that occurred more frequently in the Respreeza arm of the RAPID study than the placebo arm, none were expected to have a significant impact on HRQoL (see Section 9.7.2)
	Carer disutility is not included in the base case analysis	If carers experience a decreasing HRQoL as disease progresses, the overall benefit of Respreeza may be underestimated. This is likely to overestimate the ICER for Respreeza.

12.1.6 Define what the model's health states are intended to capture.

The overall model design and choice of health states intend to capture both the long-term costs and outcomes of A1PI deficiency and the treatment effect of Respreeza compared to BSC alone. This includes a lower health-related quality of life and increased cost associated with reduced lung function (measured by FEV_1 % predicted), a higher mortality rate associated with rapid decline and reduced lung function, reduced health-related quality of life and increased cost in the first year following lung transplant, and an improved health-related quality of life and reduction in cost in the subsequent years of lung transplantation.

12.1.7 Describe any key features of the model not previously reported.

Key features of the economic model are summarised in Table 34.

Table 34. Key features of model not previously reported

Aspect	Details	Justification
Analytical method	Semi-Markov model	A state transition model was chosen due to the progressive chronic nature of the disease.
Software used	Microsoft Excel	Microsoft Excel is a widely used software
Discount of 3.5% for costs and outcomes	Included	In line with NICE requirements.
Perspective (NHS/PSS)	NHS	Relevant perspective as specified by the scope.
Cycle length	One year	Events are expected to occur throughout the cycle length of 1 year, and therefore a half cycle correction is applied.

NHS, National Health Service; PSS, Personal Social Services

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

In regard to mortality, RAPID data were used for years 1 and 2 to inform transitions in the BSC and the Respreeza arm of the model. Data from the extension phase of this study (years three and four) was used to inform transitions for the Respreeza arm. This was undertaken by using patient counts at each year of the trial data to estimate annual transition probabilities which were applied to the first two annual cycles in the BSC arm and first four annual cycles of the Respreeza arm respectively.

To model death rates beyond the time points informed directly by the trial data, registry data was used. Death rates were taken from the registry, dividing patients into three FEV_1 states and three lung density decline rate groups.

- Curves were fitted to Kaplan-Meier plots that were produced from the UK registry. Weibull was selected based on assessment of AIC and best fit by visual inspection. Further information is provided in Section 12.2.1
- An assumption of equivalence in the mortality rates for two of the three FEV_1 groups was made based on the available evidence.

In regard to disease progression, transition probabilities between the states of the model were from a post hoc analysis of RAPID and registry data:

- Two levels of FEV_1 and the two treatments (Respreeza, BSC) were considered separately, giving four sets of transition probabilities.
- For each of the four sets, RCT data on lung density decline rate for year 1 versus year 2 were combined to give transition probabilities.
- In addition, for the two Respreeza sets of transition probabilities, RCT extension data on lung density decline rate and year three versus year four was combined with the year 1 versus year 2 data.
- These were used to extrapolate rate of lung density decline over lifetime.
- The baseline rate of transition from one level of FEV_1 to another was taken from the UK registry.
- The probability of transition from states of FEV_1 >50% to FEV_1 <50% predicted in Respreeza took into account findings from a meta-analysis of A1P1 studies (Chapman et al., 2009) (also see Section 9.9.4).
- The lung density decline rate and FEV_1 probabilities were combined for each treatment.

Each of these parameters modelled using the clinical evidence is described in detail below. The probability and case fatality of lung transplant was not derived from the RAPID trial and described in Sections 12.2.1.5 and 12.2.1.6. Health-related quality of life estimates were also not derived from the clinical trial and are detailed in Section 12.2.1.7.

12.2.1.1 Transitions to death

There were three deaths in the best supportive care arm (n=87) of RAPID and one death in the Respreeza arm (n=93) over the 2-year follow-up (HR=0.2, 95% CI 0.02-2.56, p=0.225). In addition, there was one subsequent death in the 2-year extension study in which all patients were treated with Respreeza (Table 35). Whilst these results suggest a trend towards improved mortality with Respreeza, it would not be robust to extrapolate this result to the full time horizon of the model. Therefore, the clinical trial data was only utilised in the model for the duration of follow-up. The observed annual probabilities of death from RAPID and the extension study were used for the first 2 years in the best supportive care arm of the model and for the first four years of the Respreeza arm of the model.

Table 35. Deaths observed in RAPID study (years one and two) and extension study (years three and four)

Year	Respreeza			Placebo		
	Number of patients	Number of deaths	Annual probability of death	Number of patients	Number of deaths	Annual probability of death
1	93	1	1.075%	87	2	2.299%
2	92	0	0.000%	85	1	1.176%
3	140	1	0.714%	-	-	-
4	139	0	0.000%	-	-	-

The probability of death from all subsequent time-points was based on analysis of survival from the UK registry of patients with A1PI deficiency (see Section 6.3 for details). The methods used to measure CT lung density decline in the registry were comparable to the methods used to measure CT lung density in the clinical trial for Respreeza. Patients were divided into groups based on CT density decline and FEV_1 % predicted and the relationship to survival was compared by multivariate Cox regression, with rapid CT density decline associated with subsequent death (p=0.026), whilst patients whose lung density declined slowly showed a similar trend compared to those not declining (p=0.065) [redacted] (Green et al., 2014b).

Figure 29. Cox regression curves showing impact of density decline on survival (A) FEV_1 <30% predicted, (B) FEV_1 30-50% predicted, (C) FEV_1 ≥50% predicted

(A)

(B)

(C)

These survival data were utilised in the model by digitising the survival curves and subsequent fitting parametric functions to the digitised data in order to inform cycle specific transition probabilities. Data for the different lung density decline groups with a FEV_1≥50% predicted could not be accurately detected from the graph since it was not possible to distinguish between the slow and rapid decline groups. Furthermore, the no decline group showed counter-intuitive results, likely due to the small numbers at risk (n=3). Thus, the no-decline data were omitted and the assumption was made of the same underlying rate of death associated with slow and rapid lung function decline in patients with a FEV_1≥50% predicted.

All plots were re-digitised using the DigitizeIt software (Bormann, 2012) to ensure the interpreted data points were accurate. Points were selected manually (rather than using the in-built function to take every point on the line) to ensure the most relevant points were extracted for estimating individual patient level data (IPLD). In line with NICE DSU guidelines (Latimer, 2011), IPLD has been re-created from the summary statistics reported in the literature using an algorithm generated by Guyot et al (Guyot et al., 2012). This algorithm estimates time of events and censoring based on the known number of patients at risk for each curve. Loglogistic, lognormal, Weibull, exponential, Gompertz and generalised gamma functions were fitted to the estimated IPLD using the flexsurv package in R (Jackson, 2016). Separate functions were fitted to each arm of the data.

The best fitting distribution for each curve was selected based on an assessment of AIC and visual best fit (Table 36, Figure 30 to Figure 36).

Table 36. AIC data for parametric survival functions used to fit to the UK registry data

	FEV_1 >50% predicted	FEV_1 30-50% predicted			FEV_1 <30% predicted		
		No decline	Slow decline	Rapid decline	No decline	Slow decline	Rapid decline
Weibull	88.756	17.818	65.074	48.995	33.695	56.473	65.013
Exponential	93.683	18.313	75.920	56.781	37.491	65.360	74.477
Lognormal	90.891	17.855	67.083	50.295	34.099	58.935	78.189
Generalised gamma	90.208	19.855	64.607	48.397	35.691	-	51.033
Gompertz	86.837	17.829	64.112	48.651	33.998	56.240	53.378
Loglogistic	89.297	17.937	66.967	50.687	33.877	58.336	71.948

Goodness of fit comparisons of each of these plots to the observed data are presented in Figure 30 to Figure 36.

Figure 30. Parametric survival functions for FEV_1 ≥50% predicted

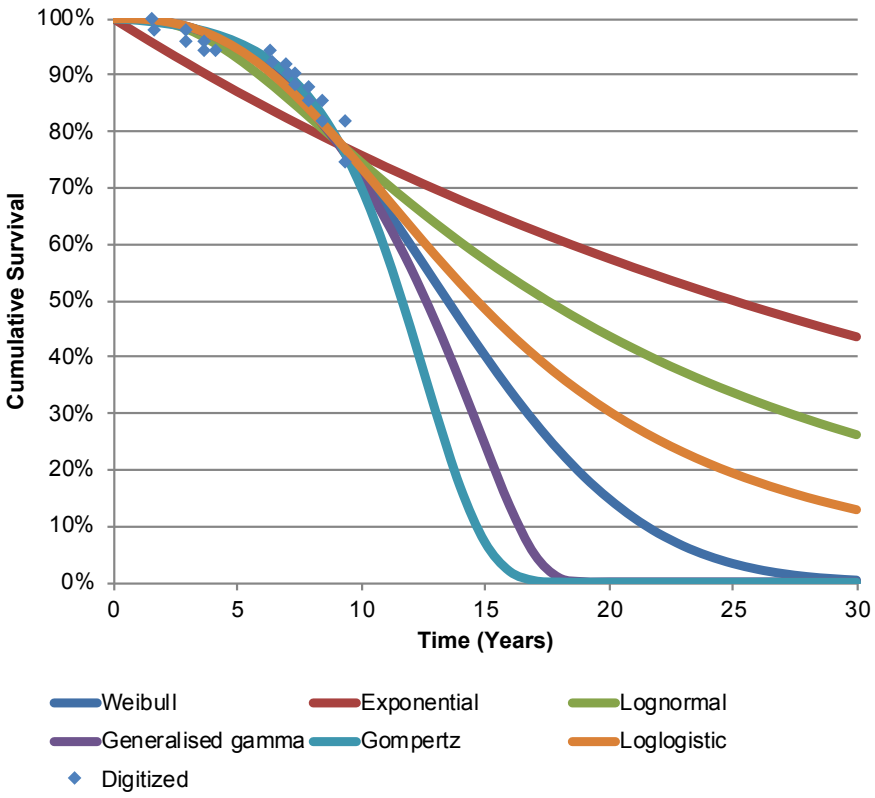


Figure 31. Parametric survival functions for FEV_1 30-50% predicted, no lung density decline

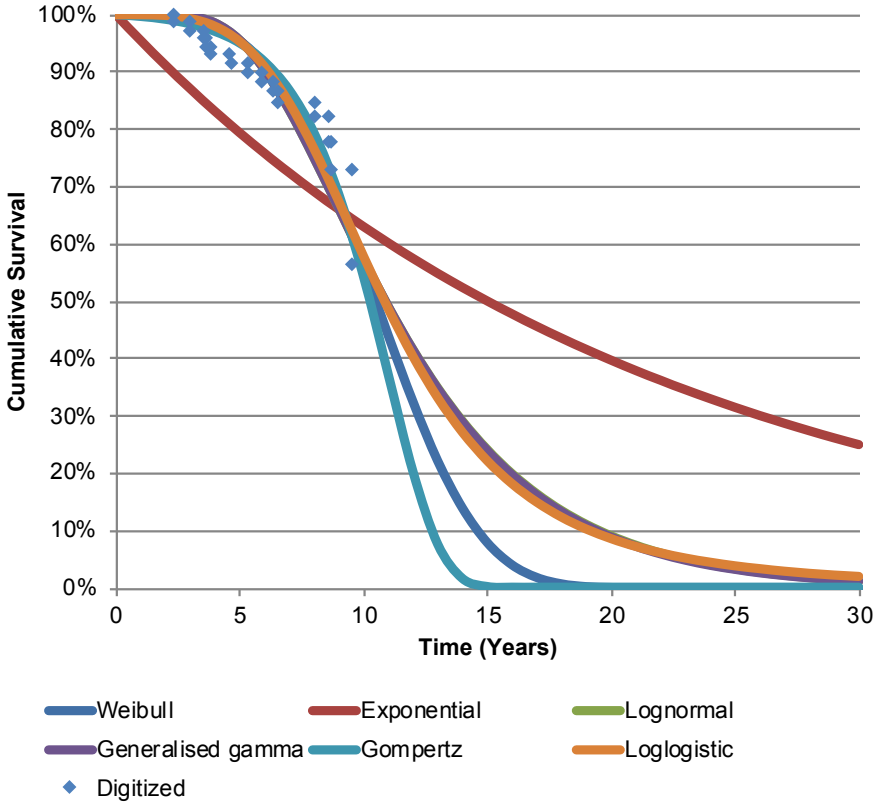


Figure 32. Parametric survival functions for FEV_1 30-50% predicted, slow lung density decline

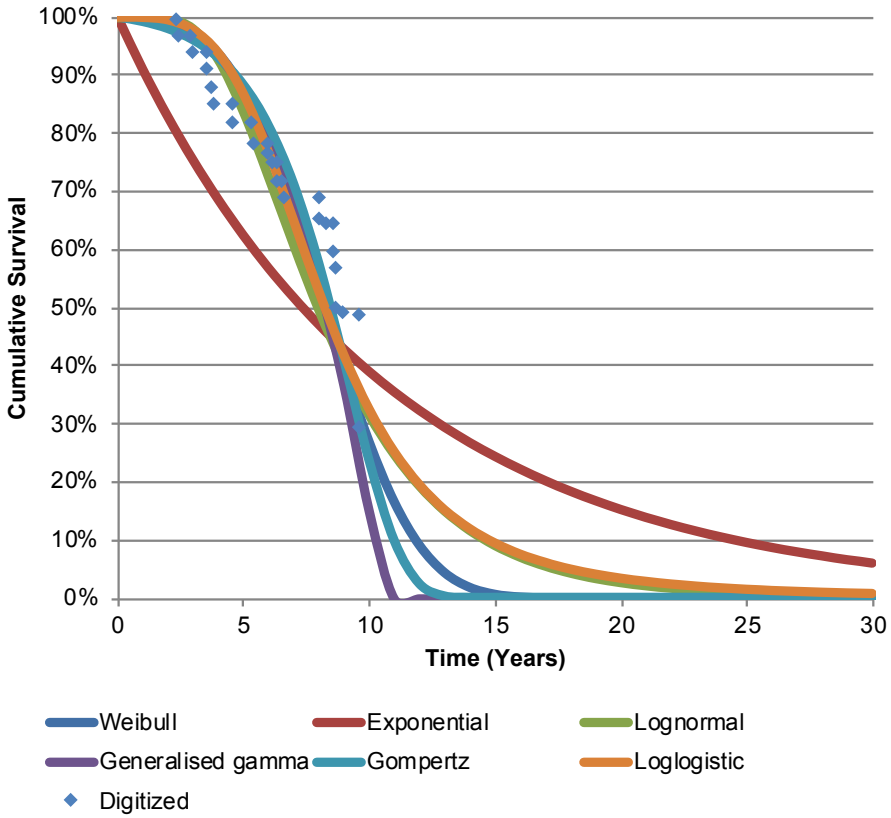


Figure 33. Parametric survival functions for FEV_1 30-50% predicted, rapid lung density decline

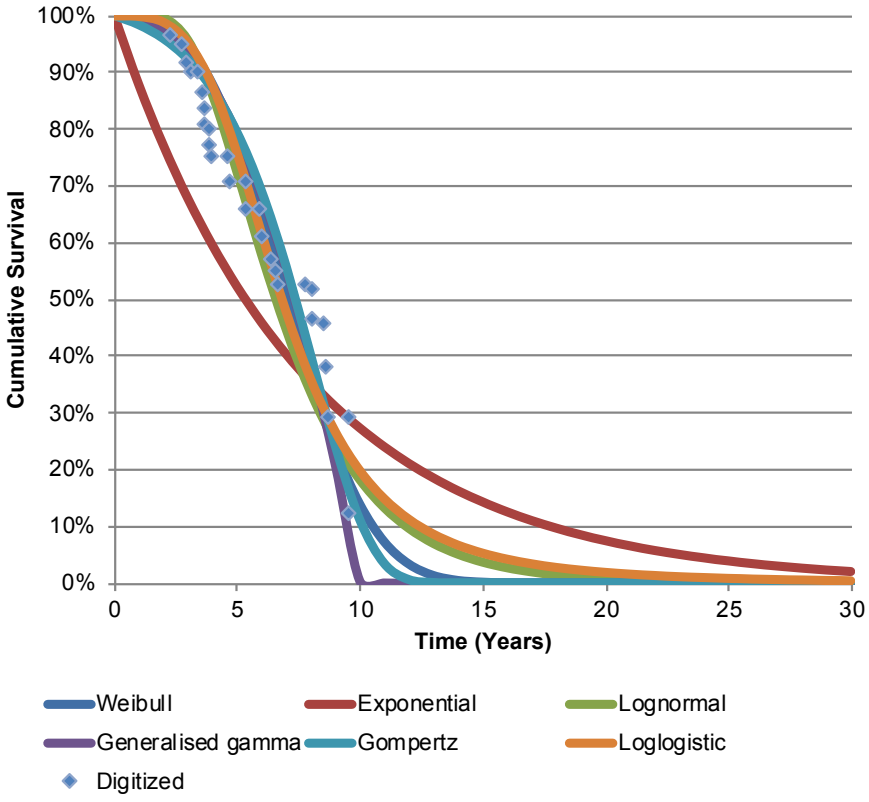


Figure 34. Parametric survival functions for FEV_1 <30% predicted, no lung density decline

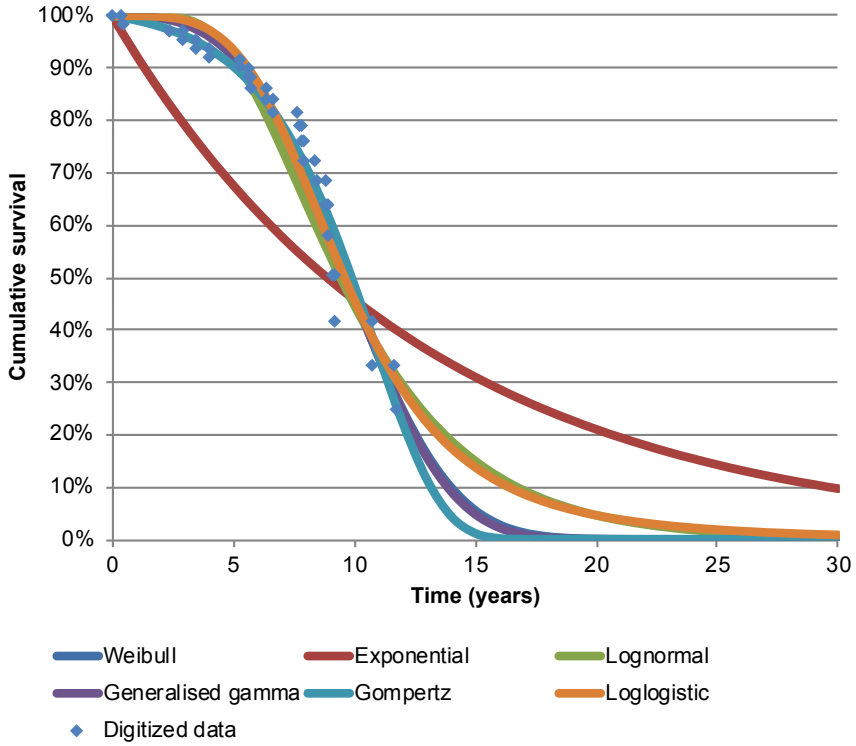


Figure 35. Parametric survival functions for FEV_1 <30% predicted, slow lung density decline

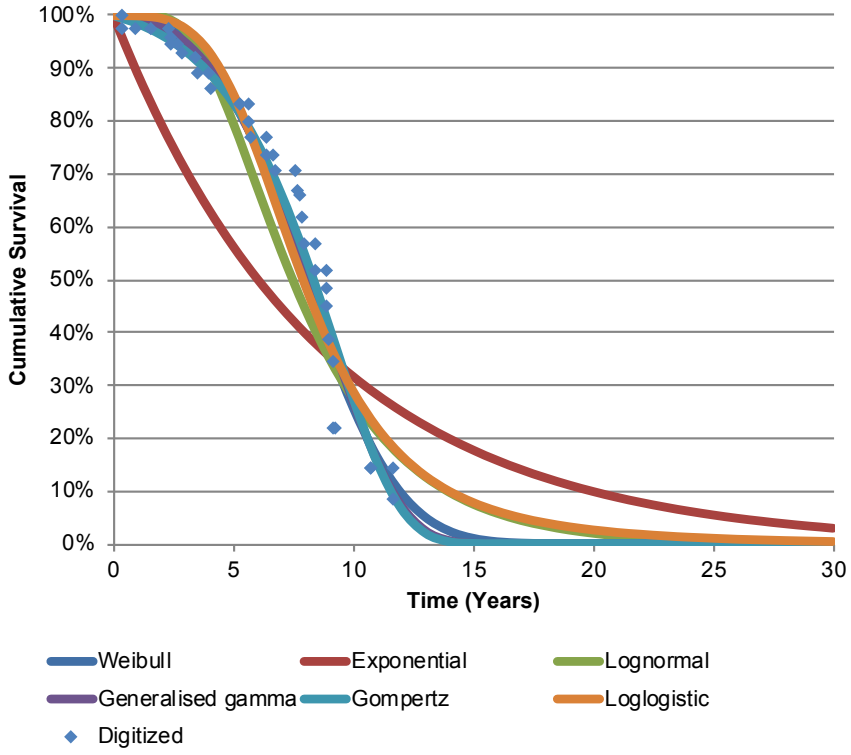
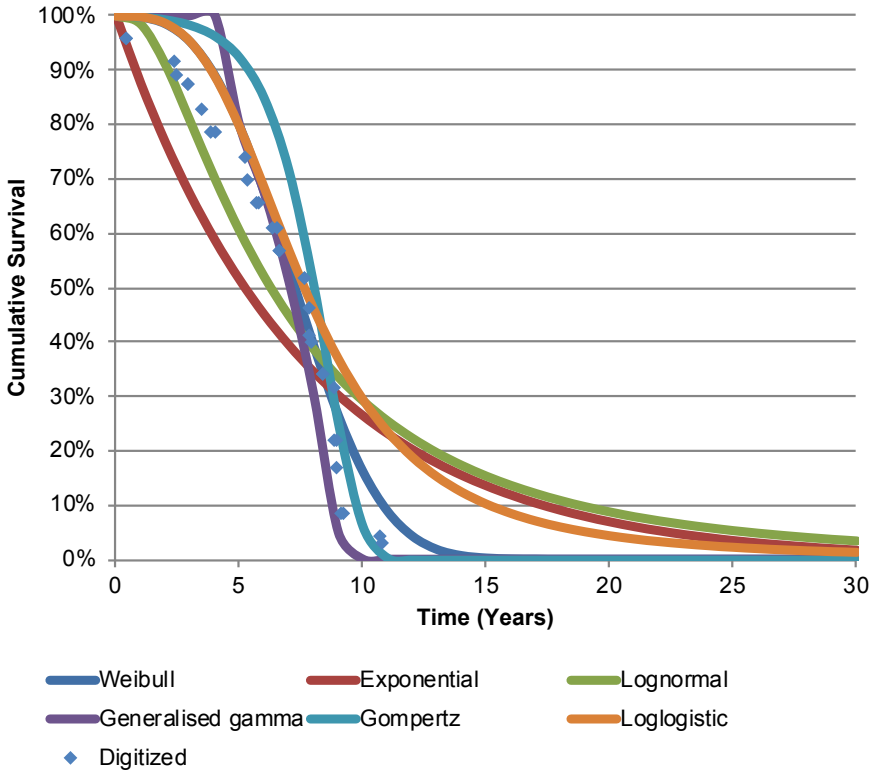


Figure 36. Parametric survival functions for FEV_1 <30% predicted, rapid lung density decline



The simplifying assumption was made that the same parametric distribution (Weibull) would be used to generate cycle specific transition probabilities for all of the seven categories. The resulting curves appear logical and clinically realistic since the FEV_1>50% of predicted curve is associated with the highest probability of survival, followed by the two states with no decline in lung density, as shown in Figure 37.

Since median survival is almost the same for FEV_1 30-50% predicted as FEV_1<30% predicted, FEV_1 30-50% predicted survival was used to represent FEV_1<50% predicted. This has the advantage of fewer health states, which means the data used to generate the transition probabilities is not reduced to small numbers. This is particularly important given the rarity of the disease and the relatively small number of patients in the trial. The final survival curves used in the model are given in Figure 38.

Figure 37. Cumulative survival functions derived from UK registry data

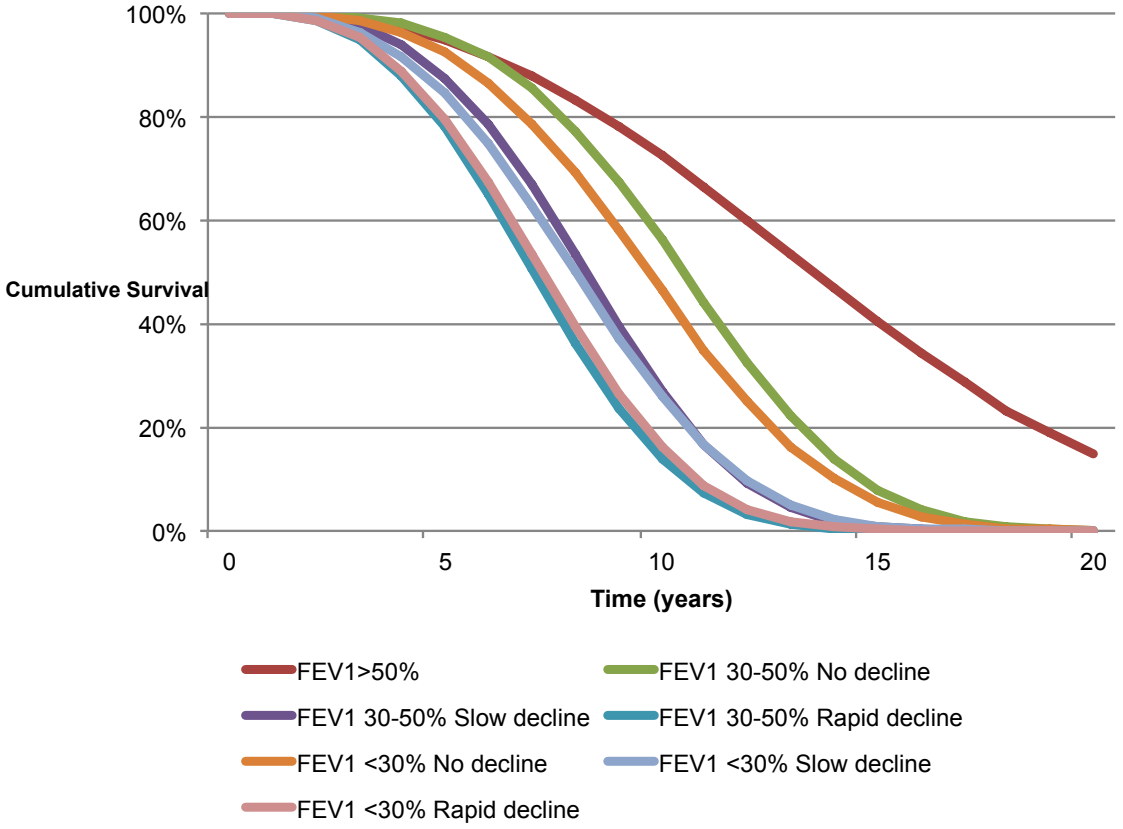
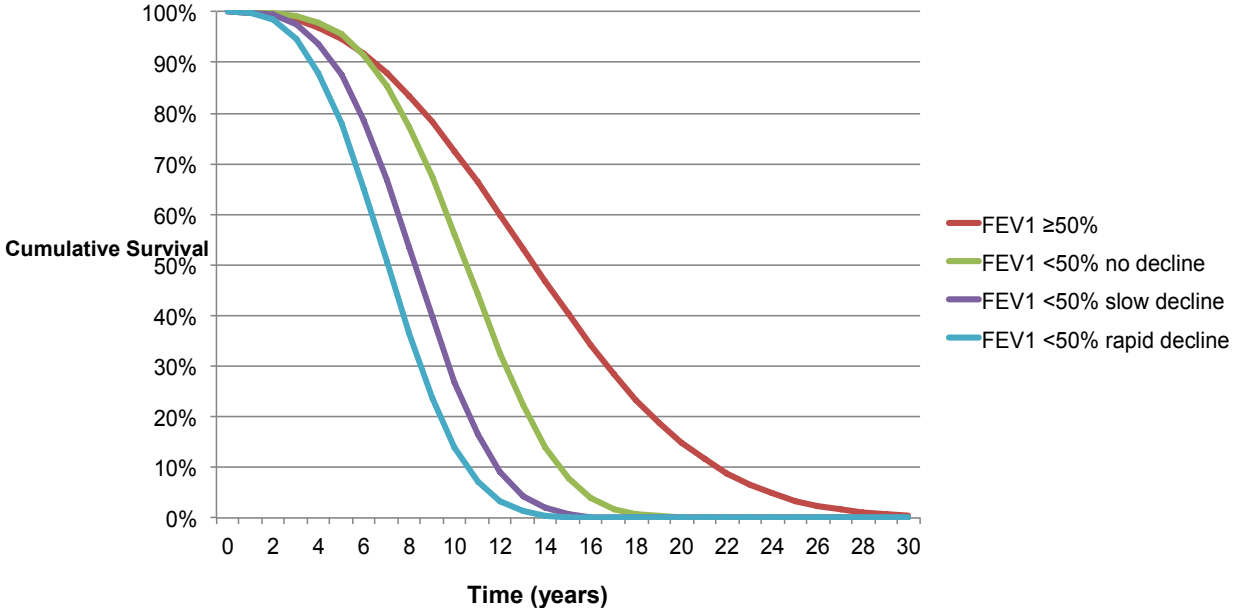


Figure 38. Cumulative survival functions used in the model



12.2.1.2 Transition probabilities between FEV_1 % predicted states

No clinically significant effect was captured in the trials to evidence that Respreeza will reduce decline in FEV_1 % predicted (see Section 9.6.1).

To power such a study would require a larger sample size than that within the RAPID Phase III study. Consequently, it is assumed that there would be no effect of treatment on FEV_1 % predicted decline. The value used in the model for the transition from $FEV_1 \geq 50\%$ predicted to $FEV_1 < 50\%$ predicted was based on data analysis of the UK registry (Stockley et al., 2014) (see Section 6.3). Average decline in FEV_1 % predicted for 406 patients with A1PI deficiency was 1.45% per year. At baseline in the RAPID study, average FEV_1 % predicted in $FEV_1 \geq 50\%$ group was 60% and average FEV_1% at baseline in $FEV_1 < 50\%$ group was 40%. Assuming a decline of 1.45% a year, it would take a patient with a FEV_1 of 60% predicted 14 years to move to an FEV_1 of 40%. Based on an exponential time to event, the annual probability of transitioning from the $FEV_1 \geq 50\%$ predicted health state to the $FEV_1 < 50\%$ of predicted health state is 7.18%.

Clinical opinion is that the probability of transitioning between these FEV_1 states would vary depending on patients' rate of lung density decline. However, data showing this effect is not yet published so the same rate of transition is applied from each lung density state. Thus, the modelled benefit of Respreeza may be underestimated.

Clinical opinion is that Respreeza would reduce the rate of decline in FEV_1% predicted over the long term. A treatment effect was applied to the baseline probability of transition from $FEV_1 > 50\%$ predicted to $FEV_1 < 50\%$ predicted using data from a meta-analysis that reported the decline in FEV_1 % predicted was slower by 13.4 mL/year among all patients receiving A1P1 treatment (Chapman et al., 2009) (also see Section 9.9.4). The pooled slope difference FEV_1 slope difference for control and augmentation therapy was 48.0 and 59.4 mL/year respectively, equating to a 19.19% reduction in decline with A1P1 therapy. Applying this effect to an annual baseline transition probability from a predicted $FEV_1 > 50\%$ to <50% of 7.18% gives an annual transition probability from a predicted $FEV_1 > 50\%$ to $FEV_1 < 50\%$ of 5.80% with Respreeza.

12.2.1.3 Transition probabilities between lung density decline states

Post-hoc analysis of the RAPID study data was conducted to generate the annual transition probability between each of the lung density decline states for patients with an $FEV_1 \geq 50\%$ predicted and those with an $FEV_1 < 50\%$ predicted for the BSC and Respreeza arms of the model. Four sets of matrices were constructed, each containing nine sets of estimated patient counts (given potential movement between any of the three states of rate of lung density of decline).

The post-hoc analysis used linear regression to estimate the expected distribution of patients across health states using data collected at different time points in the RAPID

study and RAPID extension study. From the derived distribution of patients in each state, a transition probability was derived and applied from the start of the model until the end of the lifetime horizon.

In the RAPID study, CT scans were taken at baseline, 3 months, 12 months, 21 months and 24 months to measure lung density. A linear regression was fitted to the data points at 0, 3 and 12 months for each patient to give the proportion of patients in each of the no/slow/rapid lung density decline health states at the end of year 1. A further linear regression was fitted to the data points at 12, 21 and 24 months for each patient to track their transition in the second year. The baseline characteristics of Respreeza and placebo were slightly different across arms thus the analysis is presented as a regression analysis using baseline covariate adjustment, which accounts for these slight differences.

In addition, the RAPID extension study provided further data for Respreeza. All placebo patients from RAPID enrolled into the Respreeza arm at the end of the study. All of the extension data was analysed in the same way as the main RAPID study but only using the data and time points available: 24 months, 36 months and 48 months. In line with the Markovian assumption of the model, this data was added to the 2-year analysis of the Respreeza arm of RAPID.

The resulting distributions of patients in the lung density decline states are detailed in Table 37 and Table 38 for best supportive care patients, and Table 39 and Table 40 for Respreeza patients. From these distributions an annual transition probability between each state was derived which applied across the patient's lifetime. Very few best supportive care patients experienced no decline in lung density. Comparatively, with Respreeza, patients had a higher chance of having no decline in lung density and fewer had a rapid decline. A detailed summary of the findings is as follows:

Best supportive care patients with FEV_1≥50% predicted at baseline (Table 37):

- Patients with no decline in year 1 had a slow decline in year 2.
- Most patients with slow decline in year 1 stayed as slow decliners in year 2.
- Half the rapid decliners from year 1 had a rapid decline in year 2 but the remainder only had slow decline.
- Best supportive care patients with FEV_1≥50% at baseline

Best supportive care patients with FEV_1<50% predicted at baseline (Table 38):

- Most patients with no decline in year 1 became slow or rapid decliners in year two.
- Almost half of the slow decliners had a rapid decline in year 2.
- Most rapid decliners remained rapid in year 2.

Respreeza patients with FEV_1≥50% predicted at baseline (Table 39):

- Almost half the patients with no decline in year 1 had no decline the following year.
- Most rapid decliners from year 1 only had a slow decline in year 2.

Respreeza patients with FEV_1<50% predicted at baseline (Table 40):

- Almost half of the patients treated with Respreeza with a rapid decline had a slow decline the following year, whilst most placebo patients continued to rapidly decline.

Table 37. Distribution of best supportive care patients over lung density decline health states, based on patients in the RAPID study with an FEV_1≥50% predicted at baseline

BSC		Year 1-2		
		No decline	**Slow decline**	**Rapid decline**
Year 0-1	**No decline**	0	6	0
	Slow decline	0	10	1
	Rapid decline	0	9	8

Table 38. Distribution of best supportive care patients over lung density decline health states, based on patients in the RAPID study with an FEV_1<50% predicted at baseline

BSC		Year 1-2		
		No decline	Slow decline	Rapid decline
Year 0-1	No decline	2	4	1
	Slow decline	0	17	12
	Rapid decline	0	3	12

Table 39. Distribution of Respreeza patients over lung density decline health states, based on patients in the RAPID study and extension with an FEV_1≥50% predicted at baseline

Respreeza		Year 1-2		
		No decline	Slow decline	Rapid decline
Year 0-1	No decline	13	15	2
	Slow decline	1	27	4
	Rapid decline	0	15	4

Table 40. Distribution of Respreeza patients over lung density decline health states, based on patients in the RAPID study and extension with an FEV_1<50% predicted at baseline

Respreeza		Year 1-2		
		No decline	Slow decline	Rapid decline
Year 0-1	No decline	6	15	1
	Slow decline	8	87	8
	Rapid decline	0	11	14

The annualised data for placebo from the two-year RAPID study (combined with the two years of information from the extension study in the case of estimation of the Respreeza transition probabilities) were used to extrapolate over a patient's lifetime to model the lifelong impact of treatment with Respreeza compared to placebo.

12.2.1.4 Summary of values used in the economic model

The distribution of patients across health states at the beginning of the model (Table 41) was based on the first year of placebo data from the RAPID study only (Table 37; Table 38). Since the health states are defined by the rate of decline over a year, the Respreeza data could not be used at baseline as there would be a treatment effect.

The probabilities of transitioning between the no, slow and rapid lung density decline states were combined with the probability of progressing in FEV_1% predicted to generate transition probabilities for best supportive care (Table 42) and Respreeza (Table 43).

Table 41. Distribution of patients across health states at baseline

	No decline	Slow decline	Rapid decline
FEV_1≥50% predicted	7%	13%	20%
FEV_1<50% predicted	8%	34%	18%

Table 42. Best supportive care transition matrix

		FEV_1≥50% predicted			**FEV_1<50% predicted**		
		No decline	**Slow decline**	**Rapid decline**	**No decline**	**Slow decline**	**Rapid decline**
FEV_1 ≥50% predicted	No decline	0%	93%	0%	0%	7%	0%
	Slow decline	0%	84%	8%	0%	7%	1%
	Rapid decline	0%	49%	44%	0%	4%	3%
FEV_1 <50% predicted	No decline	-	-	-	29%	57%	14%
	Slow decline	-	-	-	0%	59%	41%
	Rapid decline	-	-	-	0%	20%	80%

Table 43. Respreeza transition matrix

		FEV_1≥50% predicted			FEV_1<50% predicted		
		No decline	**Slow decline**	**Rapid decline**	**No decline**	**Slow decline**	**Rapid decline**
FEV_1 ≥50% predicted	**No decline**	41%	47%	6%	3%	3%	0%
	Slow decline	3%	79%	12%	0%	5%	1%
	Rapid decline	0%	74%	20%	0%	5%	1%
FEV_1 <50% predicted	**No decline**	-	-	-	27%	68%	5%
	Slow decline	-	-	-	8%	84%	8%
	Rapid decline	-	-	-	0%	44%	56%

12.2.1.5 Transitions to lung transplant

End-stage A1PI deficiency may be treated by transplantation (American Thoracic and European Respiratory, 2003, Wanger et al., 2005). It is assumed that only patients with an FEV_1<50% predicted with a slow or rapid decline in lung density would be eligible to receive a lung transplant. Furthermore, patients over the age of 65 rarely receive a transplant due to increased risk factors (Banner et al., 2011) thus only patients under the age of 65 are assumed eligible to receive a transplant in the model. Therefore, patients are only eligible to receive a lung transplant in the first 14 years of the model, which corresponds to age 51 to 65.

Of the 166 lung transplants performed in England last year (NHS Blood and Transplant, 2017), it is estimated that 7.2% were in patients with A1PI deficiency (Hachem et al., 2008). Based on a disease registry in the West Midlands, it is estimated that 670 people in England have emphysema caused by A1PI deficiency (Miravitlles et al., 2010). About 540 of these people (80%) will have clinically significant and progressive emphysema that requires treatment (NIHR Horizon Scanning Centre, 2014), of which 35% have an FEV_1<50% predicted (Ejiofor and Stockley, 2015), thus annual probability of a patient with A1PI deficiency receiving a transplant is 6.3% [166*7.2% / 540*35%].

12.2.1.6 Transitions from lung transplant to death

The annual probability of death from the lung transplant state was estimated at 10%, which was derived by using data reported for people who had lung transplant in 2009-2011 and had a reported 5 year patient percentage survival of 59% (NHS Blood and Transplant, 2017).

12.2.1.7 Health-related quality of life estimates

The approach used to incorporate health state preference weights (utilities) into the model was as follows:

- Quantify the age and gender adjusted general UK population norms
- Identification of health state specific health state utility values
    - Source absolute utility values associated with each health state from either the literature or the RAPID study
- Convert health state specific utility values into utility decrements
- Apply the derived utility decrements to the age and gender adjusted population norms

These steps are described in detail below. In addition, a sensitivity analysis was conducted to explore the potential impact of including A1PI deficiency emphysema on carer's health-related quality of life within the evaluation. This is briefly outlined at the end of the Section.

Quantify the age and gender adjusted general UK population norms

Age and gender adjusted general UK population health was informed by utility values reported by Kind et al (Kind et al., 1999b) (Table 44). A linear decline in utility was assumed across the age categories.

Table 44. Utility expected in the UK general population by age (Kind et al., 1999b)

Age (midpoint)	All	Male	Female	Weighted by 54% male.
All	0.86	0.86	0.85	0.86
20	0.94	0.94	0.94	0.94
30	0.93	0.93	0.93	0.93
40	0.91	0.91	0.91	0.91
50	0.85	0.84	0.85	0.84
60	0.8	0.78	0.81	0.79
70	0.78	0.78	0.78	0.78
80	0.73	0.75	0.71	0.73

Identification of health state specific health state utility values

No generic measures of health-related quality of life were captured in the Phase III study (RAPID). EQ-5D values, stratified by FEV_1% predicted, were obtained from the UK registry that provided the natural history mortality and FEV_1% predicted decline data (Table 45) (Ejiofor and Stockley, 2015). A weighted average of the utilities of

patients with a predicted FEV_1 <30%, 30-35%, 35-40%, 40-45% and 45-50% was taken to derive the utility for the FEV_1 <50% predicted in the model.

Table 45. Utilities by FEV_1% predicted from UK registry

FEV_1% predicted	Utility (EQ-5D)	Standard deviation	Number
Reported information			
<30	0.51	0.20	26
30-35	0.53	0.22	15
35-40	0.59	0.14	12
40-45	0.61	0.16	13
45-50	0.73	0.20	20
>50	0.79	0.18	158
Values used in the model			
≥50	0.79		
<50	0.59		

In the first year after a lung transplant, patients have a moderate health-related quality of life, which improves the following year (Groen et al., 2004). In an evaluation of the cost-effectiveness of lung transplantation across all respiratory disease, the EQ-5D score in a Dutch cohort of 120 transplanted patients was 0.69 one month after transplantation and 0.83-0.85 in the 3 to 12 months following lung transplant. This gives an average utility in the first year after transplant of 0.82. The score for subsequent years was 0.91 (Table 46) (Groen et al., 2004).

Table 46. Unadjusted utilities used in model

Health state	Utility (EQ-5D)
FEV_1 ≥50% predicted (all rates of lung density decline)	0.79
FEV_1 <50% predicted (all rates of lung density decline)	0.59
First year of lung transplant	0.82
Subsequent years following lung transplant (reference health state for calculating relative difference in utility between health states)	0.91

No difference in health-related quality of life between patients in different lung density decline health states were applied; HRQoL was assumed to be only driven by status in FEV_1% predicted. As well as an analysis of survival of patients in the UK registry of patients with API deficiency, an analysis of how health-related quality of life varies by rate of lung density decline was also conducted. An analysis of 58 patients in the combined group with at least 2 SGRQ scores was conducted. In Cox regression analysis, including baseline density and decline in CT densitometry as covariates, the curves separated, suggesting a trend towards worsening health-related quality of life with greater decline in CT density, although not statistically significant [redacted]. Subgroup analysis according to FEV_1 was uninformative due to sample size. Given this evidence and the intuitive clinical expectation that a decline in lung density would lead to patients being less able to breathe and therefore having a lower quality, it is highly likely that by not capturing the effect of reducing lung density decline on health-related quality of life, the effect of Respreeza is being underestimated.

Figure 39. Cox regression analysis of the combined group of patients seeking association with minimal clinically important difference of at least 4 in the SGRQ score.

In fact, although EQ-5D has shown a significant correlation with FEV_1% predicted, at best FEV_1% predicted explains about 43% of the variation in health status so factors other than FEV_1% predicted have an important impact on health status (Ejiofor and Stockley, 2015). Thus, only applying different utilities by FEV_1% predicted is unlikely to capture the full health status of A1PI deficiency patients and the benefit of Respreeza, but it is the best available data to date.

Derivation of utility decrements based on reported health state values

The utilities reported by Groen et al. (2004) suggested that utility in the first year after transplant is expected to be 0.82 and 0.91 for subsequent years (Table 46) (Groen et al., 2004). However, the population estimate for the modelled cohort is estimated at 0.84 (Table 44). Hence, the derived long term value by Groen et al. (2004) is higher than the population estimate. Therefore, adjustment to the utilities reported in the literature was made by assuming that subsequent years to lung transplant would be experienced at the same health–related quality of life as the general population who were of the same age (i.e. a decrement of zero).

The studies reporting all other utility information (Ejiofor and Stockley, 2015) (Groen et al., 2004) did not report sufficient information regarding the study population to allow comparison of the study populations between utility studies or the general population in regards to age.

The health state of “subsequent years to lung transplant” is viewed in the model as a reference category. The utility decrement between this state and other heath states was calculated using values within the literature. The population HRQoL norm according to age was assigned to the “subsequent years to lung transplant” health state, and the relative utility decrement to this reference state was applied to estimate the relative utility of other health states.

A summary of the utility decrements used in the economic model is presented in Table 47.

Table 47. Utility decrements applied to population estimates for Carer disutility

Health state	Decrement applied to population estimate
Health states where FEV_1>50% predicted	0.12
Health states where FEV_1<50% predicted	0.32
First year following transplant	0.09
Years post first year following transplant	0.00

There is currently insufficient evidence to understand how carers of people with A1P1 deficiency may be impacted by disease progression. Therefore, carer disutility could not be factored into the model base case. However, it is likely that carer health-related quality of life has a percentage reduction as disease progresses. On death of the patient, in absence of further information, it is assumed that the carer disutility is the same as advanced disease progression (where FEV_1<50% predicted). Baseline utility of the carer was approximated using population estimates of a 50 year old (which has a value of 0.85, see Table 44). Table 48 gives details of the additional utility decrement applied to each health state to account for potential carer disutility which was applied within an exploratory scenario analysis.

Table 48. Decrements applied in scenario analysis exploring carer disutility

Health state	Percentage reduction in carer health-related quality of life to baseline utility (0.85)	Utility decrement applied health state to take into account carer disutility
FEV_1>50% predicted	5%	-0.0425
FEV_1<50% predicted	10%	-0.085
First year following transplant	5%	-0.0425
Years post first year following transplant	5%	-0.0425
Post death	10%	0

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Clinical outcomes were extrapolated beyond the clinical study period. The transition probabilities informed by two years of data from the RAPID and an additional two years of data from the extension study for BSC and Respreeza respectively, and these transition probabilities were applied throughout the patient's lifetime. Transitions from a predicted FEV_1>50% to FEV_1<50% were informed by the UK registry data and a meta-analysis of studies evaluating A1P1 augmentation therapy. The use of the transition probabilities over a patient's lifetime to extrapolate assumes that rate of disease progression by health state and treatment effect is constant over time. This approach is supported by the mechanism of Respreeza which means that the treatment effect will not deteriorate. Mortality data from the two and four year Rapid and extension study was applied to the first two and four annual cycles of the model for BSC and Respreeza respectively. Thereafter survival was informed by registry data, extrapolated using a Weibull survival function. Extrapolation was undertaken using methods described above in Section 12.2.1, where the assumptions that underpin the extrapolation are explained further.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

The effect of Respreeza in the model was to change the transition probabilities between rates of CT lung density decline. This led to an indirect treatment effect on mortality since patients with lower rates of lung density decline had a lower risk of death.

Another indirect treatment effect found in the model was delayed time to lung transplant as a consequence of reduced disease progression.

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Not applicable. No adverse events were included within the model. Respreeza has a manageable side effect profile that does not require specific monitoring (Medicines.org.uk 2018). The overall adverse event (AE) profile observed with Respreeza during six clinical studies identified in the clinical systematic review was similar to that of placebo, and the types of AE reported in the clinical trials are very similar to those that arise due to the underlying disease (see Section 9.7.2).

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Please see section 10.1.10.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D5 below.

The parameters used to estimate cost and effect, alongside respective data sources are presented in the below Table 49.

Table 49. Summary of variables applied in the cost-effectiveness model (please see Section 12.4.3 for relevant range or 95% CI distribution)

Variable	Value	Source
Age	51 years	As per the RAPID trial
Male : female	54%	As per the RAPID-OLE trial
Time horizon	Lifetime	
Discount rate	3.5% for costs and benefits	
Patient distribution at baseline	**FEV_1>50% predicted** No decline 7% Slow decline 13% Rapid decline 20% **FEV_1<50% predicted** No decline 8% Slow decline 34% Rapid decline 18%	Placebo patients in the RAPID trial (Chapman et al., 2015)
Clinical inputs	**See Section 0 and 12.2.1.3**	
Annual FEV_1 decline in placebo patients	1.45	UK registry (Stockley et al., 2014)
Annual probability of transition to FEV_1<50% predicted with placebo	7.18%	UK registry (Stockley et al., 2014)
Reduction in decline with A1PI therapy	19.19%	Chapman, 2009 (Chapman et al., 2009)
Annual probability of transition to FEV_1<50% predicted with Respreeza	5.80%	Chapman, 2009 (Chapman et al., 2009)
Lung transplant	**See Section 12.2.1.5 and 12.2.1.6**	
Number of patients eligible for Respreeza in England	540	NIHR 2014 (National Institute for Health Research, 2014)
Proportion of patients with severe disease	35%	Ejiofor, 2015 (Ejiofor and Stockley, 2015)
Number of transplants between 2016-17	166	NHS Blood and Transplant 2017
Proportion of lung transplants in A1PI patients	7.2%	Hacham, 2008 (Hachem et al., 2008)
Annual probability of transplant	6.3%	Calculated
Annual probability of death following transplant	10.0%	NHS Blood and Transplant 2017
Survival	**See Section 12.2.1.1**	

Annual probability of death (Respreeza)	Year 1: 1.08% Year 2: 0.00% Year 3: 0.71% Year 4: 0.00%	RAPID study and extension (Chapman et al., 2015, McElvaney et al., 2017)
Annual probability of death (Placebo)	Year 1: 2.30% Year 2: 1.18%	RAPID study (Chapman et al., 2015, McElvaney et al., 2017)
Survival function used in extrapolation using registry data.	Weibull	See Section 12.2.2
Technology		
Variables informing treatment costs	See Section 12.3	
Dosage per week mg/kg	60	Recommended dosage
Patient weight kg	75.9	RAPID study (Chapman et al., 2015)
Vial size mg	1000	
Vials needed	4.55	Calculated
Actual vials used	5	Rounded
Number of administrations per year	52	
Costs		
Price per vial	£220	
Acquisition cost per administration	£1,100	Calculated
Acquisition cost of treatment per year per patient	£57,200	Calculated
Proportion administered via district nurse	75%	Assumption
Proportion administered via specialist clinic	25%	Assumption
Cost of district nurse per administration	£37	NHS reference costs 2016-17. District Nurse, Adult, Face to face (N02AF) (NHS Improvement, 2017)
Cost of specialist clinic per administration	£68	NHS reference costs 2016-17. Other Specialist Nursing, Adult, Face to face (N29AF) (NHS Improvement, 2017)
Cost of administration per treatment per patient	£45	Calculated

Cost of Respreeza per patient per administration, (inclusive of administering the infusion)	£1,145	Calculated
Annual cost of Respreeza per patient (assuming 52 administrations per year, inclusive of administering the infusion)	£59,526	Calculated
Variables informing disease management costs	**See Section 12.3.7**	
No lung density decline Slow lung density decline Rapid lung density decline	**FEV_1>50% predicted**: £2,254; £2,254; £2,254 **FEV_1<50% predicted**: £2,570; £2,570; £2,570	(Punekar et al., 2014) Inflated using PSSRU 2011-2017 (PSSRU, 2017)
Variables informing lung transplantation costs	**See Section 12.3.7**	
Proportion of lung transplants double	75%	Aziz,2010 (Aziz et al., 2010)
Lung transplant costs first year	Double: £76,502 Single: £77,285 Weighted cost used in model: £76,698	Anyanwu 2002 (Anyanwu et al., 2002) Inflated using PSSRU 1999-2017 (PSSRU, 2017)
Lung transplant costs subsequent years	Double: £9,294 Single: £9,157 Weighted cost used in model: £9,260	Anyanwu 2002 (Anyanwu et al., 2002) Inflated using PSSRU 1999-2017 (PSSRU, 2017)
Health-related quality of life	**See Section 12.1.2.7**	
Utility associated with FEV_1% predicted status	FEV_1>50%: 0.79 FEV_1<50%: 0.59	Derived from Ejiofor 2015 (Ejiofor and Stockley, 2015)
Utility associated with lung transplant	First year: 0.82 Subsequent years: 0.91	Derived from Groen, 2004 (Groen et al., 2004)
HRQoL for general population by age and gender	**Age / All / Male / Female** all 0.86 0.86 0.85 25 0.94 0.94 0.94 34 0.93 0.93 0.93 44 0.91 0.91 0.91 54 0.85 0.84 0.85 64 0.8 0.78 0.81 74 0.78 0.78 0.78 75+ 0.73 0.75 0.71	Kind, 1999 (Kind et al., 1999b), Table A
Utility decrement between post first year of transplant and other health states		
Difference between utility in "Lung transplant year 2 plus" and "FEV_1>50% predicted"	0.12	Calculated

Difference between utility in "Lung transplant year 2 plus" and "FEV_1<50% predicted"	0.32	Calculated
Difference between utility in "Lung transplant year 2 plus" and "Lung transplant year 1"	0.09	Calculated

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

Clinical management of the condition is likely to fall under Healthcare Resource Groups (HRG) (NHS, 2016) and PbR codes (NHS Improvement, 2018) associated with COPD (DZ65A-K). Dependent on level of complications and comorbidities, reported NHS reference costs for HRG codes DZ65A-K range from £473 for a one day stay to £5,320 in cases of multiple interventions (NHS Improvement, 2017). Admitted patient care & outpatient procedure prices in the 2017/18 National tariff report a range in reimbursement cost from £466 to £6,612 and £467 to £6,216 for elective and non-elective episodes respectively (NHS Improvement, 2018).

Because the annual cost of care will arise in the community as well as in secondary care, the model uses an annual cost of care derived from a published study of COPD patients by Punekar and colleagues (Punekar et al., 2014) (please also see Section 12.3.7 for further detail).

The only reference costs used within the model are those associated with the infusion of Respreeza, which included:

- The cost of district nurse per administration at £37 (NHS reference costs 2016-17. District Nurse, Adult, Face to face (N02AF) (NHS Improvement, 2017).
- The cost of specialist clinic per administration at £68 (NHS reference costs 2016-17. Other Specialist Nursing, Adult, Face to face (N29AF) (NHS Improvement, 2017).

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic search was conducted to identify economic and quality of life studies. From this search, two studies reporting resource use data were identified, although neither are applicable to the UK context. Please see Section 11 for further detail of the search and review inclusion and exclusion criteria.

Stoller et al. (2000) (Stoller et al., 2000) reported the resource utilisation associated with the first 712 A1PI deficient patients who entered the Alpha One Foundation Research Network Registry in the US between 1997 and 1999. No cost data was reported by the authors. Most registrants reported having the PiZZ phenotype (70.7%) and the most common lung disease was emphysema (54.2%) followed by bronchitis (35%). The registrants reported a high level of resource use overall, with a mean of 7.8 (SD 9.4) physician visits over the preceding 12 months. 35.4% of respondents reported using at least some supplemental oxygen at home. Lung-related surgery was reported by 6.5% of respondents and lung transplantation in 7.1%. The results showed that A1PI deficiency leads to considerable resource utilisation for this relatively young population.

Another study based on the Alpha One Foundation Registry for individuals with A1PI deficiency in the US assessed the impact of this disease on direct medical costs (Mullins et al., 2001). The mean annual healthcare cost among patients receiving human A1PI at the time of the research was estimated at $40,123. Lung transplant recipients reported higher mean annual costs ($67,419) than non-lung transplant recipients ($28,020).

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

There were no applicable UK studies. Since the two cost and resource use studies discussed in section 12.3.2 (Stoller et al., 2000, Mullins et al., 2001) were from US data, they were not deemed appropriate for this evaluation.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The list price of Respreeza is £220 per 1000mg vial.

12.3.5 If the list price is not used in the de novo cost-effectiveness model, provide the alternative price and a justification.

The list price is utilised in the de novo cost- effectiveness model.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Treatment costs are applied in the model in the Respreeza arm only as Respreeza is given in addition to best supportive care (present in both arms). Treatment costs comprised of intervention drug acquisition costs and administration costs of infusion. The total cost of treatment and infusion per administration per patient was calculated at £1,145. This equates to a total per person annual cost of £59,526 (which assumes 52 administrations per year and includes the cost of administering the infusion).

Acquisition costs

The drug dose and the vials required were inputted as per the summary of product characteristics (SPC) for Respreeza (Medicines.org.uk, 2018b). The average patient weight within the RAPID trial was used to determine the required dose. The required dose was combined with the drug cost per vial to obtain an overall annual treatment cost. All items utilised to determine treatment costs are included in Table 50.

Table 50. Treatment acquisition cost items (exclusive of administration cost)

Treatment cost item	Value	Source
Price of the technology	£220 per 1000mg vial	
Dose	60mg/kg once-weekly	Respreeza SPC (Medicines.org.uk, 2018b)
Patient weight	75.9kg	RAPID (Chapman et al., 2015)
Vial size	1000mg	Respreeza SPC (Medicines.org.uk, 2018b)
Number of vials required per dose	4.55	Calculated
Actual vials used	5	Rounded up to account for wastage
Cost per administration	£1100	Calculated
Annual treatment cost per patient assuming weekly infusion ((excludes cost of administering the infusion)	£57,200	Calculated

Administration Costs

The costs associated with the infusion of Respreeza were included as administration costs. Treatment was administered once a week in line with the Respreeza SmPC. Administration costs were sourced from NHS reference costs (NHS Improvement, 2017). Respreeza will be initiated within the current context of care, by specialists experienced in the management of A1PI deficiency at existing facilities. However, once initiated, home administration is likely. Therefore, administration was assumed to take place either at home with a nurse administering infusions or at a nurse-led infusion clinic. All items utilised to determine administration costs are included in Table 51.

Table 51. Administration cost items

Administration cost item	Value	Source
Proportion of nurse-administered infusion at patient's home	75%	Assumption
Proportion of nurse administered infusion at clinic	25%	Assumption
Cost of nurse-administered infusion at patient's home	£36.93	NHS reference costs, 2016-17, N02AF, District Nurse, Adult, Face to face (NHS Improvement, 2017)
Cost of nurse administered infusion at clinic	£68.12	NHS reference costs, 2016-17, N29AF, Other Specialist Nursing, Adult, Face to face (NHS Improvement, 2017)
Cost per treatment administration per patient	£44.72	Calculated
Annual cost per patient assuming 52 administrations per year	£2,326	Calculated

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in Section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

Costs associated with each of the eight health states are summarised in Table 52, with further rationale given for the choice of values below. The costs presented by health state include acquisition costs, administration costs and disease management costs.

Table 52. Summary of health states and associated costs in the cost- effectiveness model (costs applied to the proportion of people alive in each health state, expressed as cost per annum)

Health states	Item	Value	Reference
FEV_1≥50% predicted, no lung density decline FEV_1≥50% predicted, slow lung density decline FEV_1≥50% predicted, rapid lung density decline	Annual treatment cost of Respreeza	£59,526	Calculated (see Section 12.3.4 and 12.3.6)
	Disease management cost	£2,254	Punekar 2014 (Punekar et al., 2014) inflated to 2017 costs
FEV_1<50% predicted, no lung density decline FEV_1<50% predicted, slow lung density decline FEV_1<50% predicted, rapid lung density decline	Annual treatment cost of Respreeza	£59,526	Calculated (see Section 12.3.4 and 12.3.6)
	Disease management cost	£2,570	Punekar 2014 (Punekar et al., 2014) inflated to 2017 costs
Lung transplantation	First year transplant costs	£76,698	Derived from: Anyanwu 2002 (Anyanwu et al., 2002) inflated to 2017 costs Aziz 2010 (Aziz et al., 2010)
	Subsequent year transplant costs	£9,260	Derived from: Anyanwu 2002 (Anyanwu et al., 2002) inflated to 2017 costs Aziz 2010 (Aziz et al., 2010)
Death		£0	Assumed

Disease Management Costs

There are no published UK costs of managing patients with A1PI deficiency according to disease severity. Consequently, UK based costs of managing patients with COPD were used as proxy values. Emphysema is one of several respiratory diseases known collectively as COPD thus this is an appropriate assumption.

Costs were sourced from a UK a retrospective resource use analysis of over 50,000 UK COPD patients (Punekar et al., 2014). The study estimated total costs of disease management inclusive of primary care management and treatment of exacerbations. The costs were reported in terms of GOLD stages as defined at the time of publication, with Stage 2 equal to the FEV_1>50% predicted population from the RAPID study (Chapman et al., 2015), Stage 3 equal to FEV_1 30-50% predicted and Stage 4 equal to FEV_1<30% predicted. The costing study used UK NHS reference prices 2010/11. Therefore, total costs generated by the study were inflated from 2011 to 2017 using

the PSSRU pay and prices index (PSSRU, 2017). A weighted average of the costs for GOLD stages 1 and 2 was used for the cost of patients with an FEV_1>50% predicted. A weighted average of the costs for GOLD stages 3 and 4 was used for the cost of patients with a predicted FEV_1<50% (Table 53).

No costs were identified to indicate how disease management varies by rate of decline in lung density but it is expected that in clinical practice, rapid decliners would be more costly to manage than no, or slow, decliners. In light of the limited published evidence, disease management costs were only assumed to vary by FEV_1% predicted, not by lung density decline. Patients that are rapidly declining in lung density are more likely need more frequent monitoring and closer management by clinicians. Given Respreeza slows the rate of lung density decline, it is therefore likely be associated with lower disease management costs. By not capturing the differences in monitoring requirements by lung density decline, it is likely that this model is overestimating the ICER for Respreeza.

Table 53. Disease management costs

Pulmonary air flow	Value	Source
FEV_1 ≥50% predicted	£2,254	Punekar 2014 (Punekar et al., 2014) inflated to 2017 costs (PSSRU, 2017)
FEV_1<50% predicted	£2,570	Punekar 2014 (Punekar et al., 2014) inflated to 2017 costs (PSSRU, 2017)

Lung Transplant Costs

Costs of a lung transplant were sourced from an economic evaluation of lung transplantation in UK patients using data from the UK Cardiothoracic Transplant Audit (Anyanwu et al., 2002). Costs of transplant in the first year consist of assessment costs, donor acquisition costs, costs of the transplant and inpatient follow-up care. Follow up costs are also substantial owing to on-going monitoring and immunosuppressive treatment. Total annual costs for single and double lung transplants were reported in 1999 UK pounds, discounted at 6%. Undiscounted values were derived and inflated to 2017 costs using the PSSRU pay and prices index (PSSRU, 2017) to derive the cost of £76,698 which was used in the model . In comparison, the cost of lung transplant alone using 2016-17 reference cost is £ 40,076 (HRG code DZ01Z) (NHS Improvement, 2017).

A review of lung transplant in end-stage COPD patients found that 75% of patients with A1PI deficiency received a double lung transplant in 2005 (Aziz et al., 2010). Therefore, a weighted average of single and double lung transplant costs was calculated assuming 75% of patients received double lung transplants (Table 54).

Table 54. Lung transplant costs

Lung transplant cost item	Value	Source
Proportion of double lung transplants	75%	Aziz 2010 (Aziz et al., 2010)
First year double lung transplant costs	£76,502	Anyanwu 2002 (Anyanwu et al., 2002) inflated to 2017 costs (PSSRU, 2017)
First year single lung transplant costs	£77,285	Anyanwu 2002 (Anyanwu et al., 2002) inflated to 2017 costs (PSSRU, 2017)
Subsequent years double lung transplant costs	£9,294	Anyanwu 2002 (Anyanwu et al., 2002) inflated to 2017 costs (PSSRU, 2017)
Subsequent years single lung transplant costs	£9,157	Anyanwu 2002 (Anyanwu et al., 2002) inflated to 2017 costs (PSSRU, 2017)
First year transplant costs	£76,698	Calculated
Subsequent year transplant costs	£9,260	Calculated

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Respreeza has a manageable side effect profile that does not require specific monitoring (Medicines.org.uk, 2018b). The overall adverse event (AE) profile observed with Respreeza during six clinical studies identified in the clinical systematic review was similar to that of placebo, and the types of AE reported in the clinical trials are very similar to those that arise due to the underlying disease (see Section 9.7.2). In the RAPID study (Chapman et al., 2015) there were more (≥10) bronchitis, respiratory disorders, nausea and condition aggravated events in the Respreeza group than the placebo group but more cases of pneumonia in the placebo group. There was one serious TRAE in the Respreeza and one serious TRAE in the placebo arm, representing one percent of patients in each respective arm. It is therefore not expected that any of the mentioned adverse events would require specific costly treatments for Respreeza over best supportive care and therefore adverse event costs were not included within the cost-effectiveness model.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

All costs included in the model are reported in the above Sections. There are no other costs that have not been covered elsewhere.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

By delaying the time to loss of lung density and function, Respreeza is anticipated to prolong patient independence and reduce caregiver burden. This is likely to equate to care giver savings, however no evidence was identified to estimate this potential resource saving within the base case analysis. Further, if administration of treatment can be redirected from a specialised setting to the home setting, further resource savings may be made (the model assumes that 25% of administration will continue within the specialist setting). More specifically, Respreeza is administered as weekly intravenous infusions. The annual cost of administering weekly intravenous infusions in a outpatient or community setting was estimated at £1,508 per patient (see breakdown of costs Table 55).

Table 55. Breakdown of intravenous administration cost per patient per year

Item	Value	Reference
Nursing time required to administer an intravenous infusion	30 minutes	(Curtis and Burns, 2015)
Nurse patient contact cost per hour	£58	(NHS England, 2014/15)
Cost of intravenous administration per week	£29	
Cost of intravenous administration per year	£1,508	

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

Uncertainty around values of inputs have been investigated in deterministic and probabilistic sensitivity analysis, further details of which can be found in Section 12.4.2 below.

In order to test uncertainty around structural assumptions, scenario analyses were conducted, with particular inputs or assumptions being varied according to scenario.

- Discount rate: In the base case analysis, a discount rate of 3.5% was applied to both costs and benefits. In the one-way sensitivity analysis, discount rates were varied between 0% and 6%.A further analysis is conducted where a discount rate of 1.5% is applied to benefits and 3.5% is applied to costs.
- Exclude lung transplant health state
- Extrapolation function: Survival curves using next best fitting distribution (Gompertz)
- Carer disutility: A five percent reduction in carer health related quality of life was applied to patients with FEV_1 >50% predicted and in lung transplant states (i.e. a QALY loss of -0.0425 per patient per year) and a ten percent reduction was applied to all other health states including death (i.e. a QALY loss of -0.085 per patient per year). Carer utility was assumed to be 0.85 (equivalent to an average 50 year old).
- Application of reported absolute utility values to health states, rather than adjusting to population norms by decrements.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

The parameters were varied in one-way sensitivity analyses and probabilistic sensitivity analyses.

Costs, clinical inputs and utilities were varied using the upper and lower 95% confidence intervals, as reported by the literature or calculated using the distribution selected for the probabilistic analysis. Where uncertainty ranges could not be derived, range was derived to be the lower and upper bound calculated by an arbitrary 20% value of the mean, with the exception of the upper bound of the mortality rate for Respreeza in years 2 and 4 which was set to 1% (because the mean was 0%).

A number of additional scenarios were also tested by means of deterministic sensitivity analysis included:

- Administration costs: Administration through infusion clinic rather than homecare.
- Change in cost and utilities by decline in lung function density: It is expected that patients with lower decline in lung density would have higher utilities and lower costs. However, no specific evidence on the variation in utilities or costs is published so it could not be factored into the base case. A scenario is explored where patients with no decline in lung density have utilities 20% greater than slow lung density decline patients and have 20% lower costs, whilst for patients with a rapid decline in lung density, the parameters are 20% in the reverse.
- Baseline age: baseline age was varied between 30 and 60

In the probabilistic sensitivity analysis a beta distribution was chosen for transitions probabilities between FEV_1, and the lung transplant state and also for reported absolute utilities since they take a value between 0 and 1. Where utility values were varied, a maximum value in accordance to the population norm was applied. For lung density decline, a Dirichlet distribution was applied using the expected distribution of patients moving between states. A Gamma distribution was chosen for costs since costs are not expected to be negative ad the distribution is likely to be skewed to the right with high outliers.

The exceptions to the above are as follows:

- Upper value of Respreeza mortality in year 1 was set to the placebo mortality in year 1 (such that Respreeza mortality could not exceed placebo mortality).

- Upper value of Respreeza mortality in years 2 and 4 was set equal to 1%, from the base case of 0%.
- Lower value of placebo mortality in year 1 was set to the Respreeza mortality in year 1 (such that placebo mortality could not be lower than the Respreeza mortality).

12.4.3 Complete Table D24, Table D25 and Table D26 as appropriate to summarise the variables used in the sensitivity analysis.

Table 56. Variables used in one-way deterministic sensitivity analysis

Variable	Base-case value	Range of values
Discount rate on costs	3.5%	0% to 6%
Discount rate on outcomes	3.5%	0% to 6%
Discount rate costs after 30 years	3.5%	0% to 6%
Discount rate outcomes after 30 years	3.5%	0% to 6%
Clinical inputs - mortality		
Respreeza mortality year 1	1.075%	0.028% to 2.299%
Respreeza mortality year 2	0.000%	0.000% to 1.000%
Respreeza mortality year 3	0.714%	0.018% to 2.619%
Respreeza mortality year 4	0.000%	0.000% to 1.000%
Placebo mortality year 1	2.299%	1.075% to 6.309%
Placebo mortality year 2	1.176%	0.030% to 4.296%
Clinical inputs - transitions		
Transition from a predicted FEV_1>50% to FEV_1<50% placebo	7.176%	4.875% to 9.875%
Reduction in FEV_1 decline with Respreeza	19.192%	17.265% to 21.194%
Annual probability of lung transplant	6.305%	3.318% to 10.158%
Annual probability of death following lung transplant	10.015%	5.457% to 15.752%

FEV_1>50% predicted survival curve	Weibull:
	shape =2.57;
	scale = 15.57
		Lower CI
		shape = 1.40;
		and scale =10.43
		
		Upper CI
		shape = 4.71;
		scale= 23.22

FEV_1<50% predicted no decline survival curve	Weibull: shape =3.64; scale = 11.62	Lower CI: shape = 0.99 scale= 7.24 Upper CI: shape = 13.44; scale = 18.65
FEV_1<50% predicted slow decline survival curve	Weibull: shape =3.30; scale = 9.21	Lower CI shape = 1.93 scale= 7.70. Upper CI shape = 5.64; scale = 11.02.

FEV_1<50% predicted rapid decline survival curve	Weibull:
	shape =2.99;
	scale = 7.97
		Lower CI:
		shape = 1.70;
		scale= 6.37.
		
		Upper CI
		shape = 5.24;
		scale= 9.95.

Cost and resource related inputs		
Patient weight (which informs dosage calculation only)	75.9	66.00 to 84.50
Unit costs: administration per infusion	£44.72	£28.94 to £63.89
Disease management: FEV_1>50% predicted, no decline	£2,254	£1,459 to £3,220
Disease management: FEV_1>50% predicted, slow decline	£2,254	£1,459 to £3,220
Disease management: FEV_1>50% predicted, rapid decline	£2,254	£1,459 to £3,220
Disease management: FEV_1<50% predicted, no decline	£2,570	£1,663 to £3,671
Disease management: FEV_1<50% predicted, slow decline	£2,570	£1,663 to £3,671
Disease management: FEV_1<50% predicted, rapid decline	£2,570	£1,663 to £3,671
Lung transplant cost: year 1	£76,698	£49,508 to £109,276
Lung transplant cost: year 2+	£9,260	£6,015 to £13,276

Utility inputs		
Utility decrement: transplant YR 2 and FEV_1>50% predicted	0.12	0.096 to 0.144
Utility decrement: transplant YR 2 and FEV_1<50% predicted	0.32	0.255 to 0.383
Utility decrement: transplant YR 2 and YR1	0.09	0.069 to 0.104
Lung transplant YR 2	0.00	0.000 to 0.000

Table 57. Values used in scenario analyses

Analysis	Base case	Scenario
Structural assumptions		
Discount rate	Discount rate of 3.5% for outcomes and 3.5% for costs	Discount rate of 1.5% for outcomes and 3.5% for costs
Survival curves using Gompertz	Survival curves use Weibull function	Survival curves use Gompertz function
Exclude lung transplant	6.3% probability of transplant	Probability to transition to lung transplant set to 0%
Include carer disutility	No carer disutility applied	A five percent reduction in carer health related quality of life was applied to patients with a predicted FEV_1 >50% and in lung transplant states (i.e. a QALY loss of -0.0425 per patient per year) and a ten percent reduction was applied to all other health states including death (i.e. a QALY loss of -0.085 per patient per year).
Use reported absolute utilities for health states	Use utility decrements derived from reported values and apply to population norms	Use reported absolute utilities for health states
Scenario analyses		
Administration through infusion clinic rather than homecare.	25% infused administered at clinic	0% and 100% infused administered at clinic
Vary utilities and costs of lung density decline states by 20%	As per base case inputs	20% increased utilities and 20% decreased costs from no lung density decline state and 20% decreased utilities and 20% increased costs from rapid lung density decline state
Baseline age	51	30 and 60

Table 58. Variable values used in probabilistic sensitivity analysis

Variable	Base-case value	Distribution characteristics
Clinical inputs - mortality		
Respreeza mortality year 1	1.075%	Beta distribution applied; n = 93; Lower to upper bound = 0.028% to 2.299%
Respreeza mortality year 2	0.000%	Beta distribution applied; n= 92; Lower to upper bound = 0.000% to 1.000%
Respreeza mortality year 3	0.714%	Beta distribution applied; n = 140; Lower to upper bound = 0.018% to 2.619%
Respreeza mortality year 4	0.000%	Beta distribution applied; n= 139; Lower to upper bound = 0.000% to 1.000%
Placebo mortality year 1	2.299%	Beta distribution applied; n= 87; Lower to upper bound = 1.075% to 6.309%
Placebo mortality year 2	1.176%	Beta distribution applied; n= 85; Lower to upper bound = 0.030% to 4.296%
Clinical inputs – FEV_1% predicted		
FEV_1>50% survival curve	Weibull: shape =2.57; scale = 15.57	Lower 95% and Upper 95% CI: shape = 1.40 and 4.71; scale= 10.43 and 23.22
FEV_1<50% no decline survival curve	Weibull: shape =3.64; scale = 11.62	Lower 95% and Upper 95% CI: shape = 0.99 and 13.44; scale= 7.24 and 18.65
FEV_1<50% slow decline survival curve	Weibull: shape =3.30; scale = 9.21	Lower 95% and Upper 95% CI: shape = 1.93 and 5.64; scale= 7.70 and 11.02
FEV_1<50% rapid decline survival curve	Weibull: shape =2.99; scale = 7.97	Lower 95% and Upper 95% CI: shape = 1.70 and 5.24; scale= 6.37 and 9.95
Transition from FEV_1>50% to FEV_1<50% placebo	7.176%	Beta distribution applied; n= 406; Lower to upper bound = 4.875% to 9.875%
Reduction in FEV_1 decline with Respreeza	19.192%	Beta distribution applied; n= 1542; Lower to upper bound = 17.265% to 21.194%
Clinical inputs – Lung transplant probabilities		
Annual probability of lung transplant	6.305%	Beta distribution applied; n= 190.33; Lower to upper bound = 3.318% to 10.158%
Annual probability of death following lung transplant	10.015%	Beta distribution applied; SE= 128; Lower to upper bound = 5.457% to 15.752%
Costs and resource use		
Dosage per week	60.00	NA
Patient weight which informed dosage calculations	75.90	Gamma distribution applied; SE= 16.20; Lower to upper bound = 66.00 to 84.50
Respreeza cost per year	£57,200.00	Calculated
Unit costs: administration per infusion	£44.72	Gamma distribution applied; SE= 8.94; Lower to upper bound = 28.94 to 63.89

Respreeza administration cost per year	£2,325	Calculated according to the administration cost.
Disease management: FEV_1>50% predicted, no decline	£2,254	Gamma distribution applied; SE= 450.87; Lower to upper bound = 1458.91 to 3220.15
Disease management: FEV_1>50% predicted, slow decline	£2,254	Gamma distribution applied; SE= 450.87; Lower to upper bound = 1458.91 to 3220.15
Disease management: FEV_1>50% predicted, rapid decline	£2,254	Gamma distribution applied; SE= 450.87; Lower to upper bound = 1458.91 to 3220.15
Disease management: FEV_1<50% predicted, no decline	£2,570	Gamma distribution applied; SE= 514.00; Lower to upper bound = 1663.18 to 3671.02
Disease management: FEV_1<50% predicted, slow decline	£2,570	Gamma distribution applied; SE= 514.00; Lower to upper bound = 1663.18 to 3671.02
Disease management: FEV_1<50% predicted, rapid decline	£2,570	Gamma distribution applied; SE= 514.00; Lower to upper bound = 1663.18 to 3671.02
Lung transplant cost: year 1	£75,076	Gamma distribution applied; SE= 15015.25; Lower to upper bound = 48585.39 to 107239.20
Lung transplant cost: year 2+	£5,203	Gamma distribution applied; SE= 1040.60; Lower to upper bound = 3367.12 to 7432.01
Utility inputs (unadjusted to population norms)*		
Utility: FEV_1>50% predicted	0.79	Beta distribution applied; SE= 0.18; Lower to upper bound = 0.35 to 1.00
Utility: FEV_1<50% predicted	0.59	Beta distribution applied; SE= 0.19; Lower to upper bound = 0.21 to 0.92
Lung transplant utility: year 1	0.82	Beta distribution applied; SE= 0.16; Lower to upper bound = 0.40 to 1.00
Lung transplant utility: year 2+	0.91	Beta distribution applied; SE= 0.182; Lower to upper bound = 0.30 to 1.00

*a cap was placed on the sample drawn to ensure that a utility could not be drawn which was higher than a health state which is expected to have a higher HRQoL according to the values within the literature.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

The acquisition cost of Respreeza and Respreeza dosage were excluded from both sensitivity analyses since the list price was assumed to be fixed and 60mg/kg is the licensed dose. Since the probability of death with Respreeza in years 2 and 4 is 0%, a sample distribution for the probabilistic sensitivity analysis cannot be generated. On

this basis, Respreeza years one to four and placebo year's one to two mortality were excluded from the PSA.

12.5 Results of economic analysis

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

The base case results indicate that Respreeza is associated with an ICER of £342,872 per QALY gained. A breakdown of the base case results is given in Table 59.

Patients treated with Respreeza are predicted to have an undiscounted median survival of 10 years from the baseline age of 51, compared to a 7 year survival in best supportive care (please see Figure 40).

Figure 40. Predicted survival with BSC versus Respreeza

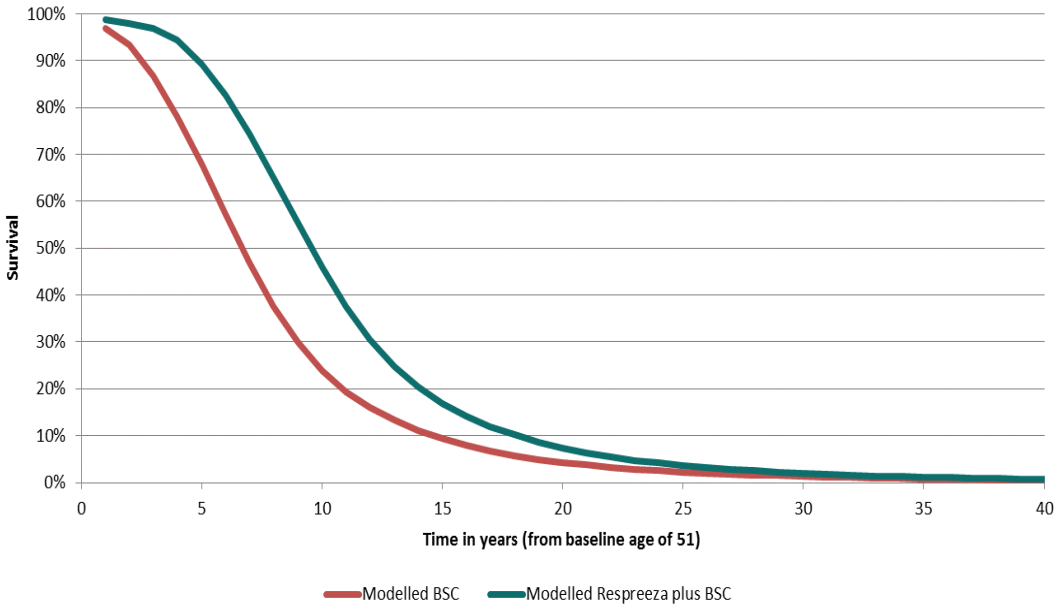


Table 59. Base-case results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Respreeza and BSC	£486,950	9.127	5.978	£447,949	2.051	1.306	£342,872
BSC	£39,001	7.076	4.672	NA	NA	NA	

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Not relevant. The clinical outcome assessed with the model is long term overall survival and prolonging the time to or obviating the need for lung transplant as a secondary clinical outcome, which cannot be compared with clinical trial data.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The trace of the proportion of people across health states is available in Table 60 to Table 63. The figures (Figure 41 to Figure 43) below provide an overview of the proportion in state for the Respreeza and BSC.

Table 60. Proportion of the patient cohort across all health states categorised by lung density decline status over time, BSC only.

Time in model (years)	Health state				
	No decline	Slow decline	Rapid decline	Lung transplant	Dead
0	9%	51%	37%	2%	1%
5	0%	31%	24%	13%	32%
10	0%	10%	4%	10%	76%
15	0%	3%	0%	6%	91%
20	0%	0%	0%	4%	96%
25	0%	0%	0%	2%	98%
30	0%	0%	0%	1%	99%
35	0%	0%	0%	1%	99%
40	0%	0%	0%	0%	100%
45	0%	0%	0%	0%	100%
49	0%	0%	0%	0%	100%

Table 61. Proportion of the patient cohort across all health states categorised by lung density decline status over time, Respreeza.

Time in model (years)	Health state				
	No decline	Slow decline	Rapid decline	Lung transplant	Dead
0	12%	58%	28%	2%	1%
5	5%	60%	11%	14%	11%
10	2%	25%	4%	15%	54%
15	0%	6%	1%	10%	83%
20	0%	1%	0%	6%	93%
25	0%	0%	0%	3%	96%
30	0%	0%	0%	2%	98%
35	0%	0%	0%	1%	99%
40	0%	0%	0%	1%	99%
45	0%	0%	0%	0%	100%
49	0%	0%	0%	0%	100%

Table 62. Proportion of the patient cohort across all health states categorised by FEV_1 % predicted status over time, BSC only

Time in model (years)	Health state			
	FEV_1 >50% predicted	FEV_1<50% predicted	Lung transplant	Dead
0	38%	59%	2%	1%
5	22%	33%	13%	32%
10	9%	4%	10%	76%
15	3%	0%	6%	91%
20	1%	0%	4%	96%
25	0%	0%	2%	98%
30	0%	0%	1%	99%
35	0%	0%	1%	99%
40	0%	0%	0%	100%
45	0%	0%	0%	100%
49	0%	0%	0%	100%

Table 63. Proportion of the patient cohort across all health states categorised by FEV_1% predicted status over time, Respreeza

Time in model (years)	Health state			
	FEV_1 >50% predicted	FEV_1 <50% predicted	Lung transplant	Dead
0	39%	59%	2%	1%
5	27%	48%	14%	11%
10	15%	16%	15%	54%
15	6%	1%	10%	83%
20	2%	0%	6%	93%
25	0%	0%	3%	96%
30	0%	0%	2%	98%
35	0%	0%	1%	99%
40	0%	0%	1%	99%
45	0%	0%	0%	100%
49	0%	0%	0%	100%

Figure 41. Markov trace for all health states for Respreeza and BSC.

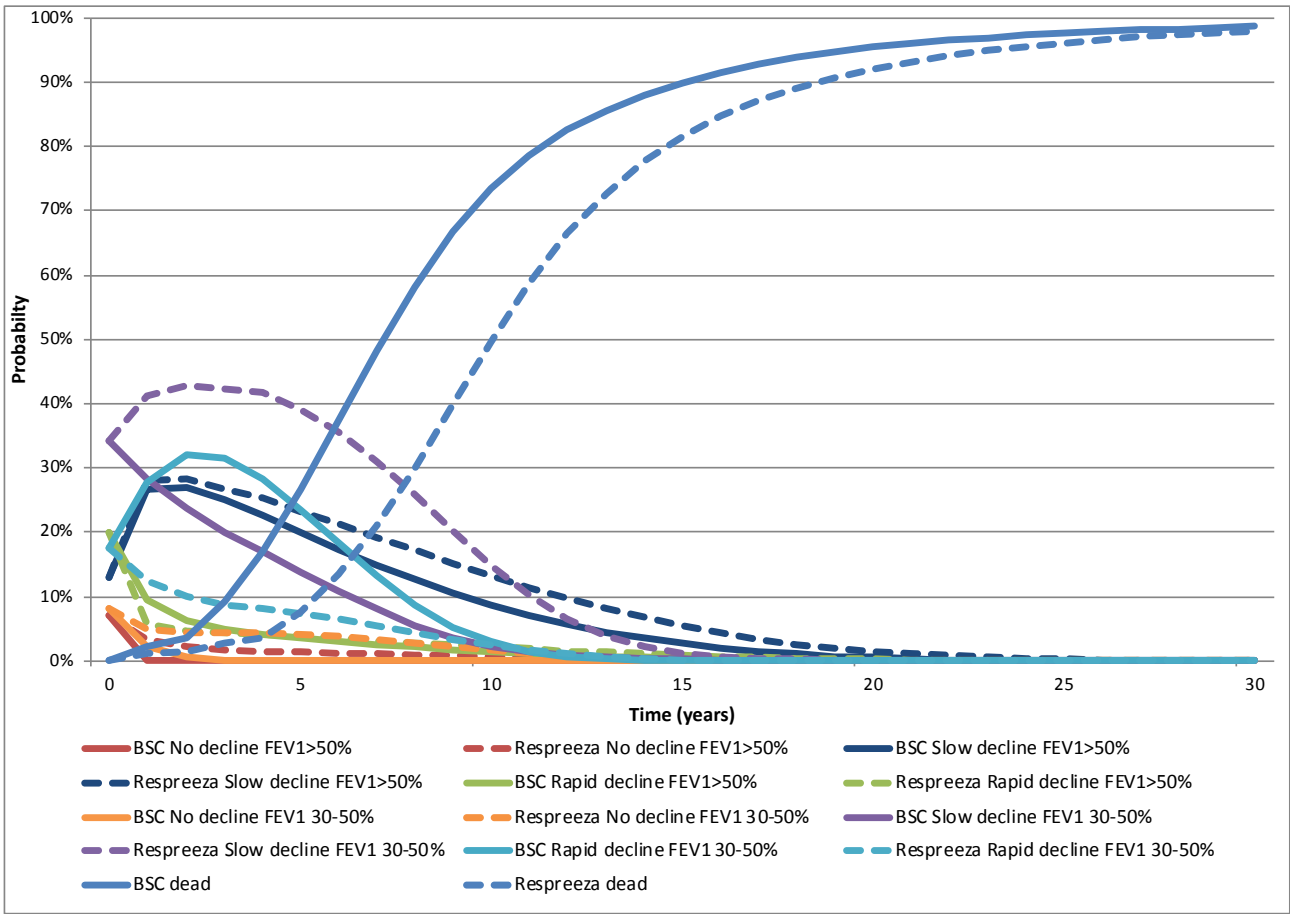


Figure 42. Markov trace by lung density decline state for BSC

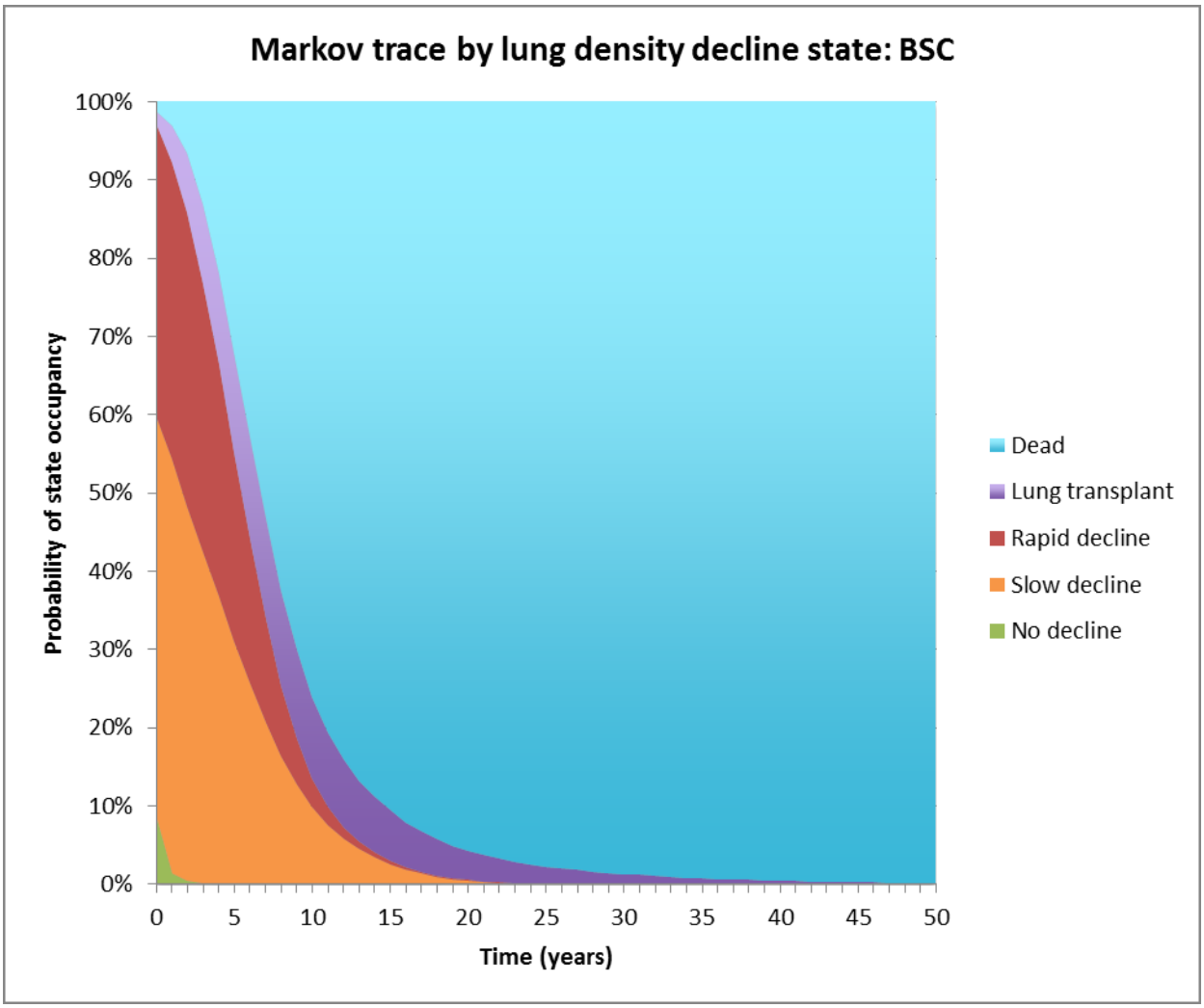
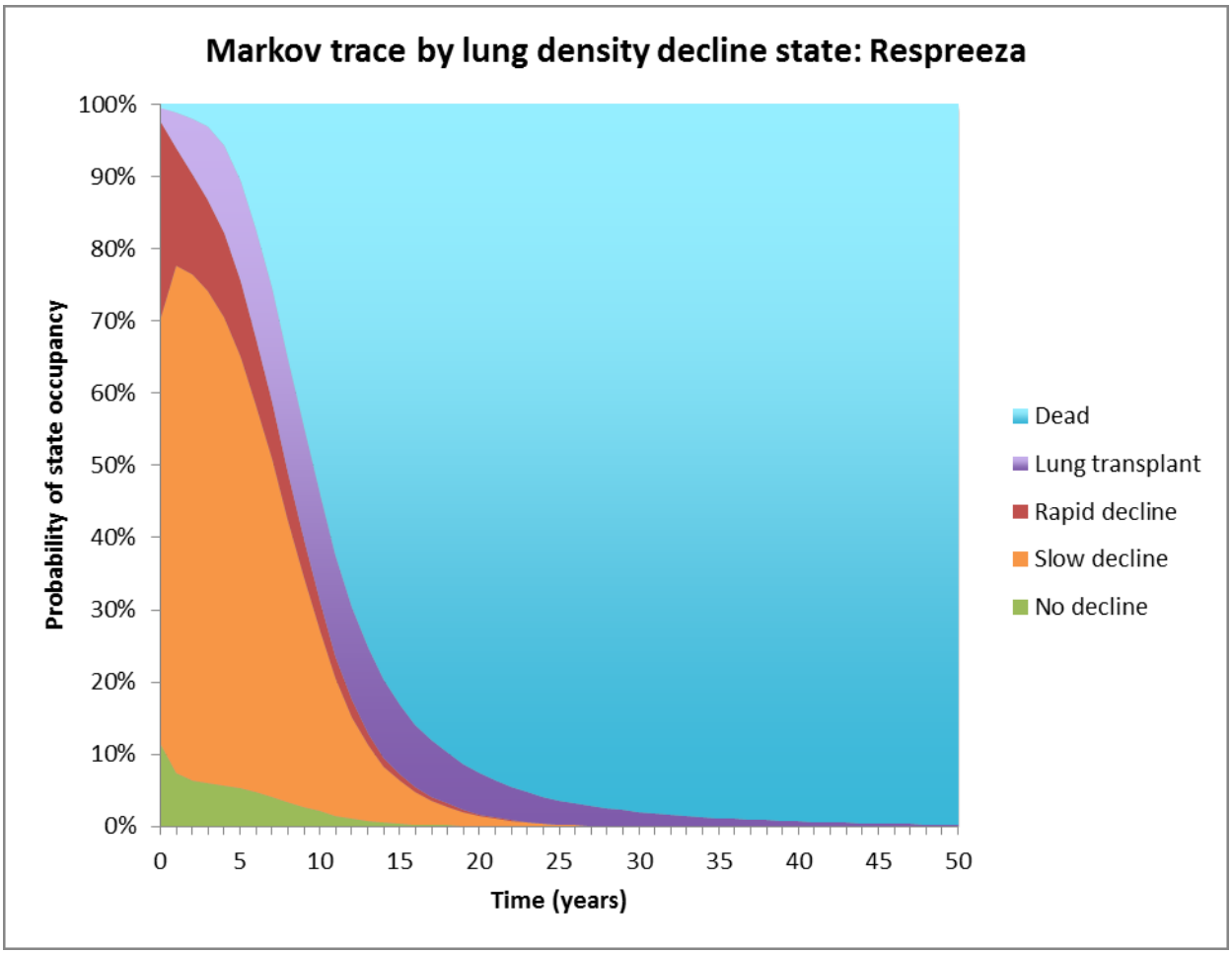


Figure 43. Markov trace by lung density decline state for Respreeza and BSC



12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table 64 and Table 65 show the trace of accrued QALYs over time by health state and intervention.

Table 64. QALYs accrued over time by health state: BSC

Time in model (years)	Total QALY accrued	Health state		
		FEV_1>50% predicted	FEV_1<50% predicted	Lung transplant
0	0.63	0.28	0.34	0.01
5	3.10	1.22	1.54	0.34
10	4.13	1.60	1.82	0.71
15	4.46	1.71	1.84	0.91
20	4.58	1.73	1.84	1.01
25	4.63	1.73	1.84	1.05
30	4.65	1.73	1.84	1.08
35	4.66	1.73	1.84	1.09
40	4.67	1.73	1.84	1.09
45	4.67	1.73	1.84	1.10
49	4.67	1.73	1.84	1.10

Table 65. QALYs accrued over time by health state: Respreeza

Time in model (years)	Total QALY accrued	Health state		
0	0.64	0.29	0.34	0.01
5	3.40	1.33	1.71	0.36
10	5.02	1.87	2.33	0.82
15	5.62	2.08	2.42	1.12
20	5.83	2.13	2.43	1.27
25	5.91	2.14	2.43	1.34
30	5.95	2.14	2.43	1.38
35	5.96	2.14	2.43	1.39
40	5.97	2.14	2.43	1.40
45	5.98	2.14	2.43	1.41
49	5.98	2.14	2.43	1.41

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The life years (LY) and QALYs accrued for each comparator, disaggregated by health state are found in the below tables (Table 66 and Table 67).

Table 66. Model outputs by clinical outcomes for best supportive care (discounted)

BSC - Discounted outcomes			
Outcome	LY	QALY	Cost (£)
FEV_1>50% predicted: No decline	0.04	1.73	£15,340
FEV_1>50% predicted: Slow decline	0.33		
FEV_1>50% predicted: Rapid decline	0.53		
FEV_1<50% predicted: No decline	0.07	0.32	
FEV_1<50% predicted: Slow decline	1.51		
FEV_1<50% predicted: Rapid decline	1.98		
Lung transplant: first year	0.19	1.55	£31,983
Lung transplant: subsequent years	0.56		
Treatment	NA	NA	£0
Administration	NA	NA	£0
TOTAL	7.08	4.67	£39,001

LY, life years; QALY, quality-adjusted life year

Table 67. Model outputs by clinical outcomes for Respreeza (discounted)

Respreeza - Discounted outcomes			
Outcome	LY	QALY	Cost (£)
FEV_1>50% predicted: No decline	0.18	1.73	£20,566
FEV_1>50% predicted: Slow decline	0.40		
FEV_1>50% predicted: Rapid decline	0.55		
FEV_1<50% predicted: No decline	0.42	0.42	
FEV_1<50% predicted: Slow decline	3.68		
FEV_1<50% predicted: Rapid decline	0.80		
Lung transplant: first year	0.15	2.06	£42,671
Lung transplant: subsequent years	0.62		
Treatment	NA	NA	£419,568
Administration	NA	NA	£2,951
TOTAL	9.13	5.98	£486,950

LY, life years; QALY, quality-adjusted life year

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table 68 below gives a summary of the expected discounted QALY gain per person by health state. This is followed by Figure 44 which shows how the QALY gain is accumulated over time.

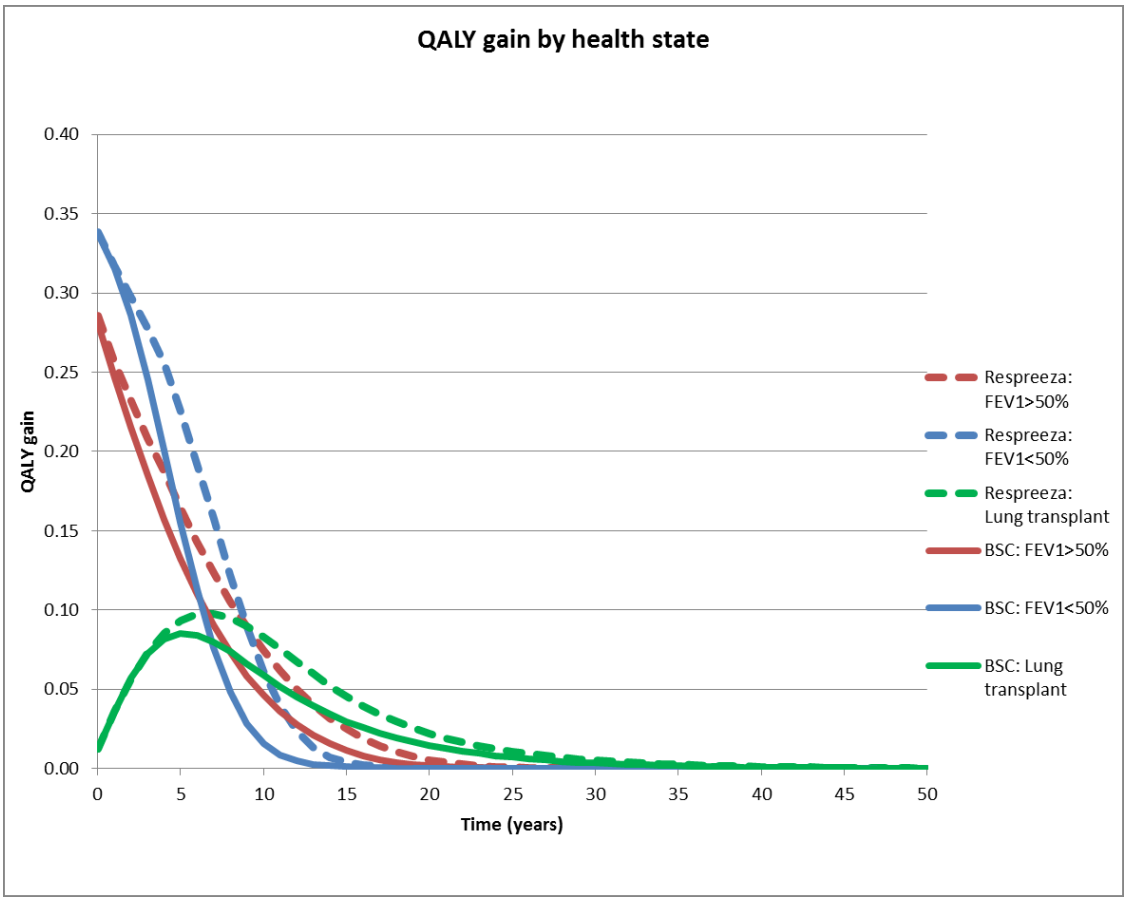
Table 68. Summary of QALY gain by health state (discounted)

Health state	QALY for Respreeza	QALY for BSC	Increment	Absolute increment	% absolute increment
FEV_1>50% predicted: No decline	0.134	0.026	0.108	0.108	5%
FEV_1>50% predicted: Slow decline	0.288	0.234	0.054	0.054	2%
FEV_1>50% predicted: Rapid decline	0.396	0.386	0.010	0.010	0%
FEV_1<50% predicted: No decline	0.235	0.041	0.194	0.194	8%

FEV_1<50% predicted: Slow decline	2.050	0.846	1.204	1.204	52%
FEV_1<50% predicted: Rapid decline	0.445	1.108	-0.663	0.663	29%
Lung transplant: first year	0.114	0.142	-0.028	0.028	1%
Lung transplant: subsequent years	0.463	0.422	0.041	0.041	2%
Total	4.126	3.206	0.920	2.301	100%

QALY, quality-adjusted life year; Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Figure 44. QALYs accrued over time by health state (discounted)



12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Table 69. Summary of QALY gain by health state (undiscounted)

Health state	QALY for Respreeza	QALY for BSC	Increment	Absolute increment	% absolute increment
FEV_1>50% predicted: No decline	0.154	0.026	0.128	0.128	4%
FEV_1>50% predicted: Slow decline	2.025	1.596	0.429	0.429	13%
FEV_1>50% predicted: Rapid decline	0.406	0.396	0.010	0.010	0%
FEV_1<50% predicted: No decline	0.240	0.042	0.198	0.198	6%
FEV_1<50% predicted: Slow decline	2.103	0.868	1.235	1.235	39%
FEV_1<50% predicted: Rapid decline	0.458	1.140	-0.682	0.682	21%
Lung transplant: first year	0.204	0.154	0.050	0.050	2%
Lung transplant: subsequent years	1.905	1.434	0.470	0.470	15%
Total	7.495	5.656	1.840	3.203	100%

QALY, quality-adjusted life year; Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.

Table 70. Summary of costs by category of cost per patient (discounted)

Item	Cost for Respreeza	Cost for BSC	Increment	Absolute increment	% absolute increment
Treatment	£419,568	£0	£419,568	£419,568	94%
Administration	£2,951	£0	£2,951	£2,951	1%
Disease management	£20,566	£15,340	£5,225	£5,225	1%
Lung transplant	£42,671	£31,983	£10,688	£10,688	2%
Total costs	£486,950	£39,001	£447,949	£447,949	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Table 71. Summary of costs by health state per patient (does not include treatment costs) (discounted)

Health state	Cost of disease management in Respreeza	Cost of disease management in BSC	Increment	Absolute increment	% absolute increment
FEV_1>50% predicted: No decline	£417	£80	£337	£337	2%
FEV_1>50% predicted: Slow decline	£905	£734	£172	£172	1%
FEV_1>50% predicted: Rapid decline	£1,243	£1,204	£39	£39	0%
FEV_1<50% predicted: No decline	£1,085	£184	£901	£901	4%
FEV_1<50% predicted: Slow decline	£9,470	£3,875	£5,595	£5,595	27%
FEV_1<50% predicted: Rapid decline	£2,048	£5,087	-£3,039	£3,039	15%
Lung transplant: first year	£20,880	£15,649	£5,231	£5,231	25%
Lung transplant: subsequent years	£22,501	£16,885	£5,616	£5,616	27%
Total	£58,549	£43,698	£14,852	£20,931	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Not applicable.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in Table D24.

Table 72 gives the cost per QALY found for each of the lower and upper bounds tested in the one-way sensitivity analysis. This information is also displayed in a tornado plot in Figure 45.

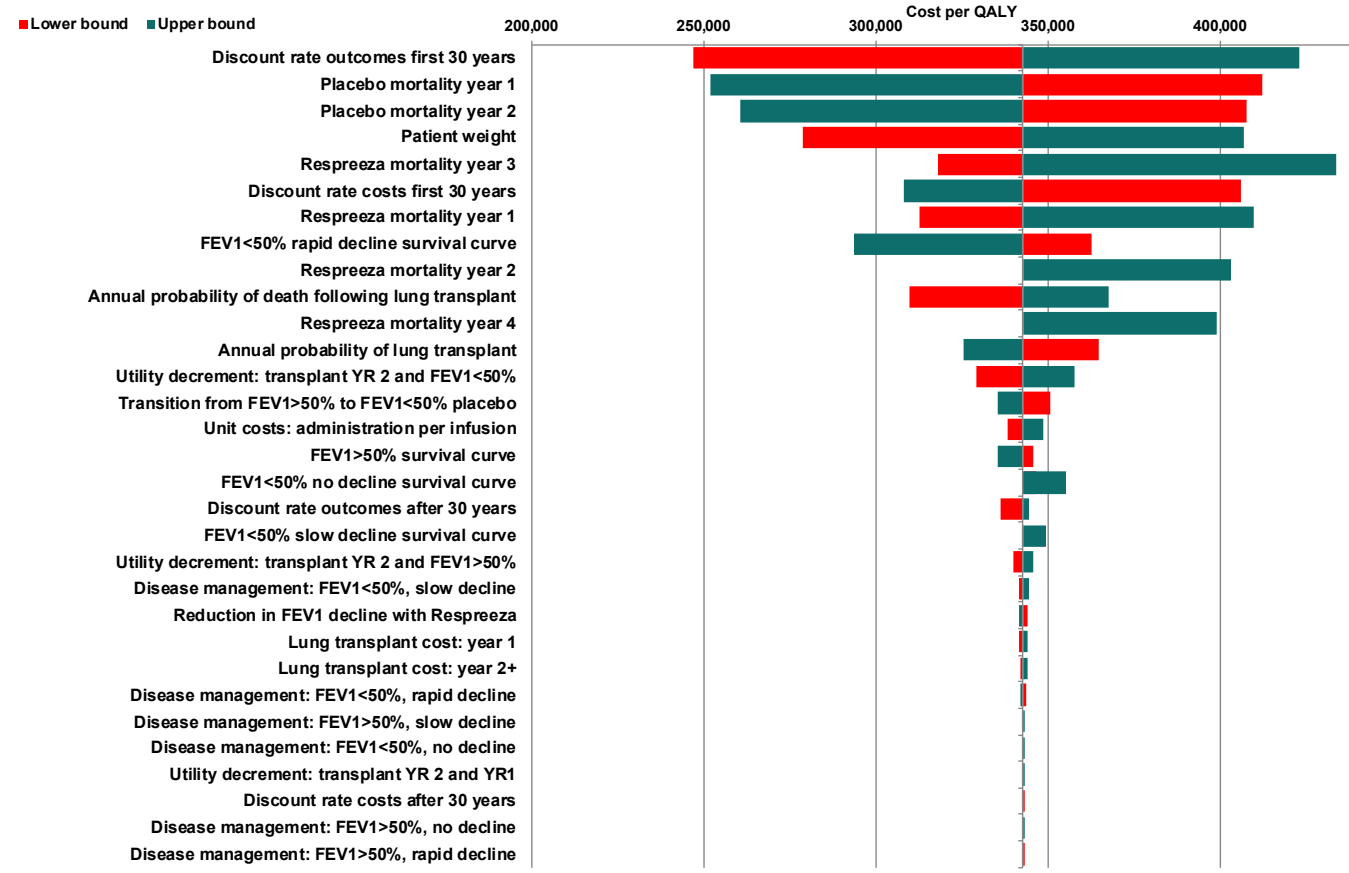
Table 72. Variables used in one-way deterministic sensitivity analysis

Variable	Base-case value	Range of values	ICER for lower bound	ICER for upper bound
Discount rate on costs	3.5%	0% to 6%	£406,102	£308,337
Discount rate on outcomes	3.5%	0% to 6%	£247,034	£422,896
Discount rate costs after 30 years	3.5%	0% to 6%	£343,152	£342,808
Discount rate outcomes after 30 years	3.5%	0% to 6%	£336,108	£344,464
Clinical inputs - mortality				
Respreeza mortality year 1	1.075%	0.028% to 2.299%	£312,849	£409,880
Respreeza mortality year 2	0.000%	0.000% to 1.000%	£342,872	£403,409
Respreeza mortality year 3	0.714%	0.018% to 2.619%	£317,910	£433,937
Respreeza mortality year 4	0.000%	0.000% to 1.000%	£342,872	£399,079
Placebo mortality year 1	2.299%	1.075% to 6.309%	£412,451	£251,994
Placebo mortality year 2	1.176%	0.030% to 4.296%	£407,568	£260,812
Clinical inputs - transitions				
Transition from FEV_1>50% to FEV_1<50% placebo	7.176%	4.875% to 9.875%	£345,684	£335,495
Reduction in FEV_1 decline with Respreeza	19.192%	17.265% to 21.194%	£346,702	£355,085
Annual probability of lung transplant	6.305%	3.318% to 10.158%	£342,305	£349,672
Annual probability of death following lung transplant	10.015%	5.457% to 15.752%	£362,538	£293,726

Predicted FEV_1>50% survival curve	Weibull: shape =2.57; scale = 15.57	Lower CI shape = 1.40; and scale =10.43 Upper CI shape = 4.71; scale= 23.22	£350,713	£335,391
Predicted FEV_1<50% no decline survival curve	Weibull: shape =3.64; scale = 11.62	Lower CI: shape = 0.99 scale= 7.24 Upper CI: shape = 13.44; scale = 18.65	£344,147	£341,540
Predicted FEV_1<50% slow decline survival curve	Weibull: shape =3.30; scale = 9.21	Lower CI shape = 1.93 scale= 7.70. Upper CI shape = 5.64; scale = 11.02.	£364,747	£325,735
Predicted FEV_1<50% rapid decline survival curve	Weibull: shape =2.99; scale = 7.97	Lower CI: shape = 1.70; scale= 6.37. Upper CI shape = 5.24; scale= 9.95.	£309,897	£367,747
Cost and resource related inputs				
Patient weight (which impacts on dosage only)	75.9	66.00 to 84.50	£278,643	£407,102
Unit costs: administration per infusion	44.72	28.94 to 63.89	£338,265	£348,466
Disease management: Predicted FEV_1>50%, no decline	£2,254	£1,459 to £3,220	£342,781	£342,983
Disease management: Predicted FEV_1>50%, slow decline	£2,254	£1,459 to £3,220	£342,604	£343,198

Disease management: Predicted FEV_1>50%, rapid decline	£2,254	£1,459 to £3,220	£342,875	£342,869
Disease management: Predicted FEV_1<50%, no decline	£2,570	£1,663 to £3,671	£342,663	£343,126
Disease management: Predicted FEV_1<50%, slow decline	£2,570	£1,663 to £3,671	£341,586	£344,435
Disease management: Predicted FEV_1<50%, rapid decline	£2,570	£1,663 to £3,671	£343,629	£341,953
Lung transplant cost: year 1	£76,698	£49,508 to £109,276	£341,786	£344,192
Lung transplant cost: year 2+	£9,260	£6,015 to £13,276	£341,996	£343,936
Utility inputs				
Utility decrement: transplant YR 2 and Predicted FEV_1>50%	0.12	0.096 to 0.144	£339,949	£345,847
Utility decrement: transplant YR 2 and Predicted FEV_1<50%	0.32	0.255 to 0.383	£329,102	£357,845
Utility decrement: transplant YR 2 and YR1	0.09	0.069 to 0.104	£342,680	£343,065

Figure 45. Tornado Plot



12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in Table D25.

Table 73 outlines the cost per QALY expected with various deterministic scenarios.

Table 73. Variables used in scenario-based deterministic sensitivity analysis

Analysis	Base case	Scenario	ICER
Structural scenario analyses			
Discount rate of 1.5% applied to benefits and 3.5% applied to costs	3.5% applied to both benefits and costs	Discount rate of 1.5% applied to benefits and 3.5% applied to costs	£283,875
Exclude lung transplant	6.3% probability of transplant	Probability of lung transplant set to 0%	£403,344
Survival curves function	Survival curve using Weibull function	Survival curves using Gompertz	£354,720
Include carer disutility	No carer disutility applied	A five percent reduction in carer health related quality	£331,653

Analysis	Base case	Scenario	ICER
		of life was applied to patients with FEV_1>50% predicted and in lung transplant states (i.e. a QALY loss of -0.0425 per patient per year) and a ten percent reduction was applied to all other health states including death (i.e. a QALY loss of -0.085 per patient per year).	
Use reported absolute utilities for health states	Use utility decrements derived from reported values and apply to population norms	Use reported absolute utilities for health states	£308,477
Scenario analyses			
Administration through infusion clinic rather than homecare.	25% infused administered at clinic	0% and 100% infused administered at clinic	£340,596 and £349,702 respectively
Scenario to explore additional cost and reduced utility as rate of lung density increases	As per base case inputs	20% increased utilities and 20% decreased costs from no lung density decline state and 20% decreased utilities and 20% increased costs from rapid lung density decline state	£301,144
Baseline age	51	30 and 60	£302,955 and £353,898 respectively

12.5.13 Present results of the probabilistic sensitivity analysis described in Table D26.

The base case of the probabilistic analysis are presented in Table 74. The probabilistic analysis of Respreeza compared to BSC alone gave an expected ICER of £378,618 per QALY.

Table 74. Summary of probabilistic results (discounted)

	BSC	Respreeza

Total Costs	£39,190	£496,680
Total QALYs	4.491	5.699
Total life years	8.76	11.572
Incremental costs	-	£457,490
Incremental QALYs	-	1.208
Incremental life years	-	2.813
Cost per QALY	-	£378,618

Probabilistic results are also summarised on in Figure 46 and a cost effectiveness acceptability curve is presented in Figure 47.

Figure 46. Cost-effectiveness plane showing probabilistic results for Respreeza compared with BSC alone

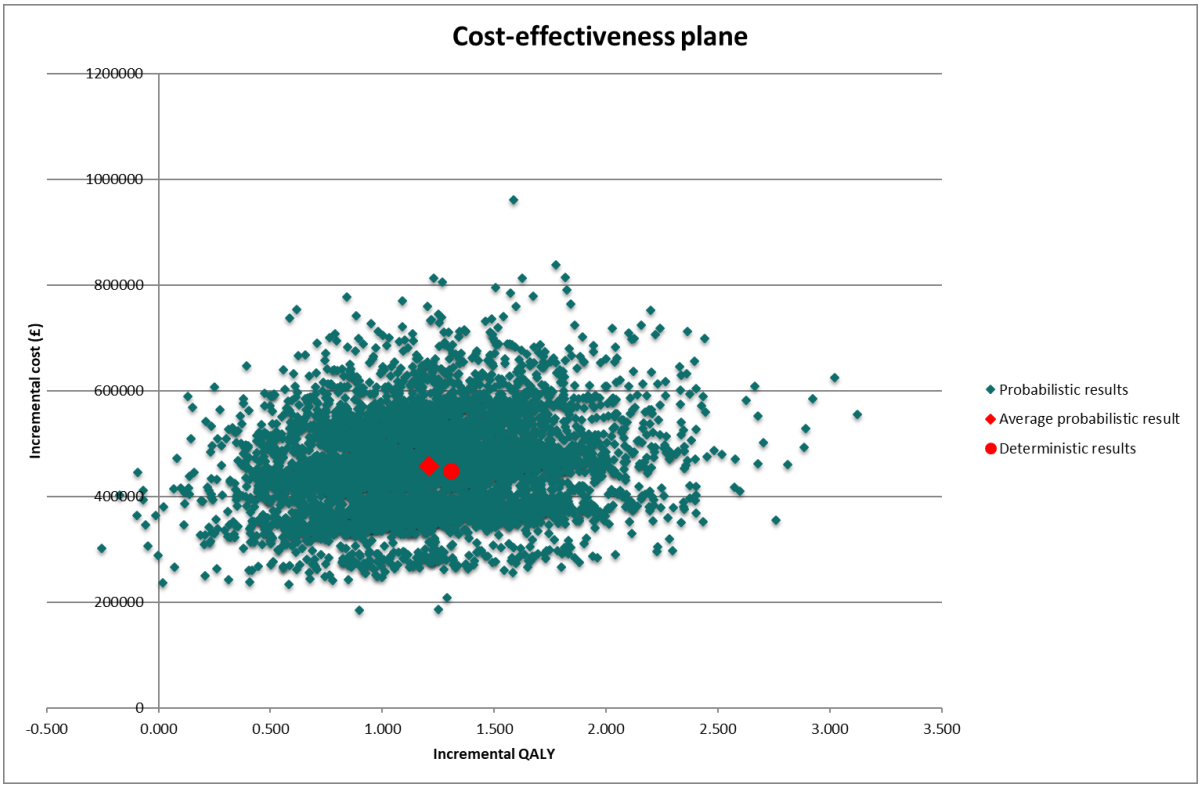
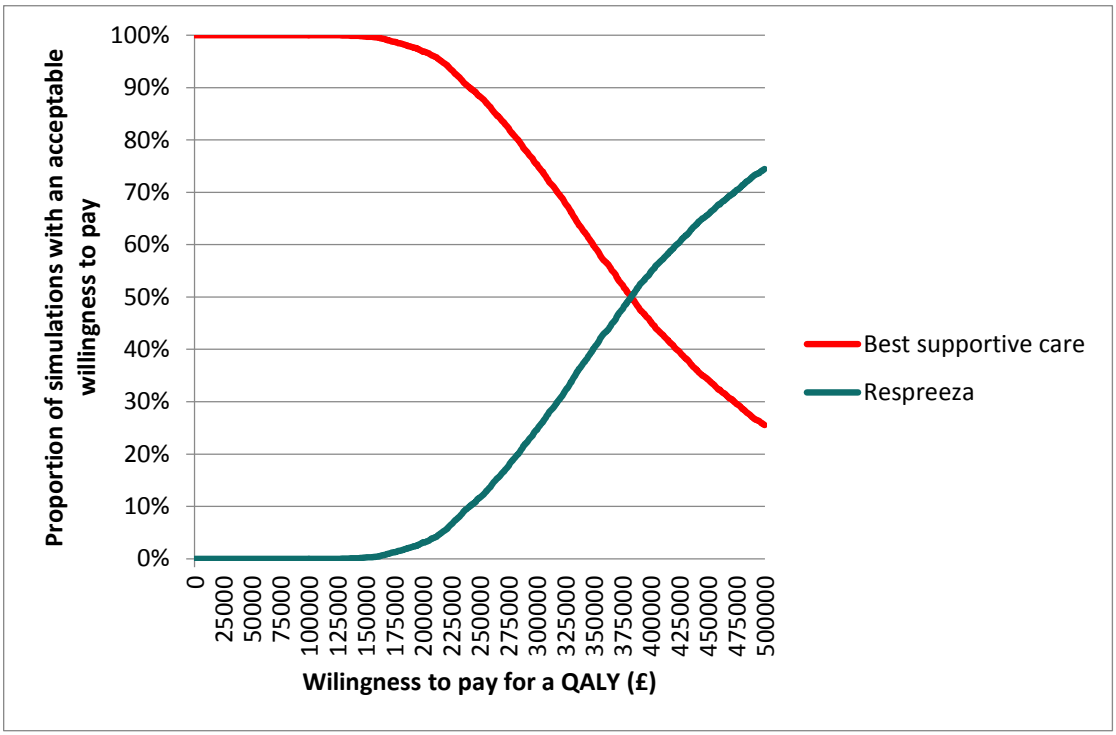


Figure 47. Cost-effectiveness acceptability curve



12.5.14 What were the main findings of each of the sensitivity analyses?

Scenario analyses were explored to test the impact of altering elements of the model structure.

The results were most sensitive changes in the discount rate on outcomes. When no discounting was applied to outcomes within the first 30 years, the ICER reduced to £247,034. A further scenario analysis found that the ICER reduced by 17% to £283,875 where discount rates were set to 1.5% for health benefits and 3.5% for costs. Consideration of this ICER is appropriate given that Respreeza may act to prolong the time to or obviate the need for lung transplant. Additionally this ICER is appropriate as many patients who would otherwise die or have a severely impaired life are able to accrue sustained long term benefits are achieved in the future with transplantation.

The ICER reduced to £251,994 and £260,812 if the upper bound of the 95% confidence interval was used for probability of mortality with BSC in year 1 and year 2 respectively.

Patient weight, and therefore the dosage and acquisition cost of Respreeza, was found to be sensitive, with the ICER reducing to £278,643 when the mean weight of 66kg was used.

Further, amendments to the shape and scale of the FEV_1<50% predicted rapid decline survival curve had potential to reduce the ICER to £293,726.

One clinically plausible scenario is that patients with lower decline in lung density would have higher utilities and lower costs. However, no specific evidence on the variation in utilities or costs is published so it could not be factored into the base case. A scenario is explored where patients with no decline in lung density have utilities 20% greater than slow lung density decline patients and have 20% lower costs, whilst for patients with a rapid decline in lung density, the parameters are 20% in the reverse. This results in an ICER of £301,144 (a 12 percent reduction in the ICER).

All other deterministic analyses resulted in the ICER being above £300,000 per QALY. Results were less sensitive to transitions between FEV_1 states, discount rates after 30 years, other survival curves and all costs. The most sensitive parameter relating to health-related quality of life was the decrement applied to estimate the utility of the predicted FEV_1<50% health state.

The results of the additional scenarios are as follows:

- Using a discount rate of 1.5% for benefits and 3.5% for costs over the lifetime horizon reduced the ICER by 17% to £283,875.
- Respreeza may act to prolong the time to or obviate the need for lung transplant in that it extends survival and therefore enables more patients to receive a lung transplant, which further increases survival and improves health-related quality of life. Excluding the lung transplant health state from the model increases the ICER by 18%.
- Alternative fitted functions for survival curves have also been explored to test the sensitivity of the results when using the 2nd best fit function, the Gompertz, resulting in an increase to the ICER of 3%.
- Including assumed decrements for reduced carer health-related quality of life reduced the ICER by 3%.
- Using utilities for health states without adjusting for population norms decreases the ICER by 10%.
- Administering Respreeza at all at home versus all in specialist clinic decreases the ICER by 1% and increases the ICER by 2% respectively.
- A sensitivity analysis which considered a five percent decrease in carer utility associated with patients in the predicted FEV_1>50% and lung transplant states, and a ten percent reduction was applied to all other health states (inclusive of death) resulted in a lower ICER of £331,653 per QALY.
- Change in baseline age from 30 to 60 years of age changes results decreases the ICER by 12% and increases the ICER by 3% respectively.

12.5.15 What are the key drivers of the cost results?

Table 75 gives the incremental total cost expected when key parameters are altered according to the bounds tested in the one way sensitivity analysis.

Key drivers of the cost result included:

- Parameters that influenced the cost of treatment, such as mean patient weight.
- The discount rate applied to costs, in particular within the first 30 years of the analysis.
- The likelihood of discontinuation and therefore a reduction in treatment costs, demonstrated by the sensitivity of total costs to a change in the following parameters:
    - The probability of lung transplant (albeit the cost of lung transplant was not found to be a driver of cost).
    - Mortality and survival probabilities when taking Respreeza

To note, costs of transplant and disease management were not demonstrated to be key drivers of cost in the deterministic analysis.

Table 75. Summary of the total incremental cost expected with each deterministic one way sensitivity analysis

Parameter Description	Lower bound	Upper bound
Patient weight	£364,036	£531,863
Discount rate costs first 30 years	£530,557	£402,830
Annual probability of lung transplant	£476,432	£416,162
Respreeza mortality year 3	£459,686	£420,505
Respreeza mortality year 1	£462,204	£426,993
Predicted FEV_1>50% survival curve	£432,774	£459,719
Predicted FEV_1<50% slow decline survival curve	£454,353	£430,356
Transition from predicted FEV_1>50% to FEV_1<50% placebo	£458,231	£438,189
Respreeza mortality year 2	£447,949	£428,663
Respreeza mortality year 4	£447,949	£429,795
Unit costs: administration per infusion	£441,930	£455,257
Placebo mortality year 1	£445,950	£452,833
Placebo mortality year 2	£446,063	£452,299
FEV_1<50% no decline survival curve	£446,261	£442,150
Disease management: FEV_1<50%, slow decline	£446,268	£449,990
Lung transplant cost: year 1	£446,530	£449,673
Annual probability of death following lung transplant	£449,740	£446,844
Lung transplant cost: year 2+	£446,805	£449,339
Disease management: Predicted FEV_1<50%, rapid decline	£448,938	£446,749
FEV_1<50% rapid decline survival curve	£448,660	£450,039
Reduction in FEV1 decline with Respreeza	£447,303	£448,631
Disease management: Predicted FEV_1>50%, slow decline	£447,599	£448,374
Disease management: Predicted FEV_1<50%, no decline	£447,676	£448,281
Discount rate costs after 30 years	£448,315	£447,865
Disease management: Predicted FEV_1>50%, no decline	£447,830	£448,094
Disease management: Predicted FEV_1>50%, rapid decline	£447,953	£447,944

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

The base case indicated that 20.5% of the patients with BSC alone compared to 27.3% of patients treated with Respreeza in addition to BSC would have a lung transplant. This suggests that Respreeza may act to prolong the time to or obviate the need for lung transplant.

12.6 Subgroup analysis

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

Not applicable: In line with the scope of this submission, no subgroups of interest were identified.

12.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable: In line with the scope of this submission, no subgroups of interest were identified.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Not applicable: In line with the scope of this submission, no subgroups of interest were identified.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in Section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with Section 12.5.7

Not applicable: In line with the scope of this submission, no subgroups of interest were identified.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable: In line with the scope of this submission, no subgroups of interest were identified.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources Sections.

Economic modelling was validated with Professor McElvaney who was consulted during development of the health economic model and ratified the model inputs. Professor McElvaney has been carrying out research into A1PI deficiency for over 20 years and is a widely published author. He founded the Alpha One Foundation in Ireland and established the first targeted detection programme in Europe. Furthermore, he was the principal investigator for the RAPID study in Ireland and continues to be a Respiratory Consultant at the Beaumont Hospital, where all Irish patients with A1PI deficiency are treated. Quality assurance was conducted by independent health economists. Please also see Section 10.1.10 – where the main detail of expert use is cited within this submission).

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Two published economic models for therapy augmentation for A1PI deficiency were identified by the systematic literature review of economic studies, but excluded as they did not evaluate Respreeza specifically. Sclar et al. (Sclar et al., 2012) used regression models, while Gildea et al. (Gildea et al., 2003) used a Markov model with health states based on FEV_1% predicted, to simulate the lifetime costs and outcomes of A1PI replacement therapy compared to best supportive care. For information, a narrative summary is given below.

Gildea et al. (Gildea et al., 2003) conducted a cost-utility analysis assessing the cost-effectiveness of different strategies for treating severe A1PI deficiency from a US healthcare perspective, using the cost of Prolastin (Bayer) at 2001 prices and Medicare reimbursement price for administration of the infusion. Effectiveness data was derived from registry data rather than a randomised control trial. The three strategies compared were: no treatment, treating A1PI deficiency patients with human A1PI for life, and treating patients until FEV_1 is below 35% predicted. A hypothetical cohort of 46 year-old patients (50% male) with FEV_1 49% predicted was followed over a lifetime horizon at yearly cycles using a Monte Carlo simulation (30,000 simulations). The five health states included were: FEV_1 50 to 79% predicted, FEV_1 35 to 49% predicted, FEV_1 below 35% predicted, post-lung transplantation, and dead. An annual discount rate of 3% was applied to costs and outcomes, and effectiveness was measured in QALYs. The ICER for lifetime treatment with human A1PI was $312,511. The ICER for lifetime treatment with human A1PI only until patients had an FEV_1<35% predicted was associated with an ICER of $207,841. In all sensitivity analyses, the ICER for lifetime treatment exceeded $100,000.

Sclar et al. (Sclar et al., 2012) also performed a cost-effectiveness analysis to ascertain the number of life-years gained, and the expense per life-year gained, associated with the use of human A1PI (Aralast, Baxter Bioscience), relative to no therapy in patients with hereditary emphysema secondary to A1PI deficiency from a US payer's perspective. The model was based on a range of published sources and US registry data (e.g. Alpha1-Antitrypsin Deficiency Registry Study Group data and NHANES III) to derive baseline and effectiveness inputs. A Monte Carlo simulation estimated the total number of life-years gained and costs of each intervention. Regression models were used to estimate FEV_1% predicted values based on individual's age, sex and height. A survival function stochastically determined mortality, but death occurred on a deterministic basis when the percent predicted FEV_1 was <15%. Use of human A1PI

was associated with an increase in life-years gained at a cost per life-year gained of $59,234 to $248,361, depending on gender and smoking history.

No study was identified in the systematic review that included Respreeza specifically. Further both identified models were constructed using a USA perspective and costing model, and thus findings have limited applicability within the UK context. Results of the published studies are therefore not directly comparable to those derived from the de novo model.

No published economic modelling studies that examined therapy augmentation for A1PI deficiency and populated using randomised control trial evidence to inform effectiveness parameters were identified. The de novo model constructed follows the NICE reference case and utilises randomised control trial evidence to inform effect. Therefore, the results from the de novo model should be given credence as it offers the best available and most applicable cost-effectiveness evidence to evaluate Respreeza compared with UK standard of care at the time of writing. This base case ICER is acceptable given that A1PI deficiency is a debilitating and fatal disease for which there are no existing licensed alternatives.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The evaluation is relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

A main strength of the de novo model is that it utilises key clinical output from a phase III trial to model the expected treatment effect of Respreeza, supplementing with secondary sources appropriately and only where necessary. The analysis was also subject to extensive sensitivity analysis.

Due to the chronic and long term nature of the condition it was necessary to extrapolate beyond the trial horizon to capture all of the potential benefits and costs over a life time horizon. This introduces uncertainty into the results. To examine the potential impact of different extrapolation functions, results were rerun using the second best fit function (Gompertz) and the general conclusions of the analysis did not change.

The model uses the best available evidence appropriate to understand efficacy as measured by CT measured lung density (and associate to FEV_1% predicted to model long term outcomes), noting that CT measured lung density is a sensitive marker of

disease progression and predictive of mortality and allows for a meaningful difference could be captured within trial duration.

The model has used observational data where necessary and in particular to facilitate population of parameters regarding a predicted FEV_1%, which is commonly used to measure disease progression. The use of observational registry data is deemed appropriate as it is unlikely further randomised control trial data would be forthcoming for timely decision modelling in this area. In particular, clinically meaningful differences defined by change in long term outcomes would be difficult to demonstrate by a trial for the following reasons:

- The slow progressive nature of disease: progression of emphysema in patients with A1PI deficiency is slow
- The small population with A1P1 deficiency available to recruit to power studies
- It is difficult to show statistically significant differences due to modest sample sizes
- The trial durations are likely to be short to allow differences in long term outcomes to materialise

Sensitivity analysis did not suggest that changes in parameter values associated with FEV_1 % predicted and that were derived using registry data, would influence conclusions of the analysis.

However, the model relies on a limited evidence base to populate HRQoL associated with the various health states, which may lead to an under estimation of cost effectiveness of Respreeza. Overall benefit could be extended to family members and carers, however, there is insufficient evidence to populate the model at the current time. It should be noted that Respreeza extends the life expectancy of the patient and therefore carer responsibilities over time. Associating a carer disutility only to the states where patients are alive therefore would give a counterintuitive result of an increased ICER. A sensitivity analysis which considered a five percent decrease in carer utility associated with patients in the predicted FEV_1>50% and lung transplant states, and a ten percent reduction was applied to all other health states (inclusive of death) resulted in a lower ICER of £331,653 per QALY.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

There is currently limited data and evidence to understand the health-related quality of life implications of treatment with Respreeza, not only for patients but also for their carers. The model is populated using HRQoL estimates from a study population not specific to the target population. The estimate of incremental QALY gain would benefit from further research in how Respreeza may improve HRQoL for both patient and carer, prior and post lung transplantation. Cost to the NHS and Personal Social Services

13 Cost to the NHS and Personal Social Services

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

It is estimated that approximately 549 people will be eligible for treatment in England. This was estimated using a 0.99 per 100,000 prevalence (derived from NIHR (National Institute for Health Research, 2014) and ONS 2014 data (Office for National Statistics, 2015)) and applied to 2016 English ONS population figures (Office for National Statistics, 2017). No published sources were identified to estimate the number of incident patients eligible for Respreeza in England. Expert opinion suggests that there would be approximately 0.17 per 100,000 population incident patients eligible for Respreeza, which equates to an English incident eligible population of approximately 95 people per year. There is insufficient evidence to suggest that prevalence and incidence rates will change over the forthcoming 5 years.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

As Respreeza is administered as a weekly infusion, it is unlikely that all patients will want treatment and thus the market uptake is only expected to be 50% on introduction and in year 1, reaching 70% in year 2 and 90% in subsequent years.

For the base case budget impact it is assumed that only the incident cohort will be offered treatment and once on a given treatment the patient will not switch to a new treatment. This equates to only 48 patients in year 1, rising to 353 patients in year five. This is summarised in Table 76, which outlines the likely number of eligible patients who take up Respreeza at the start of each year. These estimates take into account the estimated uptake of the treatment, probability of death and discontinuation due to lung transplant (estimated using the traces of the cost effectiveness model reported in Section 12.5.3).

Table 76. Summary of uptake and number of people taking up Respreeza.

Timepoint	Uptake for incident population	Number of people taking up Respreeza at start of year
Year 1	50%	48
Year 2	70%	112
Year 3	90%	196
Year 4	90%	276
Year 5	90%	353

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc.).

In addition to the cost of treatment (in terms of acquisition and administration costs), other significant costs that may be of interest to the NHS is the cost of disease management and also of lung transplantation, immunosuppressive therapies and their consequential risks.

13.4 Describe any estimates of resource savings associated with the use of the technology.

It is expected that Respreeza will be used in addition to best supportive care. In addition it is expected that Respreeza will delay disease progression, prolonging the time to or obviating the need for lung transplant, and therefore it is not expected that Respreeza will be cost saving.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The analysis does not consider potential cost savings of reduced need for care made possible with delayed disease progression and improvement post lung transplant.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

The analysis does not take a societal perspective and therefore does not consider productivity costs. A1-PI deficiency is characterised by progressive emphysema which can be debilitating and causes considerable morbidity. Patients are predominately

diagnosed in their 30s or 40s, an age at which many patients are raising a family and are in employment. The condition impacts on the patient's ability to work with the financial consequences associated with the need to take time off work due to ill-health, reduce working hours or to retire early on medical grounds. See section 7.1 (Stoller et al., 1994).

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

The budget impact of Respreeza for the NHS and PSS in England is estimated to be £2,779,196 in the first year, rising to £20,270,814 in year 5. Full budget impact results are presented in Table 77.

Table 77. Summary of the expected budget impact with the introduction of Respreeza

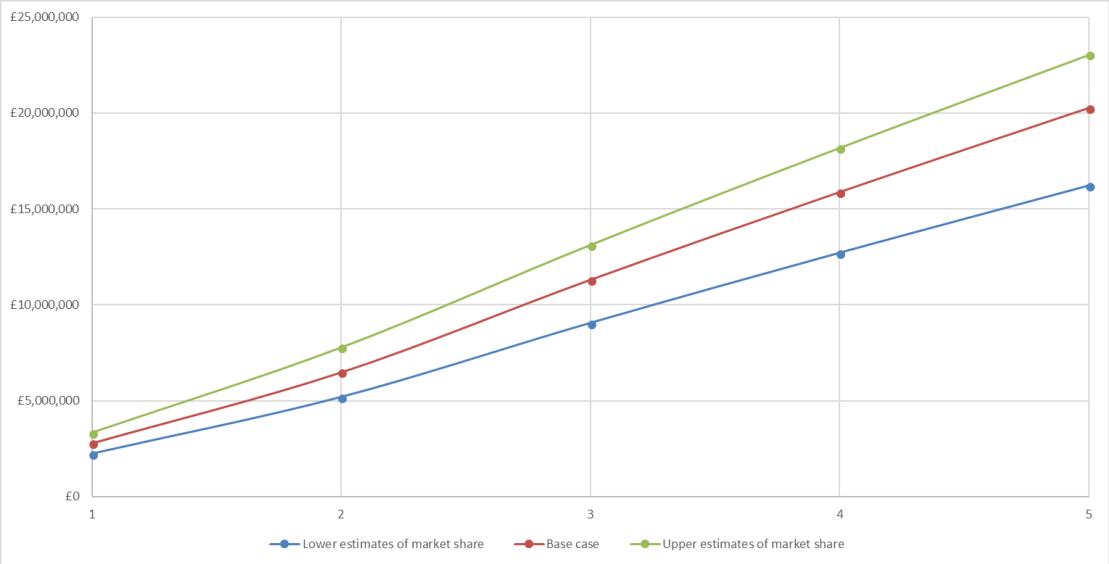
Time point	Respreeza	Best supportive care	New incremental budget impact
Year 1	£3,122,472	£343,277	£2,779,196
Year 2	£7,295,144	£815,092	£6,480,053
Year 3	£12,609,082	£1,300,979	£11,308,104
Year 4	£17,650,949	£1,767,315	£15,883,635
Year 5	£22,466,053	£2,195,239	£20,270,814

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc.).

The budget impact model is based on the progression of patients through the cost-effectiveness model. Therefore, the results are subject to the same limitations as the cost-effectiveness model, as described in Section 12. Further, the budget impact analysis assumes that Respreeza will not explicitly displace treatment costs associated with best supportive care. Instead, the model only takes into account reduced disease management costs associated with delayed disease progression. Therefore, the budget impact model may underestimate savings that could be made with Respreeza and over-estimate the overall budget impact of adopting Respreeza.

The future demand for Respreeza is uncertain. For this reason, a sensitivity analysis below (Figure 48) shows the expected incremental budget impact if market share is either 20% higher or 20% lower than the base case estimate.

Figure 48. Incremental budget impact using market share estimates which are 20% higher and 20% lower than the base case estimate.



Section E – Impact of the technology beyond direct health benefits

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

A substantial portion of the costs (savings) and benefits that will result from treatment with Respreeza are incurred outside of the NHS and personal social services. Due to the severity and chronic nature of emphysema caused by A1PI deficiency, the disease can have a highly significant economic impact on patients, their families, the healthcare service and wider society. As the patients diagnosed are in their third or fourth decade (Greene et al., 2008), an age during which full economic activity is high, they are in risk of not being able to perform at work with the immediate burden falling primarily on their family.

In an online survey of 152 respondents by alpha-1-alliance (Alpha-1 Alliance, 2013) results showed that many respondents were unable to be active and mobile as a result of shortness of breath and as the condition progresses, there is a significant impact on their ability to live a normal and fulfilled life with difficulties in performing normal everyday activities. This inability to maintain employed work has a drastic impact on economical costs. Not being able to participate in social activities leads to the burden of care being on the family which will require further services to maintain a sensible quality of life. In order for the family to provide assistance they will have to either reduced their hours or had stop working because of their caregiving responsibilities leading to high indirect and intangible costs.

Patients with A1PI deficiency tend to retire early and have to adjust to physically less demanding jobs (Section 7). Reducing patients' lung density decline will keep them in a better state of health to enable them to retain full time employment. Patients are typically diagnosed with A1PI deficiency in their 40s, which is generally the peak of a person's career and therefore the age associated with highest pay and the greatest tax contributions to society. Being in a better health state can be translated in fewer exacerbations and healthcare appointments, reducing the burden on health services, patients and carers.

Patients with A1PI deficiency treated with Respreeza have a statistically significant and clinically meaningful 34% slower rate of lung density decline compared to those

receiving placebo (-1.45 g/L in years versus -2.19 g/L, p = 0.03). This will allow patients treated with Respreeza to prolong their independence and require less support from non-healthcare services. A decrease in the rate of respiratory decline and delay in the need for lung transplantation is likely to have a positive impact on the psychological distress and caregiving burden of family and carers. Reducing patients' lung density decline is expected to enable them to retain employment and social participation for longer.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

By decreasing the rate of respiratory decline and delay in the need for lung transplantation, Respreeza could reduce the needs of both patients and carers, and thus reduce the following other non-NHS government costs through welfare (Welfare benefits, blf.org) such as those below:

- Care and mobility:
    - Personal Independence Payment (PIP)
    - Disability Living Allowance (DLA)
    - Attendance Allowance (AA)
- People unable to work:
    - Statutory Sick Pay (SSP)
    - Employment and Support Allowance (ESA)
- Universal Credit
- Conditions caused by work:
    - Industrial Injuries Disablement Benefit (IIDB)
- Carers:
    - Carer's Allowance
    - Carer's Credit
- Top-up Benefits
    - Information on Income Support
    - Tax Credits
    - Pension Credit
    - The new State Pension
    - Housing Benefit
    - Council Tax Reduction

- Prescription costs

14.3 List the costs borne by patients that are not reimbursed by the NHS.

There is a vast amount of costs incurred to patients and their carers due to the provision of care and as a consequence of large production losses. With disease progression, patients may be unable to work or may be forced into premature retirement (Karl et al., 2017). A German study by Karl et al. estimated the amount of cost not reimbursed by the NHS for COPD patients according to four groups:

- Patients with COPD without A1 antitrypsin deficiency had costs of €19,514 per year as a total of indirect costs with a human capital approach and with the number of sick days at 30.8
- Patients with COPD with A1 antitrypsin deficiency had costs of €15,541 per year as a total of indirect costs with a human capital approach and with the number of sick days at 24.8
- Patients with COPD with augmentation therapy had costs of €16,288 per year as a total of indirect costs with a human capital approach and with the number of sick days at 24.2
- Patients with COPD with A1 antitrypsin deficiency but without augmentation therapy had costs of €11,580 per year as a total of indirect costs with a human capital approach and with the number of sick days at 27.6

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

It has not been possible to quantify this.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

Respreeza is the only proven disease-modifying agent to have shown positive results in slowing down lung damage due to A1PI deficiency. The clinical trial programme for Respreeza has proven the effectiveness of the product between patients receiving treatment and placebo in delaying the decline in lung density. The EMA established

that the benefits of Respreeza by approving the medicine for use in the EU (European Medicines Agency, 2018). For now, there are no further planned or ongoing research initiatives regarding the product.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Respreeza is the first in class and only proven disease-modifying agent for A1PI deficiency. Until the development of Respreeza, this rare and commonly misdiagnosed genetic disease that is associated with significant morbidity and mortality has had no effective licensed treatment option, and certainly nothing that addresses the underlying cause of the disease. Based on the provided budget impact analysis, treatment poses a low financial impact and addresses an important unmet public health need with the promise of reducing serious and fatal events.

Treatment of A1PI deficiency may act as a catalyst for long-term benefits to the NHS based on increased research and innovation, especially the multi-systemic elements of the disease such as liver involvement.

Secretary of State for Health and Social Care, Jeremy Hunt, regarding the Industrial Strategy White Paper published in 2017 said “Today proves that life science organisations of all sizes will continue to grow and thrive in the coming years, which means NHS patients will continue to be at the front of the queue for new treatments.” (ref 2017 report). CSL Behring is a good example of such direct investment. Based on the highly innovative nature of CSL Behring's technology, being at the forefront of treatment for A1PI deficiency, CSL Behring is an ideal example of the type of company and innovative approach that the UKTI and LSIO are trying to attract to the UK.

Gaining further experience with Respreeza in clinical practice will advance clinical knowledge and strengthen the UK-reputation as a centre for world-leading research in rare lung disease. Providing access to treatments for rare diseases will encourage wider research initiatives and clinical trial programmes in the UK as well as investment in the UK pharmaceutical industry.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

CSL Behring is open to considering the need to establish or support the establishment of registries, for example, it has recently done this with and through the Pulmonology Society in Hungary.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

Respreeza has received marketing authorisation from the EMA in 2015 with a post-marketing commitment to study the effects of a higher dose. The trial design is currently being finalized with the FDA and CHMP, however results are expected post 2028 due to the large sample size in a rare disorder and an expected 4-year treatment duration.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The marketing authorisation for Respreeza mentions that the first infusion should be given under the supervision of a healthcare professional experienced in the treatment of A1PI deficiency, while subsequent infusions can be given by a caregiver or by the patient. It is expected that Respreeza, will be prescribed only by specialists with expertise in the management of the specific condition.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

Following the first infusion performed by an experienced A1PI deficiency professional, Respreeza is expected to be provided to patients via a caregiver or by the patient. Therefore, no other additional facilities, technologies or infrastructure will be required to implement the use of Respreeza.

Section F - Managed Access Arrangements

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

[redacted]

15.2 Describe the specifics of the MAA proposal

[redacted]

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

[redacted]

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17 Appendix

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- The Cochrane Library.

17.1.2 The date on which the search was conducted.

Systematic literature searches were undertaken on 9th April 2015 and were updated on 11th April 2018.

17.1.3 The date span of the search.

For the search carried out on 9th April 2015 (Edgar et al., 2017), no limits were placed on date of publication. The search carried out on 11th April 2018 was limited to publications from 9th April 2015 until the 11th Aptil 2018.

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

Table 78. ProQuest search strategy for Embase® and MEDLINE® (Searched on 11th April 2018)

	Proquest search algorithm ***MEDLINE and Embase***	**Hits using dates from Edgar et al., 2017 (1946 to 09/04/2015)**	**Hits commissioned by CSL Behring (09/04/2015 – 11/04/2018)**
#1	mesh.exact.explode("alpha 1-Antitrypsin")	8,019	345
#2	emb.exact.explode("alpha 1 Antitrypsin")	12,239	1,847
#3	ab,ti(alpha-1 antitrypsin)	13,559	1,222
#4	ab,ti(alpha 1 antitrypsin)	13,813	1,141
#5	ab,ti(alpha1-antitrypsin)	2,162	120
#6	ab,ti(alpha-1-at)	629	8
#7	ab,ti(The Alpha-1-Antitrypsin Deficiency Registry Study Group)	13,437	1,116
#8	ab,ti(alpha one antitrypsin)	1,730	241
#9	ab,ti(alfa 1 antitrypsin)	466	37
#10	ab,ti(alpha1 antitrypsin)	2,242	123
#11	ab,ti(alpha one-antitrypsin)	48	18
#12	ab,ti(AAT)	5,475	930
#13	ab,ti(A1AT)	587	245
#14	ab,ti(AATD)	418	287
#15	or/1-14	31,120	2,816
#16	ab,ti(deficien$ or lack$)	864,945	221,780
#17	15 and 16	460	100
#18	mesh.exact.explode("alpha 1-Antitrypsin Deficiency")	2,974	240
#19	emb.exact.explode("alpha 1 Antitrypsin Deficiency")	4,131	881
#20	18 or 19	7,162	905
#21	17 or 20	7,684	969
#22	limit 21 to humans	7,181	921

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

The inclusion and exclusion criteria.

Table 79. Selection criteria used for published studies

Inclusion criteria	
Population	Adults suffering from severe A1PI, circulating level of A1PI <11μmol/L and/or a genotype consistent with such levels (eg, PiZZ, PiZNull with or without a diagnosis of COPD.
Interventions	Treatment for A1PI-related lung disease including any method of treatment that has been accepted in peer-reviewed literature
Outcomes	No restrictions were placed on outcome measures.
Study design	Observational (i.e. registries) Cohort studies RCTs
Language restrictions	None
Search dates	Original search conducted by (Edgar et al., 2017): up to 9th April 2016 Update SLR commissioned by CSL Behring: 9th to 11th April 2018
Exclusion criteria	
Population	• Liver Disease • Panniculitis • Children
Interventions	No restriction
Outcomes	Outcomes must have been reported <3 months after initiation of therapy
Study design	• Animal • Individual case study reports • Letters • Comment articles • Reviews • Epidemiology

17.1.6 The data abstraction strategy.

Citations were first screened based on title and abstract supplied with each citation ('first pass'). Each citation was screened by two independent reviewers and any discrepancies between reviewers were reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded during first pass. Citations with abstracts that were unclear were included during this phase. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded. Full-text copies of all references that could potentially meet the eligibility criteria were obtained through internet search.

The eligibility criteria were then applied to the full-text citations. The list of studies included during the 'second pass' stage was screened for any RCTs evaluating A1PI augmentation therapy as an intervention

17.2 Appendix 2: Search strategy for adverse events

The following information should be provided.

17.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- The Cochrane Library.

Not applicable – search outlined in 17.1 was used to identify adverse event data.

17.2.2 The date on which the search was conducted.

Not applicable

17.2.3 The date span of the search.

Not applicable

17.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable

17.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

17.2.6 The inclusion and exclusion criteria.

Not applicable

17.2.7 The data abstraction strategy.

Not applicable

17.3 Appendix 3: Search strategy for economic evidence and quality of life data

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Embase Alert
- NHS Economic Evaluation Database (EED)
- Cochrane

Table 80. Databases searched for systematic literature review

Platform	Databases
Centre for Reviews and Dissemination	Database of Abstracts of Reviews of Effects NHS Economic Evaluation Database (EED) Health Technology Assessment Database
Cochrane	Cochrane Database of Systematic Reviews
ProQuest	MEDLINE, EMBASE, EMBASE Alert

17.3.2 The date on which the search was conducted.

Systematic literature searches were undertaken on 11th April 2016 and were updated on 9th April 2018.

17.3.3 The date span of the search.

For the search carried out in April 2016, no limits were placed on date of publication. The search carried out in April 2018 was limited to publications from 12th April 2016 to 9th April 2018.

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 81. ProQuest search strategy and hits with the addition of brand names

Domain		Proquest search algorithm	Hits until 11/04/2018
Population	#1	EMB.EXACT.EXPLODE("alpha 1 antitrypsin deficiency") OR mesh.exact.explode("alpha-1 antitrypsin deficiency") OR "alpha 1 antitrypsin deficiency" OR "A1PI deficiency" OR "AATD" OR "AAT deficiency" OR "alpha1 antitrypsin deficiency" OR "alpha 1 proteinase inhibitor deficiency" OR "alpha 1-antitrypsin deficiency" OR "antitrypsin alpha 1 deficiency" OR "deficiency, alpha 1 antitrypsin"	10,171
	#2	ab,ti("alpha 1 antitrypsin deficiency" OR "alpha-1 antitrypsin deficiency" OR "A1PI deficiency" OR "AATD" OR "AAT deficiency" OR "alpha1 antitrypsin deficiency" OR "alpha 1 proteinase inhibitor deficiency" OR "alpha 1-antitrypsin deficiency" OR "antitrypsin alpha 1 deficiency" OR "deficiency, alpha 1 antitrypsin"	6,349
	#3	#1 OR #2	10,206
Outcomes - QoL	#4	emb.exact.explode("quality of life") OR mesh.exact.explode("quality of life") OR ab,ti("quality of life")	768,046

	#5	emb.exact.explode("quality adjusted life year*") OR mesh.exact.explode("quality-adjusted life year*") OR ab,ti("quality adjusted life")	39,969
	#6	ab,ti("eq-5d" or "eq5d" or euroquol*)	19,285
	#7	ab,ti(qaly or qalys or qald or qale or qtime)	24,852
	#8	ab,ti("disability adjusted life")	3,194
	#9	ab,ti(daly or dalys)	3,148
	#10	ab,ti("health* year* equivalent*")	47
	#11	ab,ti(hye or hyes)	127
	#12	ab,ti(hui1 or hui2 or hui3)	482
	#13	ab,ti(disutil*)	721
	#14	ab,ti("standard gamble")	1,029
	#15	ab,ti("time trade off" or "time tradeoff")	1,799
	#16	ab,ti(hqol or "h qol" or hrqol or "hr qol")	36,488
	#17	ab,ti(utility or utilities)	419,976
	#18	emb.exact.explode("health care survey*" or "health survey*" or "health status") or mesh.exact.explode((health or healthcare) AND surveys*) or ab,ti(((health or clinical) AND state) or ((health or healthcare or "health care") and (survey* or status or surveillance)) or "level of health")	1,411,816
	#19	OR/#4-#18	4,502,490
	#20	#3 AND #19	424
Outcomes - economic	#21	emb.exact.explode("cost utility analysis") or mesh.exact.explode("cost-benefit analysis" or "costs and cost analysis") or ab,ti("cost-utility" or "cost-benefit" or "economic evaluation")	247,381
	#22	emb.exact.explode("cost effectiveness analysis") or ab,ti("cost-effectiveness")	203,768
	#23	emb.exact.explode("cost minimi?ation analysis") or ab,ti(cost-minimi?ation)	3,860
	#24	emb.exact.explode("cost of illness") or ab,ti("cost of illness" or cost)	851,112
	#25	emb.exact.explode("health care utili?ation") or ab,ti(("health care" or "health resource" or "health service*" or "healthcare") and (use or utili?ation))	355,342
	#26	OR/#21-#25	1,305,319
	#27	#3 AND #26	181
Total	#28	#3 AND (OR #26)	555

Table 82. ProQuest search strategy and hits for brand names only

Domain		Proquest search algorithm *SLR Results with only brand names in the search strategy*	Hits until 11/04/2018
Population	#1	EMB.EXACT.EXPLODE("zemaira" OR "alfalastin" OR "prolastin" OR "respreeza" OR "pulmolast") OR mesh.exact.explode("zemaira" OR "alfalastin" OR "prolastin" OR "respreeza" OR "pulmolast")	35
	#2	ab,ti("zemaira" OR "alfalastin" OR "prolastin" OR "respreeza" OR "pulmolast")	117
	#3	#1 OR #2	147
Outcomes - QoL	#4	emb.exact.explode("quality of life") OR mesh.exact.explode("quality of life") OR ab,ti("quality of life")	752,365
	#5	emb.exact.explode("quality adjusted life year*") OR mesh.exact.explode("quality-adjusted life year*") OR ab,ti("quality adjusted life")	38,472
	#6	ab,ti("eq-5d" or "eq5d" or euroquol*)	18,470
	#7	ab,ti(qaly or qalys or qald or qale or qtime)	23,672
	#8	ab,ti("disability adjusted life")	5,380
	#9	ab,ti(daly or dalys)	5,111
	#10	ab,ti("health* year* equivalent*")	47
	#11	ab,ti(hye or hyes)	128
	#12	ab,ti(hui1 or hui2 or hui3)	477
	#13	ab,ti(disutil*)	709
	#14	ab,ti("standard gamble")	1,025
	#15	ab,ti("time trade off" or "time tradeoff")	1,761
	#16	ab,ti(hqol or "h qol" or hrqol or "hr qol")	34,622
	#17	ab,ti(utility or utilities)	404,199
	#18	emb.exact.explode("health care survey*" or "health survey*" or "health status") or mesh.exact.explode((health or healthcare) AND surveys*) or ab,ti(((health or clinical) AND state) or ((health or healthcare or "health care") and (survey* or status or surveillance)) or "level of health")	1,391,274
	#19	OR/#4-#18	2,392,118
	#20	#3 AND #19	11
Outcomes - economic	#21	emb.exact.explode("cost utility analysis") or mesh.exact.explode("cost-benefit analysis" or "costs and cost analysis") or ab,ti("cost-utility" or "cost-benefit" or "economic evaluation")	251,834
	#22	emb.exact.explode("cost effectiveness analysis") or ab,ti("cost-effectiveness")	200,308
	#23	emb.exact.explode("cost minimi?ation analysis") or ab,ti(cost-minimi?ation)	3,874
	#24	emb.exact.explode("cost of illness") or ab,ti("cost of illness" or cost)	827,890

	#25	emb.exact.explode("health care utili?ation") or ab,ti(("health care" or "health resource" or "health service*" or "healthcare") and (use or utili?ation))	348,935
	#26	OR/#21-#25	1,280,150
	#27	#3 AND #26	15
Total	#28	#3 AND (OR #26)	22

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Given the relatively low number of records included in the Cochrane and Centre for Reviews and Dissemination databases, the search terms were kept broad.

Table 83. Search strategy for Cochrane and Centre for Reviews and Dissemination databases and hits

Platform	Search terms	Search limits	Hits
Centre for Reviews and Dissemination	(AATD) OR (The Alpha-1-Antitrypsin Deficiency Registry Study Group) OR (A1PI)	Any field	16
Cochrane	(AATD) OR (The Alpha-1-Antitrypsin Deficiency Registry Study Group) OR (A1PI)	Title, Abstract and Keywords	2

Grey literature was searched in relevant HTA agencies and conferences as described below.

Table 84. Grey literature search strategy and hits

Type of organisation	Organisation	Date searched	Hits
Clinical trials	clinicaltrials.gov	01/05/2018	0
HTA agencies	• UK: National Health For Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) • France: Haute Autorité de Santé (HAS) • Germany: Gemeinsamer Bundesausschuss (GBA) and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesenis (IQWiG) • Spain: Agencia espanola de medicamentos y productos sanitarios • Italy: Agenzia Italiana del Farmaco (AIFA)	01/05/2018	0

	• Australia: Pharmaceutical Benefits Advisory Committee (PBAC) • Canada: Canadian Agency for Drugs and Technologies in Health (CADTH) • Sweden: Tandvårdsoch läkemedelsförmånsverket (TLV) • Netherlands: Zorginstituut Nederland		
Conferences	• International Society For Pharmacoeconomics and Outcomes Research (ISPOR) • Alpha1 UK support • Alpha-1 Foundation • Alpha-1 Awareness UK	01/05/2018	0

17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Not applicable, this was covered in the search strategy shown in section 17.3.

17.4.2 The date on which the search was conducted.

Not applicable

17.4.3 The date span of the search.

Not applicable

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

17.4.6 The inclusion and exclusion criteria.

Not applicable

17.4.7 The data abstraction strategy.

Not applicable

18 Related procedures for evidence submission

18.1 Cost-consequence models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as

it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in

confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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Highly Specialised Technologies (HST)

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Dear Christian,

The Evidence Review Group, BMJ-TAG and the technical team at NICE have looked at the submission received on 25th May from CSL Behring UK Limited. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **3rd July**.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Thomas Paling, Technical Lead (Thomas.paling@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.ekeledo@nice.org.uk).

Yours sincerely,

Sheela Upadhyaya
Associate Director – Technology Appraisals and Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

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A1. **Priority question:** Please clarify how many of the people enrolled in RAPID had smoked regularly at some point in their lifetime (broken down by treatment group). If possible, please also provide subgroup analyses based on ex-smokers versus never smoked for all clinical outcomes reported in the company submission (CS). Additionally, please provide baseline characteristics for the two subgroups.

A2. **Priority question:** Please update the meta-analysis presented in Chapman 2009 based on baseline FEV_1% predicted (Figure 2) to include studies published since the RCT reported by Chapman 2005, including RAPID, and reporting results for all categories assessed in the systematic review, that is:

a) <30%;
b) 30-65%;
c) >65%
d) Total.

A3. **Priority question:** In the company submission, a criterion for eligibility for treatment with Respreeza (outlined on page 39 of the CS) is listed as, "rapidly declining lung function (FEV_1% or DL_{CO}%) or lung density decline". Please provide a definition and/or more detailed cut off points for rapidly declining lung function (in terms of FEV_1% or DL_{CO}%) and for lung density decline for eligibility for treatment.

A4. **Priority question:** Please clarify how the values of change in lung density (adjusted PD15) for TLC and FRC reported in Table 18 (page 97 of CS) have been calculated. The values reported for the two cohorts do not match those reported for the early-start and delayed-start groups in the McElvaney 2017 paper presenting the results for the RAPID-OLE study.

A5. **Priority question:** For those in the placebo group who went on to receive Respreeza during the open-label extension phase of RAPID, please provide change in mean CT lung density (shift of the 15th percentile of lung density) and in mean FEV_1% predicted at 2 years' treatment with Respreeza, based on the categorisations of no decline, slow decline, and rapid decline as determined by the CT scans collected during receipt of placebo in the trial.

A6. Please provide sensitivity analysis to assess impact of missing data using total lung capacity (TLC) state alone in the RAPID study (to match results reported in Table 21 of the CS, page 112).

A7. Please provide the Appendices associated with the Clinical Study Report (CSR). More specifically, as a minimum, please provide Appendix 16.1.9.

A8. For RAPID, please provide the following data on the occurrence of pulmonary exacerbations in the ITT population:

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a) Number of people experiencing an exacerbation per treatment group;
b) Total number of exacerbations occurring per treatment group;
c) Breakdown of exacerbations in each treatment group by severity, together with a definition of each category of severity (the paper by Anthonisen refers to criteria for treatment with antibiotics);
d) Number of exacerbations in each treatment group requiring oral corticosteroids;
e) Number of exacerbations in each treatment group requiring antibiotic treatment;
f) Number of exacerbations in each treatment group requiring hospitalisation;
g) Duration of hospitalisation of exacerbations in each treatment group.

A9. On page 180 in CS, relating to CT lung density, there is the following statement, "*The baseline characteristics of Respreeza and placebo were slightly different across arms thus the analysis is presented as a regression analysis using baseline covariate adjustment, which accounts for these slight differences*". The CSR for RAPID states that, "*linear random regression model was applied using SAS PROC MIXED, with country, inspiration state, time elapsed since Day 1 (year), treatment, and treatment-by-time interaction (i.e., a regression of Adjusted P15 on time within treatment) as fixed effects and subject and subject-by-time interaction as random coefficients. Thus, the primary efficacy model contained the subjects' individual intercept and individual slope*". Please confirm that the covariates listed in the CSR are included in the regression analysis referred to on page 180 of the CS. If not, please specify the covariates.

A10. For RAPID, please confirm that one person receiving Respreeza and one person receiving placebo underwent lung transplantation.

A11. Please clarify why CT scans were obtained for the upper zone of the lung when emphysema associated with A1PI deficiency typically affects the lower lobes of the lung.

A12. Please provide a brief description for the clinical experts' rationale for defining the following categorisations for total decline in lung density:

- no decline (no change);
- slow (0-2g/L/year);
- and rapid decline (>2g/L/year).

The Evidence Review Group could not locate a description of these rates of decline in Stockley 2015. Additionally, there is limited information provided in Green 2014. Please also outline in what way the other thresholds were assessed that were decided to be no more informative (page 161 of the CS).

A13. In the CS (page 70), it is stated that, in RAPID, weekly doses of Respreeza were given by a nurse or family doctor (other than those administered at the study centre). It is also stated that, after the first infusion, it is anticipated that Respreeza can be given by a caregiver or by the patient (page 252). However, the economic model assumes that

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home infusion will be carried out by a district nurse. Please clarify whether the company considers that home administration of Respreeza by a patient or a caregiver is viable. If so, please outline any resources the company envisages would be required to make this possible (e.g., a longline or portacath for the patient).

A14. The CS outlines (page 149) that discontinuation of Respreeza is expected to occur only when a patient receives a lung transplant or if a person dies. Please clarify whether there are any rules for cessation of treatment based on lack of clinical efficacy of Respreeza. If so, please provide details.

A15. Please provide step-by-step calculations behind the incidence (95 patients per year) and prevalence (549 patients) estimates presented in Section 13, with supporting references and justification for any assumptions. In particular, please provide a justification for the assumption that screening and case identification will not increase should Respreeza be approved for use in the NHS.

A16. Please provide reference details for the 15 studies excluded at assessment of the full publication stage, as outlined in the PRISMA flow diagram (Figure 8 of the CS) relating to the update of the systematic review initially carried out by Edgar 2017.

A17. Please specify reference details for the 12 studies identified as relevant to the review at assessment of papers at the full publication stage, as outlined in the PRISMA flow diagram (Figure 8 of the CS) relating to the update of the systematic review initially carried out by Edgar 2017.

Section B: Clarification on cost-effectiveness data

Revisions to the economic model

The ERG have identified concerns about the suitability of the model for decision-making purposes. These concerns centre on:

- the incorporation of lung density as a measure to model disease progression and severity;
- the threshold of FEV_1% cut-offs for lung transplants; and
- the exclusion of important aspects related to lung transplantation.

Therefore, the ERG request that the following revisions are made to the economic model:

B1. **Priority question:** Please restructure the base case economic model so that it includes the health states shown in the figure below. The ERG proposes that patients start the model in the FEV1%<30% predicted; ≥30%FEV1%<50% predicted; or FEV1%≥50% health states, according to the baseline distribution of RAPID patients according to their initial FEV1% status. Once patients reach the FEV1%<30% predicted health state, a proportion will be eligible for lung transplant (LT). Patients eligible for a LT will have a different probably of receiving a LT once they are on the

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waiting list for a transplant (according to the NHS Blood and Transplant 2017 report) depending if they have been on the list for one, two or three years. Tunnel states for FEV1%<30% should be implemented to capture this. Once patients move to the LT health state, they will have different probabilities of dying (according to the NHS Blood and Transplant 2017 report), depending on how much time elapses since surgery. LT tunnel states should capture this. Patients can die at any point in the model. In order to derive the necessary clinical data for the model, please:

a) Use the Stockley et al. 2014 to estimate the transitions between FEV1% states for the BSC arm of the economic model (please see question B2);
b) Use the Chapman 2009 meta-analysis update requested in question A2 to estimate treatment effectiveness of augmentation therapy on FEV1% decline (please see question B3);
c) Use Green et al. 2014 to estimate the transition between the FEV1% health states and the death state in the model (please see question B4);
d) Please conduct a search to inform the percentage of patients with an FEV1%<30% who are ineligible for a LT due to co-morbidities. Please note that the model structure below assumes that once patients move to the FEV1%<30%, 100% of these patients are put on the transplant waiting list (alternatively, patients can move to the FEV1%<30% ineligible for LT, where they will not get a LT);
e) Use the NHS Blood and Transplant 2017 report to estimate the probability of death after LT (please see question B7);
f) Use the NHS Blood and Transplant 2017 report to estimate the probability of receiving a LT once a patient is on the waiting list (please see question B8).

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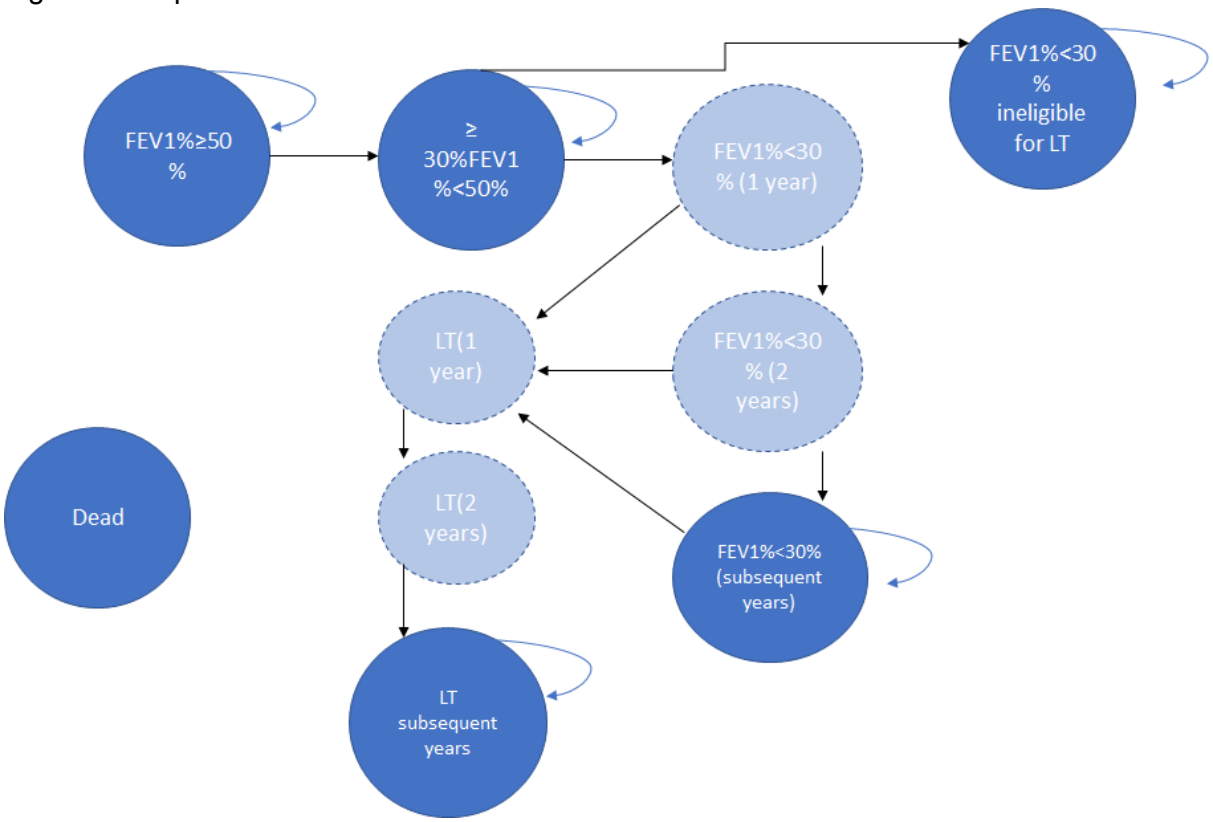
Figure 1. Proposed model structure



B2. **Priority question:** Please estimate the annual FEV1% decline between the FEV1%≥50%; ≥30%FEV1%<50%; and FEV1%<30% health states using the 1.45% annual decline (Stockley et al. 2014) as in the original model. Please take the average baseline FEV1% in each category from RAPID and estimate the number of years it will take to cross the threshold of the following FEV1% category. For example, given that the average FEV1% at baseline for the FEV1%≥50% group in RAPID is 59.76%, then at an average annual decline of 1.45%, it would take 6 years to move to the ≥30%FEV1%<50% category in the BSC arm of the economic model.

a) Please explain why the percentage of patients with different rates of FEV1% decline in Stockley et al. 2014 does not add up to 100% of the patients in the study.

B3. **Priority question:** Please use the updated Chapman 2009 meta-analysis requested in question A2 to estimate the reduction in FEV1% decline for patients with augmentation therapy, per FEV1% category. As the categories in Chapman et al. 2009 do not match the updated model categories, please use the ones provided as proxies. More specifically, in the Chapman et al. 2009 paper this would be the equivalent of taking the slope difference of 1.8 mL/y for the FEV1%<30% predicted; the 17.9 mL/Y for the ≥30%FEV1%<50% predicted; and the 3.5mL/y in the FEV1%≥50%. Please convert the slope difference into the equivalent annual reduction in FEV1% decline for Respreeza

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(compared to BSC) by assuming the same relationship between annual FEV1% decline and mls/y in the Stockley et al. 2014 paper (please see Excel sheet attached).

B4. **Priority question:** Please re-run the Green et al. 2014 analysis to obtain survival curves for the different FEV1% categories, without differentiating survival by lung density decline by CT. More specifically, please re-estimate the curves presented in Figure 29 of the company submission by the FEV1% categories provided (i.e., evaluate the fit of loglogistic, lognormal, exponential, Gompertz, Weibull and gamma) for all patients in each FEV1% category (i.e. one survival curve per FEV1% health state in the model). Please use the estimated curves from cycle 0 in the model, to estimate survival.

a) If the company has access to the more up-to-date survival data are available, as referenced during the decision problem meeting with NICE, please use this updated survival data in the model accordingly.

B5. **Priority question:** Please assess the goodness of fit (AIC; BIC; visual inspection and clinical plausibility) of the loglogistic, lognormal, exponential, Gompertz, Weibull and gamma distributions for each survival curve for the respective FEV1% category mentioned in question B4. Please use this assessment to choose the appropriate distribution for each FEV1% survival curve, instead of assuming that the Weibull distribution can be used for all curves.

B6. **Priority question:** Please include an option in the economic model (by means of a drop-down menu) so that the user can choose between the different distributions (i.e. loglogistic, lognormal, exponential, Gompertz, Weibull and gamma) to model survival, for the different health states in the model (i.e., FEV1%≥50%;≥30%FEV1%<50%; and FEV1%<30% health states).

B7. **Priority question:** Please use the estimates provided in the NHS Blood and Transplant 2017 report (page 106, table 11.21) to calculate the percentage of patients dying after LT in year 1; year 2 and subsequent years.

B8. **Priority question:** Please use the estimates provided in the NHS Blood and Transplant 2017 report (page 67, Figure 7.5) to calculate the percentage of patients receiving a LT, after having been enrolled on the transplantation list.

Resource and cost use

B9. **Priority question:** The ERG is concerned the rate of exacerbations used by Punekar 2014 differs from the rate observed in RAPID for each treatment arm.

a) Please use the disease management costs from Punekar 2014 excluding the exacerbation-related costs. More specifically, please replace the disease

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management costs taken from Table 4 according to exacerbation frequency from “All patients” to “None”;

b) Please include the rate and duration of exacerbations requiring oral steroids, antibiotics or hospitalisation by treatment arm in RAPID in the model, applying appropriate costs and benefits. Please ensure any utility decrements are not double counted as Ejiofor and Stockley 2015 may have included a proportion of patients who experienced exacerbations;

c) Apply the disease management costs for GOLD stages 2, 3 and 4 from Table 4 of Punekar 2014 to the health states relating to an FEV_1% >50%, 30-49% and <30%, respectively. As above, use disease management costs for patients with no exacerbations.

B10. **Priority question:** Clinical experts advised the ERG that a change in CT density using at least two CT scans over one year would be needed to assess eligibility for Respreeza. In the updated base case analysis, please include the cost of two CT scans to assess eligibility in the first cycle of the model (cycle 0) for Respreeza. Please consider adding any additional costs related with routinely running CT scans in specialised centre, for example, acquiring the software program required for reading densitometry, staff training, phantom scans, etc.

B11. **Priority question:** Based on your response to question A14, please include the costs to assess the rules for treatment cessation in the updated base case analysis. Also, if treatment cessation occurs, please reflect this in the economic model by applying appropriate treatment effects, costs and benefits.

B12. **Priority question:** Clinical experts advised the ERG that in order to document progressive decline, the way patients are monitored may need to change. Please include the cost of annual CT scans for patients receiving Respreeza as a scenario analysis.

B13. **Priority question:** Clinical experts advised the ERG that patients receiving high cost drugs such as Respreeza, or patients with a rare condition such as A1PI deficiency, may require additional disease management by respiratory clinics in secondary care, or expert tertiary clinics. Please justify the assumption that disease management consists of primary care alone (Punekar 2014) and is equivalent for patients receiving BSC and Respreeza.

B14. **Priority question:** Page 198 of the CS states that, “*Respreeza will be initiated within the current context of care, by specialists experienced in the management of A1PI deficiency at existing facilities*.” In the updated base case analysis, please cost the first drug administration using the cost associated with a specialist clinic.

B15. **Priority question:** Please clarify why the costs of assessment for lung transplant are only applied to patients who receive a lung transplant, rather than everyone who is

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eligible. Please provide a scenario analysis where all eligible patients incur the costs of lung transplant assessment.

B16. In the model, lung transplant costs in the first year and subsequent years are informed by a double transplant alone (Costs B37:38), rather than the weighted cost of single and double lung transplant costs, as reported in the submission. Please address this issue in the model.

B17. Please clarify why the cost of a specialist clinic per administration was informed by the cost of Other Specialist Nursing (N29AF) rather than the cost of a consultant or non-consultant led service related to respiratory medicine (service code, 340; currency code, WF01A:WF02C).

B18. Please justify the assumption that 75% of Respreeza infusions will be administered at home (Table 51 of the CS, page 199).

B19. Please clarify how Punekar 2014 was identified and chosen to inform the economic model.

B20. Please justify why non-COPD hospitalisations from Punekar 2014 are included in the costs of disease management.

Health-related quality of life

B21. **Priority question:** Please provide data extractions for the 13 studies included in the quality of life search, plus any additional studies used to inform utility data in the model. Examples of data extraction forms can be found in NICE DSU (Technical Support Document 9): http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD9-HSUV-values_FINAL.pdf

B22. **Priority question:** In the decision problem pro-forma for this submission, it was noted that evidence from an EU study including EQ-5D data was likely to become available during the evaluation. If these data are available and are appropriate to inform the model, please provide a data extraction (as requested above) and perform a scenario using the utility data for the updated economic model.

B23. **Priority question:** Please consider using the Anyanwu 2002 and Anyanwu 2001 to estimate lung transplant -related utility in the economic analysis instead of Groen 2004. This change will make the resource use data and utility data sources consistent (Anyanwu 2002) and will allow the use of the utility values reported in Table 45 of the CS (page 186), without the need for transforming these into utility decrements.

B24. **Priority question:** Please use the Anyanwu 2002 and Anyanwu 2001 papers to estimate lung transplant -related utility in the economic analysis (if not as your base

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case, then as a scenario analysis), by incorporating different utility values into the different lung transplant tunnel states.

B25. On pages 188–189 of the CS it states, "*The studies reporting all other utility information (Ejiofor and Stockley, 2015) (Groen et al. 2004) did not report sufficient information regarding the study population to allow comparison of the study populations between utility studies or the general population in regards to age*." However, the mean age of patients is reported in the study by Eijofor and Stockley 2015. Please clarify the approach taken to include utility data in the model.

B26. A Cox regression analysis is provided on pages 146–147 (marked as CiC) and 187–188 (marked as AiC). Please clarify:

a) if the analysis was undertaken by the company;
b) the confidential mark-up;
c) the source of data used to inform the analysis;
d) how covariates were chosen.

B27. Please clarify how Ejiofor and Stockley 2015 was chosen and identified to inform utilities by FEV_1% predicted.

B28. If available, please provide the number and severity of exacerbations experienced by the patients in Ejiofor and Stockley 2015.

B29. If available, please provide the treatment patients in Ejiofor and Stockley 2015 received to manage their A1PI deficiency.

Systematic literature review for health economic studies

B30. Please provide a list of excluded studies with reasons for exclusion for the economic and quality of life searches and resource use search.

B31. Please provide the inclusion and exclusion criteria used for the quality of life search and resource use search. The ERG does not consider the selection criteria in Table 30 (page 151 of CS) to sufficiently cover those types of data.

B32. If the quality of life search was limited by intervention, please justify this decision.

B33. Please provide the data abstraction strategy used for the quality of life search and resource use search

B34. Please clarify why the population in Table 30 of the CS (page 151) is restricted by country: "Emphysema due to A1PI deficiency in the UK"

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Reporting of results

B35. **Priority question:** The ERG ran PSA twice using 5,000 simulations and found notably lower life years to the results reported in Table 74 of the CS (page 233), please explain this difference.

Treatment	Total LYs		
	ERG (1)	ERG (2)	CS (Table 74)
BSC	7.228	7.204	8.76
Respreeza	9.239	9.227	11.572
Inc. LY	2.011	2.023	2.813

B36. Please clarify why correlations between lung density and lung function were not considered in probabilistic analysis.

B37. The results of OWSA on "Clinical inputs-transitions" in Table 72 of the CS (page 229) are mismatched, please correct the values in the table.

Further clarifications

If the above suggested modelling approach (questions B1 to B8) is not followed, further information relating to the existing model is required. Please note that this is not an alternative to providing a formal clarification response to questions B1 to B8 – these questions remain applicable even if the suggested approach is not followed, so please ensure full a response to each question is provided, including a rationale for the adopted approach.

If a model structure excluding lung density (questions B1 to B8) is not followed, please note the following additional clarifications and requests on those questions:

B1) If CT-based lung is retained in the model, please restructure the FEV1% thresholds included in the model to incorporate FEV1%<30%, for consistency with eligibility for lung transplantation in practice and to avoid potentially overestimating the benefits of treatment. It is noted that, although the inclusion criteria for RAPID excluded patients with a FEV1%<30% at baseline, this structure nevertheless permits patients to progress to this health state (at different rates depending on the treatment arm) in the economic model.

B2) Regardless of which FEV1% categories are included in the model, the estimation of transition probabilities between the FEV1% states should be conducted as outlined in question B2. More specifically, these should reflect the time that takes patients to transition from the mean baseline FEV1% in the starting health state to cross the threshold of the next FEV1% category (and not to reach the average baseline FEV1% in the next category as the current model does).

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B3) Please use the updated results from the meta-analysis (question A2) to estimate transitions between FEV1% categories in the model for the Respreeza arm. It is requested that the company follows the format suggested by the ERG in the Excel spreadsheet sent by the ERG together with the clarification questions.

B4) If the proposed structure is not followed, this question remains partly applicable. If lung density outcomes are retained in the model, please (either in the base case or a scenario analysis by means of a drop down menu in the model) replace the survival data from RAPID used in the current model, by Green et al. 2014 to model survival for the entire economic analysis (from cycle 0 in the model).

In addition, the following question provides the minimum additional information and amendments needed by the ERG to validate the existing economic model.

B38. **Priority question:** Please provide additional information and amendments to the economic model as follows:

a) Provide the equations used in the linear regression used to estimate transition probabilities between lung density states in the model using RAPID data (described in page 180 of the CS), together with the covariates used to adjust these data, and with a clear description of the methods and data used in this process (including the results of the statistical process for selecting covariates);
b) Provide the change in mean CT lung density per year, for Respreeza patients who received Respreeza in RAPID and carried on receiving Respreeza in RAPID-OLE (i.e. excluding the placebo patients from RAPID who crossed over to Respreeza in RAPID-OLE), over the 4-year follow-up period;
c) Use the data requested in b) to estimate transition probabilities in the economic model for Respreeza patients. More specifically, please include transition probabilities matrices estimating the probability of patients moving between the different lung density decline states in the model between year 0-1 and year 1-2; year 1-2 and year 2-3; and finally year 2-3 and year 3-4, using the 4-year Respreeza data (for the cohort of patients receiving Respreeza in RAPID and RAPID-OLE, excluding placebo patients from RAPID-OLE), for each FEV1% category included in the model;
d) Provide evidence establishing a robust predictive relationship between CT-measured lung density and FEV1% as this relationship is central to the current model and is based on the RAPID trial, where changes in FEV1% were not statistically significant. Provide evidence to allow an external validation of trial and model outcomes;
e) Incorporate into the model all the CT scans and associated costs (suggested in clarification question B10) related with performing all the CT scans informing the changes in lung density captured in the model (at least 2 scans a year as in RAPID). Please note that this does not replace the request in clarification

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question B10, relating to the CT scans necessary for the initial assessment of patients' eligibility for Respreeza.

f) The company is proposing that routine CT scanning will be introduced in the NHS and that Respreeza has the potential to change the current diagnosis pathway for A1PI deficiency in the NHS. Given the importance and cost of issues such as the requirement for redeployment of staff, training and acquisition of specialist equipment, establishing clinical appropriate criteria for diagnosis, etc. beyond the existing specialist centres, this needs to be included in the budget impact model by the company to be considered on a national level coverage by NHS England;
g) Model lung transplantation in accordance to the clinical guidelines for lung transplant and clinical expert opinion, both indicating that only patients below FEV1%<30% (and not below FEV1%<50%) are eligible for a lung transplant;
h) Link CT lung density decline with the need for lung transplant;
i) Assess the clinical plausibility of patients moving from an FEV1%>50% no lung decline to a FEV1%<50% no lung decline health state in the model, as our clinical experts consider these implausible, and substantiate the equivalent transition for a patient with slow lung density decline;
j) Capture the correlation between FEV1% and lung density in the probabilistic sensitivity analysis, as these outcomes are correlated and report the approach taken in a transparent way.

Section C: Textual clarifications and additional points

C1. Please provide the figures reported in the Green *et al.* 2014 draft manuscript (and used in the CS to provide survival by FEV_1% status) submitted by the company.

C2. Please confirm that no investigation site was located in the UK.

C3. Please clarify whether there should be a footnote in Table 11 (page 80 of the CS) to accompany the asterisk associated with "*CT lung density, adjusted PD15 g/L, mean (SD)**".

C4. Please confirm that the FEV_1/FVC ratios and accompanying standard deviations (SDs) reported in Table 11 (page 80 of the CS) should be 0.452 (0.11) and 0.432 (0.104) for Respreeza and placebo, respectively.

C5. In Table 17 of the CS (page 94), please confirm that the change in FRC for the treatment group should be -1.54 g/L per year, as reported in the full publication, rather than 0.48 g/L per year as reported in the table.

C6. The title for Table 47 in the CS (page 189) relates to carer disutility, please clarify if the title needs to be amended.

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C7. The cost of a district nurse per administration is taken from NHS reference costs 2016–17 (Table 49 of the CS, page 191) whilst the cost of administrations in an outpatient or community setting (Table 55 of the CS, page 204) is taken from the PSSRU Curtis 2017. Please clarify why the source is not consistent.

C8. Please clarify if the number of PSA simulations is 5,000 and justify the chosen number.

C9. The ERG is unable to verify the values in Tables 66, 67, 68, 70 and 71 with the results in the worksheet 'Model'. The discrepancies identified in Tables 66 and 67 are provided below. Discrepancies for Tables 68, 70 and 71 are not provided due to time constraints. Please provide corrected results for Tables 66, 67, 68, 70 and 71.

Table 66. Model outputs by clinical outcomes for best supportive care (discounted)

	BSC - Discounted outcomes			**Results in the model (cell in 'Model')**		
Outcome	LY	QALY	Cost (£)	LY	QALY	Cost (£)
FEV_1>50 % predicted: No decline	0.04	1.73	£15,340	Ok numbers match (AE58)	Ok numbers match (CA58)	£13,853 (DC58)
FEV_1>50 % predicted: Slow decline	0.33			1.88 (AF58)		
FEV_1>50 % predicted: Rapid decline	0.53			0.49 (AG58)		
FEV_1<50 % predicted: No decline	0.07	0.32		Ok numbers match (AH58)	1.84 (CC58)	
FEV_1<50 % predicted: Slow decline	1.51			1.40 (AJ58)		

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FEV_1<50 % predicted: Rapid decline	1.98			1.81 (AK58)		
Lung transplant: first year	0.19	1.55	£31,983	0.18 (AK58)	1.10 (CD58)	£25,147 (DD58)
Lung transplant: subsequent years	0.56			1.21 (AL58)		
Treatment	NA	NA	£0	–	–	–
Administration	NA	NA	£0	–	–	–
TOTAL	7.08	4.67	£39,001	Ok numbers match (AN58)	Ok numbers match (CD58)	Ok numbers match (DD58)

Table 67. Model outputs by clinical outcomes for Respreeza (discounted)

	Respreeza - Discounted outcomes			**Results in model (cell in 'Model')**		
Outcome	LY	QALY	Cost (£)	LY	QALY	Cost (£)
FEV_1>50% predicted: No decline	0.18	1.73	£20,566	Ok numbers match (AE115)	2.14 (CA115)	£17,908 (DB115)
FEV_1>50% predicted: Slow decline	0.40			2.32 (AF115)		
FEV_1>50% predicted: Rapid decline	0.55			0.48 (AG115)		
FEV_1<50% predicted: No decline	0.42	0.42		0.37 (AH115)	2.43 (CB115)	

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FEV_1<50% predicted: Slow decline	3.68			3.25 (AI115)		
FEV_1<50% predicted: Rapid decline	0.80			0.72 (AJ115)		
Lung transplant: first year	0.15	2.06	£42,671	0.23 (AK115)	1.41 (CC115)	£32,415 (DC115)
Lung transplant: subsequent years	0.62			1.56 (AL115)		
Treatment	NA	NA	£419,568			OK numbers match (CZ115)
Administration	NA	NA	£2,951			£17,059 (DA115)
TOTAL	9.13	5.98	£486,950	Ok numbers match (AN115)	Ok numbers match (CD115)	Ok numbers match (DD115)

Highly Specialised Technologies (HST)

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

This document provides responses to clarifications questions originally received by email on the 19th June 2018.

We consider that several of the requests (discussed below in each instance) go well beyond the reasonable scope of a 'clarification question' and in fact entail us performing very significant data analyses and changes to the cost-effectiveness model within a timeframe of only 10 working days.

Furthermore, the clarification questions received were themselves unclear and were contradicted by a corresponding email received at the same time on the 19th June, stating that if some elements of the requests could not be fulfilled then a separate list of questions / evidence requests in the email should be responded to.

Further to the questions being received at 18:20 on the 19th June, a teleconference (scheduled in line with the originally expected 18th June receipt date for the clarification letter) between NICE, CSL and the ERG was held at 11:30 on the 20th June. During this teleconference, we sought clear indications on which clarification questions were applicable in light of CSL having indicated during the teleconference that it did not consider to be clinically appropriate, based on clinical expert feedback and published literature, to completely alter the model structure.

The 25th June clarification letter still poses many clarification questions which are inconsistent, duplicated and/or unclear, with new questions being added to Section B after B37 (numbered B1-B4 and B38a-j). Therefore, whilst we have made our best attempts to address the clarification questions within the very short timeframe, it has not been possible to provide all responses. Furthermore, many of the clarification questions still appear to be redundant in light of our earlier indication that we do not consider a model rebuild to be clinically appropriate nor indeed possible within the timelines.

We are naturally very willing to actively engage in the appraisal process and to provide as much useful information as possible, so if we have misunderstood any of the clarification questions, then we would be happy to provide additional responses, as required, in order to ensure that the Committee has all relevant information for its decision making.

Section A: Clarification on effectiveness data

A1. Priority Question: Please clarify how many of the people enrolled in RAPID had smoked regularly at some point in their lifetime (broken down by treatment group). If possible, please also provide subgroup analyses based on ex-smokers versus never smoked for all clinical outcomes reported in the company submission (CS). Additionally, please provide baseline characteristics for the two subgroups.

The smoking history data of the patients enrolled in the RAPID study are presented in Table 1. Few patients had never smoked before (16% on treatment and 18.8% placebo, excluding unknown data) and so a robust subgroup analysis with meaningful results would not be feasible. Baseline characteristics for the two subgroups are not available.

Table 1. Smoking history of patients enrolled in the RAPID study

Smoking status	Number (%) of subjects	
	Respreeza (N=93)	Placebo (N=87)
Never	13 (14.0)	15 (17.2)
Previous	68 (73.1)	65 (74.7)
Stopped > 12 months prior to study	58 (62.4)	56 (64.3)
Stopped 6-12 months prior to study	7 (7.5)	6 (6.9)
Timepoint unknown	3 (3.2)	3 (3.4)
Unknown	12 (12.9)	7 (8.0)

Abbreviations: N = number of subjects

A2. Priority question: Please update the meta-analysis presented in Chapman 2009 based on baseline FEV_1% predicted (Figure 2) to include studies published since the RCT reported by Chapman 2005, including RAPID, and reporting results for all categories assessed in the systematic review, that is:

a) <30%;
b) 30-65%;
c) >65%
d) Total.

In order to update the meta-analysis conducted by Chapman et al. (2009) based on FEV_1, the studies listed in Tables 6, 7 and 8 of the submission (pg. 51 to 65) containing RCT and non-RCT relevant studies were reviewed in order to identify those containing FEV_1 as a measured outcome. Seven studies included FEV1 as an outcome. The outcome considered in the 2009 meta-analysis was the change in FEV_1 slope (mL per year), rather than predicted FEV_1, so slope data were required for treated and untreated cohorts. Four of the studies did not report actual FEV1 (rather than predicted) or did not report the change over a period of time (i.e. the slope) or did not report the change in each arm (treated and untreated). These studies were Dirksen et al., 2009; Campos et al., 2009; Subramanian et al., 2012; and Wewers et at., 2017.

Data extraction from each of the remaining three identified studies was conducted.

The studies identified were Tonelli et al., 2009, Barron-Tizon et al., 2012 and Chapman et al., 2015. More specifically the study by Tonelli et al., 2009 reported measurements of FEV_1 in litres for treated and untreated groups (in the categories assessed in the systematic review by Chapman et al., 2009) and the patients included in the study had a proven PiZZ genotype and at least two recorded postbronchodilator FEV_1 measurements, six months apart or more. The study by Barron-Tizon et al., 2012 reported FEV_1 outcomes in the same patients before augmentation therapy and after receiving treatment. The FEV_1 % predicted at baseline was not specifically reported, so had to be assumed in order to fit into one of the FEV_1 categories used by Chapman et al. As patients were diagnosed with severe AAT congenital deficiency (i.e. PiZZ genotypes and combinations of Z, rare and null alleles expressing AAT serum concentrations <11 μmol or 50 mg/dl) and had been receiving continuous augmentation therapy during a minimum of 18 months before being included in the study, they were assumed to be in the FEV_1 of 30-65% group. Finally, the Chapman et al., 2015 study data was extracted from the 4001 CSR, showing the difference of the FEV_1 measurements between baseline and month 24 for the ITT population.

To update the meta-analysis, we used Review Manager 5.3.5 (Cochrane Community) creating a continuous data analysis with a random effects model to be consistent with the Chapman et al., 2009 meta-analysis. Regarding the data used, the Barros-Tizon et al., 2012 and Chapman et al., 2015 studies presented results for FEV_1 in litres for the whole duration of the study, and in order to extract the appropriate data, we converted results into millilitres and divided by the study duration to gain a value of mL/year.

The first step to conduct the updated meta-analysis was to extract the data from the original Chapman et al., 2009 analysis from the FEV_1 slope data presented. The meta-analysis created, although contained the correct slope differences from extracted data, the weights were in some parts not similar to the original Chapman meta-analysis, leading to slightly different results in the pooled slope difference. This is due to Chapman meta-analysis using the individual data of patients compared to the meta-analysis presented in Figure 1 which was conducted by extracting the mean difference of the FEV_1 slope for each study (as presented in the publication).

Figure 1. Forest plot of studies included in the meta-analysis from Chapman et al., 2005

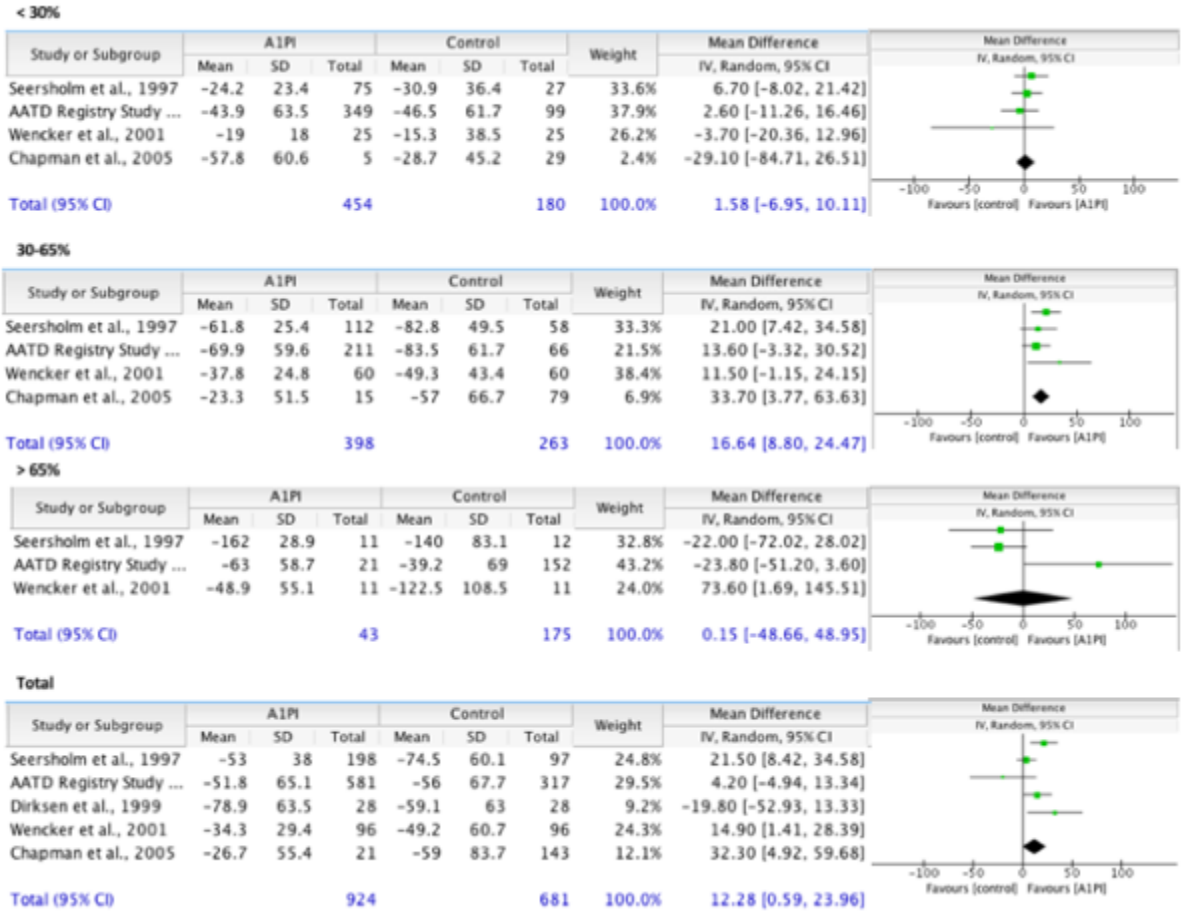
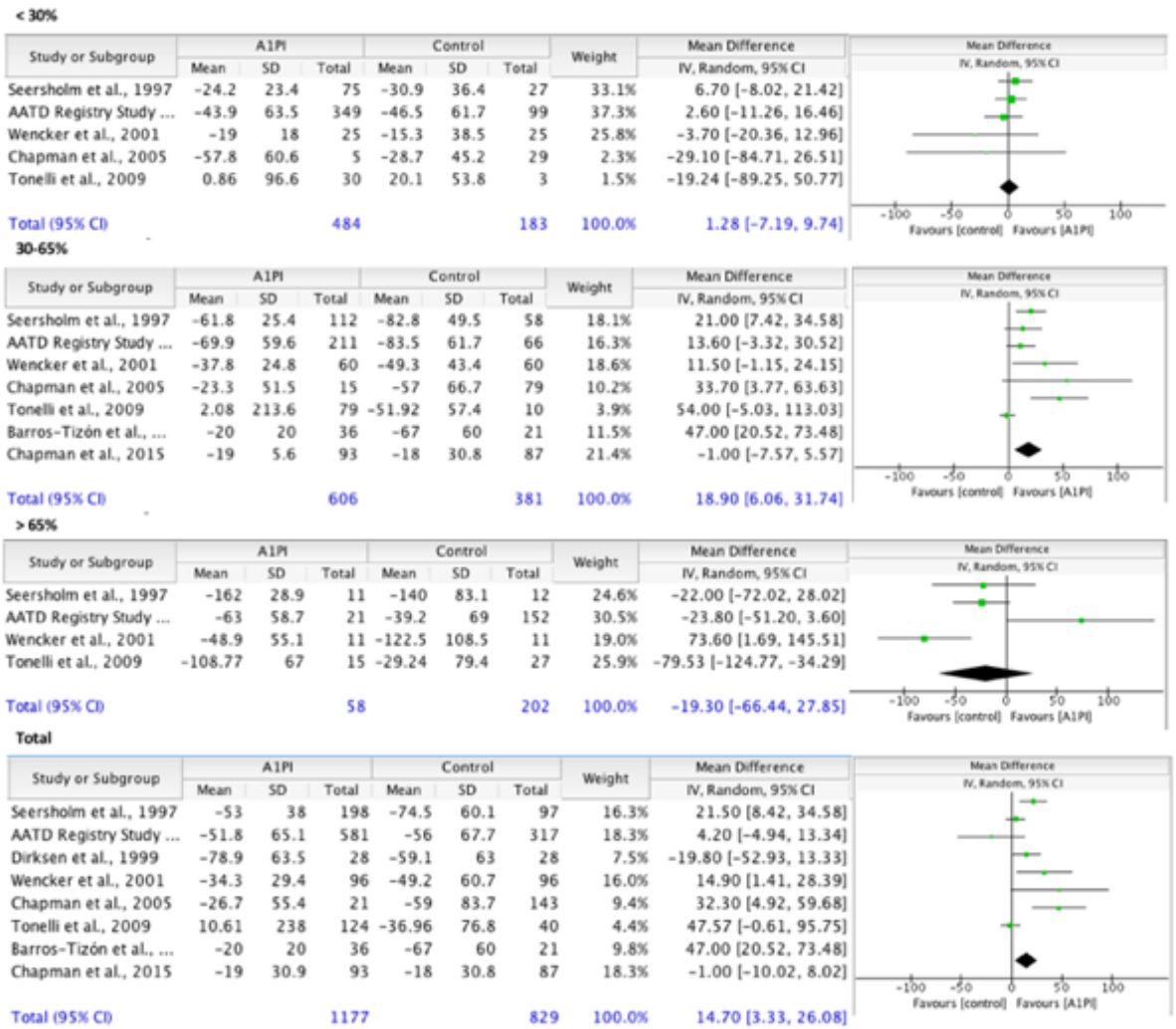


Figure 2. Forest plot of studies included in the updated meta-analysis from Chapman et al., 2005



With this aside, the updated meta-analysis (**Error! Reference source not found.**) including the three mentioned studies, did not present significant differences regarding the slope difference with the Chapman et al., 2005 publication. Although results extracted from Chapman et al., 2015 and Barros-Tizon et al., 2012 were in accordance to previous observational studies, the Tonelli et al., 2009 did contain results which were not expected. The Tonelli publication mentions that: *"It is unclear why we found an unusual increase in FEV_1 instead of a reduction in the FEV_1 decline as reported in previous studies. Possible explanations include anti-inflammatory effects of treatment with favorable effects over potential reversible processes such us bronchoconstriction and/or the use of different spirometry equipments".* Specifically, for results related to FEV_1 > 65%, Tonelli reports: *"augmented patients with an initial FEV_1 > 65% of predicted had a significant larger FEV_1 decline than nonaugmented patients, probably due to selection bias, as it is more likely to provide augmentation treatment to patients who have FEV_1 > 65% and an accelerated FEV_1 decline. Another possible explanation is based on the unusually low rate of FEV_1 decline in patients with FEV_1 > 65% who did not receive augmentation therapy (Δ FEV_1−29.24 mL/year)."*

The conclusions of the updated meta-analysis are consistent with the original analysis; namely that in the category of FEV_1 30-65%, A1PI slows the rate of lung function decline (**Error! Reference source not found.**).

A3. Priority question: In the company submission, a criterion for eligibility for treatment with Respreeza (outlined on page 39 of the CS) is listed as, "rapidly declining lung function (FEV_1% or DL_{CO}%) or lung density decline". Please provide a definition and/or more detailed cut off points for rapidly declining lung function (in terms of FEV_1% or DL_{CO}%) and for lung density decline for eligibility for treatment.

The criterion for treatment eligibility of lung disease progression (FEV_1% or DL_{CO}%) or lung density decline was determined according to the licensed indication of Respreeza. According to the SPC for Respreeza: *"Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV_1) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency."* More specific criteria could not be defined and assessment by DL_{CO}% are not excluded by this definition. Eligibility should be determined on an individual basis by clinical experts specialising in A1PI deficiency.

A4. Priority question: Please clarify how the values of change in lung density (adjusted PD15) for TLC and FRC reported in Table 18 (page 97 of CS) have been calculated. The values reported for the two cohorts do not match those reported for the early-start and delayed-start groups in the McElvaney 2017 paper presenting the results for the RAPID-OLE study.

The numbers presented in Table 18 of the submission are separated into ITT population (TLC, FRC and TLC + FRC) and complete population (TLC, FRC and TLC + FRC). Results have been taken from Figure 3 of the (McElvaney et al., 2017) publication (Figure 3).

Figure 3. Treatment comparisons for change in lung density (adjusted PD15) at different inspiration states in RAPID-RCT and RAPID OLE

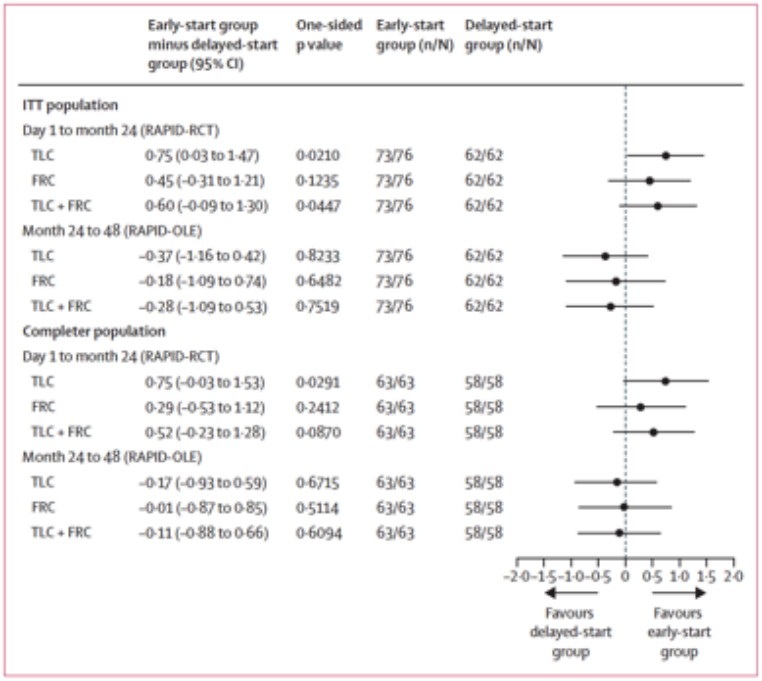


Figure 3: **Treatment comparisons for change in lung density (adjusted PD15) at different inspiration states in RAPID-RCT and RAPID-OLE**

Data are from the mixed-effects regression model applied to each trial separately. Adjusted PD15=lung volume-adjusted 15th percentile of the lung density. FRC=functional residual capacity. ITT=intention to treat. TLC=total lung capacity. OLE=open-label extension. RCT=randomised controlled trial.

A5. Priority question: For those in the placebo group who went on to receive Respreeza during the open-label extension phase of RAPID, please provide change in mean CT lung density (shift of the 15th percentile of lung density) and in mean FEV_1% predicted at 2 years' treatment with Respreeza, based on the categorisations of no decline, slow decline, and rapid decline as determined by the CT scans collected during receipt of placebo in the trial.

Those in the placebo group who went on to receive Respreeza during the open-label extension phase of RAPID are referred to as the 'delayed-start' patients. As presented in Figure 15 of the submission, those patients had change in mean CT lung density of 2.26 g/L/y when receiving placebo, and a change in mean CT lung density of 1.26 g/L/y when receiving Respreeza. These data stratified by no, slow and rapid decline are presented in Table 2 and Table 3.

Table 2. FEV_1 <50%, Treatment Delayed

	3 to 4 years		Total
	No decline	Slow decline	
2 to 3 years	2	11	13
No decline			
Slow decline	1	27	28

	3 to 4 years		Total
	No decline	Slow decline	
Total	3	38	41

Table 3. FEV_1 ≥50%, Treatment Delayed

	3 to 4 years			Total
	No decline	Slow decline	Fast decline	
2 to 3 years **No decline**	6	5	-	11
Slow decline	-	10	-	10
Fast decline	-	1	1	2
Total	6	16	1	23

A6. Please provide sensitivity analysis to assess impact of missing data using total lung capacity (TLC) state alone in the RAPID study (to match results reported in Table 21 of the CS, page 112).

There are three sensitivity analysis performed as stated in the Respreeza submission pg. 73:

- Complete-case analysis (baseline and Month 24)
- Pattern-mixture model with placebo-based pattern imputation
- Worst-case approach

The sensitivity analysis to assess impact of missing data (CSR study 4001, 11.4.1.1.3.) was performed using the primary efficacy model of physiologically Adjusted P15 values at TLC and FRC combined. As stated in the CSR, none of the sensitivity analyses indicated a statistically significant difference between the treatment and placebo group, and so we expect that performing a sensitivity analysis for TLC alone would also provide non-significant differences between these groups.

A7. Please provide the Appendices associated with the Clinical Study Report (CSR). More specifically, as a minimum, please provide Appendix 16.1.9.

The appendices are provided. In more detail we have provided Appendix 16.1.9. and related 4001 CSR appendices in the form of lab certificates.

A8. For RAPID, please provide the following data on the occurrence of pulmonary exacerbations in the ITT population:

a) Number of people experiencing an exacerbation per treatment group;

Table 23 **Rates and proportions of subjects and events with exacerbations (study CE1226_4001)**

	Number (%) of subjects				
Treatment group	**Without exacerbation**	**With ≥1 exacerbation**	**With 1-3 exacerbations**	**With 4-6 exacerbations**	**With >6 exacerbations**
CE1226 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N = number of subjects

b) Total number of exacerbations occurring per treatment group;

	Number (%) of subjects				
Treatment Group	**Reported exacerbations[a]**	**Affected subjects**	**Subject years**	**EAIR**	**Difference in EAIR[b]**
CE1226 (N=93)	[redacted]	[redacted]	[redacted]	1.70	0.28 (p=0.823)
Placebo (N=87)	[redacted]	[redacted]	[redacted]	1.42	

AE = Adverse Event; COPD = Chronic obstructive pulmonary disease; EAIR = exposure adjusted incidence rate; N = number of subjects;

[a] % of all Treatment-emergent adverse events.

[b] 2 sided Mann-Whitney-Wilcoxon test.

One of the inclusion criteria for study 4001 was according to diagnosis of emphysema due to A1PI deficiency which would mean that the average annual exacerbation rate is expected between 1 to 3 exacerbation events per year (Wise, 2014). By this, the EAIRs are well within the expected exacerbation rates.

c) Breakdown of exacerbations in each treatment group by severity, together with a definition of each category of severity (the paper by Anthonisen refers to criteria for treatment with antibiotics);

[redacted]

[redacted]

Table 25 **Rates and proportions of moderate exacerbations (study CE1226_4001)**

Treatment group	Reported moderate exacerbations n (%)[a]	Subjects with reported moderate exacerbations	% subjects reporting moderate exacerbations	Mean number of moderate exacerbations per subject	EAIR	Difference in EAIR [b]
CE1226 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

AE = Adverse Event; COPD = Chronic obstructive pulmonary disease; EAIR = exposure adjusted incidence rate; N = number of subjects;

[a] Percentage of reported exacerbations.

[b] 2- sided Mann-Whitney-Wilcoxon test.

[redacted]

Table 26 **Rates and proportions of severe exacerbations (study CE1226_4001)**

Treatment group	Reported severe exacerbations n (%)[a]	Subjects with reported severe exacerbations	% subjects reporting severe exacerbations	Mean number of severe exacerbations per subject	EAIR	Difference in EAIR [b]
CE1226 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

AE = Adverse Event; COPD = Chronic obstructive pulmonary disease; EAIR = exposure adjusted incidence rate; N = number of subjects;

[a] Percentage of reported exacerbations.

[b] 2-sided Mann-Whitney-Wilcoxon test.

Table 27 **Severe exacerbation rates in the EXACTLE study and study CE1226_4001**

	CE1226_4001		EXACTLE	
	CE1226	Placebo	Prolastin	Placebo
Severe exacerbations	[redacted]	[redacted]	[redacted]	[redacted]
Subjects randomized	[redacted]	[redacted]	[redacted]	[redacted]
Subject years	[redacted]	[redacted]	[redacted]	[redacted]
EAIR	[redacted]	[redacted]	[redacted]	[redacted]

EAIR = exposure adjusted incidence rate; EXACTLE =

[a] Based on the [redacted] of therapy for the Prolastin and placebo groups, respectively.

d) Number of exacerbations in each treatment group requiring oral corticosteroids;

[redacted]

Table 16 **Number of exacerbations and use of antibiotics and oral steroids (study CE1226_4001)**

	CE1226	Placebo
Number of exacerbations	[redacted]	[redacted]
Antibiotic treatments [a]	[redacted]	[redacted]
Oral steroid treatments [a]	[redacted]	[redacted]

[a] Temporal association of event and treatment [redacted], % of number of exacerbations.

e) Number of exacerbations in each treatment group requiring antibiotic treatment;

[redacted]

f) Number of exacerbations in each treatment group requiring hospitalisation;

[redacted]

[redacted]

Table 20 – Duration of exacerbations, duration of hospitalizations due to exacerbations, and duration of antibiotic treatment due to exacerbations (ITT population)

	Mean (SD)	
Analysis	**CE1226**	**Placebo**
	[redacted]	[redacted]
Duration of hospitalizations due to exacerbations, years	[redacted]	[redacted]
Duration of hospitalizations due to exacerbations relative to total study duration, %	[redacted]	[redacted]

N = number of subjects; SD = standard deviation.

g) Duration of hospitalisation of exacerbations in each treatment group.

[redacted]

A9. On page 180 in CS, relating to CT lung density, there is the following statement, "*The baseline characteristics of Respreeza and placebo were slightly different across arms thus the analysis is presented as a regression analysis using baseline covariate adjustment, which accounts for these slight differences*". The CSR for RAPID states that, "*linear random regression model was applied using SAS PROC MIXED, with country, inspiration state, time elapsed since Day 1 (year), treatment, and treatment-by-time interaction (i.e., a regression of Adjusted P15 on time within treatment) as fixed effects and subject and subject-by-time interaction as random coefficients. Thus, the primary efficacy model contained the subjects' individual intercept and individual slope*". Please confirm that the covariates listed in the CSR are included in the regression analysis referred to on page 180 of the CS. If not, please specify the covariates.

That is correct; the covariates listed in the CSR are included in the regression analysis referred to on page 180 of the CS.

A10. For RAPID, please confirm that one person receiving Respreeza and one person receiving placebo underwent lung transplantation.

That is correct.

A11. Please clarify why CT scans were obtained for the upper zone of the lung when emphysema associated with A1PI deficiency typically affects the lower lobes of the lung.

In contrast to typical smoking-induced COPD, emphysema in AATD subjects usually progresses from the basal region to the apices (Campos 2018). Whole lung CT scans are therefore appropriate when assessing an effect to reduce disease progression. CT lung

density assessments in the apical, central and basal regions demonstrated that although the apices were less affected in terms of the lung tissue already lost reflective in the progressively higher baseline lung densities/region (apical>central>basal), the treatment effect to preserve lung tissue was largely the same in each region at TLC: apical region 0.89 g/L/y (p=0.03), central region 0.88 g/L/y (p=0.008), basal region 0.88 g/L/y (p=0.012) (Parr et al., 2018).

A12. Please provide a brief description for the clinical experts' rationale for defining the following categorisations for total decline in lung density:

- **no decline (no change);**
- **slow (0-2g/L/year);**
- **and rapid decline (>2g/L/year).**

The Evidence Review Group could not locate a description of these rates of decline in Stockley 2015. Additionally, there is limited information provided in Green 2014. Please also outline in what way the other thresholds were assessed that were decided to be no more informative (page 161 of the CS).

The categorisation for total decline in lung density was in line with the analysis of patients in the ADAPT UK registry. The threshold at 2 g/L/year was defined by the clinical experts at the UK registry based on a stratification analysis on all available patient data. The 2 g/L/year threshold was deemed by the clinical experts as the most appropriate level by which to define slow and rapid decliners.

Further detail is not available to CSL as the analysis was conducted by the ADAPT UK registry team.

A13. In the CS (page 70), it is stated that, in RAPID, weekly doses of Respreeza were given by a nurse or family doctor (other than those administered at the study centre). It is also stated that, after the first infusion, it is anticipated that Respreeza can be given by a caregiver or by the patient (page 252). However, the economic model assumes that home infusion will be carried out by a district nurse. Please clarify whether the company considers that home administration of Respreeza by a patient or a caregiver is viable. If so, please outline any resources the company envisages would be required to make this possible (e.g., a longline or portacath for the patient).

Theoretically it is possible for Respreeza to be administered at home by the patient, after training and a comprehensive understanding of what the administration consists of. Although this may be achievable and cost saving, we conservatively assume that a nurse will be administering the drug. This conclusion is due to the fact that only 7.9% of the 555 A1PI surveyed patients in the US chose to self-administrator. Additionally, the majority of respondents who had not previously self-administered were not considering starting (90.8%) (Sandhaus and Boyd, 2018).

A14. The CS outlines (page 149) that discontinuation of Respreeza is expected to occur only when a patient receives a lung transplant or if a person dies. Please clarify whether there are any rules for cessation of treatment based on lack of clinical efficacy of Respreeza. If so, please provide details.

According to the mechanism of action, Respreeza is effective by augmentation of the protein that is lacking in patients with severe A1PI deficiency, similar to enzyme replacement therapies in other conditions. The clinical efficacy of Respreeza is not expected to lessen while there is a need to maintain appropriate anti-protease defence with A1PI augmentation.

A15. Please provide step-by-step calculations behind the incidence (95 patients per year) and prevalence (549 patients) estimates presented in Section 13, with supporting references and justification for any assumptions. In particular, please provide a justification for the assumption that screening and case identification will not increase should Respreeza be approved for use in the NHS.

Expert opinion suggests that the incidence of patients eligible for Respreeza would be approximately 0.17 per 100,000 population. This is then multiplied by the population of England of 55,619,400 equating to an English incident eligible population of approximately 95 people per year.

Prevalence estimate is 0.99 per 100,000, which is then multiplied by the population of England of 55,619,400 equating to 549 patients eligible for Respreeza (derived from NIHR (National Institute for Health Research, 2014) and ONS 2014 data (Office for National Statistics, 2015)) and applied to 2016 English ONS population figures (Office for National Statistics, 2017).

A16. Please provide reference details for the 15 studies excluded at assessment of the full publication stage, as outlined in the PRISMA flow diagram (Figure 8 of the CS) relating to the update of the systematic review initially carried out by Edgar 2017.

The relevant intervention considered in this submission is only A1PI so results of studies of COPD medical (N=12) and surgical (N=3) management found by Edgar et al, and in the update SLR, are not considered.

Table 4. References of studies excluded at assessment of the full publication stage, as outlined in the PRISMA flow diagram

Study	Reason for Exclusion
1. Barker, A., Campos, M., Brantly, M., Stocks, J., Sandhaus, R., Lee, D., Steinmann, K., Lin, J. and Sorrells, S. (2017). Bioequivalence of a Liquid Formulation of Alpha1-Proteinase Inhibitor Compared with Prolastin®-C (Lyophilized Alpha1-PI) in Alpha1-Antitrypsin Deficiency. COPD: Journal of Chronic Obstructive Pulmonary Disease, 14(6), pp.590-596.	Not Including outcome of interest
2. Barker, A., Campos, M., Brantley, M., Stocks, J., Sandhaus, R., Lee, D., Steinmann, K., Lin, J. and Sorrells, S. (2018). Comparability of a Liquid Formulation of Alpha1-Proteinase Inhibitor to Prolastin-C®: A Double-Blind, Randomized, Crossover Pharmacokinetic and Safety Study in Alpha1-Antitrypsin Deficiency. American Journal of Respiratory and Critical Care Medicine, 195, p.A7387.	Abstract reported elsewhere
3. Kirst, M., Nolte, J., Lascano, J., Rouhani, F. and Brantly, M. (2017). Effect of Short-Term Alpha-1 Antitrypsin Augmentation Therapy on the Lung Microbiota of Individuals with Alpha-1 Antitrypsin Deficiency. American Journal of Respiratory and Critical Care Medicine, 195, p.A2949.	Not Including outcome of interest
4. Choate, R., Mannino, D., Holm, K. and Sandhaus, R. (2017). Multicomponent Intervention Improves BMI in a Randomized Trial of Alpha-1 Antitrypsin Deficient Patients. American Journal of Respiratory and Critical Care Medicine, 195(A7389).	Not Including outcome of interest
5. Dasi, F., Pastor, S., Reula, A., Castillo, S. and Escribano, A. (2018). Augmentation Therapy Increases Hydrogen Peroxide Accumulation in Peripheral Blood Mononuclear Cells of ZZ Alpha-1 Antitrypsin Deficiency Patients. American Journal of Respiratory and Critical Care Medicine, 195, p.A6337.	Not Including outcome of interest
6. Chlumsky et al., (2017) Augmentation therapy for emphysema due to alpha-1 antitrypsin deficiency	Not study type of interest
7. Stone, H., Edgar, R., Thompson, R. and Stockley, R. (2015). Lung Transplantation in Alpha-1-Antitrypsin Deficiency. COPD: Journal of Chronic Obstructive Pulmonary Disease, 13(Prepared by the PSSAG Secretariat), pp.146-152.	Abstract reported elsewhere

8. McElvaney, N., Chapman, K., Burdon, J., Piitulainen, E., Seersholm, N., Stocks, J., Sandhaus, R., Vit, O., Fries, M. and Edelman, J. (2015). LATE-BREAKING ABSTRACT: Long-term efficacy of A1-PI therapy in RAPID and RAPID extension trials. 5.1 Airway Pharmacology and Treatment.	Abstract reported elsewhere
9. Torres Redondo, M., Campoa, E., Saganha, S. and Sucena, M. (2015). Health-related quality of life in patients with alpha-1 antitrypsin deficiency. 1.13 Clinical Problems - Other.	Not Including outcome of interest
10. Ochieng, P., Geraghty, P., Eden, E., Campos, M. and Foronjy, R. (2015). Alpha-1 antitrypsin protects protein phospholipid transfer protein from cleavage to counter lung inflammatory responses. 3.3 Mechanisms of Lung Injury and Repair.	Not Including outcome of interest
11. Esquinas, C., Serreri, S., Barrecheguren, M., Lara, B., Rodriguez, E., Pirina, P., Blanco, I. and Miravitlles, M. (2015). Long-term evolution of individuals with alpha1 antitrypsin deficiency from the Spanish registry. 1.13 Clinical Problems - Other.	Not Including outcome of interest
12. Lara, B. and Miravitlles, M. (2015). Spanish Registry of Patients With Alpha-1 Antitrypsin Deficiency; Comparison of the Characteristics of PISZ and PIZZ Individuals. COPD: Journal of Chronic Obstructive Pulmonary Disease, 12(sup1), pp.27-31.	Not population of interest
13. Luisetti, M., Ferrarotti, I., Corda, L., Ottaviani, S., Gatta, N., Tinelli, C., Bruletti, G., Bertella, E., Balestroni, G., Confalonieri, M., Seebacher, C., Iannacci, L., Ferrari, S., Salerno, F., Mariani, F., Carone, M. and Balbi, B. (2015). Italian Registry of Patients with Alpha-1 Antitrypsin Deficiency: General Data and Quality of Life Evaluation. COPD: Journal of Chronic Obstructive Pulmonary Disease, 12(sup1), pp.52-57.	Not population of interest
14. Gulack, B., Mulvihill, M., Ganapathi, A., Speicher, P., Chery, G., Snyder, L., Davis, R. and Hartwig, M. (2017). Survival after lung transplantation in recipients with alpha-1-antitrypsin deficiency compared to other forms of chronic obstructive pulmonary disease: a national cohort study. Transplant International, 31(1), pp.45-55.	Abstract reported elsewhere
15. Inci, I., Schuurmans, M., Ehrsam, J., Schneiter, D., Hillinger, S., Jungraithmayr, W., Benden, C. and Weder, W. (2015). Lung transplantation for emphysema: impact of age on short- and long-term survival. European Journal of Cardio-Thoracic Surgery, 48(6), pp.906-909.	Not Including outcome of interest

A17. Please specify reference details for the 12 studies identified as relevant to the review at assessment of papers at the full publication stage, as outlined in the PRISMA flow diagram (Figure 8 of the CS) relating to the update of the systematic review initially carried out by Edgar 2017.

Table 5. References of the 12 studies as outlined in the PRISMA diagram

1. Campos, M., Runken, M., Davis, A., Johnson, M., Stone, G. and Buikema, A. (2018). Impact of a Health Management Program on Healthcare Outcomes among Patients on Augmentation Therapy for Alpha 1-Antitrypsin Deficiency: An Insurance Claims Analysis. Advances in Therapy, 35(4), pp.467-481.
2. Gulack, B., Ganapathi, A., Speicher, P., Chery, G., Snyder, L., Davis, R. and Hartwig, M. (2015). Survival After Lung Transplant in Alpha-1-Antitrypsin Deficiency Recipients Compared to Other Forms of Chronic Obstructive Pulmonary Disease. The Journal of Heart and Lung Transplantation, 34(4), pp.S243-S244.
3. Ekström, M. and Tanash, H. (2017). Lung transplantation and survival outcomes in patients with oxygen-dependent COPD with regard to their alpha-1 antitrypsin deficiency status. International Journal of Chronic Obstructive Pulmonary Disease, Volume 12, pp.3281-3287.
4. Choate, R., Mannino, D., Sandhaus, R. and Holm, K. (2017). Factors Associated with FEV1 Decline in Alpha-1 Antitrypsin Deficient Patients. American Journal of Respiratory and Critical Care Medicine, 195, p.A7391.
5. Wewers, M. (2017). A Re-Analysis of FEV1 Decline and Augmentation Effects Using Stricter Slope Measurements from the NIH Alpha 1-Antitrypsin Deficiency Registry Study. American Journal of Respiratory and Critical Care Medicine, 195, p.A7394.
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7. Brantley, M., Stocks, J., Rouhani, F., Lascano, J., Jeffers, A., Nolte, J., Owens, S., Tucker, T. and Tov, N. (2017). Inhaled Alpha-1-Antitrypsin Restores Lower Respiratory Tract Protease-Anti-Protease Homeostasis and Reduces Inflammation in Alpha-1 Antitrypsin Deficient Individuals: A Phase 2 Clinical Study Using Inhaled Kamada-API. American Journal of Respiratory and Critical Care Medicine, 195(A7677).
8. McElvaney, N., Burdon, J., Holmes, M., Glanville, A., Wark, P., Thompson, P., Hernandez, P., Chlumsky, J., Teschler, H., Ficker, J., Seersholm, N., Altraja, A., Mäkitaro, R., Chorostowska-Wynimko, J., Sanak, M., Stoicescu, P., Piitulainen, E., Vit, O., Wencker, M., Tortorici, M., Fries, M., Edelman, J. and Chapman, K. (2017). Long-term efficacy and safety of α1 proteinase inhibitor treatment for emphysema caused by severe α1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE). The Lancet Respiratory Medicine, 5(1), pp.51-60.
9. Spratt, J., Brown, R., Rudser, K., Goswami, U., Patil, J., Cich, I., Shumway, S., Hertz, M. and Loor, G. (2016). Outcomes in Lung Transplant Recipients with COPD with and without Alpha-1-Antitrypsin Deficiency: Single Center Experience Over Four Decades. The Journal of Heart and Lung Transplantation, 35(4), p.S312.
10. Stone, H., Edgar, R., Thompson, R. and Stockley, R. (2015). Lung Transplantation in Alpha-1-Antitrypsin Deficiency. COPD: Journal of Chronic Obstructive Pulmonary Disease, 13(Prepared by the PSSAG Secretariat), pp.146-152.
11. Chapman, K., Burdon, J., Piitulainen, E., Sandhaus, R., Seersholm, N., Stocks, J., Stoel, B., Huang, L., Yao, Z., Edelman, J. and McElvaney, N. (2015). Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. The Lancet, 386(9991), pp.360-368.
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Section B: Clarification on cost-effectiveness data

Revisions to the economic model

The ERG have identified concerns about the suitability of the model for decision-making purposes. These concerns centre on:

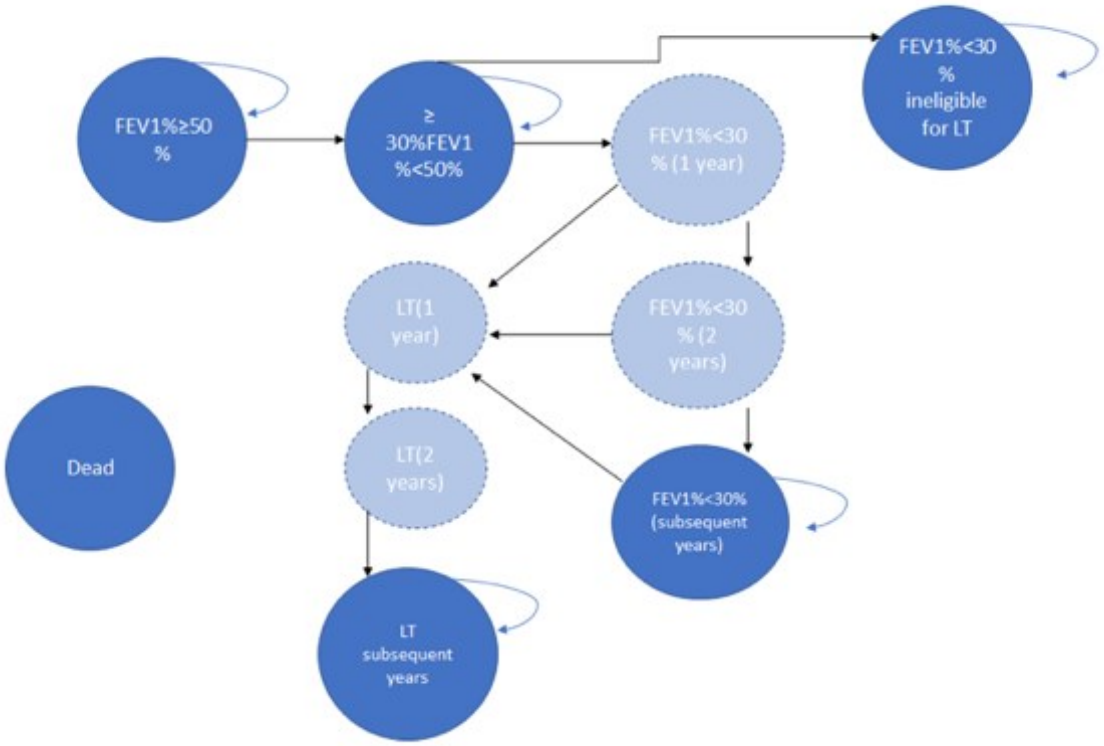
- **the incorporation of lung density as a measure to model disease progression and severity;**
- **the threshold of FEV_1% cut-offs for lung transplants; and**
- **the exclusion of important aspects related to lung transplantation.**

Therefore, the ERG request that the following revisions are made to the economic model:

B1. Priority question: Please restructure the base case economic model so that it includes the health states shown in the figure below. The ERG proposes that patients start the model in the FEV_1%<30% predicted; ≥30% FEV_1%<50% predicted; or FEV_1%≥50% health states, according to the baseline distribution of RAPID patients according to their initial FEV_1% status. Once patients reach the FEV_1%<30% predicted health state, a proportion will be eligible for lung transplant (McElvaney et al.). Patients eligible for a LT will have a different probably of receiving a LT once they are on the waiting list for a transplant (according to the NHS Blood and Transplant 2017 report) depending if they have been on the list for one, two or three years. Tunnel states for FEV_1%<30% should be implemented to capture this. Once patients move to the LT health state, they will have different probabilities of dying (according to the NHS Blood and Transplant 2017 report), depending on how much time elapses since surgery. LT tunnel states should capture this. Patients can die at any point in the model. In order to derive the necessary clinical data for the model, please:

   a) Use the Stockley et al. 2014 to estimate the transitions between FEV_1% states for the BSC arm of the economic model (please see question B2);
   b) Use the Chapman 2009 meta-analysis update requested in question A2 to estimate treatment effectiveness of augmentation therapy on FEV_1% decline (please see question B3);
   c) Use Green et al. 2014 to estimate the transition between the FEV_1% health states and the death state in the model (please see question B4);
   d) Please conduct a search to inform the percentage of patients with an FEV_1%<30% who are ineligible for a LT due to co-morbidities. Please note that the model structure below assumes that once patients move to the FEV_1%<30%, 100% of these patients are put on the transplant waiting list (alternatively, patients can move to the FEV_1%<30% ineligible for LT, where they will not get a LT);
   e) Use the NHS Blood and Transplant 2017 report to estimate the probability of death after LT (please see question B7);
   f) Use the NHS Blood and Transplant 2017 report to estimate the probability of receiving a LT once a patient is on the waiting list (please see question B8).

Figure 1. Proposed model structure from the ERG



The model structure proposed by the ERG is to remove CT-lung density as an outcome and instead structure the model only on the basis of FEV_1 as a clinical marker of progression. The proposed model structure suggest that the ERG has not fully appreciated why typical model structures for COPD are not appropriate for modelling A1PI deficiency. The justification for the use of CT-measured lung density being the primary outcome in Respreeza is detailed on pages 63-64 and 120-131 of the submission. A summary of this in the context of the model is provided here.

Taking into account the pathophysiology of the disease, emphysema is one of several conditions that are collectively known as COPD. COPD is defined by an airflow obstruction which interferes with normal breathing and is not fully reversible, whereas emphysema is characterised by a shortness of breath due to alveolar damage. In A1P1 deficiency, augmentation therapy prevents the destruction of alveolar surface tissue by binding to neutrophil elastase and inactivating its ability to degrade elastase. Destruction of parenchymal alveolar surface tissue is not detectable with FEV_1.

CT lung density has proved to be the most sensitive measurement in assessing disease progression in patients with A1PI deficiency over periods of 2-3.5 years. Lung density analyses first exclude the trachea and large bronchi prior to assessment, and the PD15 methodology effectively limits the lung density assessment to the 15% of voxels in the histogram which have lower density values reflective of lung tissue affected by emphysema. CT lung density preservation in the absence of an effect on FEV_1 establishes the ability of augmentation therapy to preserve alveolar tissue, which is why we focus on this in our submission and cost effectiveness model.

Regarding mean FEV_1 predicted results, we acknowledge that FEV_1 is an appropriate measurement to classify the severity of pulmonary dysfunction following decades of disease progression; however it is of limited use when assessing treatment response within much shorter intervals, e.g. less than 5 years, due to the fact that structural changes can only be expected to occur over extended periods of time in patients with A1PI deficiency.

The applicability and superiority of CT lung density compared to FEV_1 as the suitable parameter to monitor disease progression in A1PI deficiency has also been supported and justified by recently published reviews in high impact factor journals.

As stated in the submission pg. 135: *"The most recently updated treatment guidelines (ERS guidelines) confirm that CT densitometry has been established as the most specific and sensitive surrogate end-point for the evaluation of therapeutic benefit of augmentation therapy. Implementation of CT lung density as the primary endpoint has facilitated the collection of relevant research data in less time than trials which would necessarily attempt to recruit more than 1,100 patients into a 3-year placebo-controlled study where these trials powered to detect an FEV_1 signal. The ERS guidelines specifically cite the BPAC 2009 outcomes to establish CT lung density as a clinically meaningful endpoint and promote its use as a primary end-point in phase 4 studies (Miravitlles et al., 2017)."*

In January 2018, Chapman et al., 2018 published a review, mentioning that previous clinical studies failed to demonstrate the effect of fast lung density decline and preservation of functional lung tissue due to inadequate trial design or the use of less-sensitive clinical endpoints, such as lung function/spirometry (e.g. FEV_1). Chapman also mentions that FEV_1 is considered an inappropriate outcome measure in A1PI as FEV_1 has been shown to change slowly over time and is subject to a considerable degree of inter- and intra-patient variability. Intra-patient variability can be attributed to technical factors, such as instrument performance, as well as observer and subject procedural errors. Additionally, intra-patient factors, such as the extent of airway obstruction, changes in bronchial tone and diurnal variations in FEV_1, can contribute to further variability.

In May 2018, (Campos and Diaz, 2018) published a more recent review describing the use of CT in the evaluation of lung disease in AATD, which emphasises the fact that pulmonary function tests are unable to discriminate emphysema from airways disease, the two hallmark pathologic features of COPD (as presented by Coxson, 2014. For this reason, in recent years tools such as CT scanning have been used to further characterize the lung structure and evaluate the impact of therapeutic interventions in AATD-related COPD.

Campos et al. also highlights that CT lung densitometry is more sensitive than other measurements of emphysema progression, and that the changes in CT lung density are related to changes in lung function, providing the foundation to use this imaging tool as an endpoint for therapeutic interventions in AATD. As COPD progresses slowly with high variability in FEV_1 decline, detecting a significant decline in FEV1 would require the enrolment of hundreds to thousands of patients in a clinical trial and several years of follow-up (as presented by Schluchter, 2000. Campos et al concludes that instead of FEV_1, investigators have used CT measures of emphysema as an endpoint in AATD clinical trials with relatively smaller sample sizes and shorter follow-up times.

For the reasons outlined above, CT-measured lung density is an important outcome to be captured in the economic model. The primary endpoint of RAPID study, the pivotal trial for

Respreeza, was CT-measured lung density, which was found to decline significantly lower with Respreeza than placebo. There were no observed treatment effects on FEV_1 within the 2-year period, as would be expected for the reasons outlined above. For that reason, a model structured only on the basis of only FEV_1 would not be suitable for decision making. Consequently, we have no removed CT-measured lung density as an outcome from the model.

However, we appreciate the ERGs concerns around the health states not adequately capturing the disease status at eligibility for lung transplant. Therefore, we have updated the model structure to include three categories of FEV_1 , rather than two categories as in the original submission. The inclusion of a health state specifically for patients with an FEV_1<30% predicted enables a more accurate representation of when patients are eligible for a lung transplant. However, it should be noted that in the originally submitted analysis, the probability of receiving a lung transplant from the FEV_1<50% was already accounting for only a small percentage of the cohort transferring to the lung transplant state.

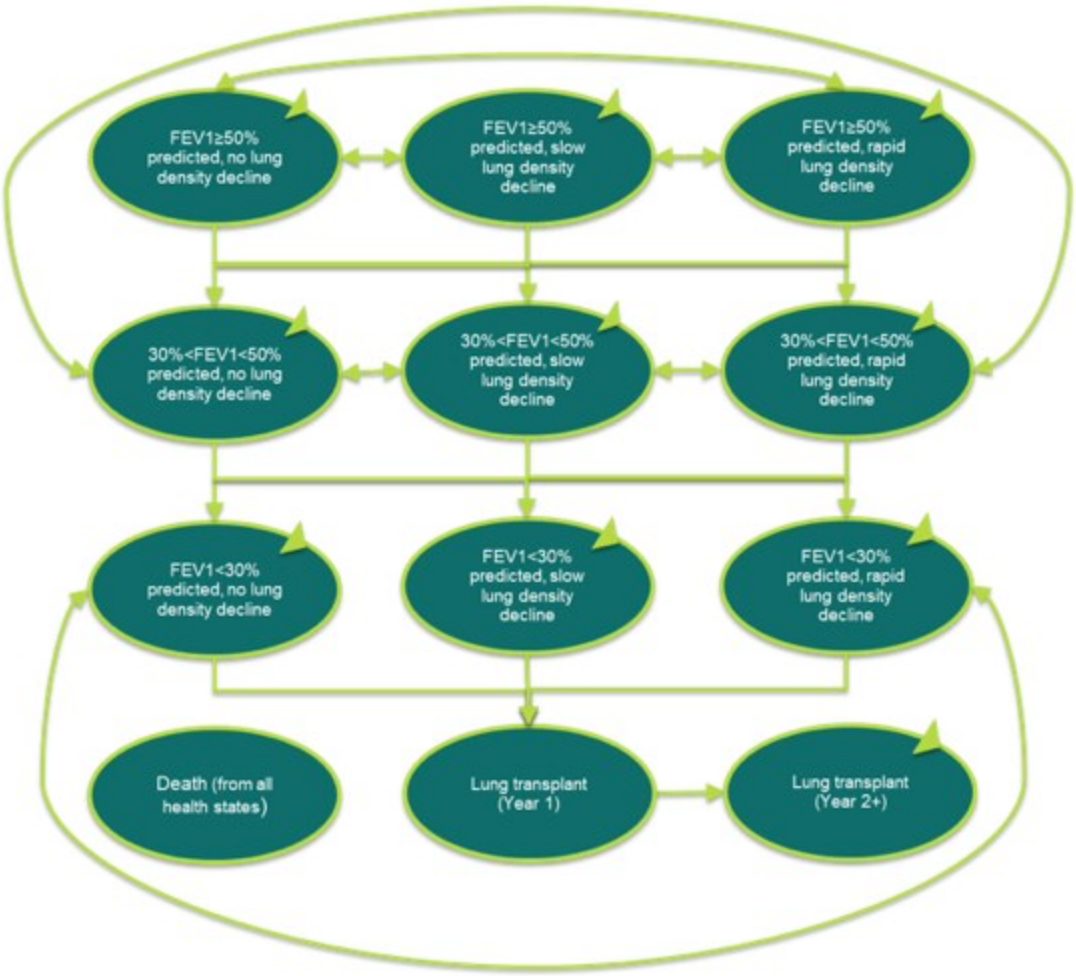
The ERGs proposed use of tunnel states for tracking patients on the waiting list and then following lung transplant would appear to be appropriate. However, practically this has not been implemented for two reasons:

1. The ERGs proposed model structure only had one state for FEV_1<30%. The updated model structure has three states for FEV_1<30% (no, slow and rapid decline). Therefore, a higher number of tunnel states would be required which would make the model computationally complex.

2. No data could be sought to provide transition probabilities for the proposed tunnel states. The NHS Blood and Transplant 2017 report provides some data to estimate some of these probabilities, but they are not specific to patients with A1PI deficiency. A literature search was undertaken but no studies have indicated what percentage of patients are ineligible for a lung transplant due to co-morbidities.

The revised model structure is illustrated in Figure 1.

Figure 1. Revised model structure



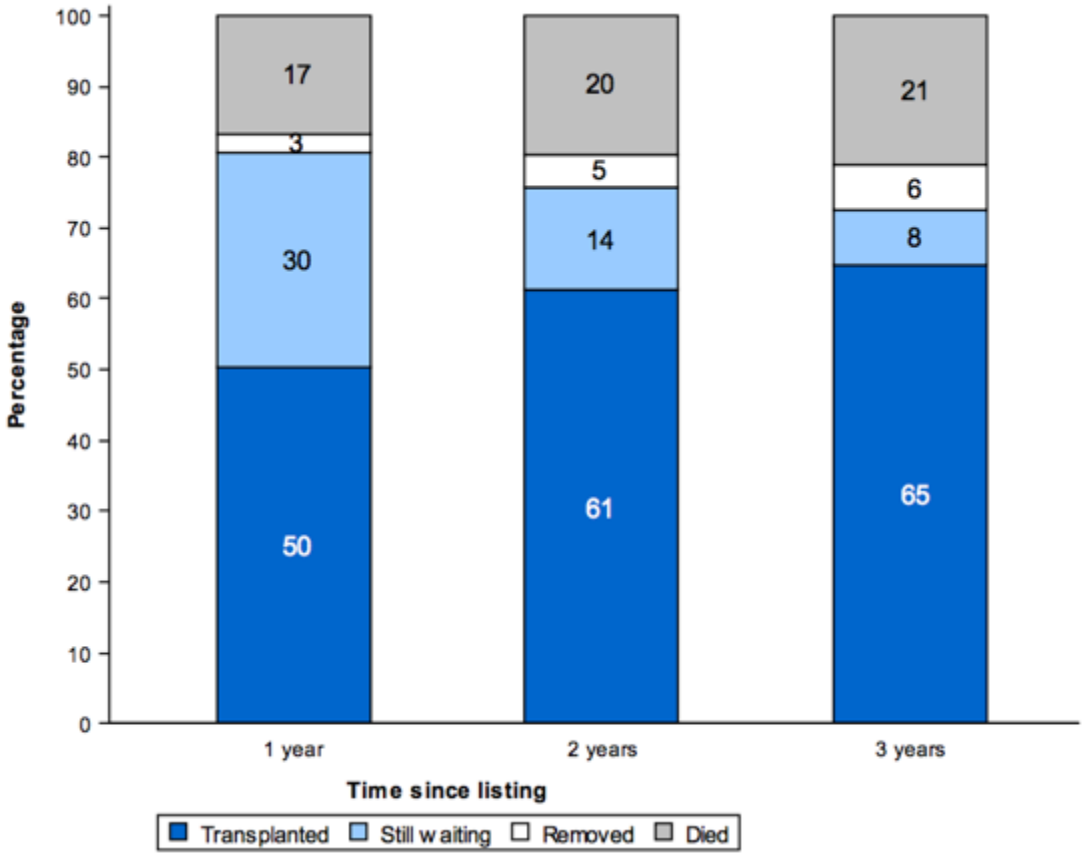
It was not possible to identify data indicating what proportion of patients with an FEV_1<30% would be ineligible for a lung transplant. The only factor which could be applied in the model was the restriction that patients should not receive a transplant over the age of 65 years. This was implemented in the original model. In addition, in the original model, only patients with slow or rapid decline as well as an FEV_1<50% were eligible for a transplant. Under the revised structure, all patients with an FEV_1<30% are considered eligible, regardless of rate of lung density decline.

The probability of receiving a transplant is highest within the year that a patient is listed, the probability declines in the second and third years (Figure 2). However, some patients die and some are withdrawn from the list (with reasons unknown). Therefore, it was assumed that patients have an equal probability of receiving a transplant regardless of how long they have been in the FEV_1<30% state. After 3 years on the waiting list, 65 of 79 patients would have received a transplant, equating to an annual probability of 43.8%.

Since this annual probability is lower that the 60% transplanted in the first year (Figure 2), then the model effectively assumes an increased risk of death since the probability of death is greater for patients with an FEV_1<30% than patients that have received a transplant. Given

Respreeza is expected to increase the proportion of patients that could receive a transplant, then assuming an equal probability in each year may be considered a conservative assumption.

Figure 2. Outcome of patients listed for lung transplantation in the UK



In the NHS Blood and Transplant 2017 report, of the 416 patients that received a transplant between 2009 and 2011, survival at one year was 82% (95% CI 78%-86%), survival at two years was 74% (95% CI 69%-78%) and survival at five years was 59% (54%-64%). The survival in year one equates to an annual probability of death of 16.47% in Year 1. The probability of death between one and two years equates to a probability of 9.8%. The probability of death between three and five years equates to an annual probability of 7.3%. Given the probability of death in the second year following a lung transplant was similar to the annualised probability of death between years 3 and 5, to reduce the number of health states, all patients entered one health state in the second year following a lung transplant. The annualised probability of death after year one equates to 7.9%.

This use of data from all lung transplantations, rather than those with A1PI deficiency can be justified since recent analysis has indicated that UK survival after lung transplant is similar for A1PI deficiency and COPD patients (Gulack et al., 2018). Based on an analysis of the Freeman Hospital in Newcastle, COPD patients make up about one third of the patients transplanted, then one third is idiopathic pulmonary fibrosis (IPF) and a quarter are cystic fibrosis (CF) patients (Fisher et al., 2017). The same analysis indicated that patients with IPF have the lowest median survival and patients with CF have the highest median survival; patients with COPD and A1PI deficiency have median survival between IPF and CF patients.

Therefore, the median survival across all transplants is similar to the survival of A1PI deficiency patients.

B2. Priority question: Please estimate the annual FEV1% decline between the FEV1%≥50%; ≥30%FEV1%<50%; and FEV1%<30% health states using the 1.45% annual decline (Stockley et al. 2014) as in the original model. Please take the average baseline FEV1% in each category from RAPID and estimate the number of years it will take to cross the threshold of the following FEV1% category. For example, given that the average FEV1% at baseline for the FEV1%≥50% group in RAPID is 59.76%, then at an average annual decline of 1.45%, it would take 6 years to move to the ≥30%FEV1%<50% category in the BSC arm of the economic model.

This has been implemented in the revised model structure. Using this analysis, it takes 6.7 years to move from the FEV1%>50% state to the ≥30%FEV1%<50% state in the BSC arm, and 6.6 years to move from the ≥30%FEV1%<50% state to the FEV1%<30% state.

a) Please explain why the percentage of patients with different rates of FEV1% decline in Stockley et al. 2014 does not add up to 100% of the patients in the study.

CSL Behring are not authors of this abstract so cannot answer this question. We had adjusted for this in our calculation (see Clinical Data sheet of model, cells D90:D93).

B3. Priority question: Please use the updated Chapman 2009 meta-analysis requested in question A2 to estimate the reduction in FEV1% decline for patients with augmentation therapy, per FEV1% category. As the categories in Chapman et al. 2009 do not match the updated model categories, please use the ones provided as proxies. More specifically, in the Chapman et al. 2009 paper this would be the equivalent of taking the slope difference of 1.8 mL/y for the FEV1%<30% predicted; the 17.9 mL/Y for the ≥30%FEV1%<50% predicted; and the 3.5mL/y in the FEV1%≥50%. Please convert the slope difference into the equivalent annual reduction in FEV1% decline for Respreeza (compared to BSC) by assuming the same relationship between annual FEV1% decline and mls/y in the Stockley et al. 2014 paper (please see Excel sheet attached).

The meta-analysis is conducted in three FEV1 subgroups: FEV1>65%, FEV1 30-65% and FEV1<30%. The derived treatment effects in the 30%<FEV1<65% group are used as a proxy for the time to transition from the FEV1>50% to the FEV1 30-50% health states. The derived treatment effects in the FEV1 <30% group are used as a proxy for the time to transition to the FEV1 <30% health states.

Using the updated meta-analysis, the difference in decline in the 30%<FEV1<65% group was 18.9 mL/y for A1PI versus the control. Utilising the ERG's preferred method of applying this difference, this equates to a relative risk compared to placebo of 64%. The difference in

decline in the FEV1<30% group was 1.28 mL/y, equating to a relative risk for A1PI of 98%. The probabilities of transitioning between FEV1 states are detailed in Table 1.

Table 1. Probabilities of transitioning between FEV1 states using updated meta-analysis

	Annual probability of transition: placebo	Difference in slope (ml/y)	Relative risk of transition with A1PI therapy	Annual probability of transition: Respreeza
30%<FEV1<50%	14.82%	18.9	63.72%	9.44%
FEV1<30%	15.07%	1.28	97.54%	14.70%

B4. Priority question: Please re-run the Green et al. 2014 analysis to obtain survival curves for the different FEV1% categories, without differentiating survival by lung density decline by CT. More specifically, please re-estimate the curves presented in Figure 29 of the company submission by the FEV1% categories provided (i.e., evaluate the fit of loglogistic, lognormal, exponential, Gompertz, Weibull and gamma) for all patients in each FEV1% category (i.e. one survival curve per FEV1% health state in the model). Please use the estimated curves from cycle 0 in the model, to estimate survival.

a) If the company has access to the more up-to-date survival data are available, as referenced during the decision problem meeting with NICE, please use this updated survival data in the model accordingly.

This question is no longer relevant given CT-measured lung density has not been removed from the model. However, a scenario analysis has been provided using the UK registry survival curves from cycle 0, rather than utilising the mortality data from the RAPID study and extension.

CSL Behring does not have access to data from the ADAPT UK registry. The data used to estimate survival in the model was obtained from a copy of a draft manuscript that was provided to CSL by the UK registry team.

B5. Priority question: Please assess the goodness of fit (AIC; BIC; visual inspection and clinical plausibility) of the loglogistic, lognormal, exponential, Gompertz, Weibull and gamma distributions for each survival curve for the respective FEV1% category mentioned in question B4. Please use this assessment to choose the appropriate distribution for each FEV1% survival curve, instead of assuming that the Weibull distribution can be used for all curves.

The model has been adapted such that the best fitting curves for each survival curve have been used, rather than assuming using the Weibull curve for all survival curves. Based on the AIC values reported in Table 33 of the submission, a Gompertz function was used for

FEV1>50%, a Weibull function was used for patients with an FEV1<50% with no decline in lung density, and a Gompertz function was used for the two remaining health states.

B6. Priority question: Please include an option in the economic model (by means of a drop-down menu) so that the user can choose between the different distributions (i.e. loglogistic, lognormal, exponential, Gompertz, Weibull and gamma) to model survival, for the different health states in the model (i.e., FEV1%≥50%;≥30%FEV1%<50%; and FEV1%<30% health states).

This has been implemented; please see response to question B5.

B7. Priority question: Please use the estimates provided in the NHS Blood and Transplant 2017 report (page 106, table 11.21) to calculate the percentage of patients dying after LT in year 1; year 2 and subsequent years.

This has been implemented; please see response to B1.

B8. Priority question: Please use the estimates provided in the NHS Blood and Transplant 2017 report (page 67, Figure 7.5) to calculate the percentage of patients receiving a LT, after having been enrolled on the transplantation list.

This has not been implemented; please see response to B1.

Resource and cost use

B9. Priority question: The ERG is concerned the rate of exacerbations used by Punekar 2014 differs from the rate observed in RAPID for each treatment arm.

- **a) Please use the disease management costs from Punekar 2014 excluding the exacerbation-related costs. More specifically, please replace the disease management costs taken from Table 4 according to exacerbation frequency from "All patients" to "None";**
- **b) Please include the rate and duration of exacerbations requiring oral steroids, antibiotics or hospitalisation by treatment arm in RAPID in the model, applying appropriate costs and benefits. Please ensure any utility decrements are not double counted as Ejiofor and Stockley 2015 may have included a proportion of patients who experienced exacerbations;**
- **c) Apply the disease management costs for GOLD stages 2, 3 and 4 from Table 4 of Punekar 2014 to the health states relating to an FEV_1% >50%, 30-49% and <30%, respectively. As above, use disease management costs for patients with no exacerbations.**

The annual number of exacerbations in the RAPID study was between 1.4 and 1.7 across the two treatment arms. In 58,589 patients with COPD, the total number of moderate or severe

exacerbations in the Punekar 2014 study was 44,293 over a 12-month period, equating to an average annual number of exacerbations of 0.76. We agree that using the average costs from (Punekar et al., 2014) of COPD patients is likely to be underestimating the costs of managing patients with severe A1PI enrolled in the RAPID study.

Given that treatment with A1PI has not been shown to reduce exacerbations in clinical trials, modelling the costs associated with exacerbations as a specific outcome is not expected to add significant value to the model. Also, exacerbations are associated with quality of life decrements which are not being specifically modelled but will likely be incorporated within the utility estimates used as they are from severe A1PI patients in the UK registry. The exacerbation rate of the patients in the ADAPT UK registry is unknown.

The disease management costs within the updated model are based on a weighted average of patients with one, two or more exacerbations within (Punekar et al., 2014) to try to reflect an average exacerbation rate of approximately 1.4 - 1.7. As requested, the FEV1>50% state is based on a Gold Stage 2, the 30%<FEV1<50% state is based on a Gold Stage 3, and the FEV1<30% state is based on a Gold Stage 4. The corresponding annual inflated costs are £3,063 for FEV1>50%, £3,227 for 30%<FEV1<50% and £3,538 for FEV1<30%.

B10. Priority question: Clinical experts advised the ERG that a change in CT density using at least two CT scans over one year would be needed to assess eligibility for Respreeza. In the updated base case analysis, please include the cost of two CT scans to assess eligibility in the first cycle of the model (cycle 0) for Respreeza. Please consider adding any additional costs related with routinely running CT scans in specialised centre, for example, acquiring the software program required for reading densitometry, staff training, phantom scans, etc.

CT-measured lung density is sometimes already measured in UK patients that are in the UK ADAPT registry (Green et al., 2014b), but not at all centres. The licensed indication for Respreeza does not require CT scans to initiate treatment. The proposed treatment initiation criteria for Respreeza is patients who either have a declining lung density measured by CT (if measured at centres), or declining lung function which is measured using more common tests such as FEV1 and DLco.

CT scans are expected to cost £71, £85 or £100, depending on the use of contrast, in the 2017/18 National tariff [RD20A / RD21A / RD22Z]. Two scans for initiating treatment would add between £142 and £200 to the incremental costs associated with Respreeza.

B11. Priority question: Based on your response to question A14, please include the costs to assess the rules for treatment cessation in the updated base case analysis. Also, if treatment cessation occurs, please reflect this in the economic model by applying appropriate treatment effects, costs and benefits.

Not applicable; no stopping rules have been proposed.

B12. Priority question: Clinical experts advised the ERG that in order to document progressive decline, the way patients are monitored may need to change. Please include the cost of annual CT scans for patients receiving Respreeza as a scenario analysis.

Please see the response to B10; it has not been proposed that CT scans are necessary for initiating or monitoring treatment, as other lung function measures can be used in the centres that are not already using CT-measured lung density. However, as a scenario analysis, patients receiving Respreeza incur the cost of an annual CT scan, costing an average of £85.

B13. Priority question: Clinical experts advised the ERG that patients receiving high cost drugs such as Respreeza, or patients with a rare condition such as A1PI deficiency, may require additional disease management by respiratory clinics in secondary care, or expert tertiary clinics. Please justify the assumption that disease management consists of primary care alone (Punekar 2014) and is equivalent for patients receiving BSC and Respreeza.

We agree that patients with A1PI deficiency would be managed in secondary care due to the complexity of their condition. Since costs associated with the management of A1PI deficiency patients was not available, the costs from Punekar et al were used as a proxy. Given patients with A1PI deficiency would be managed in secondary care regardless of whether or not they receive Respreeza, the disease management costs are not expected to be significantly different between treatment options and therefore do not drive results.

However, to better reflect that patients would be managed in secondary care, the costs of consultant led secondary appointments has been included in the revised model. The cost of a consultant-led outpatient appointment in secondary care has been estimated as £149 from NHS reference costs 2015-16 [WF01A and WF02A, non-admitted face to face, service code 340 and 341]. It is assumed that patients with an FEV1>50% would see an A1PI clinical specialist twice per year, patients with a 30%<FEV1<50% would see a specialist three times per year, whilst a patient with an FEV1<30% would see a specialist four times per year.

B14. Priority question: Page 198 of the CS states that, "*Respreeza will be initiated within the current context of care, by specialists experienced in the management of A1PI deficiency at existing facilities*." In the updated base case analysis, please cost the first drug administration using the cost associated with a specialist clinic.

This has been implemented in response to B13.

B15. Priority question: Please clarify why the costs of assessment for lung transplant are only applied to patients who receive a lung transplant, rather than everyone who is eligible. Please provide a scenario analysis where all eligible patients incur the costs of lung transplant assessment.

The costs of transplant in the first year sourced from Anyanwu et al. (2002) includes assessment costs. The costs of assessing for eligibility for a transplant are not explicitly modelled, so this requested change has not been implemented. Furthermore, in the updated model structure it was not possible to identify those that are eligible or ineligible for a lung transplant.

B16. In the model, lung transplant costs in the first year and subsequent years are informed by a double transplant alone (Costs B37:38), rather than the weighted cost of single and double lung transplant costs, as reported in the submission. Please address this issue in the model.

This has been corrected.

B17. Please clarify why the cost of a specialist clinic per administration was informed by the cost of Other Specialist Nursing (N29AF) rather than the cost of a consultant or non-consultant led service related to respiratory medicine (service code, 340; currency code, WF01A:WF02C).

As infusions would be regular, it would be appropriate to conduct them at a local hospital or infusion clinic, rather than the patient travelling to a specialist A1PI deficiency clinic. Supervision by a clinical expert would not be needed; only a nurse specialising the infusion of medicines.

B18. Please justify the assumption that 75% of Respreeza infusions will be administered at home (Table 51 of the CS, page 199).

We assumed that most patients would likely receive infusions in a home setting for convenience, but we also accounted for patients who would want to receive treatment at the hospital.

B19. Please clarify how Punekar 2014 was identified and chosen to inform the economic model.

Since costs could not be found for A1PI deficiency, COPD costs were used as a proxy. A search was conducted to identify a well-conducted large recent analysis of the costs of COPD.

B20. Please justify why non-COPD hospitalisations from Punekar 2014 are included in the costs of disease management.

The Punekar study identifies the total cost of patients with COPD, so all costs were used to represent patients with A1PI deficiency.

Health-related quality of life

B21. Priority question: Please provide data extractions for the 13 studies included in the quality of life search, plus any additional studies used to inform utility data in the model. Examples of data extraction forms can be found in NICE DSU (Technical Support Document 9): http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD9-HSUV-values_FINAL.pdf

The 13 studies included in the review are summarised in section 10.1.6 of the submission. None of the studies provided data that could be utilised for the model and so a detailed data extraction was not conducted.

B22. Priority question: In the decision problem pro-forma for this submission, it was noted that evidence from an EU study including EQ-5D data was likely to become available during the evaluation. If these data are available and are appropriate to inform the model, please provide a data extraction (as requested above) and perform a scenario using the utility data for the updated economic model.

Unfortunately, the EU study has been delayed and as such the data is no longer anticipated within the timing of the NICE process.

B23. Priority question: Please consider using the Anyanwu 2002 and Anyanwu 2001 to estimate lung transplant -related utility in the economic analysis instead of Groen 2004. This change will make the resource use data and utility data sources consistent (Anyanwu 2002) and will allow the use of the utility values reported in Table 45 of the CS (page 186), without the need for transforming these into utility decrements.

The utility value used for the first year of transplant was based on an average of the score from Anyanwu 2002 for 0-6 months and 6-18 months. The utility for subsequent years was based on an average of the utility in 19-36 months and 36+ months. With a weighted average across single and double transplants, the derived utilities were 0.76 in the first year of transplant, and 0.77 thereafter. Using these utilities, there was no need to transform the utilities into decrements.

B24. Priority question: Please use the Anyanwu 2002 and Anyanwu 2001 papers to estimate lung transplant -related utility in the economic analysis (if not as your base case, then as a scenario analysis), by incorporating different utility values into the different lung transplant tunnel states.

It is not clear how question B24 differs from B23. The utilities have been updated using Anyanwu 2002 and Anyanwu 2001; see the response to B23.

B25. On pages 188–189 of the CS it states, "*The studies reporting all other utility information (Ejiofor and Stockley, 2015) (Groen et al. 2004) did not report sufficient information regarding the study population to allow comparison of the study populations between utility studies or the general population in regards to age.*" However, the mean age of patients is reported in the study by Eijofor and Stockley 2015. Please clarify the approach taken to include utility data in the model.

Eijofor and Stockley (2015) does not report the age of patients, but given it is the UK registry of patients with A1PI deficiency it is likely to be a comparable age group to the modelled population.

B26. A Cox regression analysis is provided on pages 146–147 (marked as CiC) and 187–188 (marked as AiC). Please clarify:

a) if the analysis was undertaken by the company;

The cox regression analysis was conducted by the ADAPT registry study. We have no access to the database to undertake any further analysis.

b) the confidential mark-up;

As the cox regression analysis from Green et al., 2014a has not been published, information was presented as academic in confidence. Therefore figure 26 of the CS should be highlighted academic and not commercial in confidence.

c) the source of data used to inform the analysis;

The source of data comes from the ADAPT registry, maintained at University Hospitals Birmingham NHS Foundation Trust. The data was provided in the form of a draft manuscript.

d) how covariates were chosen.

[redacted]

B27. Please clarify how Ejiofor and Stockley 2015 was chosen and identified to inform utilities by FEV_1% predicted.

The ADAPT programme is specific to the UK population and is the only study that has reported EQ-5D data for alpha 1 patients by disease severity.

B28. If available, please provide the number and severity of exacerbations experienced by the patients in Ejiofor and Stockley 2015.

Information not available in the abstract.

B29. If available, please provide the treatment patients in Ejiofor and Stockley 2015 received to manage their A1PI deficiency.

As they are UK patients, there are no licenced A1PI. Therefore, patients receive best supportive care for the condition.

Systematic literature review for health economic studies

B30. Please provide a list of excluded studies with reasons for exclusion for the economic and quality of life searches and resource use search.

Reference	Reason
Economic	
Campos, M., Runken, M., Davis, A., Johnson, M., Stone, G. and Buikema, A. (2018). Impact of a Health Management Program on Healthcare Outcomes among Patients on Augmentation Therapy for Alpha 1-Antitrypsin Deficiency: An Insurance Claims Analysis. Advances in Therapy, 35(4), pp.467-481.	Not population of interest - US population, only COPD patients with A1PI
Sieluk, J., Levy, J., Sandhaus, R., Silverman, H. and Mullins, C. (2017). Medical Costs of Alpha-1 Antitrypsin Deficiency: Evidence From Real-World Claims Data. Chest, 152(4), p.A595.	Not population of interest - US population
Karl, F., Holle, R., Bals, R., Greulich, T., Jörres, R., Karch, A., Koch, A., Karrasch, S., Leidl, R., Schulz, H., Vogelmeier, C. and Wacker, M. (2017). Costs and health-related quality of life in Alpha-1-Antitrypsin Deficient COPD patients. Respiratory Research, 18(1).	Not population of interest - German registry, patients had diagnosis with COPD
Greulich, T., Nell, C., Hohmann, D., Grebe, M., Janciauskiene, S., Koczulla, A. and Vogelmeier, C. (2016). The prevalence of diagnosed α1-antitrypsin deficiency and its comorbidities: results from a large population-based database. European Respiratory Journal, 49(1), p.1600154.	Not population of interest - German population
Molloy, M., O'Connor, C., Fee, L., Carroll, T. and McElvaney, N. (2017). Real Life Treatment Benefit of Intravenous Augmentation Therapy for Severe Alpha-1 Antitrypsin Deficiency. American Journal of Respiratory and Critical Care Medicine, p.A7405.	Not population of interest - Ireland population
Cheng, M. and Glanville, A. (2016). Informing Patient Choices: Morbidity and Mortality 4 Years After Lung Transplantation for COPD. Chest, 150(4), p.1308A.	Not population of interest - Single centre study in Australia

Seyama, K., Hirai, T., Mishima, M., Tatsumi, K. and Nishimura, M. (2016). A nationwide epidemiological survey of alpha1-antitrypsin deficiency in Japan. Respiratory Investigation, 54(3), pp.201-206.	Not population of interest - Japan cohort
Stoller, J., Smith, P., Yang, P. and Spray, J. (1994). Physical and social impact of alpha 1-antitrypsin deficiency: results of a survey. Cleveland Clinic Journal of Medicine, 61(6), pp.461-437.	Not population of interest Potential Econ
Dawkins, P., Dowson, L., Guest, P. and Stockley, R. (2003). Predictors of mortality in 1-antitrypsin deficiency. Thorax, 58(12), pp.1020-1026.	Not population of interest Potential Econ
Holme, J. and Stockley, R. (2009). CT Scan Appearance, Densitometry, and Health Status in Protease Inhibitor SZ α 1 - Antitrypsin Deficiency. Chest, 136(5), pp.1284-1290.	Not population of interest
Piitulainen, E., Bernspång, E., Björkman, S. and Berntorp, E. (2003). Tailored pharmacokinetic dosing allows self-administration and reduces the cost of IV augmentation therapy with human α1-antitrypsin. European Journal of Clinical Pharmacology, 59(2), pp.151-156.	Not including outcome of interest
Lieberman, J. (2000). Augmentation Therapy Reduces Frequency of Lung Infections in Antitrypsin Deficiency. Chest, 118(5), pp.1480-1485.	Not including outcome of interest
Beiko, T., Kumbhare, S., Barker, A., Brantly, M., Stoller, J., Sandhaus, R., Silverman, E., Trapnell, B., Coxson, H. and Paoletti, L. (2018). Body Mass Index Predicts Exacerbation Frequency in Alpha-1 Antitrypsin Deficiency. American Journal of Respiratory and Critical Care Medicine, p.A2808.	Not including outcome of interest
QoL	
Parr, D. and Lara, B. (2017). Clinical utility of alpha-1 proteinase inhibitor in the management of adult patients with severe alpha-1 antitrypsin deficiency: a review of the current literature. Drug Design, Development and Therapy, Volume 11, pp.2149-2162.	Not study type of interest
Choate, R., Mannino, D., Holm, K. and Sandhaus, R. (2017). Increase in Exercise Activities in Alpha-1 Antitrypsin Deficient Patients: Results of a Randomized Trial. American Journal of Respiratory and Critical Care Medicine, p.A7390.	Not study type of interest - If no further details obtainable, then reject on basis no results on quality of life measures (secondary outcome measures not reported)
Stockley, R. (2016). Alpha-1 Antitrypsin Deficiency: Phenotypes and Quality of Life. Annals of the American Thoracic Society, 13(Supplement_4), pp.S332-S335.	Not study type of interest - UK focussed but comment article
Teschler, H. (2015). Long-term experience in the treatment of α1-antitrypsin deficiency: 25 years of augmentation therapy. European Respiratory Review, 24(135), pp.46-51.	Not study type of interest
Bernhard, N., Lepper, P., Vogelmeier, C., Seibert, M., Wagenpfeil, S., Bals, R. and Fähndrich, S. (2017). Intensive smoking diminishes the differences in quality of life and exacerbation frequency between the alpha-1-antitrypsin deficiency genotypes PiZZ and PiSZ. Respiratory Medicine, 130, pp.1-8.	Not population of interest - German registry
Fähndrich, S., Bernhard, N., Lepper, P., Vogelmeier, C., Seibert, M., Wagenpfeil, S. and Bals, R. (2017). Exacerbations and duration of smoking abstinence are associated with the annual loss of FEV 1 in individuals with PiZZ alpha-1-antitrypsin deficiency. Respiratory Medicine, 129, pp.8-15.	Not population of interest - German registry

Bernhard, N., Lepper, P., Vogelmeier, C., Seibert, M., Wagenpfeil, S., Bals, R. and Fähndrich, S. (2017). Deterioration of quality of life is associated with the exacerbation frequency in individuals with alpha-1-antitrypsin deficiency – analysis from the German Registry. International Journal of Chronic Obstructive Pulmonary Disease, Volume 12, pp.1427-1437.	Not population of interest - German registry
Piitulainen, E., Mostafavi, B. and Tanash, H. (2017). Health status and lung function in the Swedish alpha 1-antitrypsin deficient cohort, identified by neonatal screening, at the age of 37-40 years. International Journal of Chronic Obstructive Pulmonary Disease, Volume 12, pp.495-500.	Not population of interest - Swedish registry
Torres Redondo, M., Campoa, E., Ruano, L. and Sucena, M. (2017). Health-Related Quality of Life in Patients With Alpha-1 Antitrypsin Deficiency: A Cross Sectional Study. Archivos de Bronconeumología (English Edition), 53 (Prepared by the PSSAG Secretariat), pp.49-54.	Not population of interest - Brazilian study
Bernhard, N., Fähndrich, S., Lepper, P., Vogelmeier, C. and Bals, R. (2016). Assessment of quality of life (SGRQ) in patients with alpha-1-antitrypsin deficiency– Analysis from the German registry. 5.2 Monitoring Airway Disease.	Not population of interest - German registry
Fähndrich, S., Bernhard, N., Lepper, P., Vogelmeier, C. and Bals, R. (2016). Differences of disease phenotypes in individuals with alpha-1-antitrypsin deficiency with genotypes PiZZ and PiSZ - Analysis from the German registry. 5.2 Monitoring Airway Disease.	Not population of interest - German registry
Stolk, J. (2003). Correlation between annual change in health status and computer tomography derived lung density in subjects with 1-antitrypsin deficiency. Thorax, 58(12), pp.1027-1030.	Not population of interest Potential QoL
Needham, M. and Stockley, R. (2005). Exacerbations in α1-antitrypsin deficiency. European Respiratory Journal, 25(6), pp.992-1000.	Not population of interest Potential QoL
Barros-Tizón, J., Torres, M., Blanco, I. and Martínez, M. (2012). Reduction of severe exacerbations and hospitalization-derived costs in alpha-1-antitrypsin-deficient patients treated with alpha-1-antitrypsin augmentation therapy. Therapeutic Advances in Respiratory Disease, 6(2), pp.67-78.	Not population of interest Potential QoL
Dowson, L., Newall, C., Guest, P., Hill, S. and Stockley, R. (2001). Exercise Capacity Predicts Health Status in α1-Antitrypsin Deficiency. American Journal of Respiratory and Critical Care Medicine, 163(4), pp.936-941.	Not including outcome of interest Potential QoL
Parr, D., Guest, P., Reynolds, J., Dowson, L. and Stockley, R. (2007). Prevalence and Impact of Bronchiectasis in α1-Antitrypsin Deficiency. American Journal of Respiratory and Critical Care Medicine, 176(12), pp.1215-1221.	Not including outcome of interest Potential QoL
Manca, S., Rodriguez, E., Huerta, A., Torres, M., Lourdes, L., Curi, S., Pirina, P. and Miravitlles, M. (2013). Health-related quality of life in emphysema due to alpha-1-antitrypsin deficiency. European Respiratory Journal, 42, p.1802.	Abstract that is reported elsewhere
CEA	
Gildea, T., Shermock, K., Singer, M. and Stoller, J. (2003). Cost-Effectiveness Analysis of Augmentation Therapy for Severe α1-Antitrypsin Deficiency. American Journal of Respiratory and Critical Care Medicine, 167(10), pp.1387-1392.	20 - Not population of interest Potential CEA
Groen, H., van der Bij, W., Koeter, G. and TenVergert, E. (2004). Cost-Effectiveness of Lung Transplantation in Relation to Type of	30 - Not including outcome of interest Potential CEA

End-Stage Pulmonary Disease. American Journal of Transplantation, 4(7), pp.1155-1162.	

B31. Please provide the inclusion and exclusion criteria used for the quality of life search and resource use search. The ERG does not consider the selection criteria in Table 30 (page 151 of CS) to sufficiently cover those types of data.

The reviewed was designed to capture models, costs, resource use and utilities that could inform the cost-effectiveness model. The inclusion and exclusion criteria in Table 30 of the CS are an accurate representation of the search conducted, except that the search was not limited by intervention or country.

B32. If the quality of life search was limited by intervention, please justify this decision.

Please see the response to B31 – the search was not limited by intervention.

B33. Please provide the data abstraction strategy used for the quality of life search and resource use search

Citations were first screened based on title and abstract supplied with each citation ('first pass'). Each citation was screened by two independent reviewers and any discrepancies between reviewers were reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded during first pass. Citations with abstracts that were unclear were included during this phase. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded. Full-text copies of all references that could potentially meet the eligibility criteria were obtained through internet search. The eligibility criteria were then applied to the full-text citations.

B34. Please clarify why the population in Table 30 of the CS (page 151) is restricted by country: "Emphysema due to A1PI deficiency in the UK"

The listed inclusion criteria is incorrect; it was not limited to the UK. See the response to B31.

Reporting of results

B35. Priority question: The ERG ran PSA twice using 5,000 simulations and found notably lower life years to the results reported in Table 74 of the CS (page 233), please explain this difference.

Treatment	Total LYs		
	ERG (1)	ERG (Prepared by the PSSAG Secretariat)	CS (Table 74)
BSC	7.228	7.204	8.76
Respreeza	9.239	9.227	11.572
Inc. LY	2.011	2.023	2.813

The results were misreported.

B36. Please clarify why correlations between lung density and lung function were not considered in probabilistic analysis.

It was not possible to account for the correlation within the analysis.

B37. The results of OWSA on "Clinical inputs-transitions" in Table 72 of the CS (page 229) are mismatched, please correct the values in the table.

Clinical inputs - transitions				
Variable	Base-case value	Range of values	ICER for lower bound	ICER for upper bound
Respreeza mortality year 1	1.075%	0.028% to 2.299%	£193,115	£304,358
Respreeza mortality year 2	0.000%	0.000% to 1.000%	£236,409	£299,862
Respreeza mortality year 3	0.714%	0.018% to 2.619%	£220,305	£307,960
Respreeza mortality year 4	0.000%	0.000% to 1.000%	£236,409	£296,349
Placebo mortality year 1	2.299%	1.075% to 6.309%	£257,821	£151,948
Placebo mortality year 2	1.176%	0.030% to 4.296%	£255,638	£166,642
FEV1>50% survival curve	Weibull: shape =2.57; scale = 15.57	Lower CI shape = 1.40; and scale =10.43 Upper CI shape = 4.71; scale= 23.22	£236,794	£209,953
FEV1<50% no decline survival curve	Weibull: shape =3.64; scale = 11.62	Lower CI: shape = 0.99 scale= 7.24 Upper CI: shape = 13.44; scale = 18.65	£239,915	£247,998
FEV1<50% slow decline survival curve	Weibull: shape =3.30; scale = 9.21	Lower CI shape = 1.93 scale= 7.70. Upper CI shape = 5.64; scale = 11.02.	£197,207	£300,936

FEV1<50% rapid decline survival curve	Weibull: shape =2.99; scale = 7.97	Lower CI: shape = 1.70; scale= 6.37. Upper CI shape = 5.24; scale= 9.95.	£612,444	£140,840
Transition from FEV1>50% to FEV1<50% placebo	14.822%	11.539% to 18.433%	£240,303	£232,817
Reduction in FEV1 decline with Respreeza, FEV1 30-50%	18.90	6.06 to 31.74	£234,465	£237,798
Transition from FEV1>30% to FEV1<30% placebo	15.069%	11.761% to 18.703%	£248,795	£226,714
Reduction in FEV1 decline with Respreeza, FEV1 <30%	1.28	-7.19 to 9.74	£215,233	£265,364
Annual probability of lung transplant	43.831%	33.14% to 54.82%	£230,193	£242,455
Survival following lung transplant in Year 1	82.000%	78.17% to 85.54%	£231,884	£239,689
Survival following lung transplant after Year 1	59.000%	54.24% to 63.68%	£247,665	£223,933

Further clarifications

If the above suggested modelling approach (questions B1 to B8) is not followed, further information relating to the existing model is required. Please note that this is not an alternative to providing a formal clarification response to questions B1 to B8 – these questions remain applicable even if the suggested approach is not followed, so please ensure full a response to each question is provided, including a rationale for the adopted approach.

If a model structure excluding lung density (questions B1 to B8) is not followed, please note the following additional clarifications and requests on those questions:

B1) If CT-based lung is retained in the model, please restructure the FEV1% thresholds included in the model to incorporate FEV1%<30%, for consistency with eligibility for lung transplantation in practice and to avoid potentially overestimating the benefits of treatment. It is noted that, although the inclusion criteria for RAPID excluded patients with a FEV1%<30% at baseline, this structure nevertheless permits patients to progress to this health state (at different rates depending on the treatment arm) in the economic model.

This has been implemented; please see response to B1.

B2) Regardless of which FEV1% categories are included in the model, the estimation of transition probabilities between the FEV1% states should be conducted as outlined in question B2. More specifically, these should reflect the time that takes patients to transition from the mean baseline FEV1% in the starting health state to cross the threshold of the next FEV1% category (and not to reach the average baseline FEV1% in the next category as the current model does).

This has been implemented; please see response to B2.

B3) Please use the updated results from the meta-analysis (question A2) to estimate transitions between FEV1% categories in the model for the Respreeza arm. It is requested that the company follows the format suggested by the ERG in the Excel spreadsheet sent by the ERG together with the clarification questions.

This has been implemented; please see response to B3.

B4) If the proposed structure is not followed, this question remains partly applicable. If lung density outcomes are retained in the model, please (either in the base case or a scenario analysis by means of a drop down menu in the model) replace the survival data from RAPID used in the current model, by Green et al. 2014 to model survival for the entire economic analysis (from cycle 0 in the model).

This has been implemented; please see response to B4.

In addition, the following question provides the minimum additional information and amendments needed by the ERG to validate the existing economic model.

B38. Priority question: Please provide additional information and amendments to the economic model as follows:

a) Provide the equations used in the linear regression used to estimate transition probabilities between lung density states in the model using RAPID data (described in page 180 of the CS), together with the covariates used to adjust these data, and with a clear description of the methods and data used in this process (including the results of the statistical process for selecting covariates);

Please see the response to A9.

b) Provide the change in mean CT lung density per year, for Respreeza patients who received Respreeza in RAPID and carried on receiving Respreeza in RAPID-OLE (i.e. excluding the placebo patients from RAPID who crossed over to Respreeza in RAPID-OLE), over the 4-year follow-up period;

Please see the response to A5.

c) Use the data requested in b) to estimate transition probabilities in the economic model for Respreeza patients. More specifically, please include transition probabilities matrices estimating the probability of patients moving between the different lung density decline states in the model between year 0-1 and year 1-2; year 1-2 and year 2-3; and finally year 2-3 and year 3-4, using the 4-year Respreeza data (for the cohort of patients receiving Respreeza in RAPID and RAPID-OLE, excluding placebo patients from RAPID-OLE), for each FEV1% category included in the model;

The transition probabilities already utilise this data: the Respreeza transition probabilities are based on transitions between years 0-1, 1-2, 2-3 and 3-4 which therefore includes those that switched from placebo.

d) Provide evidence establishing a robust predictive relationship between CT-measured lung density and FEV1% as this relationship is central to the current model and is based on the RAPID trial, where changes in FEV1% were not statistically significant. Provide evidence to allow an external validation of trial and model outcomes;

Please see response to B1.

e) Incorporate into the model all the CT scans and associated costs (suggested in clarification question B10) related with performing all the CT scans informing the changes in lung density captured in the model (at least 2 scans a year as in RAPID). Please note that this does not replace

the request in clarification question B10, relating to the CT scans necessary for the initial assessment of patients' eligibility for Respreeza.

Please see response to B10.

f) The company is proposing that routine CT scanning will be introduced in the NHS and that Respreeza has the potential to change the current diagnosis pathway for A1PI deficiency in the NHS. Given the importance and cost of issues such as the requirement for redeployment of staff, training and acquisition of specialist equipment, establishing clinical appropriate criteria for diagnosis, etc. beyond the existing specialist centres, this needs to be included in the budget impact model by the company to be considered on a national level coverage by NHS England;

The company is not proposing that routine CT scanning will be introduced in the NHS. CT scanning is not necessary to initiate or monitor treatment. Please see response to B10.

g) Model lung transplantation in accordance to the clinical guidelines for lung transplant and clinical expert opinion, both indicating that only patients below FEV1%<30% (and not below FEV1%<50%) are eligible for a lung transplant;

Please see response to B1.

h) Link CT lung density decline with the need for lung transplant;

In the previous model structure that was based on health states of only FEV1 of greater than or less than 50%, only patients with a slow or rapid decline in lung density transition to the lung transplant state. Now that the model is better defined by an FEV1<30%, patients do not need declining lung function to be eligible for a lung transplant because a patient with an FEV1<30% is unlikely to be considered “stable” and therefore it is assumed that patients with an FEV1<30% with no decline within a one-year period would be eligible for a transplant.

i) Assess the clinical plausibility of patients moving from an FEV1%>50% no lung decline to a FEV1%<50% no lung decline health state in the model, as our clinical experts consider these implausible, and substantiate the equivalent transition for a patient with slow lung density decline;

It is clinically plausible that losses in FEV1% predicted would not be directly attributable to measurable lung density losses as a result of inflammatory processes reflective of exacerbations. Despite this limitation, FEV1% predicted has been considered within the model.

j) Capture the correlation between FEV1% and lung density in the probabilistic sensitivity analysis, as these outcomes are correlated and report the approach taken in a transparent way.

It has not been possible to capture the correlation between these two outcomes. Within one-year cycles, the correlation is not expected to be strong in line with the RAPID study, where a treatment effect was seen on CT lung density but not on FEV1.

Section C: Textual clarifications and additional points

C1. Please provide the figures reported in the Green *et al.* 2014 draft manuscript (and used in the CS to provide survival by FEV_1% status) submitted by the company.

The figures presented in the Green et al., 2014 draft manuscript and used in the company submission are available in pages 30-32 of the company submission document.

C2. Please confirm that no investigation site was located in the UK.

That is correct as UK experts did not support further placebo-controlled trials in this indication on the basis of existing data.

C3. Please clarify whether there should be a footnote in Table 11 (page 80 of the CS) to accompany the asterisk associated with "*CT lung density, adjusted PD15 g/L, mean (SD)".**

Yes, the footnote associated with the asterisk (*) should read:

*CT lung density values are from 90 subjects treated with Respreeza and 83 subjects who received placebo.

C4. Please confirm that the FEV_1/FVC ratios and accompanying standard deviations (SDs) reported in Table 11 (page 80 of the CS) should be 0.452 (0.11) and 0.432 (0.104) for Respreeza and placebo, respectively.

Yes, this is a typographical error. According to the 4001 CSR, Table 6, pg. 72 the FEV_1/FVC ratio and SD should be 0.45 (0.11) for Respreeza and 0.43 (0.10) for placebo.

C5. In Table 17 of the CS (page 94), please confirm that the change in FRC for the treatment group should be -1.54 g/L per year, as reported in the full publication, rather than 0.48 g/L per year as reported in the table.

According to the Chapman et al., 2015 publication: the annual rate of lung density loss at FRC alone was: A1PI -1.54 (SE 0.24) g/L per year; placebo -2.02 (SE 0.26) g/L per year; difference 0.48 (SE -0.22 to 1.18, p+0.18) g/L per year. According to this, for the separate measurement of PD15 density measures at FRC alone should be 1.54 g/L per year.

C6. The title for Table 47 in the CS (page 189) relates to carer disutility, please clarify if the title needs to be amended.

Yes, the table reflects patient utilities. The title can be changed to: Table 47. Utility decrements applied to population estimates.

C7. The cost of a district nurse per administration is taken from NHS reference costs 2016–17 (Table 49 of the CS, page 191) whilst the cost of administrations in an outpatient or community setting (Table 55 of the CS, page 204) is taken from the PSSRU Curtis 2017. Please clarify why the source is not consistent.

Both sources were considered for costing; it is not clear which is the most appropriate. The results of the analysis are insensitive to the until cost of administration.

C8. Please clarify if the number of PSA simulations is 5,000 and justify the chosen number.

That is correct. This was felt to be an arbitrarily robust figure that would produce stabilised results.

C9. The ERG is unable to verify the values in Tables 66, 67, 68, 70 and 71 with the results in the worksheet 'Model'. The discrepancies identified in Tables 66 and 67 are provided below. Discrepancies for Tables 68, 70 and 71 are not provided due to time constraints. Please provide corrected results for Tables 66, 67, 68, 70 and 71.

Table 66. Model outputs by clinical outcomes for best supportive care (discounted)

<table>
<tr><th></th><th colspan="3">BSC - Discounted outcomes</th><th colspan="3">Results in the model (cell in 'Model')</th></tr>
<tr><td>Outcome</td><td>LY</td><td>QALY</td><td>Cost (£)</td><td>LY</td><td>QALY</td><td>Cost (£)</td></tr>
<tr><td>FEV_1>50 % predicted: No decline</td><td>0.04</td><td rowspan="3">1.73</td><td rowspan="4">£15,340</td><td>Ok numbers match (AE58)</td><td>Ok numbers match (CA58)</td><td rowspan="4">£13,853 (DC58)</td></tr>
<tr><td>FEV_1>50 % predicted: Slow decline</td><td>0.33</td><td>1.88 (AF58)</td><td></td></tr>
<tr><td>FEV_1>50 % predicted: Rapid decline</td><td>0.53</td><td>0.49 (AG58)</td><td></td></tr>
<tr><td>FEV_1<50 % predicted: No decline</td><td>0.07</td><td>0.32</td><td>Ok numbers match (AH58)</td><td>1.84 (CC58)</td></tr>
</table>

FEV_1<50 % predicted: Slow decline	1.51			1.40 (AJ58)		
FEV_1<50 % predicted: Rapid decline	1.98			1.81 (AK58)		
Lung transplant: first year	0.19	1.55	£31,983	0.18 (AK58)	1.10 (CD58)	£25,147 (DD58)
Lung transplant: subsequent years	0.56			1.21 (AL58)		
Treatment	NA	NA	£0	–	–	–
Administration	NA	NA	£0	–	–	–
TOTAL	7.08	4.67	£39,001	Ok numbers match (AN58)	Ok numbers match (CD58)	Ok numbers match (DD58)

Table 67. Model outputs by clinical outcomes for Respreeza (discounted)

	Respreeza - Discounted outcomes			**Results in model (cell in 'Model')**		
Outcome	LY	QALY	Cost (£)	LY	QALY	Cost (£)
FEV_1>50% predicted: No decline	0.18	1.73	£20,566	Ok numbers match (AE115)	2.14 (CA115)	£17,908 (DB115)
FEV_1>50% predicted: Slow decline	0.40			2.32 (AF115)		
FEV_1>50% predicted: Rapid decline	0.55			0.48 (AG115)		

FEV_1<50% predicted: No decline	0.42	0.42		0.37 (AH115)	2.43 (CB115)	
FEV_1<50% predicted: Slow decline	3.68			3.25 (AI115)		
FEV_1<50% predicted: Rapid decline	0.80			0.72 (AJ115)		
Lung transplant: first year	0.15	2.06	£42,671	0.23 (AK115)	1.41 (CC115)	£32,415 (DC115)
Lung transplant: subsequent years	0.62			1.56 (AL115)		
Treatment	NA	NA	£419,568			OK numbers match (CZ115)
Administration	NA	NA	£2,951			£17,059 (DA115)
TOTAL	9.13	5.98	£486,950	Ok numbers match (AN115)	Ok numbers match (CD115)	Ok numbers match (DD115)

Revised results

When incorporated the suggested changes, the ICER has dropped from £342,872 to £236,409 (Table 6).

Table 6. Base-case results (discounted)

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
Respreeza and BSC	£422,681	9.991	6.977	£359,855	2.105	1.522	£236,409
BSC	£62,825	7.886	5.454		NA	NA	

The Tornado plot of the updated model indicates that the results are most sensitive to the survival curve of patients with an FEV1<50% and rapid decline in lung density. This is a consequence of an unstable Gompertz function, whereby the estimated survival curve results in 48% survival after 30 years which is clinically implausible.

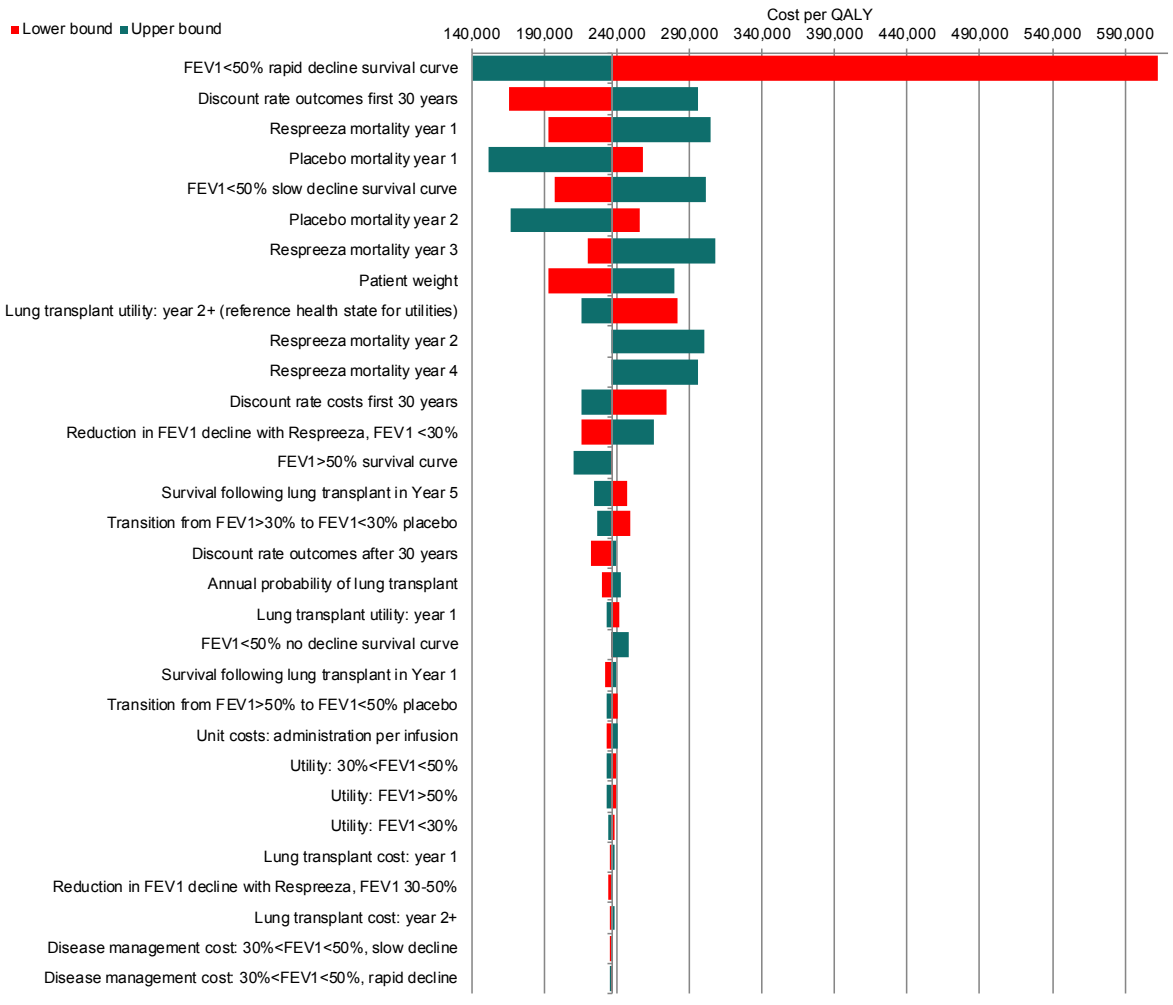


Table 7 outlines the cost per QALY expected with various deterministic scenarios.

Table 7. Cost per QALY expected with various deterministic scenarios.

Analysis	**Base case**	**Scenario**	**ICER**
Structural scenario analyses			
Discount rate of 1.5% applied to benefits and 3.5% applied to costs	3.5% applied to both benefits and costs	Discount rate of 1.5% applied to benefits and 3.5% applied to costs	£189,946
Mortality data from RAPID excluded	4-year and 2-year survival from RAPID used, followed by UK registry survival curves	UK registry survival curves only	£280,942
Include carer disutility	No carer disutility applied	A five percent reduction in carer health related quality of life was applied to patients with FEV1%>50 and in lung transplant states (i.e. a QALY loss of -0.0425 per patient per year) and a ten percent reduction was applied to all other health states including death (i.e. a QALY loss of -0.085 per patient per year).	£223,775
Adjust utilities to the general population	Use reported absolute utilities for health states	Use utility decrements derived from reported values and apply to population norms	£225,638
Scenario analyses			
Administration through infusion clinic rather than homecare.	25% infused administered at clinic	0% and 100% infused administered at clinic	£234,880 and £240,996 respectively
Scenario to explore additional cost and reduced utility as rate of lung density increases	As per base case inputs	20% increased utilities and 20% decreased costs from no lung density decline state and 20% decreased utilities and 20% increased costs from rapid lung density decline state	£207,109

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Highly Specialised Technology Evaluation

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted]

Name of your organisation: Alpha-1 UK Support Group

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

The Alpha-1 UK Support Group was founded in 1997 as a platform for patients with alpha-1 antitrypsin deficiency (AATD) and their families and carers for advice, practical support and communication. The group was registered with the HMRC as a Small UK Charity in 2010, and a Registered Charity in England & Wales and Scotland in 2012, and is dedicated to help, advise and support individuals with AATD, their families and carers. The main strategic objective of the charity is to improve patients' quality of life, and to improve access and equality of access to adequate healthcare services and effective therapies. We fund our activities predominantly through fundraising events organised by our members and supporters and from donations. We occasionally apply for donations and grants from industry, mostly to support specific events/activities of the charity.

Our charity has about 600 members. Our membership includes individuals of different AATD phenotypes, ranging from people with the genetic predisposition but no symptoms of AATD to severely affected patients at the terminal stage of the condition who are bed-bound, as well as family members and carers of AATD sufferers.

We estimate that 70-80% of symptomatic patients with AATD-associated emphysema in England are members of our group.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology? ✔

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- a carer of a patient with the condition for which NICE is considering this technology?

- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc) ✔ I am the Chair of the Board of Trustees of the Alpha-1 UK Support Group, but I am not employed at our charity. (The Alpha-1 UK Support Group has no employed staff and is run exclusively by volunteers.)

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

General comments about the data sources used this submission

This submission is made on behalf of the AATD community in England represented by the Alpha-1 UK Support Group, although not all patient contributors to this submission are affiliated with our charity. This submission has been approved by our charity's board of trustees. The information provided hereafter originates predominantly from the following sources:

1) National AATD patient survey:

In 2012/2013, our charity conducted a survey amongst English AATD patients, their families and carers to better understand the burden of AATD, patient access to both clinical specialists with expertise in AATD and optimal disease management, and the unmet need of patients living with AATD and their families. The rationale for the survey was that, unlike in other countries, no disease-specific therapies have ever been available in the UK, and no care model exists within the NHS that provides integrated clinical management for the unique needs of the different clinical aspects of AATD.
The survey was conducted online and was accessible via the main Alpha-1 patient support charities' websites. A report of the survey results was published and is available from our website at http://alpha1.org.uk/attachments/article/120/Alpha-1%20Antitrypsin%20Deficiency%20Policy%20Report%20England.pdf (referred to throughout as "Survey").

2) Individual patient interviews:

We put a call out via our closed Facebook group for patients and carers/family members willing to share their experiences for the purpose of this submission. Patients who came forward also included patients who participated in clinical trials of human alpha 1-protein inhibitor. Interviewees were individually taken through the questions in this template via telephone. Their views are reflected in the answers

throughout this document.

3) Personal experience of patients, carers/family members within our charity and/or collective knowledge within the charity

4) Telephone interviews we carried out with AATD patients in the US who have been receiving the technology as part of their routine clinical care, sometimes for many years, in order to help inform our understanding of the technology's advantages and disadvantages in a routine clinical setting.

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

About half of all patients who responded to our Survey from England experienced a delay of over 4 years after the initial onset of their symptoms before receiving the correct diagnosis of AATD. Nearly a third of all respondents reported a diagnostic delay of more than 10 years. This is in line with published data, reporting an average diagnostic delay in AATD of 5.6 years (Stoller et al. Chest. 2005 Oct;128(4):1989-94) and >6 years (Koehnlein et al. Ther Adv Respir Dis. 2010 Oct;4(5):279-87).

Testing for AATD in the NHS, according to international guidelines should be part of established NHS practice, but we know from our members that this is not the standard practice. The WHO recommends all patients with a diagnosis of COPD or adult-onset asthma should be tested for AATD (Bull World Health Organ. 1997; 75:397–415). This recommendation was confirmed in a recent European Respiratory Society Statement by a clinical expert group (Miravitlles et al. Eur Respir J. 2017; 50: 1700610). The lack of appropriate testing for AATD in the NHS contributes to the long diagnostic delay in the UK, as illustrated by this patient quote: *"I guess it was over a ten-year period that I was treated for bronchitis. I was reviewed on a yearly basis and, although I was getting shorter of breath, no more tests were done."*

Many patients consult many different doctors before finally receiving the correct diagnosis, which leaves them in a position of uncertainty as to the cause of their symptoms, sometimes for many years. The long journey that patients encounter through the healthcare system without receiving the correct diagnosis is distressing and substantially impacts on patients' quality of life. Patients feel helpless about not knowing the cause of their progressively worsening symptoms and about the lack of response to the medications that they had been prescribed and/or side effects of the inappropriate treatments, as illustrated by the following patient quotes (see Survey):

"It was like going through a tunnel with no light at the end."

"Having been diagnosed with asthma 27 years ago I've lost count of how many doctors it has taken before I was referred to a lung specialist."

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"First diagnosed with asthma aged 40 but after no signs of improvement after several years of treatment a new diagnosis of COPD was given. At age 65 I was finally sent to see a respiratory specialist who did a blood test which indicated I was an Alpha."

"I felt completely lost and deserted by the NHS."

"I had a 'mystery illness' in 1994 for which I was hospitalized for 2 - 3 weeks and although every test and scan was carried out, there was no diagnosis made."

"Years of unexplained severe long lasting chest infections treated as asthma."

"I saw 10 or 15 doctors before receiving a diagnosis. I had to ask to have the test done."

In addition, the delay in correctly diagnosing AATD delays the start of any potential intervention and treatment for the condition (albeit only interventions for symptom control are currently available in the UK, none of which slow or halt progression of the underlying disease).

The long delay in receiving the correct diagnosis of AATD may also be attributable to the lack of awareness and medical knowledge about the disease amongst GPs that our Survey highlighted. Only 22% of respondents rated their GP's level of knowledge about the condition as 'good or very good', whereas almost half of the respondents felt that their GP had 'poor or very poor' knowledge of Alpha-1. Patient quote: *"My GP was not familiar with Alpha-1. I was only diagnosed by accident by a locum GP who was concerned at the number of chest infections I was getting."*

The lack of knowledge and information about AATD in the NHS was highlighted as an area of concern in our Survey. Respondents were generally not satisfied with the level of information they receive for AATD, with 73% of patients and 84% of family members and carers feeling that the NHS does not provide sufficient information about available services and treatments for Alpha-1. This is disconcerting for patients. Patient quote: *"I was told to look on the internet. I had no information given to me by any medical professional. All my knowledge of the disorder is from online research and leaflets."*

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above (any impact the condition has had on carers and family members, specifically the ability to work and requirements to update the family home)

Physical health

AATD is a complex multi-system condition that principally affects the lung and the liver. The effects of AATD are varied and often change throughout the progression of the condition. AATD affects the lives of patients and their families at many different levels and represents a major burden for patients, their families and carers. For the purpose of this submission, we predominantly focus on the implications of the condition on the lung.

The deleterious effect of AATD on the lungs results in reduced general physical functioning consequent to the shortness of breath, which is the predominant symptom of severe AATD and associated emphysema. Due to breathlessness and the lack of oxygen saturation in their blood, patients gradually lose their physical strength and the ability to be active in all areas of life. They become increasingly immobile as the condition progresses. The lack of oxygen also results in constant tiredness. Any type of physical activity becomes exhausting at best and impossible at worst. Breathlessness increases after eating, as the stomach expands and makes breathing even more difficult. The feeling of slowly suffocating becomes patients' constant companion, even when patients become dependent on supplementary oxygen. A good analogy to simulate the shortness of breath is for a healthy person to put on a nose clip, breathe through a thin straw and start walking, climbing stairs or simply undertake everyday activities.

Patient quotes from our Survey, describing the general effect of AATD, include:

"My liver and lungs are affected, and my physical stamina has gone. Things I enjoyed doing are now history for me."

"When you can't breathe properly, life changes."

"I get severely breathless on exertion, walking up hills and carrying bags, and I feel tired most of the time."

"I am almost housebound relying on my mobility scooter to get me out & about."

Patients are more susceptible to chest infections (exacerbations), which often trigger the loss of lung function at an even higher rate than during exacerbation-free periods. Severe exacerbations may require A&E visits and hospitalisation.

As the condition progresses further, it enters the 'oxygen-assisted' phase which brings a new raft of limitations, problems and frustrations, as detailed in the following sections.

Everyday life

As the condition progresses, it significantly impacts patients' ability to live a normal and fulfilled life. Many patients struggle to perform normal everyday activities, such as getting showered and dressed, climbing stairs, doing housework such as cleaning, shopping, cooking, gardening, or just walking. The increasing lack of ability to

perform even the simplest of tasks, such as bending down to put the washing in the machine, and the associated growing dependence on carers, significantly reduced patients' quality of life:

"I am 39 and barely able to dress myself! It has only taken only five years to get to this stage."

"I can do very few 'everyday' tasks if they require any moderate exertion."

"Walking, climbing stairs, doing housework became virtually impossible."

"I have to pace myself in getting dressed or bathing."

In order to adapt to the condition, patients need to make changes to most parts of their (and their families') lives as detailed below. Patients limit their expectations and aspirations in line with what the condition allows them to do. They gradually become dependent on the help of family members and external carers and, usually at advanced stages of the condition, they require mobility equipment (e.g. wheelchairs or scooters). Support from the NHS and local care organisations for such support is limited, putting a significant burden on patients' families and carers and adversely affecting their quality of life.

Once patients have to rely on supplementary oxygen, their ability to undertake any kind of activity is further diminished. Moving around the house, shopping, driving, travelling – everything needs to be carefully planned around ensuring sufficient oxygen supply and the required logistics (oxygen cylinders, portable oxygen concentrators that have only limited battery power etc.).

Work life

Progressive shortness of breath and health problems due to AATD increasingly reduce patients' ability to engage in employed work. Desk work might be possible at an advanced stage of the condition, although often at reduced hours, as is driving (if it doesn't involve delivery/loading/unloading), whereas more physical jobs become impossible. However, such limitations can have a serious impact on a sufferer's mental outlook, particularly if they were previously used to a lifestyle of active working, regular activity and exercise.

Time off work due to exacerbations, other complications of AATD and chronic ill-health frequently results in patients' premature retirement on health grounds, as illustrated by the following quotes from our Survey:

"I had to give up work because of chronic lung problems and chest infections."

"My husband was diagnosed in his 30s in 2011, and his health declined so rapidly that he was medically retired in December 2016 and is now on the transplant list."

"I had to retire early as I was unable to fulfil my work commitments due to my breathing."

In turn, this reduces patients' ability to contribute financially to the family income. It is not uncommon for the patients' partner/spouse (who is often their carer) to be forced to reduce their working hours to care for the patients and to take on the domestic and

child-care responsibilities that the patient is increasingly unable to fulfil. This further exacerbates the family's financial situation.

Family and social life

The ability for AATD patients to have fulfilling relationships with partners, family and friends become increasingly diminished as the disease progresses. Socialising with family and friends becomes more limited, depending on locations and activity-levels; alcohol should generally be avoided (due to potential liver complications), dancing is often impossible (dyspnoea, shortness of breath). Patients are confronted with increasing limitations, such as the inability to walk and talk at the same time, the inability to participate in sports, exercise, or even play with their children as a normal parent would. As the condition progresses, many aspects of life for the patient and their family become increasingly restricted by necessity arising from increasing disability of the affected family member(s).

Due to the increased risk of AATD patients from catching chest infections, they tend to avoid big crowds or close proximity to small children, which makes it difficult and distressing for patients who are parents or grandparents.

Abstinence or moderation of alcohol (due the liver aspect of the condition) in social situations is often immediately misinterpreted as the sign of a 'drinking problem'. Stress, guilt and frustration are not uncommon and often leads sufferers to avoid such social situations completely in order not to have to explain the complexities of their condition at social events, when people are usually not in the frame of mind to discuss health problems.

Patients consistently report that they lose friends and social contacts due to their reduced physical abilities. Even talking on the telephone for extended periods of time can be challenging for AATD patients with advanced breathlessness. Patients experience increasing social and psychological isolation. Many lose their partners as they become incapable of engaging in activities that defined or enriched their relationships. Many patients report that, due to their shortness of breath, sex becomes increasingly difficult and their sex life often dies altogether.

The growing burden and dependence on partners and other family members causes a change in family dynamics and causes great feelings of guilt in patients.

Patient quotes from our Survey summarising the effect of AATD on their social life include:

"*My social life suffers, at work I struggle in many ways, sometimes I feel isolated from friends."*

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

"My circle of friends is now very small and I have lost all my old friends due to me being mostly housebound."

Emotional wellbeing

Initial diagnosis usually brings an immediate depression and fear of death, due to being diagnosed with an incurable, progressive (and therefore terminal) condition for which no treatment or cure exists. Coupled with this is usually a feeling of guilt if the sufferer has children, because they will have passed on at least one gene carrying the condition to their offspring. Conversely, the parents of the sufferer experience the same guilt, and of course the worry of going through the process of discovery to determine how seriously they may be affected by the same condition (whether partially or wholly genetically compromised).

When the disease starts to limit the ability of patients to lead self-determined, fulfilled, independent lives, their social well-being and mental health also tends to deteriorate. They feel increasingly isolated, dependent, worthless, unable to provide for their family and unable to be a fully engaged parent.

In addition, patients sometimes feel stigmatised as other people may regard the condition as somehow being 'self-inflicted', especially if the sufferer ever smoked at all. This can cause feelings of low self-esteem, guilt and frustration, even in people who have never smoked, simply because there is a public assumption that 'emphysema = smoker's disease', and almost all publicly available general literature tends to focus on the damaging aspects of smoking, whereas many severely affected AATD patients have never smoked.

Patients feel anxious about their own future and that of their families. Patient quotes from our Survey, relating to the effect of AATD on their mental health, include:

“I have severe bouts of depression.”

“I find it hard to deal with psychologically at times.”

“Mentally it’s a challenge as I have two young children that I wish to see grow up.”

“When I realised there is no effective treatment for Alpha-1 in this country, I became more and more depressed.”

“I don’t know what the future holds for me - I’m too scared to look.”

Another aspect of the condition which can result in a considerable degree of emotional stress has been described by one patient as follows: *“Families and friends of sufferers often find the effect of the condition on the patients to be quite vexing due to the obvious and apparent distress of the sufferer at times of dyspnoea, and they have a tendency to overcompensate. For the sufferer, who is usually capable of at least partially managing their oxygen-exhaustion with a variety of calming 'tricks' and techniques including 'standing still, leaning forward, breathing through pursed lips', this 'fussing' of bystanders and friends/family can in itself be rather distressing, simply because at the time, the sufferer can do nothing much more than looking or nodding. But to the bystander, they look as if they are about to die, or have a heart attack, and usually there is more panic for the bystander than there is for the sufferer, but this is good for neither party, in truth. Family and close friends usually begin to catch on after a few experiences of these extreme dyspnoea episodes and learn to let the sufferer cope with it, but for new encounters, or out in public, it can be very distressing for both the sufferer and bystanders. Afterwards, it always causes more*

frustration, more guilt and a lowering of self-esteem for the sufferer, who grows ever-increasingly tired of such encounters, and will sometimes strive to avoid them, even to the point of becoming reclusive."

Our Survey showed that many patients feel distressed about losing their independence and becoming a burden for their families, often at a young age and at the time they are trying to bring up a family. Quotes include:

"I struggle to stay at home and look after the kids whilst my wife single-handedly supports the family."

"It's heartbreaking having your family worry about you, becoming a nuisance to them, seeing the fear in their eyes when you are poorly."

"It is very difficult for my husband who is trapped in my same world."

"I am pretty much housebound these days and need oxygen 24/7. I have been struggling to breathe now for over 20 years and some days it all seems a bit too much. I can no longer drive my car and I have to rely on my son to take me anywhere."

"I have found it hard to get others to do so many of things for me that I routinely did just a year or two ago."

Other issues

Impact on spouses, family members and carers:

Most carers of AATD patients are family members who, as a direct consequence of the condition of their loved ones, experience a significant impact on their own ability to have a productive and fulfilling life. In our survey, family members and carers reported that the flexibility in their own work and social lives was significantly reduced by having to care for an AATD patient. They also reported experiencing anxiety about the effects of the disease on the patient, and on their families.

"I can't keep a job as I had to keep taking time off to look after my daughter, I have

to be her nurse as well as her mum."

"It means having to take a lot of time off work for hospital appointments, sickness etc."

"The constant worry about my children's health and welfare is stressful and not good for my health either!"

"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."

"I have to care for her full-time and am not able to return to work."

"There aren't many things we can still do together."

A spouse and carer of an AATD patient shared her story with us which is representative of the high burden that AATD has on partners and carers: *"Over the*

last three years my husband has gone from using a mobility scooter and getting out and about to being housebound, needing oxygen 24/7, morphine, antidepressants and drugs for anxiety. He now remains in his bedroom all of the time. He had to retire early, so I've had to work full-time to manage financially. But the pressures of his ill health have meant my own health has suffered and I've had to cut my hours to part-time so that I can care for him. I cannot leave the house before 11am as it takes 2 ½ hours to get him out of bed, washed, breakfasted and medicated. It also takes about an hour in the evening to get him to bed, which starts at around 8.30pm so I can't ever go out for an evening. I have to help him through the night, so I have many nights with broken sleep so get incredibly tired myself. I can't leave him for any more than 5 hours at a time on clinical advice and I was also very worried about him to leave him any longer. I cry alone as I don't want to worry him. We have had no holidays for two years as it's too stressful. My social life has suffered as a consequence and I do very little. If my husband's brother and other family members didn't live close to us I wouldn't be able to work or go out anywhere at all. My daughter has moved from her home in London to live closer as she was aware that my health was suffering caring for her father. Every day I wonder if today is going to be the day that I will lose him. I can't give up work because if my husband dies I will lose his private pension and I wouldn't be able to find another job. There is an increased financial burden to buy things like mattresses and cushions to make him more comfortable. I have to do everything, paying bills - it's like being on your own but you're not. I don't talk to anyone about how I feel, it is so difficult, as nobody understands."

Out of pocket expenses:

Many of the direct and indirect expenses incurred by patients and/or their family members are not reimbursed and have to be borne by the patients themselves. These can amount to sizeable figures and put enormous financial pressure on patients and their families and include costs for equipment or mobility aids (e.g. most types of portable oxygen concentrators, mobility scooters etc.), loss of earnings due to reduced working hours or having to take time off work to attend medical appointments or to routinely care for patients, parking at frequent hospital visits, additional child care expenses, or high insurance premiums.

Miscellaneous - travel, oxygen, insurance, assistance, seasonal variations:

As the disease progresses, choices have to be made as to whether to make trips, go on holidays, fly in an aircraft (a serious problem for AATD patients, as oxygen saturation levels are reduced in aircrafts). The need for in-flight oxygen and the very real fear of suffering a spontaneous pneumothorax during a flight (a potentially fatal occurrence) are a significant limitation and deterrent to undertaking travel by airplane.

Dependence on supplementary oxygen results in a string of other associated problems and limitations, such as restrictions on the amount of time being away from home for shopping or days out meaning patients become increasingly reclusive. Booking and taking flights when dependent on oxygen treatments requires a lot more

planning, often with forms to be completed by the clinician, and oxygen supply needs to be organised at the travel destination.

Moderate to severely affected AATD patients have severe difficulties in obtaining affordable travel insurance due their increased risk of falling ill whilst travelling, with insurance premiums being as high as several thousand pounds for single trips. Many patients can therefore no longer travel abroad.

There are dilemmas to face with regards to applying for things like Disability Blue Badges; AATD sufferers at moderately advanced stages of the disease are often not considered 'bad enough' for a Blue Badge that would enable close-proximity parking. However, depending on weather and temperature conditions, daily form and physical condition, distances and terrain (flat versus hills, steps, stairs, etc.), an AATD sufferer can find themselves every bit as immobile and handicapped as a person who physically cannot walk. This is often not recognised, and can cause great stress, often resulting in sufferers simply avoiding going out of the house. This, in turn, can lead to a chronic lack of exercise and activity, thus causing general health risk from lack of fitness, higher oxygen consumption. It's a vicious circle.

The physical condition of AATD patients is very dependent on the weather, air temperature, humidity and seasons, which is extremely burdensome or even dangerous for patients. Cold and wet winter months are often much more restricting, and patients tend to avoid going outside or using public transport.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages
(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Patients expect the technology to slow the loss of lung tissue and, in turn, slow or halt the progression of breathlessness, which is the principle cause of the multiple affects of AATD on all aspects of patients' lives described in Section 1 above.

Based on information from patients in other countries where human alpha1-proteinase inhibitor has been available for many years, we would also expect this technology to reduce the severity of exacerbations which, in turn, would also slow disease progression.

Patients expect the technology to help them to remain physically and socially active for longer, continue working for longer, thereby being able to provide for the family for longer, be a dependable member of the family for longer, generally lead a fulfilled life for longer and have a better quality of life for longer.

These advantages would not only benefit the patient but also their family and carers, who would experience a lower burden as a consequence of an improvement/decelerated worsening of the condition in the patient.

Ultimately, the expectation is that the human alpha1-proteinase inhibitor provides patients with a higher quality of life for longer and even extends life.

We are fully aware that this technology is not a cure, but we expect that it does at least create a 'holding pattern' situation and hope for patients and their families which would result in a much improved emotional and mental state for all parties impacted directly or indirectly by AATD.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

AATD is generally a slowly progressing condition; we therefore expect that most benefits of the technology will be enjoyed in the long-term.

However, one patient in the UK who participated in the clinical trial of another, but biologically identical, human alpha1-proteinase inhibitor product, experienced significantly less severe and less frequent chest infections whilst being in the trial compared to before the trial. After the trial was completed, his rate and severity of exacerbations increased again almost immediately. This observation is in line with one of the secondary outcomes in this trial. We therefore expect a fairly immediate reduction in frequency and severity of exacerbations. This is likely to lead to a reduction in hospitalisations, less requirement for medication to treat exacerbations, and slower progression of symptoms (as these usually decline faster after an exacerbation).

The following benefits of the therapy were consistently reported by AATD patients in the US who have been receiving the technology as part of their routine clinical care:

- 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 dependency 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

As the standard of care in the US and in the UK are very similar (with the sole exception of access to this technology), we expect that patients in England would enjoy the same benefits.

3. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

The potential need to travel to a regional hospital in order to receive the weekly infusions might be an inconvenience for patients and carers (if they provide transport) and might adversely impact on the ability to work full-time. However, most patients who are eligible for the therapy are unlikely to be in full-time employment in any case.

Another, minor, potential concern is an uncomfortable localised reaction at the infusion site.

Patients have strongly expressed their view that these potential disadvantages massively outweigh the expected benefits from the therapy.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

The patient community is well aware of the fact that this technology is not a cure and, at the very best, may be able to halt disease progression. However, the AATD patient community in the UK is unanimous in their opinion that this technology would be a step-change in the management of AATD and, for the first time, provide a specific treatment option for patients.

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

The issue of patient sub-groups has been an issue of discussion for some time among the clinical and patient communities. Anecdotal evidence from patients who have been receiving the therapy in other countries, suggests that it is particularly efficacious in patients who experience periods of fast decline of certain lung function parameters, FEV1 and/or KCO.

The effectiveness of AAT augmentation therapy has not been assessed prospectively in sub-groups but there is evidence that the effect of treatment is most pronounced in the lower parts of the lung, which is where emphysema is usually seen in patients with AATD (Parr et al. Resp Res. 2009:10:75) and in patients who are classified as 'rapid decliners' (Wencker et al. Chest. 2001;119:737-744).

6. Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

The standard practice for the management of severe AATD does not differ significantly from the management of patients with usual COPD and is primarily aimed at symptom control.

Typical management includes daily use of inhaled drugs to relieve breathlessness (bronchodilators and steroids), depending on the severity of the breathlessness. Some patients receive pulmonary rehabilitation, although our Survey has shown that access to this therapy varies greatly across England. As the condition progresses, supplementary oxygen is prescribed, either for ambulatory or continuous use.

Exacerbations are usually treated with antibiotics and steroids. Depending on the severity of the exacerbation and the severity of the underlying emphysema, hospital admission may be necessary.

No disease-specific treatments that impact the underlying cause of the condition are available in the UK.

The treatment of last resort is lung transplantation, although the patient community generally does not view this treatment as an acceptable or valid standard of care for reasons detailed below under the section *Other Issues*.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

We would expect the technology to be used in addition to the current standard of care, rather than replacing any elements of the current management regime for AATD. Advantages we expect this technology to deliver over current standard of care are summarised in Section 2 above.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

Depending on how the setting in which the treatment would be given (hospital, local surgery, at home), having to travel for long distances to receive it could be a problem, particularly for patients who live in remote areas or for patients who are still working full-time and have to take time off work in order to receive the treatment once weekly. However, patients indicated a strong preference for accepting this potential 'inconvenience' in return for the expected benefits that the technology delivers (as detailed in Section 2ii)).

We do not believe that the technology has any other disadvantages.

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

We are not aware of significant differences between the patient experience with the technology in the clinical trial setting versus routine clinical care settings.

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

We are not aware of any adverse effects of the treatment that have become known since the treatment has become available. Human alpha1-proteinase inhibitor (from different manufacturers) has been available for treating AATD-associated emphysema in other countries for many years. Its safety profile has been extensively studied, and the treatment has been reported by many patients worldwide to be well tolerated.

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

We are not aware of any research that we have not referred to in this submission that would be relevant to an evaluation of this technology.

8. Availability of this technology to patients

(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

Having access to this therapy is considered to be life-changing for many patients. Being able to stabilise the condition, slow its progression and reduce the rate and severity of exacerbations would not only significantly improve the quality of life of patients, but also of their family members and carers, as it would positively impact on many areas of life that are detrimentally affected by AATD, as detailed in Section 1 above.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

Patients feel that, without this treatment, their condition will continue to decline, shorten their lives and their lives will continue to be impacted, as detailed above.

It is extremely frustrating for patients in the UK to know that the treatment has been available in many other countries in Europe, whilst no specific treatment options are available for AATD patients in the UK. Patients in the UK are well connected with patients from other countries and, consequently, hear about the positive impact the treatment has on the lives of patients and their families. Continuing to not have access to human alpha1-proteinase inhibitor would significantly increase the feeling of hopelessness across the entire AATD patient population in the UK, particularly as no other specific treatments for AATD-associated emphysema are expected to become available within the next 10 years.

Not making this treatment available in the NHS would further increase the inequality of access to optimal treatment across Europe and would not be in line with the consensus expert statement on the diagnosis and treatment of pulmonary disease in α1-antitrypsin deficiency recently published by the European Respiratory Society which recommends the use of human alpha1-proteinase inhibitor in patients with the ZZ phenotype or other rare phenotypes resulting in severe AATD (Miravitlles et al. Eur Respir J. 2017; 50: 1700610).

(iii) Are there groups of patients that have difficulties using the technology?

None of the patients we interviewed who received the treatment during a clinical trial have reported any difficulties. If the technology could only be administered in secondary or tertiary hospitals, having to travel long distances for weekly infusions could pose a problem for immobile patients.

(iv) Are there any situations where patients may choose not to use this technology?

Regular travel would not deter patients wanting to receive the therapy. However, the opportunity to receive the treatment by home infusion or in a local NHS facility would be much preferred, particularly by patients who would have to take time off work or organise additional child care in order to be able to make weekly trips to the hospital.

Patients with young children specifically said that they would accept any inconveniences associated with receiving this therapy rather than consider a lung transplantation due to the high risks and short average survival associated with such a major procedure.

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9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Based on data from a large AATD registry in the UK, we estimate the number of patients with AATD-associated emphysema to be around 650 patients, with 400-450 of those being eligible for the therapy under evaluation.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment] is licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

We are not aware of any potential equality issues in relation to the technology under consideration.

Other Issues

Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Contrary to the listed comparators in the final scope for this evaluation, we do not agree that lung transplantation and lung volume reduction surgery are viable comparators for the technology under evaluation. Although lung transplantation is a recognised treatment option for AATD patients with terminal respiratory failure due to severe emphysema, where the only alternative options are death or intolerable breathlessness, we would not consider it as a standard treatment available to patients for the following reasons:

a) The shortage of available donor organs results in inequitable access to this intervention and, in reality, transplantation is therefore only available to a small number of AATD patients. Patients may also not survive on the waiting list because of limited organ availability.

b) Many patients in our charity who had positive lung transplantation assessments, have decided not to be added to the transplant waiting list, as they feel unable to cope with the psychological impact of such a major decision and risky intervention.

Similarly, for AATD patients with predominantly basal emphysema, lung volume reduction surgery (LVRS) is also a symptomatic treatment option that may reduce breathlessness. It should be noted, however, that the suitable patient population is very small, and the durability of the benefits derived from LVRS in patients with AATD seems inferior to that of patients with usual COPD and it is not generally recommended (Donahue and Cassividi. Thorac Surg Clin. 2009; 19(2):201-208). We had reports from patients who were declined for lung transplantation due to prior LVRS, which further limits the available treatment options.

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Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: British Thoracic Society

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? No
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
No links

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What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Approx 1500 known cases PiZZ/Znull AATD, of whom 200-250 potentially eligible for treatment based on criteria discussed below, could be more dependent on FEV1 threshold chosen and whether confirmed decline is a required feature for prescription (as it could be if we wish to ration in order to limit cost burden to the NHS). FEV1 limits are discussed below and could be confirmed in a national guideline.

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

AATD patients have access to some clinics where the consultants have expertise in AATD, through the NIHR network. However most patients attend general respiratory clinics and not a specialist service. No specialist services are commissioned and all patients who see experts in AATD do so through the general respiratory outpatient tariff. Birmingham is the largest service in the UK and sees approx. 10 patients/week; other centres seeing significant patient numbers are in Southampton, London, Cambridge and some smaller patient cohorts are seen by consultants with AATD expertise in Leicester and Coventry.

Treatment of AATD lung disease in the UK at present is limited to best practice for COPD in the UK – ie inhaled therapies, smoking cessation and pulmonary rehabilitation. Some centres also offer endobronchial valves for emphysema to highly selected patients. This is no different from other patients with COPD.

Worldwide intravenous augmentation therapy is used in AATD patients who have emphysema and with circulating levels that are <11um and PiZZ/Znull genotype. Some countries select on the basis of FEV1, others do not, and the range of eligible FEV1 also varies by country with Canada using FEV1 25-80% predicted and others ranges 30-65%. It is generally accepted by the AATD community that augmentation therapy is of value to reduce emphysema progression, as described in the recent European Respiratory Society Working Party statement (Miravitlles et al, ERJ (2017)) and in an NIHR funded systematic review of the therapy done by a UK group (Edgar et al, Int J COPd (2017)).

There are no alternatives to augmentation at this time.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Subgroup published data focuses on FEV1 30 -65%. However: a) below FEV1 = 30%, gas transfer is a better index of disease progression, and b) the phenotype of

emphysema with relatively preserved spiromety is well recognised – some patients with FEV1 > 65% may show rapid progression with a substantial impairment in gas transfer and symptoms. Clinicians should have the freedom to treat patients outside the FEV1 thresholds above when there is evidence of progression on gas transfer or lung density. Risks of the technology do not differ by subgroups.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

If augmentation were in regular use in the UK specialised services would need to be commissioned to allow them to run with the time and additional features needed to assess for augmentation and see patients more regularly; for example lung function monitoring allied to clinic appointments would need to be supported by an appropriate clinic tariff and CNS support to clinics would need to be widely available to assess patient suitability for remote treatment (hub/spoke model of iv delivery), whether they could self-administer treatment, or whether they should attend a major national centre such as those where NIHR network AATD clinicians are based for all doses. Iv dosing in a hub/spoke model outside major centres would likely key into existing community services that deliver iv drugs but additional staff training may be needed.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Augmentation therapy is not available routinely in the UK, and it is therefore not being used outside license. A few patients receive it for panniculitis (skin lesions related to AATD) but there are probably <10 who do.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Systematic reviews were used in the ERS working party statement mentioned previously; a copy can be provided if desired. A similar US guideline using systematic review methodology was published in J COPD Foundation, and similar conclusions were drawn regarding augmentation to the more recent ERS document.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

It is the opinion of the NIHR network that if therapy were not altering emphysema progression, as defined by CT scanning, then the treatment could possibly be stopped, but this is not usual practice worldwide. If we were to make this criterion then facility for CT scanning with quantitative analysis would need to be available in the NHS – it is not at present, and software plus staff training might be needed to allow this. Research centres in the UK are familiar with it, several of which lie in the NIHR AATD network

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Augmentation is not used in the UK, but practice worldwide is largely consistent with the trials. Limited real life data exists on whether response to treatment outside trials is the same as in them; the Birmingham AATD group have several funded research studies looking at this at present comparing matched augmented patients in the US to untreated ones here. These studies will look at mortality, quality of life and exacerbations and will complete in the next 6-18 months (exacerbations data and QOL data takes longer than mortality as is being done prospectively). Dr Turner can provide more info on these studies if desired.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Side effects are rare and generally linked ot infusion reactions as this is a blood derived product. No new effects became apparent in the various national registries that are available and use augmentation.

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

N/A. All major trials and systematic reviews are in the public domain. Please check the ERS working party statement for all major citations of evidence.

This response has the support of the NIHR AATD Group.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

If recommended national centres would need to be established and funded appropriately; these exist via the NIHR network and centres named previously but funding and recognition of the service would need to be approved. A national guideline would then be appropriate which the NIHR network could provide. CT scanning analysis equipment and iv delivery services as mentioned previously would be required.

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Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Equality of access between countries within the UK may be an issue as some devolved nations have already made a decision on this technology (specifically Wales)

NICE National Institute for Health and Care Excellence

Clinical expert statement

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **x**☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x**☐ other (they didn't submit one, I don't know if they submitted one etc.)-they did not submit one
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes **N/A**

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To delay progression of emphysema associated with severe PiZZ or PiZ null alpha 1 antitrypsin deficiency. The severe lack of circulating A1AT in individuals with A1ATD leaves the lungs exposed to proteolysis leading to lung destruction. This therapy augments the small amount of A1ATD in the blood to levels that are protective- hence delaying the progression of lung disease.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Delay in progression of emphysema in an individual with A1ATD as evidenced by reduction in slope of lung function decline and reduced rate of CT densitometry decline.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes- there is a massive unmet need. This genetic condition currently has no specific treatment anmd affected individuals (often on the 3rd-4th decade of life) suffer with progressive loss of lung function and develop severe intractable breathlessness, disability and ultimately death. Augmentation therapy has been available in many other countries for many years – this slows the rate progression of disease.. Patients in the UK have not had access to this therapy.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Current treatments are those for usual COPD and are only supportive and symptom based (inhalers, oxygen therapy, pulmonary rehabilitation. These treatments do not target the underlying disease or prevent progression of emphysema- unlike augmentation therapy. Current treatment is therefore inadequate and would be improved massively by access to augmentation therapy for those who would benefit.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The European Respiratory Society statement on AATD has been published recently Eur Respir J. 2017 Nov 30;50(5). pii: 1700610. doi: 10.1183/13993003.00610-2017. Print 2017 Nov. This advocates augmentation therapy for those who would benefit. GOLD guidance and ATS guidance both advocate augmentation therapy.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are centres of expertise in Birmingham, Cambridge, Coventry, Royal free, Southampton, Brompton. We all link through the NIHR A1ATD network and agree on pathways. I am not aware of any significant disagreements in this area. The ERS statement above details the pathways for lung disease. There is geographical variation in access of patients to clinical experts, however, PSSAG has agreed that the commissioning pathway should sit with specialised commissioning, hence specialist centres will be formally commissioned and provide better access to appropriate care for patients.
• What impact would the technology have on the current pathway of care?	Augmentation therapy would have a major beneficial impact on the pathway for patients- giving them a therapy that targets the underlying disease and therefore significantly delaying onset of disability and reducing exacerbations .
11. Will the technology be used (or is it already used) in	No. Assessment and monitoring for Respreeza is highly specialised therefore Specialised centres would assess and select individuals for the therapy. Such specialist centres would be commissioned by usual commissioning processes.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The technology delays lung function decline associated with A1ATD as such it delays the introduction of therapies such as inhalers, long term oxygen, non-invasive ventilation, lung transplantation and reduce admissions rates and hospital admissions and improves quality of life and prolong survival
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Designated Specialist centres alone should be responsible. AATD is rare and the clinical impact of AATD on lung function is variable and therefore requires specialised assessment.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The introduction of specialised centres will provide the necessary commissioned expertise- clinical, lung physiology and radiology (ct scan). All these requirements are currently available in current centres of expertise but there needs to be better geographical coverage. To allow access to appropriate care. Pathways for delivering the IV therapy would have to be developed – this should be straightforward as these pathways already exist for other drugs e.g. IV immunoglobulin therapy.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Absolutely. There is currently no therapy currently that will allow the rate of progression. This technology provides the exciting prospect for the first time of making a meaningful difference to A1ATD individuals
• Do you expect the technology to increase	Yes – see above by delaying the rate of progression of disease

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes- by delaying lung function progression and therefore reducing the onset of disability and QOL.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those who would benefit are - Those with PIZZ or PI Znull NOT PI SZ or PI MZ phenotypes of A1ATD. Phenotyped and /or genotyped in a recognised laboratory, with evidence of emphysema and progression of emphysema and lung function decline faster than age related decline. As evidenced by CT densitometry and lung function. - Non smokers - No other comorbidities that would confound outcomes –e.g. advanced renal/liver cardiac failure, progressive cancer significantly affecting QOL.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	It will require IV therapy which should be straightforward- as above. Home care through local providers may be required. Monitoring for efficacy through the specialist centres-lung function, QOL, CT densitometry-this is only available in centres of expertise.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Initiation as above-evidence of emphysema related to A1ATD- not smoking related emphysema Progression of emphysema on CT densitometry and/or lung function decline greater than normal age related rate of decline in those who have stopped smoking. Serial monitoring with lung function (annually) and CT (every 3-5 years) these need to be done in specialised centres In those who do not show an improvement in the rate of decline consider reasons why and consider stopping treatment. Those with very advanced disease MRC grade 4,FEV1 <20% consider carefully benefits before initiation.

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes- reduced exacerbations, and health care utilisation as the rate of decline will be lower.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Absolutely. I strongly recommend its availability for use in A1ATD specialist centres. It is highly novel and will produce a change in the paradigm of care and clinical outcomes.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any	Yes- there is no current disease modifying treatment.

particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No significant issues
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	No- as we don't have access to therapy. We in the UK have close working relationships both clinically and research – see ERS statement Assessment in other countries using augmentation therapy does reflect UK practice in specialist centres.
• If not, how could the results be extrapolated to the UK setting?	It is highly likely that the same benefits will be generated in the UK
• What, in your view, are the most important outcomes, and were they measured in the trials?	Change in the rate of lung function decline and reduced loss of lung tissue- CT densitometry- these were measured in the trials

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	It is likely that reduction in rate of decline in lung function will have benefits long-term- less disability and improved mortality.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There may be benefit from contacting the National AATD registry in Birmingham re epidemiology of the condition in the UK
21. How do data on real-world experience compare with the trial data?	Patient groups included in trials reflect the current population in the UK
Equality	
22a. Are there any potential equality issues that should be	Yes- it is important that individuals and patients with rare genetic diseases have access to specialist care and to therapy. This is currently being denied them.

taken into account when considering this treatment?	There should also be equality in access to specialists and augmentation therapy- PSSAG's recommendation that A1ATD be specialised will ensure the latter. A core function of these specialised centres will be to treat appropriate patients. Therapy is personalised and relies on a great degree of experience in management of AATD.
22b. Consider whether these issues are different from issues with current care and why.	Currently AATD individuals in the UK do not have equality of care with those in many other countries in the EU and NORTH America. – for the reasons above.
Topic-specific questions	
23a. Would surgical treatment options such as lung transplantation or lung reduction surgery suitable comparators in the population being considered?	No- these treatments are not suitable comparators.. These interventions unlike Respreeza do not prevent progression of disease but only treats patients once they have established advanced disease and are already disablked.. This, the key difference with augmentation therapy is that is prevents progression to the advanced stage. Furthermore transplantation and LVR have a high morbidity and mortality and highly selective criteria.
23b. Do you expect that respreeza will be used as a bridge to surgical treatments?	Respreeza should delay the progression of the disease to reduce the need for LVR and transplantation.

24. Is lung density predictive of survival and health related quality of life in this population? (e.g. is it an appropriate surrogate for disease severity and mortality in people with emphysema)	Yes, It is the best parameter in AATD related emphysema. This is only available in specialist units.
25. Do you expect long term outcomes to be dependent on the brand of A1PI used? (e.g. is it reasonable to draw conclusions from long term evidence relating to other brands of A1PI)	Unlikely.-There may be small differences in activity of A1AT preparations- but several studies with different preparations of A1AT have shown a benefit. In my opinion, the Respreeza data is the most convincing due to the study design and endpoints, but it is unlikely that there are major differences in efficacy between preparations.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Respreeza slows the rate of progression of AATD related emphysema-
- This is a highly novel technology that radically alters the treatment for A1ATD- there is no other therapy that slows progression of disease and currently no treatment for AATD.
- I strongly support that Respreeza is made available for use in carefully selected PiZZ or Pi Znull patients through specialist AATD centres with strict criteria for use
- Patients with this genetic condition should have access to this disease modifying therapy as soon as possible
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.) **I don't know who nominated me**
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Augmentation therapy for AATD aims to slow disease progression; ultimately it aims to stop progression altogether but the available evidence only shows slowing. By preventing some of the decline in lung function disability may be delayed or prevented
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The majority of trials of treatment (as opposed to real-life data) has shown outcome in terms of CT density of the lung. There is no formally accepted minimal clinically important difference in this outcome, but it has been shown both cross-sectionally and longitudinally to associate with other important outcomes such as mortality (Dawkins et al, Resp Med (2009)) and lung function, consequently any reduction in lung density decline should prevent deaths in the long run. Minimal evidence from real-life data in the NHLBI registry supports this assertion, and my group has an ongoing collaboration and research project with the USA (where augmentation is used routinely) to assess this in data from US treated patients and data from untreated AATD patients in the UK registry. My group have also conducted a systematic review of the clinical utility of CT density measurements (Crossley et al, Int J COPD (2018)). 112 studies were included, with 82 papers being suitable for meta-analysis, the largest meta-analysis including 18984 patients. Our data showed that association between CT density and other clinical parameters deemed suitable as outcomes for airways disease trials (eg, FEV1, SGRQ) were consistently significant, and furthermore there was a clear and consistent relationship to mortality. This suggests that CT density is an appropriate surrogate outcome measure in studies of emphysema, like those conducted in AATD. My group have also used the systematic review data and that from the UK AATD registry to try and derive a minimum clinically important difference in CT density change per year (PD15 g/l/year). This data is under submission and as yet only published in abstract form (Crossley et al, AJRCCM (2018) – American

	Thoracic Soc conference, San Diego); there are several ways to calculate an MCID and we have done this using all methods, then validated by looking for associations between the various potential MCID generated and outcomes such as FEV1 and mortality in the UK registry patients who have serial CT scan data available. The MCID appears to lie at/below -2g/l/year. If NICE would like me to provide the submitted paper and relevant figures from all analyses I am happy to do so, provided the paper is kept confidential since it is not yet in the public domain.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is no specific treatment for AATD available in the NHS, unlike other European countries and the USA (amongst others). There is also no national commissioning of specialist assessment services for AATD, so most patients attend general respiratory clinics and may or may not see an expert in their condition – this is a further unmet need which would warrant addressing if augmentation were made available, to ensure that the most appropriate patients were selected for it. Some NHS Trusts have established tertiary clinics, recognising the need for specialist multidisciplinary services for these patients; many did so after the NIHR AATD network was established a few years ago, and the NIHR centres would be a reasonable starting point for AATD centres if national commissioning were made available. Some non-NIHR network Trusts have capability too (eg Coventry), largely due to their consultants having been trained either in the Birmingham centre or in a relevant non UK centre. There is a European Respiratory Society statement on quality care for AATD (to which I contributed) which could guide service specifications if required.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients generally receive non-specific treatments aimed at COPD or liver cirrhosis, these being the 2 conditions to which AATD predisposes. This may be in a general respiratory outpatient clinic +/- hepatology outpatient clinic, or in a tertiary service such as that in Birmingham. The Birmingham service is set up to offer a one-stop clinic incorporating lung function, liver assessment and clinical review on the same day to smooth the pathway for our patients who travel from all over England and Wales to us. Multispeciality clinics are available for those patients who need them (hepatology and dermatology support). We have to complete named patient applications for some CCGs to allow them to come, which adds an administrative burden.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	European Respiratory Society statement (ERJ (2017) is the most recent. Whilst not termed a guideline it was generated using systematic review methodology and provides recommendations for practice. A US based version was also published in the J COPD Foundation (2016), although was perhaps a bit less extensive in the topics covered and literature reviewed.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is certainly guidance on this but the lack of national commissioning and variable funding for patients to attend tertiary centres due to this means that those seen in less experienced places may not be getting ERS standard care. Those centres in the NIHR AATD network are in general agreement on the fact that national specialist centres would be a good thing and most support use of augmentation, at least in some patients. The pathway at the moment probably goes something like this • Patient gets tested for AATD either because of early onset COPD or liver disease • Gets managed by a local respiratory physician in a normal outpatient service (or hepatology service) • May or may not get referred to a tertiary centre • Followed up annually by local +/- tertiary centre giving best supportive care, and non specific treatments such as inhalers for COPD • If disease progression occurs may be referred to lung/liver transplant
• What impact would the technology have on the current pathway of care?	If introduced I think national centres would need to be established to assess patients for treatment, which could then work in a hub-spoke model with other hospitals/community services across the UK to deliver the treatment. In this model the hubs (specialists) would assess the patient and determine if they were deteriorating sufficiently to warrant augmentation, then would recommend prescription to a spoke centre closer to where the patient lives. Spokes would adminster the infusions weekly, and/or teach patients to infuse themselves. In the USA most patients either infuse themselves or receive infusions in a community setting (AlphaNet, personal communication – I have requested detailed data on proportions receiving in each setting and should have this by the 23rd Aug) Ideally the NHS would train the hubs in CT density measurement (many will already have experience through research studies) and fund the software required to do this, so that pre-treatment disease

	progression and on-treatment disease progression can be assessed. This would allow assessment of response to treatment quicker than other clinical measures and potentially provide an exit strategy for patients who do not respond (the number of these individuals is not easy to determine in published trial data).
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is not currently available therefore N/A
• How does healthcare resource use differ between the technology and current care?	Patients will require weekly infusions of Respreeza, and the first one will need to be in a supervised environment due to the (very low) risk of a reaction. More detailed assessment of disease progression may be needed to determine eligibility to start and continue treatment. Since the treatment affects disease progression there would be a rationale for establishing progression first, either through past lung function data or serial CT scans over ~2 years, before starting treatment and possibly using similar measures to stop it. If rationing were required this would be one way to do it
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Assessed in specialist clinics, working in hub-spoke as described above, with infusions largely delivered in community settings. Note that many places have home iv antibiotic services and this could fit in with existing providers of such.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	1) Formal establishment of national centres, with ability for all areas to send for tertiary review (see prior comments on 'postcode lottery') – could this be via national commissioning, as for other areas of respiratory that have high cost drugs? (CF, severe asthma etc) 2) Ideally ability for these centres to do quantitative CT – training/software provision. Second best would be to use gas transfer measurements, which capture 80% of patients whose CT density is deteriorating (unlike FEV1 which only captures half (Green et al, Resp Med, 2016). 3) Negotiation with local providers of home intravenous drug services to gain agreement to use them for delivery
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes – in trials it has been shown to slow the decline in CT lung density, a measure which has been shown both cross-sectionally and longitudinally to associate with mortality (Dawkins et al, Resp Med (2009)), consequently any reduction in lung density decline should prevent deaths in the long run. Minimal evidence from real-life data in the NHLBI registry supports this assertion. My group have also conducted a systematic review of the clinical utility of CT density measurements (Crossley et al, Int J COPD (2018)). 112 studies were included, with 82 papers being suitable for meta-analysis, the largest meta-analysis including 18984 patients. Our data showed a clear and consistent relationship to mortality. This suggests that CT density is an appropriate surrogate outcome measure in studies of emphysema, like those conducted in AATD.
• Do you expect the technology to increase health-related quality of	Whilst our systematic review referenced above showed a clear relationship between measures of quality of life (eg SGRQ) and CT density our other meta-analysis of the effects of augmentation (Edgar et al, Int J COPD (2017)) did not show a significant difference in SGRQ between placebo and actively treated patients – the direction of effect was toward benefit but the range was such that it crossed the line of no effect and therefore uncertainty remains. (Small and non-significant changes in health status were observed in both

life more than current care?	groups demonstrating greater worsening in SGRQ on placebo 0·83 (-3·55 to 1·89; p=0·55). Logically I would expect improvement given the biological effect and relationship to CT density in large cohorts cross sectionally and longitudinally, however this remains unproven in trials due to the large size that would be required to prove benefit. Real-life cohorts of treated and untreated patients provide another potential source of this data, and my group were awarded funding by the American Thoracic Society this year (contract being finalised) to analyse this. The ERS have also recently funded a Europe wide registry of AATD patients which might be a mechanism to look at this longitudinally in a second group of patients.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients should be similar to those in the trials ie PiZZ genotype or equivalent in terms of AAT level/function. These people generally have an AAT level <11micromol. Those whose lung disease is demonstrably progressing either in terms of lung function (FEV1 or gas transfer) or CT density would be most likely to benefit, since this is the measure which treatment benefitted in trials. Sub-cut data in trials and in real-life datasets (see also Q21) suggests that those with an FEV1<30% predicted may benefit less, however this is probably because the FEV1 has bottomed out at this point, and in such patients my group have shown that gas transfer decline is more marked (Pillai et al, Annals ATS (2015)). Gas transfer is arguably a better measure of emphysema than FEV1 hence if gas transfer is getting worse then so is the emphysema. Consequently it would not be logical to set FEV1 limits if disease was still progressing by density or gas transfer decline. We have also looked to see how many patients FEV1 and gas transfer pick up, of the total number of patients who have progression on CT – FEV1 picks up around half and has transfer approx 80% (Green et al, Resp Med 2016). Thus serial data on both measures rather than a single cut off value is probably the gold standard to pick up deteriorating patients.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	Please see my answer to Q11 – in short it will be more difficult, but not very much so if existing specialist centres are formally recognised and funded as such. Monitoring requirements would not change a lot within

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	tertiary care (annual) but more local reviews might be needed for patients having regular infusions, to ensure no issues with iv sites etc.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	We could use CT density decline as a stop measure ie if no effect of the drug on density decline then stop it. This is not a measure in use anywhere else in the world but is logical given that the major effect is on disease progression by this measure. This would require CT scans perhaps annually, or once every 2 years, once on treatment.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	Patients may be able to continue working, thus gains to the wider economy. If lung transplants are delayed to beyond the age where lung transplantation is generally offered (age 60-65 maximum) then more lungs may be available for those with other progressive conditions occurring at younger ages (eg CF)

quality-adjusted life year (QALY) calculation?	Patients in the UK are very aware of the fact that they do not get treatment but many other places in the world do, and as such mental health benefits could accrue too should treatment be available – even if not for everyone.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, as delineated by my previous answers on clinical benefits. However it is not a panacea and further research into optimal patient selection, either through registries or biomarker studies in future clinical trials are still likely to be needed Need would be met by (a) establishing of national centres (b) giving treatment to those most likely to benefit, such that their disease progression slows, disability and death are delayed
• Is the technology a 'step-change' in the management of the condition?	Yes – at present we have no specific treatment in the UK, and this would change that.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – there are no treatments that adequately (or even inadequately) reduce lung disease progression in AATD in the NHS at present

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are no major side effects; difficulties with iv access are not generally seen in the countries which have been using similar products for years, but this is a theoretical possibility
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Mostly – in that patients were non-smokers (ie they had to stop prior to treatment or had never smoked), and had other treatments (non-specific ones) optimised first, and were seen by a specialist. Visits were perhaps more frequent than the usual care pathway in the UK, which would typically have 6-12 monthly outpatient clinics, only increasing to 3 monthly in the most unwell people.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	CT density, FEV1, gas transfer (DLCO or KCO), mortality, exacerbations, quality of life – all were looked at in trials, but only powered for CT density.
• If surrogate outcome measures were used, do they adequately predict	Please see my answer to Q8

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There is quite a lot of registry data out there, and systematic reviews limited to RCTs would obviously not include this. Our systematic review of augmentation therapy was not limited to RCTs (unlike Cochrane, for instance), hence provides a summary of this other data (Edgar et al, Int J COPD (2018). In short, registry data and that from large cohorts provides some evidence of benefit on mortality and exacerbations, which was not able to be shown in trials. Naturally uncertainty is there, and some of my groups ongoing research aims to address this uncertainty.
21. How do data on real-world experience compare with the trial data?	Generally supportive of the trial data, as per comments above. Below is an extract from the relevant section of our systematic review, which describes the observational controlled cohort data. There were six eligible controlled observational studies, comprising 2610 participants. AEs and reasons for starting/stopping therapy were reported by one registry; severe events occurred at a rate of 9·5% (69/720 infusions).[32] The largest observational study analyzed data from 1129 patients in the US AATD registry split into three groups "always receiving" (n=390), "partly receiving" (n=357) or "never receiving" (n=382) augmentation.[33] Dosing was not standardized with only 51·3% being dosed weekly throughout the study. A survival analysis was conducted, but excluded 81 subjects (55 deaths) due to missing data, such that results could have been biased. Overall mortality was 18·1% (n=204); it was significantly higher for subjects who never received augmentation therapy (as opposed to sometimes or always) when FEV_1 <50% predicted ($p < 0·001$). Mortality rates were low for other subjects and did not

	differ between augmentation-therapy groups. FEV_1 decline was calculated using a slope equation in 927 patients with n=202 excluded due to insufficient data; patients receiving augmentation with mean FEV_1 values of 35-49% predicted had a slower rate of FEV_1 decline (-73·7±6·8 v -93·2±8·9; p=0·03) though this was not seen in the whole group. Three other studies investigated the effect of AAT augmentation on FEV_1 decline.[34-36] Seersholm *et al* undertook a non-randomized surveillance study in two cohorts. A statistically significant difference in FEV_1 annual decline was observed -53 (48–58) v -75 (63–87)ml/year in treatment v placebo; p=0·02).[34] The other two studies concurred with this result. Wenker *et al* conducted a pre-post study of augmentation, using an inclusion criteria of ≥2 lung function measurements prior to augmentation and two following commencement of therapy within a minimum period of 12 months.[36] FEV_1 declined significantly slower (-34·3±29·7mL/yr. v 49·2± 60·8 mL/yr., p=0·019) after starting augmentation. Tonelli *et al* compared 124 augmented PiZZ patients to 40 non-augmented patients who had a median of 2 spirometry measurements over a mean follow-up of 41·7±2·6 months.[35] Again FEV_1 decline was worse in untreated patients (+10·61± 21·4 v -36·96 ± 12·1 mL/yr.; p=0·05). All three studies stratified patients to groups by their FEV_1 at presentation - FEV_1 <30%; 30%-65% and >65% predicted.[34-36] Patients with FEV_1<30% were consistently observed not to benefit from augmentation in terms of FEV_1 decline. Two of the three studies showed those with an FEV_1 >65% to have statistically significant reductions in FEV_1 decline when on augmentation (-122·5±108·4 v-48·9±54·9mL/yr.; p=0·045 and −108·7 ± 17·3 v −29·2 ± 15·29 mL/yr.; p=0·0006).[35,36] Treatment effect was restricted to patients with FEV_1 >30 and <65% (-62 (57–67) v -83 (70–96) mL/yr.; p=0·04) in one study.[34] When FEV_1 at commencement of therapy was used to group patients, a statistically significant decrease of rate of decline during treatment was seen if FEV_1<30% (53·4±45·3 to 22·1±16·0mL/yr. (p<0·0001)).[36] Sub-grouping the FEV_1>65% group demonstrated marked benefit in those deemed rapid decliners (FEV_1 decline pre v post augmentation -255·7±70·4 v 52·7±61·3mL/yr. (p=0·0016)). The most recent study, by Barros-Tizón *et al*[37] was a retrospective medical records review of 127 participants evaluating the effect of augmentation on exacerbation rate. Seventy five patients had ≥1 exacerbation during the 18 months follow up required prior to commencement of augmentation. Dosing regimens were not standardized with an average dose of 60·7 ± 3·8 mg/kg/week(Supplementary Table1) different to other studies[33], and many patients had missing data. Fewer exacerbations were seen (1·2±1·6 v 1·0±2·2 pre v post treatment; p<0·01), an effect more marked in those exacerbating previously (2·0 ± 1·6 v 1·4 ± 2·7; p<0·01).
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Treatment is currently inequitable across Europe and the world with some countries using and others not. Other than the fact that even limited use in the NHS would address this inequality I cannot think of any equality issues of note
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23a. Would surgical treatment options such as lung transplantation or lung reduction surgery suitable comparators in the population being considered?	There is no evidence of benefit of LVRS in AATD patients from trials and the data in real-life is extremely limited (see also our systematic review (Edgar et al, as before). This treatment would therefore not be a sensible comparator. Below is an extract from our review describing evidence for LVRS in AATD Six studies investigated the use of LVRS in AATD. Five studies (n=71 patients) used an open surgical technique[56-60] and all demonstrated improvements in either physiological measurements or dyspnea. Benefits were inferior and shorter in duration than usual COPD patients in all studies. One small RCT randomized participants to LVRS (n=10) or medical treatment (n=6); higher 2 year mortality (20% v 0%) occurred in the surgical group, albeit alongside improvements in SGRQ.[59] There was one published study using endobronchial valves which demonstrated their safety in AATD patients with significant benefits in mean FEV_1 at six months, one and two years (p=0·0022, p=0·0067 and p=0·033 respectively).[61] The generalizability of this study is not evident as this cohort included strict inclusion criteria including sever heterogeneous emphysema demonstrated by CT scan and scintigraphy, RV≥140%, FEV_1 15-45% and optimal lobe selection. This resulted in fewer than half of referrals meeting this criteria

	Lung transplant is offered to patients with a BODE score greater than or equal to 8, and generally to patients with FEV1 and gas transfer measurements both at around 30% predicted or less. This population appear to benefit less from augmentation (although see also my answer to Q13) than others thus this would not be a sensible comparator, because most patients receiving treatment would not have FEV1 in this range. Furthermore if this comparator were used then the age limits around transplant could bias results (patients aged 60-65 are generally the upper age limit for transplant) and introduce inequity for augmentation based on age, which RCT results would not suggest to be warranted.
23b. Do you expect that respreeza will be used as a bridge to surgical treatments?	Yes. It may delay the need for referral to transplant. The evidence on use of LVRS in AATD is so limited that it would be unlikely to be a bridge to this in many patients; individual assessment is the norm for this as the emphysema distribution and other CT parameters may identify rare patients whose characteristics suggest LVRS might benefit them in the same way to usual COPD
24. Is lung density predictive of survival and health related quality of life in this population? (e.g. is it an appropriate surrogate for	Yes, please see my answers to Q8 and Q12

disease severity and mortality in people with emphysema)	
25. Do you expect long term outcomes to be dependent on the brand of A1PI used? (e.g. is it reasonable to draw conclusions from long term evidence relating to other brands of A1PI)	No. I think all brands of augmentation therapy are likely to be similar – this is supported by low heterogeneity of results in the meta-analysis we did (Edgar et al, as before) which included studies of Prolastin and Respreeza for the RCTs and other brands as well in the observational cohorts
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- AAT augmentation therapy, whether using Respreeza or other brands, demonstrably reduces disease progression as measured by CT density, supported by systematic review and meta-analysis
- CT density is a good surrogate outcome because it relates to FEV1, QOL and mortality; systematic review evidence of this exists
- Patients should be selected for AAT augmentation by specialist centres, most likely after a period of observation to demonstrate that disease is progressing. This will require agreement, such as national commissioning, to ensure equity across the NHS
- Patients with AATD, confirmed by genotyping, and progressive disease should receive a trial of augmentation, and if no effect is shown on disease progression then consideration could be given to stopping it
- Introduction of augmentation to the NHS would be possible through existing AATD specialists, linking to existing intravenous drug services, provided training in CT analysis and adequate funding for a hub-spoke model service were available

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): nominated by Alpha-1 UK Support Group for patients with the condition and their families.
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of intravenous human alpha1-proteinase inhibitor therapy is to retard or prevent the progression of emphysema secondary to AATD. Through the reduction of protease activity in the lung and the consequent reduction of proteolytic tissue damage and protease-induced inflammation in the lung, it is intended to preserve lung tissue and, thereby, maintain functional ability for longer, and to reduce the severity of exacerbations. The onset of disability and mortality would, therefore, be delayed by long-term usage of the treatment.
8. What do you consider a clinically significant treatment	Published data from a controlled study, in which patients were randomly allocated to the treatment or placebo, have shown that the rate of decline in lung density measured using computed tomography (CT) densitometry is

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	slowed by 33%. Lung density decline was reduced from 2.19 g/L/year in the placebo treated patients to 1.45 g/L/year in the patients treated with the technology (a reduction of 0.74 g/lLyear). I consider this to be a highly significant clinically-relevant response that will have a significant beneficial impact on the natural history of the disease. There is a linear relationship between the decline in CT lung density and the reduction in FEV_1 over time. This relationship enables an approximate estimation of the equivalence of lung density decline in terms of the loss of lung function. Previously published data would suggest that 10g/L loss in lung density equates to approximately 1 litre loss in FEV_1. Application of this relationship to the trial population would represent a treatment benefit of an annual preservation in FEV_1 of 74 ml. In comparison, observational data of a cohort of patients without access to anti-protease therapy attending the UK National Registry demonstrated a mean annual decline in FEV_1 of 90 ml in patients with moderate disease and 52 ml / year in patients with severe disease (Dawkins et al. Eur Respir J. 2009 Jun;33(6):1338-44. doi: 10.1183/09031936.00061208). A linear relationship also exists between the decline in lung density and worsening health status over time. This relationship indicates that preservation of lung density also equates with preservation of health status. Previously published data have shown that anti-protease therapy also reduces the severity of exacerbations. Since exacerbations are associated with worsening disease progression, worsened quality of life, increased healthcare resource use (particularly hospital admission) and increased mortality, I would expect the technology to have a significant beneficial impact on these outcomes in the long-term. I would expect the above treatment benefit to be transferable to the population of AATD patients in England and to translate into preservation of lung function, health status and reduced mortality with long-term use.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The burden of disease is high and no specific treatment for AATD is available in the UK. Based on my experience of caring for patients with AATD in England and my communications and collaborations with AATD experts and AATD patients in countries where anti-protease treatment is prescribed, I consider that there is a significant unmet need for patients with AATD and healthcare professionals managing these patients in England.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients with severe AATD in England receive only symptomatic treatment for the partial alleviation of breathlessness. There are no specialised treatments targeted at AATD currently available in England. Consequently, patients suffer the effects of faster disease progression than they would otherwise experience if they had access to a disease-modifying treatment to retard or halt disease progression. The general approach is to use treatments recommended in usual COPD, extrapolating the evidence from guidelines for usual COPD.

	In the absence of specific treatments for AATD, the standard of care is that of primary and secondary prevention with smoking cessation therapies, inhaled bronchodilators, which may include long-acting beta2 agonists and long-acting muscarinic antagonists, to relieve the symptoms of breathlessness, inhaled corticosteroids to reduce airway inflammation (and, potentially, exacerbation frequency but at the expense of an increased risk of pneumonia) and pulmonary rehabilitation. Ambulatory and long-term oxygen therapy are prescribed in patients with respiratory failure associated with severe disease. Surgical options are of limited use in AATD (please see Q23). The evidence-base for the use of medicines licensed for the treatment of usual COPD in patients with AATD is extremely limited and the application of this approach is, therefore, based largely on the premise that there is a degree of commonality in pathogenesis and pathophysiology. However, there are important differences between AATD and usual COPD in the pathogenesis, pathophysiology, clinical phenotype and natural history of the diseases. AATD is associated primarily with the development of early onset, panlobular emphysema predominantly affecting the basal lung regions, whereas in usual COPD-associated emphysema centrilobular emphysema develops in the upper parts of the lung (although many patients with usual COPD have no emphysema). Emphysema associated with AATD typically progresses at a faster rate than emphysema associated with usual COPD.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The most recent international guidelines for the management of patients with AATD was published in 2003 (American Thoracic Society; European Respiratory Society. Am J Respir Crit Care Med. 2003 Oct 1;168(7):818-900.). NICE clinical guidance 101 for the management of COPD does not include any detailed information on the management of patients with AATD. The use of human alpha1-proteinase inhibitor is not recommended but this guidance was last updated prior to the publication of critical data demonstrating the benefits of this treatment. Consequently, these guidelines are currently not a suitable reference for optimal clinical management of AATD. CG 101 is currently under review by NICE. More recently, the ERS commissioned a European group of experts in AATD to produce recommendations on the management of AATD (Miravitlles et al. Eur Respir J. 2017 Nov 30;50(5). pii: 1700610. doi: 10.1183/13993003.00610-2017).
• Is the pathway of care well defined? Does it vary or are there differences of opinion	AATD is a rare, genetically inherited condition and the essential expertise that can only be obtained through regular and frequent clinical exposure to patients with the condition is, consequently, largely limited to four

between professionals across the NHS? (Please state if your experience is from outside England.)	centres in England (Birmingham, Cambridge, Coventry and London). There is a general consensus on the management of AATD and the pathway of care within these four centres. However, knowledge and experience of AATD varies greatly across primary and secondary care. Consequently, patient experience differs widely, according to chance, rather than design. Misdiagnoses and delayed diagnoses are common. On average, patients are seen by 7 doctors and experience a delay of >5 years before the correct diagnosis is made. There are well-described diagnostic pathways for the genetic testing of AATD but testing is regularly undertaken by primary care and secondary care physicians who do not follow these algorithms. Conformity to genetic testing standards also varies. Patients who have been tested outside of the specialist AATD centres are often confused by the paucity of pre-genetic testing counselling and clinician understanding of the results of their phenotyping and genotyping tests, and the clinical implications for their health and that of their 'blood' relatives. The subsequent clinical management is also heterogeneous and may not involve any referral to an expert tertiary centre but remain under the care of the local primary care and secondary care physicians who may have little if any previous experience of the condition. Unless referred to one of the expert tertiary centres, most patients report a journey that starts with recurrent primary care visits over several years with symptoms that are usually ascribed incorrectly to asthma. Genetic testing is rarely undertaken in primary care but, when performed, is rarely accompanied by pre-test counselling and informed explanation of the results. Diagnostic uncertainty may lead to referral to secondary care where it is more likely that a diagnosis of COPD will be made and, if the clinical picture does not conform to the typical presentation of usual COPD, AATD testing will be undertaken. Subsequent patient experience depends on local expertise and knowledge. When patients subsequently attend an expert clinic, they usually report that the information provided previously did not provide answers to many of their questions and was often inaccurate. Clinical management in secondary care follows usual COPD guidelines, as described in Q10. Outpatient management is usually provided in general respiratory clinics (or, if the liver is involved, in hepatology clinics). Patients may only be seen by junior doctors in these clinics. Pharmacotherapy and oxygen prescribing is usually guided by secondary care. Exacerbations occur more frequently as disease progresses and is more likely to require Emergency Department attendance and hospital admission. Advanced disease leads to intractable symptoms, the need for long-term oxygen and consideration for palliative care or surgical alternatives. Transplantation is undertaken at several centres in England and requires patient travel for assessment, surgery and post-transplant care, usually on a shared-care model with the their local physicians.

	There is a clear disparity in available service provision and treatment options between patients with AATD in England and those in other European countries. Patients in other European countries (eg Spain, Portugal, Italy, Austria, Germany, Switzerland) and in the US and Canada receive human alpha1-proteinase inhibitor with the intention of reducing the rate of disease progression. In some of these countries, management decisions and care are orchestrated by the regional or national epxert centre using a hub and spoke design. No formal specialised NHS service for patients with AATD-associated disease exists in England and, consequently, the management of these patients is somewhat *ad hoc* and dependent on whether patients are managed by their local physicians or at one of the four aforementioned expert centres. In 2017, the Prescribed Specialised Services Advisory Group's (PSSAG) recommendation that NHS England should directly commission severe or complex alpha-1 antitrypsin deficiency services, received ministerial approval. Commencement of these specialised services was planned to be in place from 1 April 2018, however, service specification do not yet appear to be in development.
• What impact would the technology have on the current pathway of care?	The technology would represent a significant advantage over the current management strategy, which is restricted to symptom alleviation through the application of management therapies for 'usual COPD'. Access to human alpha1-proteinase inhibitor would be a step-change in the management of AATD-related emphysema, because this would be the first time that patients in England would be able to receive a treatment that would modify their disease and reduce the rate of emphysema progression. Availability of the technology would further justify the establishment of NHSE nationally-commissioned Specialised AATD services, which would be the most appropriate setting for all aspects of patient management and follow-up as well as the assessment of individual patient suitability for treatment with intravenous anti-protease and treatment initiation. Standardisation of the clinical care pathway would also be achievable through the management of patients and the co-ordination of their care by Specialist AATD centres. Current international and national guidelines on the testing for AATD are not widely applied which is likely to reflect the current perception in England that the diagnosis of AATD does not greatly affect management strategy. The opportunity to modify the course of disease would greatly incentivise testing and increase the onus of responsibility on primary care and secondary care physicians to diagnose AATD earlier in the course of disease, refer patients to expert centres and commence a suitable management strategy earlier. This would be of benefit to eligible patients who would gain access to relevant clinical expertise and a disease-modifying therapy before the onset of severe disease and its associated morbidity. I would expect long-term use of the

	technology to reduce the required resources in primary and secondary care through improved disease control, reduced symptoms, reduction or avoidance of hospital admission, delayed morbidity and mortality.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is not currently in use in NHS clinical practice but could be easily integrated into current care.
• How does healthcare resource use differ between the technology and current care?	Intravenous therapies are currently delivered in hospital day-case facilities and, using ambulatory care teams, in 'community' settings. Weekly (or, if required, fortnightly) infusions of the technology would be possible in either setting without the need for a significant additional healthcare resources. I would not envisage a significant alteration to the use of clinical investigations to monitor disease progression / response to treatment. There is no clinical need to monitor the clinical safety of the technology, since the side effect profile of the technology is well-established, through long-term use, as being very favourable.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	I would advocate that the assessment of the suitability for use of the technology in individual patients should be undertaken in one of the four existing expert centres in England or, in the future, designated specialist centres within the NHSE Specialised AATD service. Treatment initiation should be given in a hospital setting by a clinician experienced and trained in the use of the technology. Routine administration of the technology after initiation would be best delivered locally, in either a hospital day-case facility or, preferably, with a home-care arrangement. There is only one centre in England where experience of regular use of the technology exists (where a respiratory physician works with almost 20 years of experience in using the technology in routine clinical care in another EU country). Two centres in England have used the technology within a clinical trial setting.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The infrastructure for hospital day-care is likely to exist currently in the majority of secondary care facilities and the low number of patients receiving treatment with the technology in each local catchment area should be easily accommodated in these pre-existing units. Training of infusion nurses and home-care teams would be required, and it would be a reasonable expectation for the investment of home-care arrangements to be funded by the company that provides the treatment.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Human alpha1-proteinase inhibitor therapy has the advantage of providing missing anti-protease which will reduce the proteolytic destruction of lung tissue and reduce lung inflammation. Evidence from clinical trials has shown that the technology provides clinically meaningful benefits through the reduction in the rate of emphysema progression and the severity of exacerbations. Current standard of care does not provide these treatment benefits. Studies which have compared outcomes in countries where therapy is available with those where it is not available demonstrate superior outcomes in those countries where the technology is available.
• Do you expect the technology to increase length of life more than current care?	The technology will retard the progression of emphysema by delaying the onset of respiratory failure and maintaining the ambulatory capacity of patients for longer. I expect that long-term use of the technology will prolong life compared to current standard of care through the retardation of disease progression and the reduction in exacerbation severity.
• Do you expect the technology to increase health-related quality of life more than current care?	I would expect that the technology will increase HRQoL compared to current care. It would maintain ambulatory capacity and independent living, including the ability to undertake everyday activities and self-care, reduce breathlessness, malaise and fatigue, maintain the ability to continue paid employment and ability to lead an active and fulfilled family and social life for longer and improve the emotional and mental health of patients. By reducing exacerbation severity, consequent hospital admissions are likely to be avoided.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is no published data that indicates differential efficacy in subgroups of people with AATD but there is evidence of a more pronounced treatment effect in the basal lung regions, which is where emphysema is usually seen in patients with AATD (Parr et al. Resp Res. 2009:10:75) and in patients who are classified as 'rapid decliners' (Wencker et al. Chest. 2001; 119:737-744). ‘Frequent exacerbators’ may experience greater benefit. Patients who continue to smoke are expected to benefit less than the general population.
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Current care does not employ the routine use of intravenous therapy. Patients would receive weekly (or fortnightly) infusions. Administration could initially be given in hospital on an ambulatory / outpatient basis. I would favour the use of home administration and this arrangement is also usually the choice of patients. Centres that have not had previous experience from using the technology would require some familiarisation with reconstitution and delivery of the drug. Weekly intravenous cannula access can be a deterrent for some patients for whom venepuncture is unacceptable, or in patients who have poor venous access because of idiosyncratic venous anatomy (but the number of patients for whom this will constitute a significant obstacle is likely to be very small). The technology is not suitable for patients with IgA deficiency who are at risk of developing hypersensitivity reactions (as per SmPC).
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There is no expert consensus on the use of stopping or starting rules for the technology. Patient acceptance of the need for weekly infusions and continued smoking abstinence would be necessary. I would advocate an approach of starting treatment in patients who are over the age of 18, have severe AATD (serum concentration less than 11μM), who are never-smokers or ex-smokers for at least 6 months, with pulmonary emphysema demonstrated by chest CT imaging. Monitoring of disease progression would require further testing of lung function and CT imaging. It is unlikely that repeated tests to monitor levels of alpha1-antitrypsin in the blood would be required on a routine basis.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Patients commenced on treatment with the technology have reported improvements in their general physical and psychological well-being to me which may not be (fully) captured in the QALY. It is specifically reported that they experience less breathlessness and greater exercise tolerance (eg ability to climb stairs, walk further etc) and are less susceptible to catching chest infections and suffering exacerbations. The symptoms of exhaustion, fatigue, muscle and joint discomfort are also reported by many patients to improve following commencement of treatment with the technology. Treatment is also reported to alleviate depression, feelings of anxiety, guilt and foreboding which relate to the fear of significant morbidity and early mortality. However, these beneficial effects have not yet been systematically studied or captured in trials.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on	The technology would represent an innovative therapeutic option for English AATD patients even though it was first introduced in 1987 following approval by the US Food and Drug Administration. Since then, it has been available to thousands of patients around the world. I consider that the technology will provide substantial and significant benefits to patients by reducing or halting disease progression, thereby prolonging their physical and

health-related benefits and how might it improve the way that current need is met?	mental health. This will improve their potential ability to increase working hours or avoid early retirement due to the condition, thereby lessening the detrimental effect of the condition on their earning potential. The technology would also reduce the impact of AATD on families and carers of patients with advanced disease who experience the substantial burden of caring. In particular, I would consider the technology to have a beneficial effect on partners/spouses who would otherwise have to reduce their working hours and limit career potential, resulting in loss of earnings as a consequence of having to care for patients. The technology would also improve the ability of patients to participate in family life and reduce the detrimental effect their condition has on partners and, particularly, their children.
• Is the technology a 'step-change' in the management of the condition?	The technology would represent a step-change in the management of the condition. Patients with AATD in England currently receive only symptomatic treatment for the alleviation of the symptoms of breathlessness. However, this approach does not influence the natural history of disease, which is that of inexorable progression.
• Does the use of the technology address any particular unmet need of the patient population?	Patients currently experience accelerated disease progression, recurrent hospital admissions, leading to worsening health status, premature employment cessation and disability, followed frequently by premature death. This disease course could be significantly modified through use of this technology, which is currently available in other other European countries, the US, Australia and Canada, This disparity and inequality across different countries, particularly within Europe, is considered unacceptable by patients, who believe that they are subject to discrimination, and by their physicians who wish to have the option of prescribing the same therapy that is available to specialists in other countries.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile is very favourable, and a list of adverse reactions collected from six clinical studies are listed in the SmPC. Hypersensitivity reactions, including anaphylaxis, have been reported. I would avoid home administration in the event of a previous hypersensitivity reaction and stop treatment following an anaphylactic reaction. Transmission of infective agents cannot be totally excluded but data collected over the last 30 years demonstrates that the risk of transmission is extremely low.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials on the technology reflect current UK clinical practice for the management of AATD patients in that the trial populations were representative of UK patients and the standard of care during the trials reflected UK standard of care.

• If not, how could the results be extrapolated to the UK setting?	Not applicable.
• What, in your view, are the most important outcomes, and were they measured in the trials?	I consider that the most important outcome for these trials was CT lung densitometry. Other important outcomes are lung function (FEV1, gas transfer), walking distance, health status and exacerbations. These were measured in the trials but they lack sensitivity (and specificity) and it is not feasible to power a study in AATD to demonstrate treatment effects on these outcomes.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	CT lung densitometry is a surrogate outcome measure that was approved as the primary outcome for use in emphysema-modifying studies in AATD patients by the FDA in 2007. It was validated and developed primarily for this purpose and is now used extensively in studies of emphysema. It is the most sensitive and specific clinical measure of emphysema and has enabled the completion of a study that is suitably powered for this population.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any adverse events that were not apparent in clinical trials but have come to light subsequently.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Patients receiving the technology in countries where it is available have reported to me and to other experts that they experience an improvement in general health and well-being, a reduction in fatigue and malaise and, in the case of frequent exacerbators, a dramatic reduction in the frequency and severity of exacerbations coincident with commencement of the technology. Withdrawal of the technology has also been reported by patients to lead to a relapse of their symptoms.
21. How do data on real-world experience compare with the trial data?	AATD-associated emphysema is a chronic disease that slowly progresses over the course of adult life. Trial data will consequently be unable to detect benefits in health status, lung function and survival arising from the technology, which will only be evident in a long-term study.
Equality	
22a. Are there any potential equality issues that should be	There are no potential equality issues.

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
23a. Would surgical treatment options such as lung transplantation or lung reduction surgery suitable comparators in the population being considered?	Surgical treatment options do not represent suitable comparators in the population being considered. Lung volume reduction is used in patients with severe disease with grossly over-inflated lungs to relieve breathlessness. Lung volume reduction surgery and endobronchial lung volume reduction devices (eg valves and coils) have been studied in usual COPD and shown to be of benefit only in a limited number of patients. Benefit is seen in usual COPD patients with severe hyperinflation due to emphysema, particularly patients with heterogeneous distribution of emphysema and a predominance of emphysema in the upper lung. These features are seen only in patients with very severe emphysema. Lung volume reduction surgery is now used much less frequently, following the introduction of endobronchial lung volume reduction techniques. Use of the techniques is less well evidence-based in AATD. They appear to be of less benefit in AATD than in usual COPD and this is, in part, because the pattern of disease in AATD tends to be homogeneous emphysema that is typically distributed in the lower lung. The insertion of foreign bodies to obstruct the airways (as in the use of endobronchial valves or coils) poses a theoretical risk of infection and inflammation, which would be of concern in patients with reduced blood levels of anti-protease inhibitor. Lung transplantation is an option only for a small number of patients with end-stage disease but is limited by organ availability. It is employed when patients experience breathlessness that is intractable and intolerable despite optimal treatment, or where death may be imminent. Acceptance onto transplantation programmes is subject to stringent criteria and patients may be ineligible for reasons of co-morbidity, age or other exclusion criteria (such as previous thoracic surgery, chronic lung sepsis etc). It does not represent a curative solution to terminal lung disease but is, in effect, the exchange of one series of clinical problems for another and is often viewed by patients as an unacceptable alternative to death.

23b. Do you expect that respreeza will be used as a bridge to surgical treatments?	Retardation of emphysema progression through the use of Respreeza will delay the onset of end-stage disease and potentially avoid the need for surgical treatments. However, it is not envisaged that this technology would be utilised for the purpose of acting as a bridge for surgical treatments.
24. Is lung density predictive of survival and health related quality of life in this population? (e.g. is it an appropriate surrogate for disease severity and mortality in people with emphysema)	Cross-sectional studies have demonstrated good correlation between lung density and quality of life (Dowson et al. Eur Respir J. 2001 Jun;17(6):1097-104; Dowson et al. Am J Respir Crit Care Med. 2001 Nov 15;164(10 Pt 1):1805-9;). Longitudinal data indicates that lung density decline correlates with decline in health status (Stolk et al. Thorax. 2003 dec;58(12):1027-30). Lung density predicts mortality better than physiological measures and health status (Dawkins et al. Thorax. 2003 Dec;58(12):1020-6).
25. Do you expect long term outcomes to be dependent on the brand of A1PI used? (e.g. is it reasonable to draw conclusions from long term evidence relating to other brands of A1PI)	It is not expected that the brand of A1PI will influence long term outcomes. Biochemical equivalence has been demonstrated between different brands and it is reasonable to accept evidence obtained on the use of these alternative anti-protease therapies.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- I consider that the technology delivers tangible clinical benefits, which would be a step change for the management of AATD in England and would bring our clinical management in line with other countries with modern healthcare services.
- The technology is the first and only disease-modifying treatment in AATD-associated emphysema.
- The technology would be easily incorporated into the existing treatment paradigm and any additional resources would be easily manageable.
- I consider that the benefits of the technology hugely outweigh any potential disadvantages and that the safety profile is excellent.
- Based on experience in countries where treatment is available, I would expect patients to experience reduced disease progression, reduced exacerbation severity, increased levels of activity and improved quality of life compared to standard care.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Alpha-1 UK Support Group
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:

Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	I first presented with severe shortness of breath at age 15 and was diagnosed, at that time, with asthmatic hay fever. From the age of 30 I was more breathless than friends of a similar age upon exertion but I didn't think anything of it at the time, although I saw doctors regarding my asthmatic hay fever during the summer months as I frequently had chest infections caused by my allergies. I was treated for some years for asthmatic hay fever. Although I presented many times for treatment of numerous chest infections, nobody ever investigated or indeed asked about my breathing or breathlessness. By the age of 40 my use of inhalers for asthmatic hay fever had increased and I was also using them when I had chest infections. Each and every cold would always quickly develop into a serious chest infection, and these exacerbations increased with frequency, duration and intensity over time. I was by the age of 40 walking noticeably slower than my peers, getting short of breath walking upstairs and inclines and generally upon exertion. I had for many years managed to hide my breathlessness from people but this became impossible, and I would often find people looking at me quizzically wondering why such a young person was struggling to breathe upon such little exertion! One particular chest infection absolutely terrified me. I spent the entire night quite literally gasping for each and every breath just lying in bed, and I thought I was going to die. I made an emergency appointment with my respiratory nurse the following day who wanted to admit me to hospital as my symptoms were so extreme. I was given steroids for the first time and the usual antibiotics to treat the chest infection. Once the infection had cleared, my respiratory nurse did lung function tests and reversibility tests. She advised me that my lungs had deteriorated to the equivalent of those of a 100-year old. She also wanted to test me for AATD purely to "rule it out as it is so rare you aren't going to have that". 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. The information I found on AATD suggested that most alpha's die within 5 years of diagnosis. This was totally devastating. I initially hid my diagnosis from my family and friends as I struggled to come to terms

	with the diagnosis of a condition that would kill me and for which there was no cure, treatment or specialist care I could get or a clinician to whom I could be referred. As neither of my parents smoked and, as I am an only child to them, I didn't tell them about my condition until I was left without any choice and I couldn't hide my increasing breathlessness and frequent chest infections anymore. My mother has been struggling with an immense amount of guilt knowing she has passed on a genetic condition to me - she feels responsible and completely powerless, especially as there is no treatment available in this country. It is difficult for her to see her own daughter being in worse health than she is, despite being much older than me. My father remains unaware that AATD is a genetic condition as we know that this knowledge would worsen his own health and we have still not told him.
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also	My severe breathlessness has had a major negative impact on all areas of my life. Everyday tasks such as showering and getting dressed and undressed exhaust me and I find them increasingly difficult to cope with. Any kind of household tasks, for example laundry, general housework, or changing my bed or cooking are activities that I struggle to undertake and that require more energy and take me longer every month. I dread shopping; it needs careful planning and could take me half a day - can I park nearby, will there be a lift, how and where do I best load and unload the trolley, can I get help with packing the bags and getting them to the car? Unpacking and putting the shopping away when I get home is exhausting. I now have to use ambulatory oxygen for all activities that result in even minor exertion, for example walking, shopping, climbing the stairs, cooking and housework. Climbing a single flight of stairs leaves me breathless on a good day. Walking on the smallest of incline at a very slow pace leaves me breathless, and I have to stop frequently. I have to choose between even the simplest of physical exertion tasks and talking … I simply cannot do both at the same time any longer. I even get out of breath just talking! I have to carefully plan how much energy to put into each day, if I do too much today, then tomorrow I will not be able to do very much at all and will have to rest as I get so tired and exhausted. Normal life ceased to exist when I was diagnosed with a condition for which there is no cure or treatment. Increasingly everything that involves physical exertion or carries the risk of me getting a chest infection are becoming distant memories – social events, simple days out, holidays, they all require careful planning and involve other people who might carry simple infections. Being very limited in the kind and frequency of social activities I can participate in has had a dramatic effect on friends and family too. I feel increasingly isolated. The very real fear of catching another cold and consequently getting another

include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	exacerbation with the inevitable lung function decline means that people who are infectious often take significant offense when I ask them to keep away! Using oxygen is extremely restrictive and embarrassing for such a young person. It is a constant cause of anxiety: Will I have enough battery power to last? Will I be able to recharge the battery anywhere? Do I have an alternative plan in case of an oxygen concentrator failure? The oxygen concentrators that last more than 1 ½ hours are very heavy, and I am now finding my shoulder is going to need medical attention due to carrying it around all of the time – and this is after only a year of being oxygen-dependent! Air travel requires additional planning; will the airline permit my oxygen device onboard; my clinician has to complete MEDIF Forms for each and every flight, which are different for each airline, before I can fly even if I merely want to carry my oxygen concentrator onboard and don't need to use oxygen during the flight; I have to organise Special Assistance at the departing and arrival airports, this often means sitting around waiting for somebody to come and escort me to and from the aircraft; the delay of the Special Assistance team has meant that I have missed flights which causes much anxiety, stress and additional exhaustion. I cannot walk even short distances without oxygen anymore and I am completely reliant upon a machine to help me breathe and remain at my already substantially limited activity capacity. Using oxygen doesn't stop me getting out of breath, in such instances I am often offered a glass of water by people who don't know what else they can do to help! As for many alpha's, my deteriorating physical health and the effect on the long-term future prospects of my life caused the breakdown of my marriage. I became increasing reliant upon my husband's support in most areas of life in which I could no longer manage on my own. We had planned to have children later in life … sadly my declining health made this then impossible. The prospect of my husband becoming my carer meant he found another model able to give him all the things I couldn't any longer! I am too embarrassed at my physical inability to have sex due to my breathlessness, so forming personal intimate relationships are a thing of the past for me. Equally, who would want to form a close relationship with someone knowing they would quickly become their carer rather than an equal partner. I was professionally successful before AATD forced me to first reduce my working hours and subsequently, to take early retirement due to ill-health. I haven't been able to work as an IT trainer for 7 years now as I do not have enough energy or breath to teach.

	The fairly recent breakdown of my marriage means I am now entirely dependent upon benefits. Due to financial pressure, I now share a home with my mother who has had to become my carer at the age of 74! When anything happens to her I do not know how I will manage! As my health has deteriorated due to AATD so has my quality of life. Hobbies and things I used to enjoy doing have either become increasingly difficult to do or impossible. I used to enjoy water skiing and scuba diving, playing squash, swimming and going for long walks for example – all of these are a very distant memory of many years ago due to my breathing problems. I was an extremely keen cook and host of regular dinner parties, now just feeding myself is a major challenge and I often cannot manage anything more than reheating something ready-made! I used to be a social butterfly with a very active social life, now my social life only exists from behind a computer screen!
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	There is currently no disease specific medication on the NHS. My AATD is treated with inhalers typically used for COPD, antibiotics and sometimes steroids for exacerbations but these only treat the symptoms of my condition and do not address the root cause of my deteriorating lungs! Pulmonary rehabilitation is extremely beneficial at improving one's fitness level but the effect is rather short-lived and, again, it does not address the root cause of AATD. There are long waiting lists for pulmonary rehabilitation and it is not readily available to all patients, and once the course is finished, continuation programmes are even more limited which means that patients quickly lose the benefit they gained. Attending regular fitness sessions offered in gyms and fitness centres is not an option for me as the sessions are not designed for people with limited ability and the type of health problems I have. In addition the fitness instructor would not be specifically trained so as to know if, and when, I was putting my health at risk or not. There is also the element of embarrassment I would encounter due to my very limited ability and becoming so breathless upon little exertion. I know the time is approaching when I will need to have the conversation about lung transplantation with my clinician, and indeed with myself and my parents. Transplantation is a very frightening prospect and is the absolute last resort for me and many others. I know from others who have been, or are currently going through the lung transplantation assessment process that it will not be an easy decision to make. Many patients are deemed not eligible for a transplantation. Many do not make it through the operation. Some live 6 months after the operation, some get a little or much longer, but there are absolutely no guarantees.

	Many transplantees swap their breathlessness for a lot of other medical problems which are equally debilitating. And many patients die on the waiting list! One needs to be able to have a support network in place to assist after the transplantation in order to qualify…I don't even know who I could ask for support if that time ever came!
11. Is there an unmet need for patients with this condition?	Yes, there is a huge unmet need for AATD. There is currently no treatment available in the UK for the treatment of AATD.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	Retaining every little bit of lung function is of paramount importance to me, when you can't breathe nothing works, except perhaps my bladder! My fear of contracting a simple cold or being near potentially lung damaging pollutants means I avoid many social events - the therapy would give me confidence knowing that my lungs have at least some protection, and I am not potentially putting my life at risk by further damaging my lungs every time I leave the house. 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. Receiving the therapy would mean I could continue with my limited social life and not become totally housebound. I hope I would be able to continue walking my dogs, albeit incredibly slowly and not very far. I would hope I would be able to retain my already very limited lung function for longer. I would hope that I would be able to delay the dreaded transplant conversation indefinitely. The retention of my current abilities, although incredibly limited, is preferable to a rapid deterioration and early death. The therapy is the light at the end of a very dark tunnel living with a condition which dominates my life and which will be life-limiting. Without this therapy, my health will continue to deteriorate both physically and psychologically at a fast rate.

13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	I would hope to be able to receive treatment at a location close to my home or, ideally, at home. However, travelling further to be able to receive the therapy, would not deter me at all.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	I don't see any disadvantages.
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so,	I understand that those patients who are classed as "rapid decliners" (in terms of their rate of lung function decline) may respond better to therapy.

please describe them and explain why.	
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	I don't think so.
Other issues	
17. Are there any other issues that you would like the committee to consider?	No.
Key messages	

18. In up to 5 bullet points, please summarise the key messages of your statement:

- Augmentation therapy will reduce the rate of progression of lung tissue loss and the severity and frequency of exacerbations thereby reducing the rapid decline of lung function and improving quality of life
- There is a high unmet need for AATD patients as there is currently no alternative treatment available targeted at delaying the disease progression
- The therapy is very safe and could be given locally or at home
- Lung transplantation is a last resort for AATD patients that is only available to few and not always an option that patients choose
- Without being able to receive this therapy, the health of AATD people will continue to decline both physically and psychologically

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	[redacted]

4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: I have been an active member of one of the UK's patient groups for AATD (Alpha-1 Awareness UK) and have heard many other patients describe their experiences. I am also drawing on the experience of one specific patient from that patient group who was resident in Spain at the time of her diagnosis, and has been receiving AAT therapy there for a number of years now.
Living with the condition	
8. Did you have any difficulty or delays in receiving a	Compared to many others who are initially misdiagnosed (often as having asthma) and don't receive the correct diagnosis for around seven years, I was quite lucky, and I was correctly diagnosed as having

diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	Alpha-1 Antitrypsin Deficiency within about six months of presenting with a persistent cough and abnormally-long cold or flu symptoms including fatigue, shortness-of-breath, easy exhaustion, and difficulty with things like climbing stairs, which my wife urged me to get dealt with. During that initial phase, though, my GP struggled to isolate the true cause, and was confounded by various signals which caused him to consider my thyroid, possible liver issues (he asked whether I drank alcohol much, and luckily believed me when I explained that I did not). He did a full 'MOT' test and ruled out diabetes, hypertension, prostate cancer (which my father died of), heart issues, etc. but was still concerned about my lungs, so arranged for a chest X-ray to be done at the local hospital. Once this had been done, he was still unsure, but felt there was something wrong enough to seek a referral to a Respiratory Consultant at the hospital. During that initial consultation with the referred Consultant, I was very quickly diagnosed with COPD, and my spirometry had revealed a pattern which the Consultant felt was most likely emphysema. I initially assumed that this was as a result of having previously smoked because I had been a low-to-moderate level smoker for a number of years but had given up a year prior to start of the unshiftable cold/flu symptoms that had caused me to go to my GP in the first place. Given my 'pack years' and my age at presentation of emphysema, the Consultant explained that he had taken a blood sample to rule out a condition which he described as having a 'less than two percent chance' of being relevant to me… namely, Alpha-1 Antitrypsin Deficiency (AATD). I thought nothing of that, at that time, but was of course deeply affected by the diagnosis of emphysema/COPD, which rocked my world, and that of my family. At that time, my wife and I had been married only three years or so, and first child, Samuel, was a matter of about three or four months old. My immediate expectation was that I was not going to live to see him grow up. A few weeks later, my GP explained the test results and I learned that I had AATD and thus began my 'new regime' as an affected sufferer. My immediate reaction was that it was a death sentence; given that all information I could find about it termed it as 'incurable, progressive' and advised that there were no treatments for it in the UK. Obviously, this knowledge was very depressing, especially given that there was very little concrete information available for sufferers at that time. Worse was the knowledge that I had passed it on to my son, and at that stage, had no idea what ramifications this would have for my young family. Luckily my wife was more successful in sifting the 'horror-stories' out of the facts, and discovering two patient support groups in the UK, and fortunately, one was holding an 'information day'

	nearby shortly after I received the diagnosis. We attended that, and learned much from some researchers in the field, and I was able to regain a more positive composure with regards to the future. Similarly, my Respiratory Consultant was more positive, and explained that I would not 'die instantly' or even 'any time soon', providing I continued to abstain from cigarettes (which I have done). He was confident that we had caught this in time to establish a period of stability which might last a long time, and so far that does seem to have been the case. However, in terms of impact to my life, and my family's, this initial period was without doubt the most worrying, terrifying stage, and one which still troubles me to recount. The feeling of isolation and frustration is palpable, the belief that your life is over, that you're going to die a horrible, strangulated, drowning death, gasping for air (in the way that you feel when suffering from a dyspnea attack), is utterly nightmarish. The knowledge that you've had it all your life, niggling away but without realising, that you inherited it from your own parents and have passed it on to your child, and that it might kill them too, merely adds guilt to the equation. I am so lucky that my wife is a more optimistic and proactive person, and that her forays into the internet brought useful reward; my own detective-work brought only more terror and horror-stories, whereas hers brought constructive avenues like support groups.
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to	Living with the condition is pretty awful, but a lot depends on how seriously one is affected, and at what stage in the progression one is. For me, I'm about 43% FEV1-predicted, so I am not as badly affected as many others; however, my life is still quite heavily affected. I have difficulty climbing stairs and hills, and I cannot talk whilst walking (even on the flat) anymore. This causes embarrassment and fear, when in public; dyspnoea attacks are truly terrifying, even when used to them. It's like drowning out of water – or inhaling hot sand – there's no other way to describe it. I cannot play any sort of sport with my children (I have two boys now, aged 9 and 7); I could not teach them how to ride bicycles, because it is impossible to run alongside supporting them, and neither yet knows how to do this simple thing, which causes me much guilt and regret. We have never 'had a kickabout in the park', or anything like that. I have to watch while others play with my children in this way; my friends, my wife, my colleagues in Scouts, etc – and whilst I am glad to have so many good friends, it always, always causes me a massive pang of regret, guilt and frustration when this happens.

school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	My wife has become my carer and does so much for me that I would be lost without her. I see the effect that it has had on her, though; she strives so hard to provide for us (she is the chief bread-winner in the house now), and she manages all the manual tasks that would take me an age to achieve; washing, lawn-mowing, cleaning, etc. I still try to do what I can, but she hates to see me struggling, and will often cut in and take over; and I feel so guilty when I realise I am grateful that she does. I do my best, but sadly, as a family, we cannot rely on that alone anymore. I work from home and provide occasional IT support services as a consultant to a couple of firms that I have dealt with for a long time, but the work is tailing off now. Partly, this is because I now lack the capability to rush out and meet them at their locations, whereas this is required in my line of work. Similarly, I no longer have the drive to turn my business into something bigger, as I had once intended, simply because I would not have the energy and stamina required to handle expansion into offices, going into public and dealing with my condition or inflicting it upon others. I have become a little bit of a recluse in this regard. Consequently, I earn very little these days, haven't earned enough to pay income tax for three or four years, and am only technically self-employed for my own vanity/sanity and demonstrable proof that I am not so 'over the hill' to be reliant on the State for support. In reality, although I am still self-employed, and do a few desk-jobs per year, I am reliant on my wife's income for support, and this causes me a great deal of anxiety and guilt. As a family, we manage; just about. And we make the best of it, but it is not a good situation. I fear for the future, and what will happen when my condition progresses to the point where I can no longer take care of myself properly. Showering can sometimes be an issue even now, and it can take an age to get dressed. Everything I do has to be slowed-down due to constant breathlessness, and I have to plan for that in advance, or I get 'rushed', and then it's impossible to meet expectations (my own or other people's), which causes more tension and guilt – often on all sides. My children are currently not fully aware of the ramifications of their condition, and hopefully won't suffer it as greatly as I do… but they are aware that 'daddy is not well', and that he cannot do all the things normal dads can do. This has caused a few embarrassing moments or tears in the playground when other children have said things like "your dad will die soon" and other heartless things. I'm sure all kids say stuff like this, but in our case, obviously, these comments cut way deeper than normal. In terms of social life, I am far less active in this regard than I used to be, largely because I live in fear of

	catching colds or other infections from my friends. Most of them have been briefed, but many of them forget, or don't fully understand the implications that their simple cold might have for me, in terms of faster damage progression, and tissue loss that I will never regain. In many cases, it's easier to make my excuses and be a 'no-show', rather than subject them to the 'has anyone got colds?' questioning that can be a bit embarrassing to put everyone through, every time there is a social gathering.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	Current treatments largely consist of inhaled airway dilators that attempt to reduce the effects of the airway obstruction and breathlessness. Whilst these can be moderately effective in reducing some (but by no means all) symptoms, they do not even begin to approach the treatment of the condition itself. They do not provide any protection for the lungs to damaging pollutants and oxidative stress, per se, they do not address the ongoing elevated liver enzyme blockages, they don't reduce the likelihood of infection, nor do they assist the lungs in fighting infection without causing further damage to themselves. They do not provide one iota of protection against future progression of the damage, and further destruction of the lungs over time. Everything about them is entirely 'reactive' not proactive, and they do not improve my quality of life at all; yet it's all we are given, and other, more effective treatments (that happen to be expensive) are simply not available on the NHS. I have been referred for a 10-week period of pulmonary rehabilitation which has been useful, and improved my ability to cope with breathlessness, but its effects are rather 'short-term'. Exercising at home alone after the course has finished has proven difficult. Efforts to try and secure some cheap or free access to gyms with trainers qualified to handle COPD patients has proved impossible, and I have not been able to get access to 'GP-prescribed exercise'. I cannot financially afford to join a gym, and I would be frightened and embarrassed to exercise with normally-fit people. I understand that at some point in the future I may be offered a lung or liver transplant (or both), but currently I am in denial about the prospect of these. I currently do not meet the criteria, so it is a moot point, but I have lost several Alpha friends who opted for transplantation and have died either after the operation as a result of failures in their anti-rejection medication, or who have simply died on the operating table. I am aware that, if successful, I might have a new lease of life – but at the moment, considering transplantation feels rather like playing "Russian Roulette" to me.

11. Is there an unmet need for patients with this condition?	Very definitely. At best, we need a cure, and at worst we need access to the only available treatment proven to hold off the damaging progression long enough for us to receive a cure when one finally might be available. So that unmet need is for augmentation therapy (the technology under evaluation); providing the body the protein which it cannot supply to the lungs due to it being misfolded and caught up in the liver. It's a pretty simple equation, really. Stop the lungs from being damaged by neutrophil elastase, by supplying the 'missing' alpha-1 antitrypsin intravenously. Slow the progression of lung-damage, prevent further destruction of lung tissue which causes reduction in oxygen absorption, and thereby reduce the strain on the pulmonary and cardiac systems. Live longer, and (if caught at the right time) in a more stable, sustainable way with a better quality of life. Whilst it is true that augmentation therapy will not magically fix past damage, it seems absolutely ludicrous that we would not want to stop more damage from occurring, if we could. Instead, we are given inhalers that will merely 'open up our pipes'… which is tantamount to simply 'flooring the accelerator whilst ignoring the oil-leak', in a hope that we can sustain our speed.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends	Advantages include the primary aim; slowing down of the progression-rate of destruction of alveolar tissue, and that has to be the main goal, regardless of whether current spirometry or CT density measurements are able to determine precise changes. We know that boosted levels of AAT protein in serum will, and do, prevent neutrophil elastase from causing as much harm to lung tissue as reduced or non-existent AAT levels do. In terms of physical symptoms, I do not expect any immediate miraculous change; my lungs are already compromised, and no amount of augmentation therapy will fix them, and they will not heal themselves. Similarly my pain and mobility levels are unlikely to improve immediately upon receiving AAT treatment, because my oxygen-absorption rates will continue to be dependent on the amount of lung tissue that I currently have. However, I would certainly benefit from the ability to keep safe that which remains! From a mental and emotional point of view, the knowledge that I am no longer declining in health as fast as before, and that I have a chance to live longer and in a better condition than expected, will make a massive difference to my outlook on life. Being able to think more positively about the future, and at least take stock of my life during this prolonged 'holding pattern' stage, rather than fretting about constant

and participate in school and social life.	decline, would potentially enable me to focus on 'living' again. I would be able to think about developing my business as planned, and being more socially-active and less reclusive –because my fear of infection would be virtually removed, knowing that I had the AAT protection that my body required.
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	Currently, it involves an infusion which can be done at a hospital or clinic. Usually it is administered weekly, sometimes monthly (depending on the patient and their proximity to their treatment centre). There will be some minor impact in terms of having to turn up regularly for infusions, but this is more than offset by the protective effects of the treatment, the expected benefits and the peace of mind received from having them. The ability to receive the treatment at home would be a plus but is by no means a necessity.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	The actual process itself is fairly innocuous and causes no real issues, from what I have heard. It can make you a little tired and feel a little cold, but that doesn't last long, and is no barrier to wanting to receive treatment. There may be issues in terms of travel costs if treatment centres are far away, but this is likely to be rare, and no different from many other forms of regular treatment, or comparable with current prescription-cost levels. Most families are unlikely to suffer as a result, and in terms of expense, it's likely to be one that is considered worthwhile by the recipient. Any cost involved is likely to be small when compared to its benefits.

Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	There was an early paper which suggested that some type of alpha sufferers (termed 'fast-FEV1-decliners') might have received a greater benefit from this treatment than patients with a lower rate of decline.
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	No
Other issues	
17. Are there any other issues that you would like the committee to consider?	No
Key messages	

18. In up to 5 bullet points, please summarise the key messages of your statement:

- There is currently no treatment being given for AATD that curtails lung-damage or reduces progression.
- AAT therapy will reduce ongoing progression of lung-damage and maintain patients' quality of life for longer.
- There are significant impacts caused as a result of non-treatment of progression,which affect patients and their families alike.
- The benefits of AAT therapy by far outweigh any potential disadvantage.
- The positive effects reported by patients receiving AAT therapy do not appear to have been reflected in the clinical trial outcomes of Respreeza.

Thank you for your time.
Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ **X** commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no NHS England guidelines for the treatment of emphysema.
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	There is no well defined pathway for the care of patients with alpha$_1$-proteinase inhibitor deficiency.

experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	We would need to create a clear pathway for the use of alpha$_1$-proteinase inhibitor, if approved.
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	Not currently commissioned by NHS England
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Prescribing should be restricted to a small number of specialist centres, but the mechanism for identifying these centres would have to be developed. A full commercial procurement would be disproportionate.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Some investment in training for use of a new intravenous product.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	The answer to this depends on what guidance for the product is issued by NICE.
10. What is the outcome of any evaluations or audits of the use of the technology?	None available.
Equality	

11a. Are there any potential equality issues that should be taken into account when considering this treatment?	
11b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Human alpha 1-proteinase inhibitor for treating emphysema

HST REPORT

This report was commissioned by the NIHR HTA Programme as project number 15/121/01

BMJ Technology Assessment Group

Title: Human alpha 1-proteinase inhibitor for treating emphysema

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Samantha Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Kayleigh Kew	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Victoria Wakefield	Drafted the section covering submissions from stakeholders, patient groups and patients

All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
A1PI	Alpha-1 proteinase inhibitor
AE	Adverse event
AIC	Akaike Information Criterion
AUC	Area under the curve
BIC	Bayesian Information Criterion
CE	Cost effectiveness
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
D_{LCO}	Diffusing capacity of the lung for carbon monoxide
EMA	European Medicines Agency
eMC	Electronic medicines compendium
EPAR	European public assessment report
ERG	Evidence Review Group
FDA	US Food and Drug Administration
FEV1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ISWT	Incremental shuttle walking test
ITT	Intention to treat
K_{CO}	Transfer coefficient for carbon monoxide
KM	Kaplan–Meier
MCID	Minimal clinically important difference
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office of National Statistics
OS	Overall survival
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year

QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of product characteristics
STA	Single technology appraisal
SVC	Slow vital capacity
TEAE	Treatment-emergent adverse event
TLC	Total lung capacity

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of the human alpha-1 proteinase inhibitor (A1PI) Respreeza® (hereafter referred to as Respreeza; CSL Behring) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of Respreeza in the management of emphysema secondary to severe A1PI deficiency.

The goal of treatment with human A1PIs, such as Respreeza, is to augment the level of the protein in the blood of those who have a genetic mutation that disrupts production of A1PI by the liver. Respreeza was granted marketing authorisation by the European Marketing Authorisation (EMA) on 20 August 2015 as a maintenance treatment, to slow the progression of emphysema in adults with documented severe A1PI deficiency. Respreeza has been approved for use in the USA for 15 years (as Zemaira®), as well as being approved for use in several other countries.

The evidence on clinical effectiveness and safety of Respreeza presented in the company's submission (CS) is primarily derived from a randomised controlled trial (RCT), RAPID, and a subsequent open-label extension phase, RAPID-OLE. Corroborative evidence on the effectiveness of intravenous augmentation therapy with an A1PI, including but not limited to Respreeza, in those with A1PI deficiency comes from two systematic reviews, both of which report meta-analyses for several clinical outcomes, including annual change in CT lung density, and change in FEV1.

RAPID was designed to assess the efficacy and safety of Respreeza compared with placebo in adults who were currently non-smokers (had to not have smoked in the 6 months prior to recruitment) and had severe A1PI deficiency (a serum concentration of A1PI of <11 μM or <80 mg/dL) and a baseline forced expiratory volume in one second (FEV1) of 35 to 70% predicted. Both the Respreeza and placebo groups concomitantly received established treatments used for the clinical management of symptoms. The final scope issued by NICE specified the population of interest to be adults with severe A1PI deficiency who have progressive lung disease, with no specification of thresholds for severe deficiency or for progressive lung disease. The Evidence Review Group's (ERG's) clinical experts confirmed that a serum level of A1PI <11 μM or <80 mg/dL is a widely accepted threshold.

The ERG notes that no study site for RAPID was located in the UK. However, the ERG does not consider this a limitation in this case. The ERG determines that it is difficult to draw conclusions on the representativeness of the people enrolled in RAPID to people in England with emphysema secondary to severe A1PI deficiency likely to be eligible for treatment with Respreeza. The ERG's clinical experts fed back that there is considerable variation across people with the condition in terms of their FEV1% predicted, age, and functional capacity at diagnosis. Also, because of the rarity of A1PI deficiency,

epidemiological data for the population are limited. Considering other RCTs assessing clinical effectiveness of A1PI augmentation therapy in severe A1PI deficiency, the baseline characteristics of those enrolled in RAPID are as generalisable as those enrolled in other trials to the population of interest in England. Therefore, the population in RAPID is considered to be relevant to the decision problem.

In RAPID and RAPID-OLE, Respreeza was infused intravenously at the licensed dose of 60 mg/kg body weight on a weekly basis, with infusion taking typically around 15 minutes (about 0.08 ml of solution per kg body weight each min). Evidence is available that suggests administration of Respreeza at a dose of 60 mg/kg per week could be a suboptimum augmentation dose for some people with A1PI deficiency. Two studies evaluating clinical effectiveness of A1PI at a dose of 120 mg/kg per week are ongoing. One study is an RCT (SPARTA) comparing A1PI 60 mg/kg versus 120 mg/kg given once weekly over 156 weeks. Results are not yet available for the study. Based on the licence for Respreeza, the ERG considers the evidence presented to be relevant to the decision problem.

The comparator in RAPID was placebo. In the final scope issued by NICE, various interventions given to ameliorate the symptoms of progressive lung disease were specified as comparators of interest to the decision problem. As highlighted by the company and the ERG's clinical experts, clinical management of progressive lung disease is dependent on the symptoms with which a person presents, and may involve administration of a single therapy or a more complex combination of interventions. The company highlights that the treatments listed as comparators are clinically equivalent to BSC in lung disease and that it would be more appropriate to view the interventions as a collective rather than individual comparators, an opinion with which the ERG's clinical experts agreed. Therefore, the ERG considers placebo to be an appropriate comparator.

All clinically relevant outcomes were reported in the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

RAPID is an international, randomised, double-blind, phase III/IV trial with a primary objective of assessing the change in lung density by CT on A1PI augmentation with Respreeza compared with placebo in people with emphysema secondary to severe A1PI deficiency. RAPID involved 180 people, with 97 and 83 people allocated to Respreeza and placebo, respectively. After 2 years of follow-up, all patients located outside the USA entered an open-label 2-year extension phase, RAPID-OLE, during which everyone received Respreeza. The ERG notes that RAPID did not include a "run in" period during which rate of deterioration in lung function could have been monitored.

The primary measure of clinical effectiveness in RAPID was annual change in lung density as measured by computed tomography (CT), with the value adjusted to account for lung volume. Spiral CT scans

were taken at baseline and after 3, 12, 21, and 24 months of follow up. At the request of regulatory authorities, rather than capture lung density solely at total lung capacity (TLC), CT scans were taken at both TLC and functional residual capacity (FRC) and the primary outcome was a combined assessment of recordings at each inspiration state.

In RAPID, Respreeza was associated with a lower rate of annual decline in CT lung density (adjusted PD15 for combined TLC and FRC) compared with placebo at 2 years of follow-up, but the difference did not reach statistical significance. However, the difference between Respreeza and placebo in decline in CT lung density was statistically significant for the TLC inspiration state, and, again, favoured Respreeza:

- TLC plus FRC: mean difference of 0.62 g/L per year (95% CI: –0.02 g/L to 1.26 g/L; p=0.06);
- TLC alone: mean difference of 0.74 g/L (95% CI: 0.06 g/L to 1.42 g/L; p=0.03);
- FRC alone: mean difference 0.48 g/L (95% CI: –0.22 g/L to 1.18 g/L; p=0.18).

Sensitivity analyses to account for missing data generated similar results to the primary efficacy analysis. Meta-analyses of results from three RCTs, one of which was RAPID, evaluating intravenous A1PI augmentation therapy in severe A1PI deficiency support findings from RAPID in terms of effect on deterioration of CT lung density. Two systematic reviews analysing the same three RCTs reported statistically significant differences between A1PI and placebo in decline in CT lung density at the TLC inspiration state, with results favouring A1PI treatment:

- Edgar 2017: mean difference 0.79 g/L (95% CI: 0.29 g/L to 1.29 g/L; p=0.02);
- Gotzsche 2016: mean difference 0.86 g/L (95% CI: 0.31 g/L to 1.42 g/L; p=0.002).

In the longer term, results from RAPID-OLE indicate that the effect of Respreeza in reducing rate of lung density decline is sustained. Those initially receiving Respreeza, referred to as the early-start group, had a similar level of annual decline in CT lung density (TLC only) in the 2 years follow-up of RAPID-OLE (1.51 g/L [Standard error {SE} 0.25] for day 1 to month 24 versus 1.63 [SE 0.27] in months 24 to 48). By contrast, those who switched to Respreeza from placebo, referred to as the delayed start group, had a substantially lower rate of annual decline in the 2 years of active treatment compared with the 2 years prior to start of treatment (mean loss of 2.26 g/L [SE 0.27] for day 1 to month 24 versus 1.26 [SE 0.29] in months 24 to 48). The company reports that, in a mixed model that assessed lung density decline across RAPID and RAPID-OLE, the annual lung density decline rate was reduced by 0.52 g/L (p=0.001) when switching from placebo to Respreeza in the delayed-start group. The authors of the study concluded that those in the delayed-start group did not regain the lung tissue that had been

lost during the previous 2 years of treatment with placebo, and that the result underscores the importance of early interventional treatment with an A1PI.

Various secondary outcomes were assessed in RAPID. The key secondary outcomes were deemed to be those that would help explain the clinical relevance of the primary objective of change in lung density as measured by CT scan and were listed in the European Public Assessment Report (EPAR) as:

- change in exercise capacity assessed by incremental shuttle walking test (ISWT);
- change in symptoms score assessed by the St. George's Respiratory Questionnaire (SGRQ);
- risk of pulmonary exacerbation assessed by the annual rate of exacerbations.

Other secondary outcomes assessed included the key spirometry variables of FEV1 and gas transfer.

No statistically significant differences were reported between Respreeza and placebo for the identified secondary outcomes, with the direction of effect favouring Respreeza in some outcomes. However, for ISWT, FEV1, diffusion capacity of the lung for carbon monoxide (D_{LCO}) and, unexpectedly, rate of pulmonary exacerbation, the direction of effect favoured placebo:

- ISWT: change from baseline at 24 months: 10.8 m (SD 139.8) with Respreeza versus 16.1 m (SD 101.6) with placebo; least square mean difference of –13.9 m (p=0.48);
- total SGRQ score (higher score is less favourable): change from baseline at 24 months: 1.4 (11.1) with Respreeza versus 2.2 (11.7) with placebo; least square mean difference of –0.19 (p=0.91);
- annual number of exacerbations: risk ratio for Respreeza versus placebo of 1.26 (95% CI 0.92 to 1.74) (risk ratio greater than 1 indicates increased risk of exacerbation with Respreeza);
- FEV1% predicted: change from baseline at 24 months: –3.1% (SD 10.7) with Respreeza versus –2.3% (SD 13.1) with placebo; least square mean difference of –2.26% (p=0.21);
- D_{LCO}: change from baseline at 24 months: –2.2% (SD 18.2) with Respreeza versus –1.5% (SD 19.5) with placebo; least square mean difference of –1.31% (p=0.64).

Syntheses of data from three RCTs, including RAPID, generated similar results to those from RAPID, with meta-analyses reported by Edgar 2017 and Gotzsche 2016 indicating no statistically significant differences between Respreeza and placebo for change in FEV1, D_{LCO}, and health status assessed by SGRQ. For FEV1 and D_{LCO}, direction of effect favoured placebo. By contrast, for health status, direction of effect favoured Respreeza. The ERG notes that a meta-analysis presented in one systematic

review indicated a statistically significant difference between treatments in terms of annual patient-reported exacerbation episodes, with Respreeza associated with a significantly higher rate of exacerbation than placebo (2 RCTs, 257 people: mean difference: 0.29; 95% CI: 0.04 to 0.54).

Overall, the total number of adverse events reported in RAPID was higher in those receiving Respreeza compared with placebo (1,298 with Respreeza versus 1,068 with placebo). Most people (99%) forming the safety population experienced a treatment-emergent adverse event (TEAE). There were four deaths during the RAPID study (1 in the Respreeza group and 3 in the placebo group), and one additional death during RAPID-OLE. Based on preferred terms, the company noted that headache was the most common TEAE reported in RAPID. Other TEAEs reported by ≥10% of people and occurring more frequently in the Respreeza group than in those receiving placebo included COPD (32% with Respreeza versus 23% with placebo), oropharyngeal pain (24% versus 12%), condition aggravated (22% versus 16%), and cough (22% versus 8%). By contrast, more people in the placebo group developed pneumonia (12% with Respreeza versus 14% with placebo).

COPD exacerbation was also captured as a TEAE. As part of the application to the EMA for marketing authorisation, the company submitted safety data from 6 studies, two of which were RAPID and RAPID-OLE. The EPAR for Respreeza reported that, during the first 6 months of treatment, exacerbation of COPD was recorded in 40 people from a total pool of 221 people having taken Respreeza (18.1%). By contrast, 11 out of 149 people taking placebo experienced an exacerbation of COPD (12.6%). The overall incidence rate for exacerbation of COPD was 0.59 and 0.36 events per patient year for Respreeza and placebo, respectively, and the odds of experiencing the event were statistically significantly higher with Respreeza (odds ratio 1.66; 95% CI: 1.24 to 2.23). The EPAR reported that the definition of COPD exacerbation and serious COPD exacerbation differed for the safety and the efficacy components of the submission. The EMA concluded that the number of COPD exacerbations was not lowered following treatment, and commented that, as COPD is an end stage of lung disease, the statistically significant higher rate of COPD exacerbation recorded for Respreeza was unexpected.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

In the CS, the company discussed two systematic reviews evaluating the clinical effectiveness of treatments for A1PI deficiency that were published in the past 2 years. The CS does not include a discussion of the methods followed to identify the systematic reviews. The company carried out a literature search to identify potentially relevant studies published subsequent to the search date of their chosen review. The ERG considers the company's approach and the systematic review methods followed to be appropriate and is confident that all relevant RCTs have been identified.

RAPID, and the subsequent open-label extension, represent the largest study to date evaluating the effects of A1PI augmentation therapy, specifically Respreeza, on slowing the progression of emphysema secondary to severe A1PI deficiency. The ERG considers RAPID to be predominantly well-designed and well-conducted and at a low risk of bias.

Baseline characteristics of people enrolled in RAPID were predominantly well balanced across the Respreeza and placebo groups, with the exception of baseline CT lung density (adjusted PD15). Those allocated to Respreeza had a baseline value of 46.6 g/L (SD 15.6 g/L) for the combined measure of TLC and FRC compared with 49.8 g/L (SD 15.0 g/L) in those receiving placebo. The company presents research to support the proposal that those with a decrease in CT lung density of 2.0 g/L or greater annually are deemed to be in rapid decline, and likely to achieve a greater benefit from treatment with Respreeza compared with those who experiencing no or slow decline in lung density. The ERG notes that the thresholds proposed for rate of decline, at this time, have not been validated and could be considered arbitrary cut offs that are at risk of bias. The ERG has concerns about the imbalance in CT lung density at baseline because the primary measure of clinical effectiveness in RAPID was annual change in lung density as measured by CT, with the value adjusted to account for lung volume. CT lung density was assessed at both the TLC and FRC inspiration states and the results combined to give a value for TLC plus FRC.

Considering the assessment of FEV1 per cent predicted, the ERG considers it important to note that administration of a bronchodilator before assessment of FEV1, as is advised by GOLD for COPD, was not compulsory in RAPID: the protocol for RAPID initially stipulated use of a bronchodilator 4 hours before CT scan, but was subsequently amended to use of bronchodilator only on interruption of treatment for emphysema. The ERG considers that it is unclear whether results presented for FEV1 include results with and without pre-test use of bronchodilator. Neither the CS nor the Clinical Study Report (CSR) provides details on the frequency of use of bronchodilator, or whether the results have been adjusted to account for the disparity in use of FEV1. The ERG considers the direction of potential bias arising from variation in bronchodilator use prior to FEV1 measurement to be unclear.

1.4 Summary of cost effectiveness evidence submitted by the company

The population considered by the company comprises adults with severe alpha-1 proteinase inhibitor (A1PI) deficiency who have progressive lung disease. In the base case model, the baseline distribution of patients across FEV1 and lung density decline categories is based on RAPID data. In scenario analysis, the company used age and gender distribution reportedly from RAPID, however the mean age does not match that of RAPID patients. The company used different sources of clinical effectiveness data in the model, the majority of which were based on the UK registry dataset, ADAPT, looking at patients with A1PI deficiency. The ERG considers the modelled population broadly reflective of the

NICE final scope, and with the exception of gender distribution, notes that the UK registry population and RAPID patients have similar baseline characteristics (54% males in RAPID, and 62% males in ADAPT).

Patients with an FEV1<30% at baseline were excluded from the trial population, and therefore not included as starting patients in the model (although patients can progress to this FEV1 category in the company's model). The ERG's clinical experts highlighted that there may be a rationale for initiating treatment with Respreeza in patients with a FEV1<30%, to salvage remaining lung function of patients who are either ineligible, or on the waiting list for a lung transplant.

The NICE final scope sets the intervention under consideration as human alpha 1-proteinase inhibitor in addition to BSC. In return, the company defined the intervention as Respreeza in addition to BSC; however, the company only included the cost of Respreeza in the model. This departs from the NICE scope, as it excludes BSC as a concomitant treatment to Respreeza.

The modelled intervention is Respreeza, formulated as 1,000 mg powder and indicated for intravenous infusion at a dose of 60 mg/kg once weekly. The company assumed that 75% of patients would receive treatment at home, with a nurse administering infusions, and 25% of patients would be treated at a clinic.

The NICE final scope sets the comparator as BSC (bronchodilators, corticosteroids, oxygen therapy, among others). Similar to the intervention arm, the company did not estimate any costs of BSC for the comparator arm. The company justifies not including BSC costs in either treatment arms as these would cancel out. The ERG disagrees with this statement because patients survive, and get lung transplants (hence stopping treatments) at different rates across treatment arms, therefore the BSC costs in both arms will not be exactly the same. The ERG included the costs of BSC in both treatment arms and presents the results in Section 5.4.10.

The company developed a *de novo,* state transition, semi-Markov model in Microsoft Excel®. The model includes twelve health states: three FEV1 states, comprising of FEV1≥50%; 30%≤ FEV1<50%; and FEV1<30%, each combined with three categories for lung density function decline: no decline (ND); slow decline (SD); and rapid decline (RD). The company defined lung density function decline as:

- No lung density decline: decline of <0 g/L/year in lung density measured by CT scan;
- Slow lung density decline: decline of 0-2 g/L/year in lung density measured by CT scan;
- Rapid lung density decline: decline of >2 g/L/year in lung density measured by CT scan.

The model also includes two lung transplant states, one of which is a tunnel state. Patients receive life-long treatment with Respreeza until they move to the FEV1<30% states, were they stop treatment. The cohort is allocated to the FEV1≥50% (ND, SD and RD) and to the 30%≤ FEV1<50% (ND, SD and RD) states at the beginning of the model. Including lung density decline in all health states of the model implied that patients' baseline rate of decline had to be estimated. Once patients reach the FEV1<30% category in the model, they cannot move within the category and across the different lung density states. If patients' FEV1 is below 30%, they are eligible for a lung transplant in the model. Patients can die at any point in the model.

A life time horizon of 49 years is adopted in the analysis and time is discretised into annual cycles. A half-cycle correction was applied in the model. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

The company's semi-Markov method uses transitions probabilities to determine patients' flow through the different health states in the model. As discussed in Section 5.4.4, the company desegregated the relationship in the evolution of the hybrid FEV1 and lung density decline outcomes, by using different data sources to estimate transition probabilities between FEV1 and lung density decline, even though these outcomes are contained within the same health states in the model.

The company used two different data sources to estimate FEV1 progression; one for the BSC arm, and another for the Respreeza arm of the model. In order to estimate FEV1 progression for BSC patients, the company used Stockley *et al*. 2014, who predicted the annual decline (by linear regression) in FEV1% predicted values in 406 patients with A1PI deficiency in a UK registry database (ADAPT), who had never received augmentation therapy and for whom at least 4 consecutive annual data points were available to determine FEV1 decline. The company estimated a weighted average of 1.45% annual decline in FEV1 and used it to calculate BSC patients' transitions across FEV1 states in the model by taking the average baseline FEV1 for each FEV1 category in RAPID and calculating how many years it would take BSC patients to cross the threshold to the next category, with an annual decline of 1.45%. Patients in the FEV1≥50% category had a baseline FEV1 of 59.76% predicted in RAPID, therefore, at an annual decline of 1.45%, it would take these patients 6.7 years to transition to the 30%≤ FEV1<50% category. Patients in the latter category had a baseline FEV1 of 39.60, thus it would take them 6.6 years to cross to the FEV1<30% category at a 1.45% annual decline. The company then converted these estimates into the annual probability of patients crossing the FEV1 thresholds in the model. The company estimated that the annual probability of BSC patients transitioning from the FEV1≥50% category to the 30%≤ FEV1<50% category is 14.82%, while the probability of patients in the latter category transitioning to the FEV1<30% category is 15.07%.

The company used the updated meta-analysis (described in Section 4.4) to estimate the treatment effectiveness of Respreeza in delaying FEV1 progression. After the clarification stage, the company used the 18.90 ml/y effect size and the 1.28 ml/y value to predict FEV1 progression in the Respreeza arm of the model, by applying these estimates of treatment effectiveness to the BSC annual probabilities of crossing the FEV1 thresholds in the model. The company used the average decline in ml/y reported by Stockley *et al*. 2014 (52.10 ml/y) to be able to apply the meta-analysis results, also reported in ml/y, instead of annual decline in FEV1. It then estimated the relative risk of FEV1 decline with Respreeza vs BSC, to then apply to the annual probability of BSC patients crossing between FEV1 thresholds. The company estimated that the annual probability of Respreeza patients transitioning from the FEV1≥50% category to the 30%≤ FEV1<50% category is 9.44%, while the probability of patients in the latter category transitioning to the FEV1<30% category is 14.79%.

The company reports that *post-hoc* analysis of the RAPID data was conducted to generate patient counts in each lung density decline state, according to the company's definition of lung density decline. The company reports fitting a linear regression to data points at 0, 3 and 12 months for each patient, to obtain the proportion of patients in the ND, SD and RD heath states at the end of year 1. A further linear regression was fitted to the data points at 12, 21 and 24 months for each patient to track their transition in the second year. The company reports that the baseline characteristics of Respreeza and placebo patients were slightly different in RAPID thus the analysis used baseline covariate adjustment, which is reported to account for these differences.

In addition, the company reports using the RAPID extension study, RAPID-OLE, to estimate lung density decline for Respreeza patients. The company states that all of the extension data were analysed in the same way as the main RAPID study, using the data and time points available: 24 months, 36 months and 48 months. The company adds that in line with the Markovian assumption of the model, the data were then added to the 2-year analysis of RAPID data, for the Respreeza arm of the model.

The company ran the regression analysis for two patient groups in RAPID, the FEV1≥50% group and the FEV1<50% group. Therefore, transition probabilities were also derived for these two populations, and used in the model for the corresponding FEV1≥50% health states, while the FEV1<50% data were used for 30%≤ FEV1<50% and the FEV1<30% health states in the model.

The company combined the FEV1 and lung density decline estimates to calculate the transition probabilities between the hybrid FEV1 and lung density decline health states in the economic model.

The company used RAPID and RAPID-OLE data to model mortality for the duration of the trial follow-up period (four years Respreeza patients, and two years for BSC patients). Thereafter, the company used the analysis by Green *et al.* (unpublished manuscript) to extrapolate mortality in the long-term

economic analysis. Green *et al.* analysed UK registry (ADAPT) data for patients with A1PI deficiency, and categorised lung function decline using the same thresholds as the company. Mortality data in the study were analysed in a multivariate Cox regression by lung function decline (ND, SD and RD) and FEV1 categories (≥50%, ≥30%-<50% and <30%).

The company didn't report how the "transition" from using the trial data to the registry data was modelled in their analysis. At year 4 in the Respreeza arm, and year 2 in the BSC arm, the company matched patients' cumulative survival from RAPID (Table 40) to its closest next value in the registry cumulative survival data. The company then took the corresponding death hazard for the following year in the registry data. From that year on, the company applied the registry hazards to model patients' survival in the economic analysis.

As no generic measures of HRQoL were captured in the RAPID trial, the quality of life analysis was informed by published utility data. However, as described in Section 5.3, the company did not identify any relevant utility data from the SLR to i nform the model. As a result, the company obtained EQ-5D utility values from the ADAPT UK registry dataset (Ejiofor and Stockley 2015), which provides EQ-5D values by FEV1 predicted state, for patients with A1PI deficiency.

The company assumed no difference in HRQoL between patients in different lung density decline health states (no, slow and rapid decline). Therefore, the company assumed that HRQoL is driven only by FEV1 predicted in the model, but stated that this is unlikely to capture the full quality of life of patients with A1PI deficiency.

After a clarification request from the ERG, the company used the Anyanwu *et al.* 2001 study to estimate the impact of lung transplant on patients' quality of life. Anyanwu *et al.* 2001 collected EQ-5D data from 185 UK patients and reported utility values according to the type of lung transplant (single or bilateral) and further according to the number of months after transplantation, up to 36 months after transplantation.

The costs included in the model consist on the following:

- Acquisition and administration costs associated with the intervention (Section 5.4.10.1);
- Disease management costs (Section 5.4.10.2);
- Lung transplant costs (Section 5.4.10.3).

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

Clinical

The CS included a systematic review that used appropriate methodology to identify and appraise evidence relevant to the use of Respreeza in the management of emphysema secondary to severe A1PI deficiency. The ERG considers the evidence identified and included in the submission is appropriate to the decision problem and NICE scope. The ERG is confident that all relevant RCTs and relevant extensions were included in the submission.

The key findings were derived from a large, well-designed and well-conducted study, RAPID. Corroborative evidence on effect of A1PIs as a class was derived from two systematic reviews that included RAPID in their analyses. Results from the systematic reviews were consistent with the results reported from RAPID.

Economic

The formulae within the economic model are generally sound and the economic model is broadly well constructed.

1.5.2 Weaknesses and areas of uncertainty

Clinical

The ERG notes that data on rate of deterioration in lung density or lung function pre-treatment are not available for RAPID, as RAPID did not include a "run in" period to establish that those potentially eligible for the trial were experiencing progressive decline in lung disease. The ERG appreciates that monitoring lung function before treatment was not part of the design of other RCTs evaluating A1PI therapy. However, given that the company proposes that those who are experiencing rapid deterioration in lung disease, which, based on reported research, the company proposed to be reached at an annual decline of ≥2.0 g/L in CT lung density, could potentially achieve greater benefit with Respreeza, the ERG considers that it would be appropriate to identify those whose lung density is declining at a rate of 2.0 g/L or more annually. Alternatively, if people of any categorisation of rate of decline in CT lung density are eligible for treatment, it would be appropriate to stratify randomisation by the categories of rate of decline to ensure balanced groups at baseline for this characteristic.

Although inclusion criteria for RAPID are well-defined, the ERG has reservations about the lack of clearer definition of progressive lung disease, or eligibility criteria for treatment. Based on the eligibility

criteria for RAPID, one of the ERG's clinical experts has fed back that everyone with emphysema secondary to A1PI deficiency will be eligible for treatment with Respreeza. More guidance on eligibility for treatment, for example, a threshold for starting treatment in terms of rate of annual decline in CT lung density or annual decline in spirometry measures (e.g., FEV1 per cent predicted, K_{CO}, and D_{LCO}) would be welcome. The EPAR for Respreeza outlines that an expert panel agreed that the appropriate target population in clinical practice for A1PI replacement would be patients presenting with a combination of risk factors, based on significant lung density decline, severity of emphysema, deficient level of A1PI (<11 μM), and phenotype or genotype at risk. The ERG notes that, at this time, no minimal clinically important differences (MCIDs) have been established for CT lung density, FEV1 or gas transfer.

Additionally, as clarified by the company, there is currently no guidance when it is appropriate to stop treatment with Respreeza. The company highlighted that, as the goal of treatment is to restore serum levels of A1PI to ≥11 μM, continuous treatment with Respreeza would be necessary. However, the ERG's clinical experts highlighted that, potentially, there could be people, for example, those whose CT lung density continues to deteriorate at the same rate or increases after treatment with Respreeza. Clinicians might want to consider stopping treatment for those who do not appear to be achieving a benefit from treatment.

The primary outcome in RAPID of deterioration in lung density by CT is a surrogate outcome measure for progression of lung disease, as is change in FEV1. Although deterioration in CT lung density is seen as an appropriate clinically meaningful outcome to assess effectiveness of augmentation therapy on progression of emphysema, FEV1 is typically the preferred measure in clinical practice in the UK as it is less expensive and easier to assess. Where FEV1 tests respiratory health in terms of airway obstruction, CT lung density and gas transfer capture changes in the alveolar structure, and thus the pathology of the condition. However, in contrast to gas transfer, CT is costly and requires specialist equipment and software. At this time, there is uncertainty around how changes in CT lung density correlate with spirometric measures, HRQoL and mortality. Thus, clinicians in England are likely to want to base decisions to treat people with Respreeza on CT densitometry, as was carried out in RAPID, as well as using CT lung density to monitor progression of emphysema.

Economic

The ERG's main concerns are related to the use of RAPID data to estimate baseline lung density decline and treatment effectiveness on CT lung density decline; the estimation of lung function-related mortality in the model; the benefits associated with lung transplant; the proposed value of Respreeza, and finally, the use of CT scanning in the NHS. These issues are discussed in detail below, together with other topics worthy of consideration:

1. Eligibility criteria for treatment with Respreeza: One of the company's proposed eligibility criteria for treatment with Respreeza is a, "*rapidly declining lung function, measured by predicted values for FEV1 or gas transfer ($D_L$co), or lung density decline*". However, the marketing authorisation for Respreeza does not include any specifications on the rate of lung function decline for treatment initiation. Despite there being no clinically established definition of rapid lung function decline, the company has defined rapid decline as a deterioration in CT lung density of more than 2 g/L/year in their analysis of treatment effectiveness, within the economic model. Inconsistent with the former, the company did not apply their own "starting rule" in the economic model for the administration of Respreeza, as all patients in the intervention arm receive treatment, regardless of having no, slow, or, rapid baseline lung density decline.

   Clinical expert opinion sought by the ERG confirmed that there would need to be demonstrable evidence of decline in patients' lung function for them to prescribe Respreeza, as they would not want to give it to patients with no decline in lung function. The experts added that, as the company is not proposing any definition of "rapid decline" in their eligibility criteria, if Respreeza is recommended, everyone with emphysema secondary to A1PI will be eligible for the treatment, as the former disease implies an inevitable decline in lung function. Furthermore, the EPAR expert panel recommended that the appropriate target population for Respreeza should have evidence of significant lung density decline.

   Finally, patients with an FEV1<30% at baseline were excluded from the trial population, and therefore not included as starting patients in the model. The ERG's clinical experts highlighted that there may be a rationale for initiating treatment with Respreeza in patients with a FEV1<30%, to salvage remaining lung function of patients who are either ineligible, or on the waiting list for a lung transplant.

2. Treatment stopping rules: In reply to an ERG clarification question, the company confirmed that stopping rules for Respreeza have not been proposed, and that such rules are not specified in the drug's marketing authorisation. Nonetheless, the company applied a stopping rule in the model, as all patients progressing to an FEV1<30% state stop treatment, thus underestimating the costs associated with Respreeza. Clinical experts advising the ERG explained that they would not necessarily stop treatment with Respreeza when patients' FEV1 falls below 30%, as for most of these patients there will be no treatment options left. The impact of implementing a stopping rule for Respreeza in the final ICER is considerable.

3. Modelling approach using the hybrid FEV1 and lung density decline health states: The ERG is concerned that by estimating FEV1 progression and lung density decline separately, and then

aggregating these in the model, the company is breaking an implicit relationship between clinical outcomes to them; artificially manipulating it through the use of different assumptions and data sources, without any means of validating its approach nor its results. As acknowledged in the CS, there is a considerable evidence base documenting the correlation between FEV1 and CT lung density measurements, however, there is no robust evidence to establish a predictive relationship between the two outcomes. The ERG is, therefore, concerned that the pillar of the economic model (patients' movement through the hybrid states of FEV1 and CT lung density decline) is based on a method which artificially decomposes the relationship in the evolution of FEV1 and CT lung density. This introduces a paramount degree of uncertainty in the cost-effectiveness results, which has not been appropriately accounted for through probabilistic sensitivity analysis, as the latter did not correlate FEV1 and lung density decline outcomes.

Alternatively, the company could have taken a modelling approach based on either FEV1 or lung density decline outcomes. Given that most economic outcomes, such as disease management costs and eligibility for lung transplant are linked only to FEV1 status, and that quality of life and mortality are also easily linked to FEV1 outcomes, the ERG proposed, during the clarification stage, that the company built an alternative model based only on FEV1 outcomes. The company disagreed with the proposed approach, and stated that, "*FEV1 is considered an inappropriate outcome measure in A1PI as FEV1 has been shown to change slowly over time and is subject to a considerable degree of inter- and intra-patient variability*". The company added that, *"The most recently updated treatment guidelines (ERS guidelines) confirm that CT densitometry has been established as the most specific and sensitive surrogate end-point for the evaluation of therapeutic benefit of augmentation therapy* […]*."*

Other literature sources are in accordance with the superiority of CT measurements of lung decline function. For example, Green *et al.* 2016 found that around half of patients in their study (ADAPT registry) who exhibited no significant decline in FEV1 (i.e. normal ageing), had whole lung CT density decline.[1] The ERG acknowledges the fact that CT densitometry is a superior measurement of emphysema progression in A1PI deficiency, and of the therapeutic benefit of augmentation therapy. Nonetheless, it points to the contradiction in the company's approach of stating that FEV1 is an inappropriate outcome measure in A1PI, but still including it as a clinical outcome in their economic model. The ERG considered the feasibility of an economic model based on lung density decline outcomes only: treatment effectiveness measures would be available from RAPID; mortality and quality of life data would be available from Green *et al*.; the challenge would be to cost lung density decline outcomes and judge patients' suitability for

lung transplant. The ERG concluded that more research is needed to assess the feasibility, and surpass the initial barriers associated with such models.

4. Use of CT scanning: The company, in their reply to the ERG's clarification questions, state that it is not proposing that routine CT scanning is introduced in the NHS if Respreeza is recommended, as the latter is not necessary to initiate or monitor treatment.

   From a current clinical practice perspective, the ERG is concerned that CT lung density is rarely measured in the clinical management of A1PI, as explained by the ERG's clinical experts and discussed in Section 4. Consequently, the ERG is concerned that in order to prescribe, and monitor patients on Respreeza, clinicians would have to use CT scanning. The clinical experts advising the ERG have different views on this topic. While one of the experts stated that lack of access to CT scanning would not prevent the prescribing or monitoring of patients on Respreeza; the other explained that he would want to "replicate" the RAPID trial measurements, in order to be able to assess patients' response to the drug, therefore requiring CT scanning.

   Green *et al.* concluded that use of serial spirometry to select patients most likely to benefit from augmentation, would miss many at risk individuals. Serial gas transfer would be a more reliable marker of the emphysema process detected by density change, but would still miss around 20% of patients with a declining CT scan. The authors added that even though some of the study patients did not decline at all, over the period when density was monitored, none of the standard measures taken in clinical practice differentiated these patients clearly from decliners. The authors therefore, suggest that serial CT densitometry would be the most reliable way to identify progressing high risk A1PI patients for more aggressive treatment (i.e. augmentation), and lower risk A1PI patients, who could safely be monitored, therefore bringing A1PI management closer to a personalized, risk-based approach. The authors advise that if the NHS were to move to routine use of densitometry, hospitals/clinics would either need to buy software and train staff, or commission services from external providers of CT studies and analysis, to ensure consistency and accuracy.

   Furthermore, the ERG cannot fail to acknowledge the inconsistency in the company's need to have a CT lung density-based economic model to appropriately assess the cost-effectiveness of Respreeza, and the company's view that CT lung density assessments will not be necessary in clinical practice if the drug is recommended.

   Given the opposite views of the ERG's clinical experts on the subject, it is difficult to anticipate if the use of Respreeza in the NHS would have to be accompanied by routine use of CT lung

density. If that is the case, then the company's analysis of cost-effectiveness is underestimating the costs associated with Respreeza.

5. Estimation of treatment effectiveness on FEV1 progression: The company used the Stockley *et al.* 2014 to model FEV1 decline for BSC patients in the model. However, the source is an abstract, therefore, the ERG could not assess the full analysis. Furthermore, using the Stockley *et al.* 2014 analysis assumes that patients on BSC have the same probability of decline in FEV1 status, regardless of their current FEV1 value, which might be overly simplistic and clinically implausible.

   The company used their updated meta-analysis to estimate the probability of patients' decline in FEV1 status for the Respreeza arm of the model, compared with BSC patients. From a conceptual point of view, the ERG disagrees with the company's choice of treatment effect estimates from the meta-analysis, to be used in the economic model. The company used the 18.90 ml/y effect size and the 1.28 ml/y value to predict the annual probability of Respreeza patients transitioning from the FEV1≥50% category to the 30%≤ FEV1<50% category, and the probability of patients in the latter category transitioning to the FEV1<30%, respectively. However, given the outcome of the meta-analysis reflects the effect of augmentation therapy versus placebo on the annual change in FEV1 decline, measured by ml/y, for the specific FEV1 categories of FEV1>65%; 30%-65% and <30%, the ERG notes that the 18.90 ml/y, and the 1.28 ml/y effect sizes correspond to the effect of Respreeza on slowing patients' FEV1 decline within the 30%≤ FEV1<50% category, and within the FEV1<30%, respectively. In their exploratory analysis, the ERG used the 18.90 ml/y effect size (instead of 1.28 ml/y) to reflect the effect of augmentation therapy in reducing the decline in FEV1 in patients in the 30%≤ FEV1<50% health states in the model. This results in the estimation of an annual transition probability of 9.60% for Respreeza patients, compared with 15.07% for BSC, for patients moving from the 30%≤ FEV1<50% to the FEV1<30% states in the model.

   Given the effect size for the FEV1>65% group in the meta-analysis is, not only non-statistically significant, but also counterintuitive (as it is a negative value, suggesting augmentation therapy is detrimental compared to placebo), the ERG used a relative risk of 1, which suggests that augmentation therapy does not have an effect, compared with placebo, in the FEV1≥50% group in the model.

6. Estimation of baseline lung density decline in the model: Including lung density decline in all health states of the model implied that patients' baseline rate of decline had to be estimated (with the exception of the FEV1<30% health states, which have no patients at the beginning of the model). In order to estimate baseline decline, the company used the results of their

regression analysis and took the year 0 to year 1 estimates for the number of patients in the ND, SD and RD categories in the placebo arm of RAPID, in the FEV1≥50% and FEV1<50% categories. The company's decision to use data from the RAPID placebo arm, and use it to estimate decline for both the BSC and the Respreeza arms of the model, implicitly assumes that the baseline lung density decline in placebo patients in RAPID is representative of the baseline decline in Respreeza patients, before they start treatment. This raises considerable concerns, given the company's acknowledgment of an imbalance in patients' baseline characteristics in the trial. The company does not provide more details on the baseline imbalance issue; however, the ERG is particularly concerned with the imbalance in baseline CT lung density, with Respreeza patients having a mean 46.6 g/L at baseline, and placebo patients having a lung density of 49.8 g/L. In the company's own definition of lung density decline, a 2 g/L annual decline is classified as rapid decline, thus, the difference and bias in baseline CT lung density across both treatment arms (3.2 g/L) should not be ignored. The direction of the bias is not clear to the ERG, as it could be argued that patients starting with a lower CT lung density are expected to have worse outcomes than patients with a higher lung density, but it could also be argued that the former are simply at a later stage of the disease and therefore might have "less room" for deteriorating, compared to the latter. Given that the real baseline CT lung density decline for the Respreeza group in RAPID is unknown, it is not possible to draw comparisons on baseline rate of decline, but only on absolute baseline lung density.

7. Estimation of treatment effectiveness on CT lung density decline: During the clarification stage, the ERG requested that the company provided, "*the equations used in the linear regression used to estimate transition probabilities between lung density states in the model using RAPID data (…), together with the covariates used to adjust these data, and with a clear description of the methods and data used in this process (including the results of the statistical process for selecting covariates)*". The company did not comply with the ERG's request, and instead confirmed that the covariates used in the RAPID analysis of change in CT lung density reported in the clinical study report (CSR), were used by the company in their assessment of CT lung density decline (defined with the 2 g/L threshold). The covariates listed in the CSR are [redacted].

   The list referred by the company does not include baseline CT lung density, which the ERG considers to be the more obviously imbalanced baseline characteristic in RAPID, and an important prognostic factor as it has been linked with mortality, FEV1 decline and other important clinical outcomes (Green *et al.* 2016). As the company's declined to provide the

information requested by the ERG, this essentially renders the company's analysis of treatment effectiveness a "black box".

Furthermore, the company reports using a linear regression to estimate lung density decline and the clinical expert advising the ERG noted that the decline in lung function outcomes over time is unlikely to be linear, therefore, the use of linear regression analysis might be inappropriate.

The ERG is also concerned with the fact that the thresholds used by the company to define lung density decline are not based on clinically standardised thresholds, and therefore are arbitrarily categorising Respreeza's measure of treatment effectiveness. The ERG is concerned that if the thresholds of lung density decline were defined differently, the measure of Respreeza's treatment effectiveness might also change considerably. This would have a direct impact on the final ICER, as one of the key model drivers is mortality, which in its turn is driven by patient's change in lung density decline (i.e. ND, SD or RD).

The ERG is concerned with the fact that the company is using the RAPID extension study data, which includes patients who crossed-over from the placebo arm of RAPID to treatment with Respreeza in the extension study. The company does not mention any data adjustments, and it reports that it is in line with the Markovian assumption of the model to add the data extension to the 2-year analysis of RAPID data, for the Respreeza arm of the model.

The ERG interprets the company's justification as a mention to the memoryless characteristic of the Markovian assumption. However, the ERG has not seen any evidence that patients whose disease has progressed for two years longer than other patients, are expected to have identical clinical outcomes as patients diagnosed earlier.

During the clarification stage, the ERG requested the company to provide the change in mean CT lung density per year, for Respreeza patients who received Respreeza in RAPID and carried on receiving Respreeza in RAPID-OLE (i.e. excluding the placebo patients from RAPID who crossed over to Respreeza in RAPID-OLE), over the 4-year follow-up period. The company instead provided the data for the placebo group in RAPID who went on to receive Respreeza during the open-label extension phase of RAPID.

The ERG also asked the company to use the requested Respreeza data (which the company did not provide) to calculate transition probabilities matrices estimating the probability of patients moving between the different lung density decline states in the model between year 0-1 and year 1-2; year 1-2 and year 2-3; and finally year 2-3 and year 3-4, using the 4-year Respreeza data (for the cohort of patients receiving Respreeza in RAPID and RAPID-OLE, excluding placebo patients from RAPID-OLE), for each FEV1% category included in the model. The

company replied that, "*The transition probabilities already utilise this data: the Respreeza transition probabilities are based on transitions between years 0-1, 1-2, 2-3 and 3-4 which therefore includes those that switched from placebo*.", therefore ignoring the ERG's request to exclude placebo patients from the 4-year data analysis of Respreeza.

8. Final transition probabilities used by the company: In terms of FEV1 decline, the company's estimated transition probabilities show that on average, patients on Respreeza are less likely than BSC patients to transition from the FEV1≥50% to the 30%≤ FEV1<50% category, every year. Patients in the latter FEV1 category have a similar probability of transitioning to the FEV1<30% category across treatment arms.

   The transition probabilities resulting from the ERG's exploratory analysis show that patients on Respreeza are equally likely as BSC patients to transition from the FEV1≥50% to the 30%≤ FEV1<50% category, every year. Conversely, Respreeza patients on the 30%≤ FEV1<50% category have a lower probability of transitioning to the FEV1<30% category compared with BSC patients. From a clinical point of view, this is a more likely scenario than the one translated from the company's analysis given the ERG's clinical experts' opinion that most patients presenting in clinical practice with symptoms are in the 30%≤ FEV1<50% category.

   Furthermore, it is the ERG's opinion that the transition probabilities estimated by the ERG are more consistent with the company's proposed benefit of Respreeza, which is to slow down patients' lung function decline and therefore, avoid the need for (or delay) lung transplant. Given that only patients with an FEV1<30% are eligible to receive a lung transplant in the model, it is by preventing them crossing from the 30%≤ FEV1<50% to the FEV1<30% states that lung transplants can be avoided in the economic analysis.

9. Lung transplants in the model: Throughout the CS, it is stated several times that one of the anticipated benefits of Respreeza is to delay, or obliviate the need for lung transplant. However, in their reply to a clarification question, the company states that Respreeza is expected to increase the proportion of patients that could receive a transplant. The ERG points to the inconsistency in the company's proposed value of Respreeza with regards to lung transplant, and reinforces the need for clarification around this issue. The impact of Respreeza on patients' need for lung transplant is one of the model key drivers. This, however, is related to the expected benefits associated with lung transplant, which also need discussing.

   For the subsequent years after lung transplant, the company took the 59% survival at five years from the NHS Blood and Transplant (NHS BT) 2017 report, and estimated an annual probability of death of 7.90%. Clinical expert opinion provided to the ERG was consistent in

reporting that survival after lung transplant is generally poor, with one clinical expert saying that the expected survival at year 5 is 50%, and the other clinical expert advising that on average, transplanted patients are expected to live between 5 and 10 years. Furthermore, Anyanwu *et al.* 2002, an economic evaluation of lung transplantation in UK patients which used 15 years of data from the UK Cardiothoracic Transplant Audit, suggests that survival at year 5 is around 50%, while survival around year 10 is 37% for double lung transplants.

The 1-year survival estimate used by the company (82%) is quite different from the ones estimated in Anyanwu *et al.* 2002 (around 70%).The 5-year survival estimate used by the company (59%), and that suggested by the ERG's clinical experts and Anyanwu *et al.* 2002 (50%) is not dissimilar. However, given that this is one of the key drivers in the economic model, the difference in these estimates has a paramount effect on the final ICER.

10. Lung function-related survival: The ERG is concerned with the lack of transparency in the company's reporting of its modelling approach for mortality. The ERG has several concerns with the company's approach:

    a. Firstly, the ERG disagrees with using survival RAPID data given that only five events were observed over the 4-year follow-up period (two in the Respreeza arm and three in the BSC arm). The use of trial data is further compromised by the ERG's concerns around baseline imbalances, and placebo patients crossing over to the Respreeza arm of RAPID-OLE after 2 years, without any data adjustments;

    b. Secondly, the company's approach to "transitioning" from the trial survival to the registry survival curve leads to a paramount overestimation of the survival benefit associated with Respreeza. In addition to the survival gain derived from the trial data during the first 2 years of the model (where data for both Respreeza and BSC patients are available), the company is artificially giving Respreeza patients extra years to "catch up" to BSC patients' death rate. This underestimates survival in the BSC arm, and overestimates survival in the Respreeza arm of the model. Given the ERG's consideration that RAPID data should not be used in the analysis, the ERG did not explore other transition methods from the RAPID to the registry survival data.

    c. Thirdly, the company's approach assumes that survival in the RAPID, and in the ADAPT registry populations is the same, as patients simply join from RAPID survival curves into registry survival curves from ADAPT, without any data adjustments. However the ERG considers that survival data are not comparable in these sources, and

thus cannot be used interchangeably, possibly because survival estimates from RAPID are unreliable, given the extremely small number of events.

The ERG asked the company to run a scenario analysis using only registry data to model survival. However, the company implemented its scenario analysis incorrectly, as patients in the Respreeza and in the BSC arms of the model were still joining the registry survival data at different points in the curve, therefore implicitly assuming a survival benefit with Respreeza. Therefore, the ERG corrected the company's scenario analysis and applied only the registry survival data to the model. Using only the Green *et al*. data to model lung density-related survival in the model is consistent with the company's proposed value of Respreeza, which is that it delays lung density decline in patients, which in turn reduces patients' mortality.

Nonetheless, the ERG also has several issues with the use of registry data by Green *et al*. and the company's reporting of the latter. The company did not acknowledge that the survival data used in the model are based on the analysis by Green *et al*. which concluded that when survival data were analysed by FEV1 category, CT density decline [redacted]. Instead, the company reports results of statistical significance between rapid CT lung density decline and death (p=0.026) but does not specify that the latter analysis, also by Green *et al*., refers [redacted] In fact, [redacted]

Contrarily to the company's view, the ERG concludes that the measure of the impact of declining CT lung function, by FEV1 group, on mortality is not well established, and neither is the impact of augmentation therapy on the latter. Therefore, caution is needed when interpreting the survival outcomes in the economic analysis.

Finally, the ERG notes that despite its the request for the company to include an option in the model to choose between the loglogistic, lognormal, exponential, Gompertz, Weibull and gamma distributions, to model lung function-related survival in the analysis, the company excluded the gamma distribution from the list. This is particularly relevant, given the ERG's assessment (based on AIC criteria), that the gamma distribution might be a better fit to the survival curves for the rapid decline categories, instead of the Gompertz distribution, used by the company.

11. Synergies in the economic model: In the company's base case, where RAPID survival data are included in the analysis, patients who receive Respreeza accrue incremental life years in all the FEV1 lung density decline states, as well as in the lung transplant states (Table A).

Removal of RAPID survival data from the analysis

When the ERG included only registry survival data in the model, the incremental life years gained decreased overall (as the company's base case overestimates survival with Respreeza and underestimates survival with BSC), and the incremental life-years in the FEV1<30% categories become close to zero (Table B). Fewer Respreeza patients move to the 30%≤ FEV1<50% category, compared to BSC patients, therefore, also accruing fewer life years in that state. The biggest drop in life-years gained from the company's base case analysis, to the ERG's analysis, is in the lung transplant state, which decreased from 1.39 to 0.03 incremental life-years with Respreeza. Given that the ERG only changed the estimation of lung function-related mortality, the change in life-years gained after lung transplant is a direct consequence of fewer Respreeza patients reaching the FEV1<30% state, where patients become eligible for transplant.

The life-years gained in the ERG scenario are consistent with the company's base case transition probabilities, which suggest that patients on Respreeza are less likely than BSC patients to transition from the FEV1≥50% to the 30%≤ FEV1<50% category, but that patients on the latter FEV1 category have a similar probability of transitioning to the FEV1<30% category across treatment arms. Therefore, removing the RAPID survival data from the analysis, and more importantly, removing the company's approach of allocating Respreeza and BSC patients to different points in the registry survival curves, removes "noise" from the company's analysis and leads to a generation of incremental life-years consistent with the company's base case transition probabilities.

The change in ICER caused by the removal of RAPID survival data (from £236,409 to £940,650) also shows how, perhaps counterintuitively, avoiding lung transplants in the Respreeza arm of the model is detrimental to the company's ICER (i.e. the ICER increases). This is because lung transplant in the model is associated with a considerable improvement in quality of life and survival, and the total costs of lung transplant are not enough to offset this gain when considerably more patients in the Respreeza arm receive lung transplants than patients in the BSC arm.

Table A. Undiscounted life years gained in company's base case analysis (ICER £236,409)

Health state	Undiscounted life years		
	BSC	Respreeza	Incremental
FEV1>50%: No decline	0.04	0.17	0.13
FEV1>50%: Slow decline	1.33	2.04	0.71
FEV1>50%: Rapid decline	0.39	0.44	0.05

Total	**1.76**	**2.65**	**0.89**
30%<FEV1<50%: No decline	0.07	0.33	0.26
30%<FEV1<50% Slow decline	1.46	2.92	1.47
30%<FEV1<50% Rapid decline	1.79	0.66	-1.13
Total	**3.32**	**3.91**	**0.60**
<30% ND	0.01	0.10	0.09
<30% SL	0.37	0.90	0.53
<30% RD	0.56	0.19	-0.37
Total	**0.93**	**1.18**	**0.25**
Lung transplant: first year	0.35	0.47	0.12
Lung transplant: subsequent years	3.59	4.85	1.27
Overall total	**9.94**	**13.07**	**3.13**

Table B. Undiscounted life years gained in ERG's scenario using registry mortality data (ICER £940,650)

Health state	**Undiscounted life years**		
	BSC	**Respreeza**	**Incremental**
FEV1>50%: No decline	0.04	0.17	0.13
FEV1>50%: Slow decline	1.56	2.04	0.47
FEV1>50%: Rapid decline	0.43	0.43	0.01
Total	**2.03**	**2.64**	**0.62**
30%<FEV1<50%: No decline	0.07	0.29	0.23
30%<FEV1<50% Slow decline	1.57	2.57	1.00
30%<FEV1<50% Rapid decline	1.88	0.59	-1.29
Total	**3.52**	**3.45**	**-0.07**
<30% ND	0.01	0.09	0.08
<30% SL	0.40	0.74	0.34
<30% RD	0.58	0.15	-0.43
Total	**0.99**	**0.98**	**-0.01**
Lung transplant: first year	0.37	0.38	0.00
Lung transplant: subsequent years	3.84	3.87	0.03
Overall total	**10.75**	**11.32**	**0.57**

Use of different meta-analysis estimates

Using the ERG's proposed results from the meta-analysis, but maintaining the company's approach to using RAPID survival data, shows that Respreeza patients still accrue more life years in all the FEV1 states, including the lung transplant states (Table C). However, the gain in life-years shifted from the FEV1≥50% to the 30%≤ FEV1<50% category, compared with the company's base case (Table A). This is broadly in line with the ERG's corrected transition probabilities, which show that patients on Respreeza are equally likely to transition from the FEV1≥50% to the 30%≤ FEV1<50% category as BSC patients, and that the latter have a lower

probability of transitioning to the FEV1<30% compared with BSC patients. Nonetheless, the life-years gained in the economic analysis are not perfectly consistent with the ERG's transition probabilities, until the ERG included only registry mortality data in the model.

Use of UK registry data and different meta-analysis estimates

The combination of both changes to the company's model (Table D, dominated ICER of -£5,898,567) decreased the overall survival benefit with Respreeza (overestimated in the company's base case analysis) and increased the survival benefit with BSC, and indeed generated no incremental life-year in the FEV1≥50% category as expected, given the ERG's use of a relative risk of 1 for Respreeza and BSC patients progressing from the FEV1≥50% to the 30%≤ FEV1<50% category.

The biggest gain in survival with Respreeza is derived in the 30%≤ FEV1<50% category, as more Respreeza patients stay in these states than BSC patients. More patients in the BSC arm of the model spend time in the FEV1<30% states, and therefore, there are more lung transplants in the BSC arm of the model, than in the Respreeza arm.

The utility associated with FEV1<30% is lower than the utility associated with 30%≤ FEV1<50% category (0.63 vs 0.51); however, the utility associated with lung transplant after 2 years is higher than both (0.77). Moreover, survival in the lung transplant state is higher than in the FEV1<30% states, therefore, the treatment that allocates more patients to lung transplants, is the most likely to generate an additional clinical benefit in the economic analysis. Ironically, avoiding lung transplants is one of the outcomes that the company proposes as Respreeza's biggest benefit (i.e. to slow down disease's progression and avoid lung transplants), however, contradicted by the company during the clarification stage.

Use of UK registry data; different meta-analysis estimates, and reducing the proportion of patients eligible for lung transplant

Reducing the number of patients eligible for lung transplant by 30% (Table E, dominated ICER) means that overall, more patients stay in the FEV1<30% state, thus overall, fewer patients receive a lung transplant. Therefore, the negative incremental life-years and QALYs associated with Respreeza decrease from -0.15 to -0.07, but still generating a dominated ICER for Respreeza.

Use of UK registry data; different meta-analysis estimates; reducing the proportion of patients eligible for lung transplant, and reducing the survival benefit associated with lung transplant

When the survival benefit associated with lung transplant is reduced, the incremental QALYs become positive in the model (Table F, ICER £10,468,323). The ERG replaced the company's survival estimates at year 1 and year 5 (82% and 59%, respectively), by an approximation of the Anyanwu *et al.* 2002 and ERG's clinical experts' estimates (around 70% for year 1 and 50% for year 2). Reducing the survival benefit associated with lung transplant means that the benefit derived by Respreeza patients in the 30%≤ FEV1<50% category is enough to offset the benefit derived by BSC patients in the lung transplant states.

It is therefore, crucial that the Committee discusses which health state – the 30%≤ FEV1<50% or the post-lung transplant states – is likely to be associated with higher benefits in terms of quality of life and survival. It is also important to discuss if the goal of treatment with Respreeza is: i) to maintain patients in the 30%≤ FEV1<50% state for the longest time possible, avoiding lung deterioration to FEV<30% and, thus, lung transplant (which the ERG's adapted model demonstrates); or ii) to allow more patients to transition to a lung transplant.

Given the small QALY gain generated with Respreeza in the 30%≤ FEV1<50% state, and the very high costs associated with treatment, the ICERs generated in the ERG's analysis are unlikely to be considered cost-effective.

Table C. Undiscounted life years gained in ERG's scenario using different meta-analysis results (ICER £316,685)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.33	1.54	0.20
FEV1>50%: Rapid decline	0.39	0.35	-0.03
Total	**1.76**	**2.03**	**0.27**
30%<FEV1<50%: No decline	0.07	0.43	0.37
30%<FEV1<50% Slow decline	1.46	3.92	2.46
30%<FEV1<50% Rapid decline	1.79	0.85	-0.94
Total	**3.32**	**5.20**	**1.88**
<30% ND	0.01	0.08	0.07
<30% SL	0.37	0.75	0.38
<30% RD	0.56	0.15	-0.41
Total	**0.93**	**0.98**	**0.05**
Lung transplant: first year	0.35	0.38	0.04

Lung transplant: subsequent years	3.59	3.95	0.36
Total	**9.94**	**12.54**	**2.60**

Table D. Undiscounted life years gained in ERG's scenario using registry mortality data and different meta-analysis results (ICER -£5,898,567)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.07	0.06
<30% SL	0.40	0.60	0.19
<30% RD	0.58	0.12	-0.46
Total	**0.99**	**0.79**	**-0.21**
Lung transplant: first year	0.37	0.30	-0.08
Lung transplant: subsequent years	3.84	3.05	-0.79
Total	**10.75**	**10.60**	**-0.15**

Table E. Undiscounted life years gained in ERG's scenario using registry mortality data, different meta-analysis results and reducing the proportion of patients eligible for lung trabsplant by 30% (ICER -£37,189,197)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.09	0.08
<30% SL	0.51	0.75	0.23

<30% RD	0.72	0.15	-0.57
Total	**1.24**	**0.99**	**-0.26**
Lung transplant: first year	0.32	0.26	-0.07
Lung transplant: subsequent years	3.31	2.64	-0.67
Total	**10.42**	**10.35**	**-0.07**

Table F. Undiscounted life years gained in ERG's scenario using registry mortality data, different meta-analysis results, reducing the proportion of patients eligible for lung trabsplant by 30% and decreasing lung transplant-related survival (ICER £10,468,323)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.09	0.08
<30% SL	0.51	0.75	0.23
<30% RD	0.72	0.15	-0.57
Total	**1.24**	**0.99**	**-0.26**
Lung transplant: first year	0.32	0.26	-0.07
Lung transplant: subsequent years	2.88	2.30	-0.59
Total	**9.99**	**10.01**	**0.02**

12. Estimation of quality of life in the model: The company stated that the benefits of Respreeza may be underestimated by not capturing its effect of reducing lung density decline on patients' quality of life. The company presented one of two analyses from the Green *et al.* looking at the impact of lung density decline in HRQoL. The analysis reported by the company found [redacted] The second analysis in the manuscript, not reported by the company, showed [redacted]

[redacted]

Although the second analysis is based on smaller patient numbers, and given that the definition of lung density in Green *et al.* is the same as the definition used by the company in its analysis of lung density decline, the ERG is concerned that the company did not use this source to model differences in HRQoL, according to baseline lung density and lung density decline. Instead, the company states that there are no available data to conduct such analysis, and argues that the benefits of Respreeza may be underestimated in the analysis, without additional modelling to try and mitigate its concerns. The company's approach is also inconsistent with its overarching rationale for including lung density outcomes in the health states of the economic model, and in the overall economic analysis.

Finally, a scenario analysis was explored by the company to account for age-adjusted utilities, but the ERG disagrees with the company's implemented approach. Therefore, the ERG recommends that the company uses the published algorithm by Ara *et al.* 2010 to estimate age-adjusted utilities, which is based on a published, peer-reviewed methodology. Due to time constraints and limitations regarding the model structure, the ERG did not implement this in the model.

13. Treatment costs with Respreeza: Patients in the Respreeza arm of the model are assumed to have a mean weight of 75.9kg, which translates into 5 required vials per patient, per treatment (including wastage). However, the weight range in RAPID was quite broad (47.0 to 170.8kg) and, therefore, the number of vials of Respreeza required would change according to weight categories in RAPID. For example, for a patient with 88kg, 6 vials would be required. Hence, the ERG recommends that the company look at patients' weight categories in the trial, and assesses the proportion of patients requiring a different number of vials.

    Furthermore, the clinical experts advising the ERG noted that it could be challenging for patients to receive Respreeza at home, based on the availability of community nurses to administer treatment. Therefore, the ERG a conducted scenario analysis to assess the impact of assuming 100% of patients receive treatment in a clinic, instead to assuming that 75% of patients get treatment at home.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The ERG corrected the company's estimated probability of death in the first year after lung transplant (16.47%) and replaced it with 18% in the model. Results are provided in Table G and show an increase from the company's base case ICER of £236,409 to £237,822 per QALY gained.

Table G. Results of company's base case analysis corrected by the ERG

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
BSC	£62,457	5.424	-	-	-
Respreeza	£422,198	6.936	£359,741	1.513	£237,822

1.7 ERG exploratory analysis

The scenario analyses undertaken by the ERG consist on the following:

1. The ERG used the 18.90 ml/y effect size (instead of 1.28 ml/y) to reflect the effect of augmentation therapy in reducing the decline in FEV1 in patients in the 30%≤ FEV1 <50% health states in the model. Given the effect size for the FEV1>65% group in the meta-analysis is, not only non-statistically significant, but also counterintuitive (as it is a negative value, suggesting augmentation therapy is detrimental compared to placebo), the ERG used a relative risk of 1. This results in the estimation of an annual transition probability of 14.82% for Respreeza and BSC patients moving from the FEV1≥50% to the 30%≤ FEV1 <50% category;

2. The ERG removed the RAPID survival data from the analysis and replaced it with the UK registry survival data;

3. The ERG removed the treatment stopping rule applied in the model so that Respreeza patients who move to the FEV1<30% category continue to receive treatment, until they receive a lung transplant or die;

4. The ERG applied an age cap for lung transplant, so that patients above 65 years would not be eligible for a transplant in the model;

5. Clinical experts advising the ERG reported that 30% of patients would be expected to be ineligible for lung transplant due to co-morbidities. Therefore, the ERG decreased the population eligible for lung transplant in the model by 30%;

6. The ERG replaced the company's lung transplant survival estimates at year 1 and year 5 (82% and 59%, respectively), by an approximation of the Anyanwu *et al.* 2002 and ERG's clinical experts' estimates (70% for year 1 and 50% for year 2);

7. The ERG assumed that 100% of drug administrations take place at a clinic.

Results from the ERG analysis are reported in Table H. The two key drivers of the model are the source and method used to estimate FEV1, including the treatment effect on FEV1 progression taken from the meta-analysis, and lung density decline-related mortality. The change in the former increased the corrected base case ICER from £237,822 to £940,871, while changing the latter increased the corrected base case ICER to £317,053 per QALY gained.

Nonetheless, as discussed in Section 5.4.7.2, when all the changes are combined, there are synergies in the model which affect the final ICER. Therefore, even though the ERG is not presenting a preferred "ERG base case", the individual and cumulative ICERs (incorporating all the changes in Table H), are reported in Table I. The ERG's cumulative exploratory ICER amounts to £8,573,535 per QALY gained, with incremental QALYs of 0.046 and an incremental cost of £393,162.

The ERG ran the company's PSA on the ERG's cumulative analysis, and estimated a probabilistic ICER of approximately £3,000,000. The ERG notes that PSA results are unreliable, potentially due to the lack of correlating FEV1 and lung density declines in the analysis.

Table H. Results of the ERG's exploratory analysis

Analysis from list	Results per patient	Respreeza (1)	Best supportive care (2)	Incremental value (1-2)
0	**Company's corrected base case**			
	Total costs (£)	£422,198	£62,457	£359,741
	QALYs	6.936	5.424	1.513
	ICER		**£237,822**	
1	**Using different results from the meta-analysis**			
	Total costs (£)	£446,278	£62,457	£383,821
	QALYs	6.634	5.424	1.211
	ICER		**£317,053**	
2	**Using the UK registry survival data**			
	Total costs (£)	£388,548	£66,733	£321,815
	QALYs	6.177	5.835	0.342
	ICER		**£940,871**	
3	**Removing stopping rule for treatment with Respreeza**			
	Total costs (£)	£482,002	£62,457	£419,545
	QALYs	6.936	5.424	1.513

Analysis from list	Results per patient	Respreeza (1)	Best supportive care (2)	Incremental value (1-2)
	ICER		**£277,359**	
4	**Applying an age cap for lung transplant (65 years)**			
	Total costs (£)	£421,764	£62,456	£359,308
	QALYs	6.919	5.424	1.495
	ICER		**£240,298**	
5	**Reducing the population eligible for lung transplant by 30%**			
	Total costs (£)	£417,047	£56,811	£360,236
	QALYs	6.804	5.239	1.565
	ICER		**£230,196**	
6	**Using alternative survival estimates for lung transplant**			
	Total costs (£)	£418,090	£59,324	£358,766
	QALYs	6.595	5.164	1.432
	ICER		**£250,584**	
7	**The ERG assumed that 100% of drug administrations took place at a clinic**			
	Total costs (£)	£429,180	£62,457	£366,723
	QALYs	6.936	5.424	1.513
	ICER		**£242,438**	
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.				

Table I. Cumulative results of ERG's exploratory analysis

	Results per patient	Respreeza (1)	BSC (2)	Incremental value (1-2)
0	**Company's corrected base case**			
	Total costs (£)	£422,198	£62,457	£76,638
	QALYs	6.936	5.424	1.02
	ICER		£237,822	
1	**Using different results from the meta-analysis**			
	Total costs (£)	£446,278	£62,457	£383,821
	QALYs	6.634	5.424	1.211
	ICER (compared with base case)		£317,053	
	ICER with all changes incorporated		**£317,053**	
2	**Using the UK registry survival data**			
	Total costs (£)	£388,548	£66,733	£76,010
	QALYs	6.177	5.835	1.02
	ICER (compared with base case)		£940,871	
1+2	ICER with all changes incorporated		**Dominated (-£6,764,471)**	
3	**Removing stopping rule for treatment with Respreeza**			
	Total costs (£)	£482,002	£62,457	£75,929
	QALYs	6.936	5.424	0.95

	Results per patient	Respreeza (1)	BSC (2)	Incremental value (1-2)
	ICER (compared with base case)	£277,359		
1+2+3	ICER with all changes incorporated	**Dominated (-£7,580,023)**		
4	**Applying an age cap for lung transplant (65 years)**			
	Total costs (£)	£421,764	£62,456	£77,261
	QALYs	6.919	5.424	1.02
	ICER (compared with base case)	£240,298		
1+2+3+4	ICER with all changes incorporated	**Dominated (-£7,338,875)**		
5	**Reducing the population eligible for lung transplant by 30%**			
	Total costs (£)	£417,047	£56,811	£80,079
	QALYs	6.804	5.239	1.02
	ICER (compared with base case)	£230,196		
1+2+3+4+5	ICER with all changes incorporated	**Dominated (-£72,940,369)**		
6	**Using alternative survival estimates for lung transplant**			
	Total costs (£)	£418,090	£59,324	£358,766
	QALYs	6.595	5.164	1.432
	ICER (compared with base case)	£250,584		
1+2+3+4+5+6	ICER with all changes incorporated	**£8,399,246**		
7	**The ERG assumed that 100% of drug administrations took place at a clinic**			
	Total costs (£)	£429,180	£62,457	£366,723
	QALYs	6.936	5.424	1.513
	ICER (compared with base case)	£242,438		
1+2+3+4+5+6+7	ICER with all changes incorporated	**£8,573,535**		

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

2.1.1 Overview of the condition

The company provides an overview of alpha-1 proteinase inhibitor (A1PI) deficiency in Section 6 of their submission. The Evidence Review Group (ERG) notes the population defined in the final scope issued by the National Institute for Health and Care Excellence (NICE) to be adults with severe A1PI deficiency who have progressive lung disease. Neither severe A1PI deficiency nor progressive lung disease are defined in the NICE final scope (see Section 3.1).

A synopsis of information provided in the company submission (CS), including pathophysiology, symptoms, and diagnosis, is provided below with supplementary information about the impact of smoking:

- A1PI is a protein produced in the liver, which is circulated in the bloodstream and found in all body tissues. The primary role of A1PI is to protect tissue, particularly in the lungs, from damage arising from the action of neutrophil elastase and other proteolytic enzymes that are released by neutrophils or macrophages in response to pathogens or tobacco smoke;[2,3]

- Severe A1PI deficiency most commonly manifests as emphysema, a form of chronic obstructive pulmonary disease (COPD) that causes damage to the alveolar, because tissues are poorly protected from the neutrophil elastase produced in response to smoking, infections, and other environmental toxins (e.g. fumes, dust);[4] individuals are also at risk of liver and skin problems;[5, 6]

- The development and characteristics of emphysema secondary to A1PI deficiency vary considerably, suggesting an interplay between genetics and environmental exposures (e.g., smoking, pollution);[7]

- The company states that a threshold of 11 μmol/L (hereafter referred to as <11 μM) is commonly used to indicate severe deficiency in circulating A1PI levels,[8] which was corroborated by the ERG's clinical experts;

- Functional or defective genetic variants of the A1PI gene 'PiM' can cause A1PI deficiency. Risk of developing symptoms is dependent on circulating A1PI levels, which is associated with, but not reliant upon, the underlying genotype;

- Genotypes most commonly associated with severe A1PI deficiency (PiZZ (95%),[9] PiZ(null) and Pi(null,null))[10] are carried by between 1 in 5,000 and 1 in 1,600 of babies born in the UK (0.02 to 0.07%).[11] Genotype frequency varies substantially across countries and regions[12] and those associated with severe deficiency are highest in individuals of white European descent.[12]

- Around 25,000 people in the UK are thought to be carriers of defective variants, many of whom remain undiagnosed; many carriers have sufficient circulating A1PI or are not exposed to enough damaging substances for lungs to suffer substantial damage;[4]

- Emphysema associated with A1PI deficiency tends to have an early onset – typically between 20 and 50 years old[13] – and progresses more rapidly than it does without deficiency, particularly in previous or ongoing smokers;[14]

- Respiratory symptoms are akin to those of emphysema which is not secondary to A1PI deficiency; symptoms include breathlessness during exercise, long-lasting cough, sputum, wheezing, and recurrent chest infections;[4, 13]

- Emphysema secondary to A1PI deficiency is often misdiagnosed or diagnosis is delayed[15] due to overlap in symptoms with more common respiratory disorders and lack of awareness and screening; 1 to 2% of people with COPD have severe A1PI deficiency, although, because A1PI deficiency as a diagnosis is rarely considered, up to 95% of symptomatic cases will not be attributed to the underlying genetic cause;[16]

- Patients may be diagnosed with emphysema secondary to A1PI deficiency through routine monitoring if their carrier status was picked up incidentally (e.g., through screening of family members or due to paediatric jaundice);

- The ERG's clinical experts indicated that screening in England is not conducted in line with standards outlined by the World Health Organisation[17] (that is, all patients with COPD), and that serum concentration testing may be prompted by young onset symptoms of emphysema and dominant lower lobe disease;

- If suspected, emphysema secondary to A1PI deficiency is usually confirmed through serum concentration and phenotyping for common alleles. The ERG's clinical experts indicated that full genetic sequencing is rarely conducted in UK clinical practice.

2.1.2 Number of patients eligible in England

The company provides an estimate of the prevalence and incidence of symptomatic A1PI deficiency in England to calculate the number of patients who may be eligible for Respreeza should it be approved.

The company proposes that eligibility for Respreeza will be based on severity of A1PI deficiency (serum concentrations <11 μM) and evidence of progressive lung disease.

The ERG's clinical experts highlighted that any estimate of the eligible population will be subject to substantial uncertainty, because:

- Neither criteria for progressive lung disease nor thresholds for rate of decline are defined in the scope (see Section 3.1); in UK clinical practice, eligibility would currently be based on clinical judgement according to repeated observations of lung function, gas exchange (e.g., D_{LCO}) and physical function (e.g., impaired walking capacity);

- There is no national commissioning for A1PI deficiency in England, and so no national prevalence data;

- Patient registries associated with specialist UK research centres (e.g., Birmingham, London, Cambridge) are valuable but may not be representative of the total eligible population (e.g., because they are more likely to include patients who are willing or able to travel to a specialist centre).[18]

The company estimates prevalence and the size of the eligible population in England from a National Institute for Health Research (NIHR) horizon scanning report[11] and a West Midlands registry of people with A1PI deficiency (ADAPT).[11] Despite the limitations of registry data, the ERG's clinical experts agreed that it represents the best available evidence on which to base England prevalence estimates. Genotype frequency data are an unreliable estimator of the size of the eligible population because, while some genotypes are more commonly associated with severe A1PI deficiency, genotype alone does not associate closely with risk of developing progressive lung disease (Section 2.1.1).[11]

The company outlines that prevalence of symptomatic A1PI deficiency in England is estimated using a 0.99 per 100,000 prevalence derived from the NIHR report[11] and Office for National Statistics (ONS) data,[19] which are together applied to English ONS population figures (55,619,400).[20] The NIHR report[11] estimates prevalence of symptomatic A1PI deficiency at 1:123,284, translating to 670 people, of whom 549 (80%) are assumed to have clinically significant symptoms that would be eligible for Respreeza (see Sections 6.2 and 13).

The ERG could not validate the method used by the company or the NIHR report[11] to estimate the size of the eligible population; details were not provided in the CS about the size or coverage of the ADAPT registry, and how it was used with ONS 2014 data to derive a prevalence of 0.99 per 100,000. While the NIHR report cited by the company states that the calculations are based on 69 people identified from ADAPT, of whom 80% were deemed to have clinically significant symptoms, it does not give

details of the characteristics used to select the relevant population in ADAPT (e.g., genotype, serum concentrations, respiratory symptoms). The ERG requested step-by-step methods and assumptions from the company at the clarification stage, but the information provided by the company did not clarify the calculations.

The incidence of patients eligible for Respreeza presented in the CS was 0.17 per 100,000 population, based on expert opinion. At the clarification stage, the company stated that the expert estimate was applied to 2016 England population data to calculate an incident population of 95 patients per year (i.e., 0.17/100,000, multiplied by 55,619,400). The ERG considers the calculation valid, and is unaware of more reliable empirically derived incidence on which to base the estimate. At the clarification stage, the ERG asked the company to justify the reasoning for assuming incidence would remain stable should Respreeza be approved. The company did not respond to the ERG's question.

The ERG considers there to be substantial uncertainty associated with estimating prevalence and incidence, but appreciates that the West Midlands ADAPT registry constitutes the best available data given the rareness of the condition. The ERG's clinical experts suggested the population under care for severe A1PI deficiency and progressive lung disease may be larger than the company have estimated (up to 600 to 700). Moreover, the availability of Respreeza – a drug aimed at the underlying A1PI deficiency which currently remains unidentified in many cases (see Section 2.1.1)[12, 16] – may incentivise screening within the wider population with emphysema and substantially increase the size of the population. The ERG is unaware of before and after data from countries where A1PI augmentation has been introduced that could be used to inform projections for budget impact.

2.1.3 Life expectancy

The company present evidence about the impact of emphysema secondary to severe A1PI deficiency on survival, highlighting that it is a serious and chronic condition that profoundly reduces life expectancy (CS, Section 6.3). Life expectancy estimates for people with severe A1PI deficiency as presented by the company are based on Danish,[21] Spanish[22] and Swedish[23] registries, which indicate median survival of 54.5, 59 and 67 years, respectively. An equivalent estimate of median survival for patients with severe deficiency in the UK ADAPT registry was not presented in CS Section 6.3. Based on data from the ADAPT registry over a 9-year period (July 1996 to July 2005), mortality in those with A1PI deficiency (PiZ phenotype) in the UK (and therefore not receiving A1PIs) was 2% per year and was associated with lung function impairment and emphysema severity on CT scan.[24]

In the absence of median survival for the population of interest in England, the ERG sought the opinions of clinical experts. The experts indicated that survival varies widely for patients with severe A1PI deficiency in England but expected the median to be towards the upper end of the range across the European registries. The ERG's clinical experts highlighted that detection and management of A1PI

deficiency in the UK has improved since the establishment of specialist research centres, which is likely to have impacted the prognosis of patients with emphysema secondary to A1PI deficiency.

Information provided by the ERG's clinical experts and an analysis provided by the company suggest median survival across the population is likely to mask important variation in prognosis within the population of interest. The ERG's clinical experts outlined that patients with A1PI deficiency without progressive lung disease are likely to have similar life expectancy to the general population, and it is the development of emphysema that is life limiting. Survival within the population who develop progressive lung disease is heavily dependent on the age at which symptoms first arise, smoking history,[21] and the rate of lung function and density decline thereafter.[1]

The company presents a survival analysis of 110 patients from the ADAPT registry to identify predictors of survival for patients with severe A1PI deficiency, all of whom were naïve to A1PI therapy and had at least two CT scans at least a year apart. [redacted] results from multivariate analyses showed that age, baseline lung density and lung density decline >2 g/litre/year remained significantly associated with mortality. The ERG's clinical experts highlighted uncertainty associated with the arbitrary cut-off of >2g/litre/year to indicate rapid decline, but considered the results to indicate potentially important subgroup differences for consideration in the assessment of survival in this population.

2.1.4 Quality of life

Section 7 of the CS outlines the impact of severe A1PI deficiency on health-related quality of life (HRQoL), and how the technology may benefit patients and their families. The ERG highlights that Section 7 of the CS provides a narrative overview based largely on selected surveys,[18,25] observational studies,[26,27] and anecdotal evidence,[28] and does not present a systematic review of the HRQoL literature in the population of interest. Evidence cited in Section 7 includes a 2013 survey conducted by the Alpha-1 Alliance (N=162),[18] a 1994 survey conducted in the USA (N=398),[25] accounts published by Alpha-1 Awareness UK, two observational studies of patients with A1PI deficiency (N=35 and N=922 in Europe and the USA, respectively), and one randomised controlled trial of augmentation therapy[29] (N=77). A more in-depth consideration of the HRQoL evidence base, including data from the primary trial of Respreeza, is presented in Section 10 of the CS.

The ERG provides a summary of the company's overview in Section 7 of the CS below, with supplementary information from valuable statements from stakeholders and patient experts submitted to NICE in relation to this evaluation:

- Progressive lung disease secondary to A1PI deficiency can cause considerable physical and psychological morbidity, most notably severely restricted mobility and independence due to extreme breathlessness and frequent exacerbations;

- Effects on HRQoL vary depending on stage of progression and are most distinct when substantial lung function and mobility has been lost, often causing patients to become housebound and dependent on supplementary oxygen;

- Severe breathlessness due to progressive lung disease causes considerable distress; patients commonly report mental health issues, social isolation and guilt from increasing reliance on carers, loss of independence, and inability to engage in hobbies, activities and travel with children, friends, and partners;[28]

- Progressive lung disease secondary to severe A1PI deficiency tends to occur earlier than COPD (see Section 2.1.1), which heightens the social and financial impact of symptoms on family life and work commitments for both patients and their carers; in the 1994 US survey, 44.4% of respondents retired early and 19.1% changed to a physically easier job;[25]

- Most people with progressive lung disease secondary to A1PI deficiency have at least one exacerbation a year (91.5% of 922 patients during a 1-year follow-up),[27] which is distressing to endure and associated substantial healthcare resource utilisation;

- The ERG's clinical experts outlined that the A1PI population tend to be younger, fitter, and have fewer comorbidities than the general COPD population; conversely, age at symptom onset amplifies the impact of the disease on family life, employment, and wider society compared with the older smoking-related COPD population;[26,5, 18]

- The company proposes that Respreeza slows rate of lung density decline, which may enable patients to maintain independence, employment and social participation for longer, delay the need for lung transplantation, and improve psychological distress and fatigue of patients and carers (see Table 1); the ERG provides a critique of lung density as an outcome for A1PI deficiency and evidence relating it to patient important outcomes in Section 3.4.

2.2 Critique of company's overview of current service provision

2.2.1 Current clinical pathway

The ERG provided information in Section 2.1.1 to supplement the company's outline of the diagnostic pathway for emphysema secondary to A1PI deficiency. Briefly, the condition is often misdiagnosed or diagnosis is delayed[15] due to overlap in symptoms with more common respiratory disorders, and lack

of awareness and screening. While as much as 1 to 2% of people with COPD will have underlying severe A1PI deficiency, it will not be identified in up to 95% of cases.[16] The ERG's clinical experts explained that screening in the UK falls below the standards recommended by WHO, which advises that all patients with a diagnosis of COPD should be screened once, especially in areas with high prevalence of A1PI deficiency.[17]

The ERG's clinical experts also explained that, while there is likely to be variation in clinical practice, factors that commonly trigger A1PI serum concentration testing in England include young onset emphysema and dominant lower lobe lung disease. Additionally, patients' lung disease may be monitored routinely if A1PI deficiency is picked up incidentally, such as through family screening or due to paediatric jaundice. As outlined in Section 2.1.1, suspected A1PI deficiency is usually confirmed through serum concentration followed by phenotyping for common alleles in UK clinical practice, and full genetic sequencing is rarely conducted.

The company outlines that, once A1PI deficiency is diagnosed, management of the resulting lung disease generally follows standard COPD guidance (CS Section 8.1) because there are currently no treatments aimed at the underlying A1PI deficiency recommended for use in the NHS. The ERG's clinical experts agreed that this is the case, and explained that patients with A1PI deficiency are currently managed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[30] because the international guidance is more current than existing NICE guidance which was last updated in 2010.[31] The ERG's clinical experts highlighted that the NICE update (GID-NG10026) was out for consultation during the writing of this report, and that A1PI replacement therapy is not recommended for people with A1PI deficiency: guidance is due to be published in December 2018.[32] The company outlines that intravenous A1PI augmentation therapy is not currently recommended by NICE, and results of the RAPID trial for Respreeza were not available at the last update of CG101. However, the company outlines that routine screening of patients with COPD and A1PI augmentation therapy is recommended in statements issued by the European Respiratory Society (ERS),[33] a specialist group in the USA,[34] and the Canadian Thoracic Society.[35]

GOLD recommendations for general COPD management are broadly in line with the company's outline of care from the current NICE guideline for COPD. Both recommend that all smokers with COPD are counselled to stop smoking, and that all patients should receive regular influenza vaccine.[30, 31] GOLD and NICE outline the aims of pharmacologic therapy are to control symptoms and prevent exacerbations, which follows a step-wise approach guided by lung function (post-bronchodilator forced expiratory volume in one second [FEV1]), exacerbation history, and patient symptoms (e.g., dyspnoea, cough, sputum). Maintenance therapy primarily consists of inhaled short- and long-acting bronchodilators (beta-agonists and/or muscarinic antagonists) and inhaled corticosteroids, and, less commonly, oral theophylline or a mucolytic. Both guidelines acknowledge strong evidence for

pulmonary rehabilitation. Treatment for acute exacerbations is usually with oral corticosteroids or antibiotics, although some require emergency or inpatient treatment. In the later stage of COPD, patients may require long-term oxygen therapy, lung transplantation, or lung volume reduction.[30, 31]

In addition to the information outlined by the company in Section 8 of its submission, the ERG consulted clinical experts about how patients with severe A1PI deficiency are monitored, and the decision process for lung transplant. The experts advised that, at least through specialist centres, patients are reviewed each year to monitor symptoms and lung function decline with FEV1 and gas exchange (D_{LCO} or K_{CO}), which may prompt changes in treatment. Although most centres have a CT scanner, CT is not routinely used in clinical practice to monitor and assess progressive lung disease, at this time, results do not influence clinical management of the condition. Few patients are considered suitable for lung transplant, which is generally assessed using the BODE index to indicate approximate 4-year survival.[36] The BODE index considers a patient's percentage predicted FEV1, 6-minute walk distance, dyspnoea score and body mass index. The ERG's clinical experts outlined that it is common to die while on a transplant waiting list, and 5-year survival after lung transplant is less than 50%. As such, a primary aim of management is to slow the progression of lung function decline, and delay the need for transplant.

The ERG's clinical experts explained that patients who are monitored and managed through a specialist research centre may receive a higher standard of care than those who are not (e.g., closer monitoring and more sophisticated tests and scans).[18] The company notes that NICE guideline CG101 recommends that patients with A1PI deficiency be offered referral to a specialist centre.[31] However, the ERG's clinical experts explained that the lack of national commissioning for patients with A1PI deficiency in England means that specialist services have grown on an *ad hoc* basis, which has created inequality of access. As a result, most patients do not live close to a specialist centre and are not managed by a specialist in A1PI deficiency. In their submission, the company outline ongoing plans to transfer severe A1PI commissioning to NHS England to improve the quality and coverage of services across England (see Section 2.2.3).

2.2.2 Description of technology under assessment

The company states the approved name of the technology under assessment to be 'human alpha1-proteinase inhibitor' (brand name Respreeza®), which is the active substance: to avoid confusion with other commercially available A1PIs, the technology under assessment is hereafter referred to as Respreeza. Human A1PI is obtained from human blood and works by augmenting the level of protein in the blood of individuals with a genetic mutation that has led to A1PI deficiency (see Section 2.1.1).

Respreeza was granted marketing authorisation by the European Marketing Authorisation (EMA) on 20 August 2015 for, "*maintenance treatment, to slow the progression of emphysema in adults with documented severe A1PI deficiency*". Respreeza has been approved for use in the USA for 15 years (as

Zemaira®) and several other countries. In Section 3.3 of the CS, the company outlines efforts to acquire data on the long-term use of augmentation therapy from the US National Heart, Lung and Blood Institute (NHLBI) registry and that the data would be made available to NICE (CS Section 3.3), but these were not available by the time this report was submitted. As outlined in Section 3.4 of the CS, Respreeza is currently available off-label in England for panniculitis, a skin condition also associated with A1PI deficiency. Should it be approved by NICE for the current indication, it would be made available based on a maximum NHS list price agreed with the Department of Health and Social Care in 2016.[37]

Section 2.3 of the CS indicates that Respreeza is formulated as 1,000 mg powder and solvent for solution. Respreeza is indicated for intravenous infusion at a dose of 60 mg/kg body weight once weekly as a long-term chronic therapy, in addition to patients' standard treatments (e.g., bronchodilators). The summary of product characteristics (SmPC) for Respreeza details the administration procedure, which the company propose could be done at home or in a near home facility by a community nurse, family member or carer, or the patients themselves.

The ERG's clinical experts expected that most patients would be motivated to receive and remain compliant with weekly infusions, particularly if sufficient resources were in place to allow safe home or self-administration. The experts explained that progressive lung disease in people with severe A1PI deficiency generally has a much earlier onset, typically between 20 and 50 years of age,[13] meaning flexible administration around work and other commitments would be appealing to many patients. However, the ERG's clinical experts were concerned that the cost of community nurses for home administration, and the possible safety implications of procedures required for frequent home infusions (e.g., portacath or long line) have not been considered adequately. In their response to the ERG's clarification questions, the company outlines that it is theoretically possible for Respreeza to be administered at home by the patient after comprehensive training but noted that only 7.9% of 555 patients surveyed in the USA chose to do so.[38] No additional information was provided regarding the feasibility of weekly nurse home visits, or the safety implications of procedures required for frequent home administration.

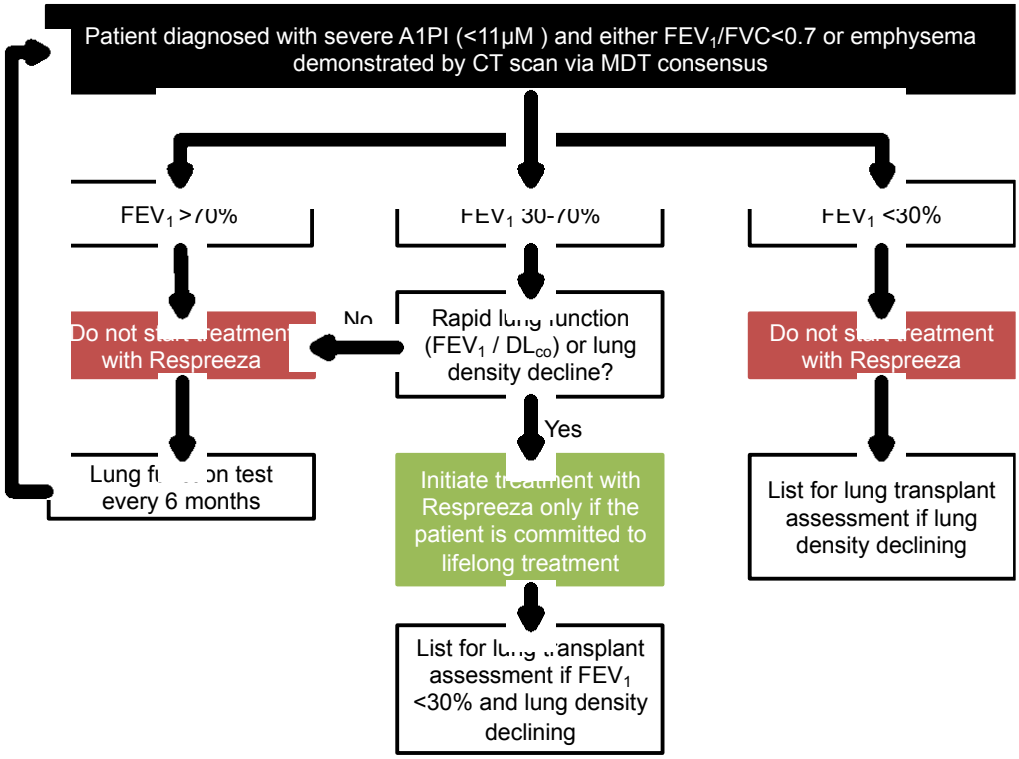
2.2.3 New pathway of care

The company are proposing that Respreeza be used in addition to existing treatments (outlined in Section 2.2.1) for patients meeting all the following criteria (Figure 1):

- Diagnosis of severe A1PI deficiency, indicated by serum concentrations less than 11 μM;
- FEV1/forced vital capacity (FEV1/FVC) less than 0.7, indicating airways obstruction, or emphysema demonstrated by CT scan via multi-disciplinary team consensus;

- FEV1 between 30 and 70% of the predicted value (which accounts for sex, race and height);
- Rapidly declining lung function, measured by predicted values for FEV1 or gas transfer (D_{LCO}), or lung density decline.

Figure 1. Proposed treatment initiation criteria for Respreeza (reproduced from CS, Figure 1)



The ERG's clinical experts generally agreed with the company's placement of Respreeza in the clinical pathway, but highlighted that the lack of a definition for rapid lung function decline may lead to variability in the judgement of treatment eligibility in clinical practice. The experts indicated that FEV1 and D_{LCO}/K_{CO} are currently used to monitor decline every 6 to 12 months, but both are variable, and most centres do not have the equipment or training required to measure CT lung density. The company does not propose the level of decline required (e.g. 500 mL FEV1 decline over 5 years[32]) for a patient to be eligible for treatment. The ERG's clinical experts suggested that 2 or 3 measures over a couple of years may be required to assess decline reliably, but it may be considered unethical to delay treatment for 6 months to obtain a second measurement if a patient met the other criteria.

The ERG notes that existing recommendations for intravenous A1PI augmentation therapy outline different lung function eligibility criteria. The US clinical practice guideline recommends treatment for patients whose FEV1 is less than or equal to 65% of the predicted value,[34] and the Canadian Thoracic Society's recommendation is for patients with FEV1 between 30 and 80% of the predicted value.[35] The ERG's clinical experts highlighted that there may be a rationale for giving Respreeza below the 30%

FEV1 predicted cut-off proposed, to salvage remaining lung function of patients who are either ineligible or on the waiting list for a lung transplant.

The company states that no additional monitoring of patients will be required for patients taking Respreeza, which the ERG's clinical experts considered reasonable (CS, Section 8.7). The ERG's clinical experts highlighted that the primary measure of efficacy in the Respreeza trial, CT lung density, is not commonly used in clinical practice to assess lung function, and clinicians may feel uncomfortable initiating and continuing treatment without evidence of lung density decline. CT densitometry requires specialist software and staff training and is currently used primarily as a research measure rather than in clinical practice. In their response to the ERG's clarification questions, the company stated that the licensed indication for Respreeza does not require CT scans for treatment initiation or monitoring, so no change to current practice would be required. The ERG's clinical experts also anticipate that screening practices may change should Respreeza be approved, because it would be the first treatment aimed at improving underlying A1PI deficiency rather than treating symptoms (see Section 2.1.2).

The company outlines ongoing plans for a new, highly specialised service for people with severe A1PI deficiency, irrespective of Respreeza being approved (CS, Section 8.6), that aims to coordinate the delivery of services and resolve existing inequality of access. The ERG provides a summary of the service outlined by the company below:

- NHS England are working towards taking responsibility for the commissioning of clinical services for patients with severe A1PI deficiency from April 2019, based on the Department of Health and Social Care's Prescribed Specialised Services Advisory Group recommendations;[39]

- The service would integrate clinical care through multidisciplinary teams (respiratory, hepatology, transplantation, genetics, dermatology, renal and paediatrics), with the aim of improving the diagnosis and management of severe A1PI deficiency, reducing morbidity and mortality, and ensuring equity of access across England;

- Three to five specialist centres would see patients to conduct diagnostic tests, initial assessment, and risk stratification, and commission existing secondary care service providers for some elements of the patient's pathway (hub and spoke model).

- Depending on individual patient risk, specialist centres would provide personal management plans, annual or quarterly reviews to track progression and guide treatment, and elective inpatient management as required;

- The service would also provide specialist advice for local providers; transition clinics, a phone advice line; tightly controlled access to current and future therapies, and preventative advice for family relatives.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE), together with their rationale for any deviation from the final scope (Table 1).[40] The company highlights that the submission differs from the final scope in terms of specification of eligibility parameters for the population and relevant comparators: reasons for variation from the final scope are discussed in greater detail below.

Table 1. Summary of decision problem as outlined in the company's submission (reproduced from CS, Table 1 [pg. 16])

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	Adults with severe alpha-1 proteinase inhibitor deficiency who have progressive lung disease.	As per scope. Adults with severe alpha-1 proteinase inhibitor deficiency (A1PI deficiency, also known as alpha-1 antitrypsin deficiency, AATD) who have progressive lung disease. In clinical practice, the population is defined as: patients with a serum A1PI level <11 µmol/L. This is typically patients with genotypes PiZZ, PiZ(null) and Pi(null,null). Some patients with genotype PiSZ have severe disease and more than 150 rare variants have been described. Evidence of progressive lung disease can be a lower forced expiratory volume in one second (FEV1) % predicted or D_{LCO} % predicted, impaired walking capacity or increased number of exacerbations as evaluated by a healthcare professional experienced in the treatment of A1PI inhibitor deficiency.	N/A – equivalent
Intervention	Human A1PI in addition to established clinical management.	A1PI (Respreeza) in addition to best supportive care (BSC).	N/A – equivalent
Comparator(s)	Established clinical management without A1PI, which may include but is not restricted to: • short-acting bronchodilators; • long-acting beta2 agonists; • long-acting muscarinic antagonists; • inhaled corticosteroids; • oral therapy with slow-release theophylline or a mucolytic; • pulmonary rehabilitation; • oxygen therapy; • lung transplantation; • lung volume reduction.	Established clinical management without A1PI as listed in the scope is clinically equivalent to best supportive care (BSC) and so should not be listed as standalone comparators. Most patients with A1PI deficiency will receive a combination of corticosteroids, oxygen therapy and/or bronchodilators to treat the symptoms, which have short-term benefits but do not address the underlying problem of the deficient protein. The placebo arm of the pivotal study is representative of patients receiving BSC. End-stage disease may be treated by lung transplantation and/or lung volume reduction surgery. Respreeza may act to prolong the time to or obviate the need for lung transplant. Therefore, lung transplant and/or reduction surgery should be considered	Agreed with NICE and ERG on decision problem meeting call.

		as downstream options within the treatment pathway as opposed to a standalone frontline comparator.	
Outcomes	The outcome measures to be considered include: • incidence, duration and severity of acute exacerbations, including hospitalisation; • change in lung density; • lung function; • symptom control (e.g., shortness of breath); • exercise capacity; • mortality; • adverse effects of treatment; • health-related quality of life (for patients and carers).	As per scope. However, it is not feasible to conduct a clinical trial powered to observe statistically meaningful changes in either mortality or health related quality of life in such a rare condition. Such a study would require a larger number of patients than could feasibly be recruited and would have to be conducted over many years to detect significant treatment effects. Therefore, outcomes such as mortality and health-related quality of life will not be based on trial outcomes but derived indirectly using published data.	N/A
Subgroups to be considered	If evidence allows, consideration may be given to subgroups based on the characteristics and progression of the disease (including for example, speed of decline, distribution of disease, and frequency of exacerbations)	None.	Subgroup analysis of patients in the pivotal study using primary and key secondary outcomes has not suggested that there is a group of patients in which the treatment provides greater clinical benefits.
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care; • Impact of the disease on carer's quality of life; • Extent and nature of current treatment options.	As per scope.	N/A
Impact of the new technology	Listed as 'Clinical Effectiveness' in the final scope: • overall magnitude of health benefits to patients and, when relevant, carers;	As per scope.	N/A

	• heterogeneity of health benefits within the population; • robustness of the current evidence and the contribution the guidance might make to strengthen it; • treatment continuation rules (if relevant).		
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year; • Patient access schemes and other commercial agreements; • The nature and extent of the resources needed to enable the new technology to be used.	As per scope.	N/A
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health; • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services; • The potential for long-term benefits to the NHS of research and innovation; • The impact of the technology on the overall delivery of the specialised service; • Staffing and infrastructure requirements, including training and planning for expertise.	As per scope. By delaying the loss of lung density and function, Respreeza is anticipated to prolong patient independence as well as prolonging the time to or obviating the need for lung transplant. Respreeza will be initiated within the current context of care, by specialists experienced in the management of A1PI deficiency at existing facilities. Home administration is likely. Although Respreeza is expected to reduce caregiver burden, there was limited evidence available to quantify the impact of this and also the costs to patients or costs to society outside of healthcare/PSS.	N/A
Special considerations, including issues related to equality	Listed as 'Other considerations' in the final scope: • Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements	A positive review of Respreeza will enable equity of access to licensed treatment for a minority group with a rare genetic disease.	N/A
Abbreviations: A1PI, alpha-1 proteinase inhibitor; CS, company submission; D_{LCO}, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in one second; N/A, not applicable; NHS, National Health Service; pg, page, PSS, Personal Social Services.			

3.1 Population

As highlighted in Section 2.2.2, Respreeza has a marketing authorisation for use as a maintenance treatment to slow the progression of emphysema in adults with documented severe alpha-1 proteinase inhibitor (A1PI) deficiency and progressive lung disease, and who are receiving optimal clinical management,[41] which is in line with the population of interest to the decision problem (Table 1). However, a concentration for a severely deficient level of A1PI was not specified in the final scope. The company reports that, in clinical practice, severe A1PI deficiency is defined as a serum concentration of A1PI of <11 μM, which was an inclusion criterion in the key study forming the evidence base and which the Evidence Review Group's (ERG's) clinical experts advised is a widely accepted threshold.

Data submitted in support of the clinical effectiveness of Respreeza as a maintenance treatment for adults with severe A1PI deficiency and who have progressive lung disease are primarily derived from one randomised controlled trial (RCT), the RAPID RCT,[42] and an open-label extension of RAPID, RAPID-OLE.[43] Corroborative evidence on the effectiveness of augmentation therapy with an intravenous A1PI in those with A1PI deficiency comes from two systematic reviews, both of which report meta-analyses for several clinical outcomes.[44, 45] Data are synthesised for different human A1PIs, including Respreeza. Other A1PIs included in the meta-analyses are outside of the scope of this Highly Specialised Technology report.

RAPID was designed to assess the efficacy and safety of Respreeza compared with placebo, in addition to best supportive care (BSC), in adults who were non-smokers and had severe A1PI deficiency (a serum concentration of A1PI of <11 μM) and a baseline forced expiratory volume in one second (FEV1) of 35 to 70% predicted.[42] The ERG notes that the design of RAPID did not allow for monitoring of FEV1 over a period of time prior to enrolment in the study to establish that lung function was declining, as would be done in clinical practice, before commencement of treatment with Respreeza or placebo. Thus, people with stable lung disease could potentially have been enrolled in RAPID: discussed in greater detail in Section 4.

In addition to not defining severe A1PI deficiency, the final scope does not specify a lower or upper limit of FEV1 per cent predicted as a baseline level for the population relevant to the decision problem (Table 1). As outlined in Section 2, the company is proposing that the population who would receive treatment with Respreeza are those with a FEV1 of between 30 and 70% of the predicted value, which differs from the inclusion criteria of RAPID and international clinical guidelines (US and Canadian guidance recommend commencing Respreeza at FEV1 of 65% predicted,[34] and between 30 and 80% predicted,[35] respectively).

In addition to FEV1 30 to 70% predicted and a serum concentration of A1PI of <11 μM, to be eligible for treatment with Respreeza, as outlined in Section 2, the company proposes that those with A1PI deficiency also have:

- FEV1/forced vital capacity (FEV1/FVC) less than 0.7 or emphysema demonstrated by computed tomography (CT) scan via multi-disciplinary team consensus;
- rapidly declining lung function, measured by predicted values for FEV1 or gas transfer (D_{LCO}), or lung density decline.

The ERG's clinical experts fed back that, in current practice, most clinicians would likely use a combination of change in gas transfer (D_{LCO}) and FEV1 per cent predicted to ascertain rate of lung function decline as only a minority of facilities have access to the specialist equipment required to carry out and interpret CT scans of lung density, which includes software and trained personnel. Gas transfer measures are more closely related to lung density than FEV1 but are associated with greater variability. Additionally, minimal clinically important differences (MCIDs) in gas transfer measures, or in CT lung densitometry, to indicate progressive lung disease have not been established.

The ERG notes that the CS does not outline limits for categorising rapid decline in lung function as assessed by change in FEV1 per cent predicted or gas transfer (D_{LCO}), or decline in CT lung density. The ERG's clinical experts commented that there are no accepted thresholds to categorise a person's rate of decline in lung function, and that they would most likely start treatment with Respreeza in those with worsening lung function, irrespective of rate of decrease. In terms of FEV1 and K_{CO}, categories for rate of decline expressed as an annual change in per cent predicted have been proposed: consistent with normal aging, <–0.1% predicted; slow decline, –0.1% to <–0.5%; moderate decline, –0.5% to <–1.0%; rapid decline, >–1.0%.[46] Comparable classifications have been suggested for rate of decline determined by CT lung density: no decline is equal to no change; slow decline, decrease of 0–2g/L/year; rapid decline, decrease >2g/L/year.[47] As part of the clarification process, the ERG asked the company to define rapid decline. In their response, the company did not provide a threshold for rapid decline, commenting that, "*More specific criteria could not be defined and assessment by D_{LCO}% are not excluded by this definition. Eligibility should be determined on an individual basis by clinical experts specialising in A1PI deficiency*". The European Public Assessment Report (EPAR) for Respreeza outlines that an expert panel agreed that the appropriate target population in clinical practice for A1PI replacement would be patients presenting with a combination of risk factors, based on significant lung density decline, severity of emphysema, deficient level of A1PI (<11 μM), and phenotype or genotype at risk.[41]

In summary, given the population characteristics of the evidence base, together with the parameters proposed by the company before starting treatment with Respreeza, the ERG considers the population informing the decision problem to be narrower than that outlined in the NICE final scope and the marketing authorisation for Respreeza. However, considering feedback from its clinical experts, the ERG considers the population from which evidence is derived to predominantly reflect the population most likely to be treated with Respreeza and to be relevant to the decision problem, with the caveat that it is unclear that all those participating in the trial had progressive lung disease at enrolment into RAPID.

3.2 Intervention

As outlined in Section 2, the goal of treatment with A1PIs, such as Respreeza, is to restore serum concentration of A1PI to levels above 11 μM and, ideally, to normal levels of 25 to 50 μM. The Summary of Product Characteristics (SmPC) for Respreeza indicates the recommended dose of Respreeza to be 60 mg/kg body weight, given intravenously once weekly.[48] In RAPID and RAPID-OLE, Respreeza was infused intravenously at the recommended dose once weekly, with infusion taking typically around 15 minutes (about 0.08 ml of solution per kg body weight each min).[48] In a *post-hoc* analysis, the authors of the full publication of the RAPID study reported an inverse relationship between trough A1PI serum concentration achieved and clinical efficacy as measured by rate of lung density decrease, with no evidence of a plateau to the dose–response relationship.[42] Based on the lack of a plateau, the authors inferred that administration of Respreeza at a dose of 60 mg/kg per week could be a suboptimum augmentation dose for some people with A1PI deficiency. Two studies evaluating clinical effectiveness of A1PI at a dose of 120 mg/kg per week are ongoing. One study is an RCT (SPARTA) comparing A1PI 60 mg/kg (Prolastin®) versus 120 mg/kg given once weekly over 156 weeks,[49] whereas the second is a single arm Phase 2 study in which A1PI (Respreeza) is given at 60 mg/kg per week for 4 weeks, with dose increase to 120 mg/kg per week for the subsequent 4 weeks, followed by a return to 60 mg/kg for the last 4 weeks of the study.[50] Results are not yet available for either study.

In those with A1PI deficiency, endogenous production of A1PI cannot be restored, and, therefore, treatment with A1PIs, such as Respreeza, if a person is eligible for treatment, would be required for the natural lifetime of the person, or until they meet criteria for a lung transplant. The ERG's clinical experts highlighted that, should a person's FEV1 decline to less than 30% predicted, they would likely continue treatment until lung transplantation. Additionally, neither the CS nor SmPC provides guidance on when it is appropriate to stop treatment with Respreeza, other than when a person experiences an adverse effect, undergoes lung transplantation, or dies. To avoid exposing a person to unnecessary risk of adverse effects, the ERG's clinical experts queried whether it would be appropriate to cease treatment with Respreeza, for example, should there be no change in rate of deterioration of lung function, or

should a person's lung function stabilise. As part of the clarification process, the company reported that stopping rules for Respreeza have not been proposed.

In summary, the ERG considers the intervention for which evidence is presented in the CS to be consistent with the NICE final scope, with the caveat that the licensed dose might not be appropriate for all people with A1PI deficiency, with some people requiring a higher dose.

3.3 Comparators

Various interventions given to ameliorate the symptoms of progressive lung disease (e.g., emphysema and chronic obstructive pulmonary disease [COPD]) are specified as comparators of interest to the decision problem (Table 1). As highlighted by the company and the ERG's clinical experts, clinical management of progressive lung disease is dependent on the symptoms with which a person presents, and may involve administration of a single therapy or a more complex combination of interventions. The company highlights that the treatments listed as comparators are clinically equivalent to BSC in lung disease and that it would be more appropriate to view the interventions as a collective rather than individual comparators, an opinion with which the ERG's clinical experts agreed. The key trial presented in the submission, RAPID, provides direct evidence comparing augmentation established clinical management of emphysema with Respreeza versus with placebo.[42]

In summary, given the population for which evidence has been submitted, the ERG and its clinical advisors agree with the company that placebo is the most relevant comparator in the setting of augmentation of BSC in treatment of A1PI deficiency.

3.4 Outcomes

In the CS, the company presents evidence on most of the outcomes specified in the NICE final scope (Table 1), with the exception of:

- symptom control (e.g., shortness of breath);
- health-related quality of life (HRQoL) of carers.

The primary outcome of RAPID was annual reduction in CT measured lung density (15th percentile), summing CT density values calculated at both total lung capacity (TLC) and functional residual capacity (FRC). During the study, lung density was measured by CT at baseline, 3, 12, 21, and 24 months.[42] Previous studies focused on lung density at TLC, but, at the request of regulatory authorities, the primary outcome of RAPID was assessment of combined TLC and FRC, with results for the individual components reported separately, and the combined value adjusted to take into account lung volume.[42] Secondary outcomes evaluated in RAPID were:[42]

- number of exacerbations, as defined by the Anthonisen criteria;[51]
- exacerbation duration and severity;
- FEV1;
- single-breath diffusion capacity;
- baseline and achieved A1PI concentrations (functional and antigenic assays);
- incremental shuttle walk test results;
- health status established with the St George's Respiratory Questionnaire (SGRQ; high scores represent increased disability);
- body-mass index;
- mortality;
- adverse events.

Assessment of FEV1 and deterioration in lung density by CT are both surrogate outcome measures for progression of lung disease, with FEV1 often regarded as the preferred measure. Where FEV1 tests respiratory health in terms of airway obstruction and is easy to measure, CT lung density and gas transfer capture changes the alveolar structure, and thus the pathology of the condition. However, in contrast to gas transfer, CT is costly and requires specialist software and personnel trained in interpreting the scans. Although spirometry measures, such as FEV1 and gas transfer, are frequently the desired outcomes, it is recognised that establishing clinical effectiveness of treatments in A1PI deficiency based on these clinical outcomes is challenging.[52] The rarity and chronic nature of A1PI deficiency renders it impractical to carry out a clinical trial adequately powered to detect statistically significant changes in FEV1, gas transfer, HRQoL and mortality.[52] A study focusing on FEV1 would require a minimum of 1,000 people and to be carried out over at least 5 years to capture a clinical benefit of augmentation with A1PI over placebo.[52] Moreover, pathological studies have shown that up to a third of the lung tissue is destroyed in emphysema before spirometric measures become abnormal.[53]

Given the difficulties in establishing a clinical benefit of augmentation therapy in A1PI deficiency based on spirometric measures, in 2009, the US Food and Drug Administration approved CT lung density as an appropriate clinically meaningful outcome to assess effectiveness of augmentation therapy on progression of emphysema.[54] CT lung density is now used extensively in studies evaluating treatments for emphysema. However, there remains uncertainty around how changes in CT lung density correlate

with spirometric measures, HRQoL and mortality. Considering FEV1, as outlined by the company (Table 4 [pg. 45] of the CS), correlation coefficients (r) for the association between decline in CT lung density and decrease in FEV1 of 0.286 to 0.52 have been reported. The correlation coefficient is a measure of the strength and direction of a linear relationship between two variables, and the value of r always lies between –1 and +1. The closer the value of r to ±1, the greater the strength of the association between the two variables. The correlation coefficients reported for FEV1 suggest a weak to moderate association between decrease in CT lung density and decline in FEV1. Although the reported correlation coefficients suggest, at best, a moderate relationship between CT lung density and FEV1, the authors of a systematic review of use of CT densitometry in assessing progression of emphysema associated with COPD, irrespective of A1PI deficiency, found that the association between CT lung density and other clinical parameters implemented as outcomes for studies in respiratory conditions, for example, FEV1 and SGRQ, were consistently statistically significant, and there was a relationship with mortality.[53] However, the authors went on to comment that various biases make it difficult to draw definitive conclusions about the exact strength of each association. However, the ERG considers it noteworthy that a correlation between two variables does not necessarily indicate that one variable causes the other.

The ERG considers it important to note that the authors of a systematic review identified considerable variation in methods implemented to perform the CT scans as a source of heterogeneity among studies utilising CT densitometry.[53] More specifically, there was considerable disparity in the choice and combination of reconstruction algorithm, slice thickness and software program used to analyse data. The authors of the review concluded that the considerable identified heterogeneity and lack of longitudinal data contributed to the inability to determine how the sensitivity and specificity of changes in CT density relate to time or interventions. The authors called for, "*international consensus be reached to standardise CT conduct and analysis in future emphysema studies*".

Clinical experts consider change in CT lung density a validated outcome to assess progression of emphysema in RCTs but, in line with comments from the ERG's clinical experts, the technique is not currently routinely used in UK clinical practice to determine worsening lung disease: as highlighted in Section 2, many facilities likely to be involved in treating people with A1PI deficiency will not have access to the specialised equipment and personnel necessary for carrying out and interpreting CT densitometry. Moreover, the company is not advocating routine scanning of CT lung density to either diagnose eligible patients or monitor disease progression.

In summary, the ERG considers the outcomes presented in the CS to be clinically relevant to the decision problem and to be aligned with the final scope issued by NICE, but has reservations about the uncertainty around the correlation of CT lung density with other clinical outcome measures in A1PI deficiency.

3.5 Other relevant factors

In the CS, the company highlights an equity consideration pertaining to granting access to a licensed treatment for those with a rare genetic disease that is not currently a treatment option for those in the UK but is available in most countries in Europe. The ERG does not consider the issue highlighted by the company to relate specifically to people who are protected by equality legislation.

4 CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of Respreeza in the treatment of alpha-1 proteinase inhibitor (A1PI) deficiency. Details, together with the Evidence Review Group's (ERG's) critique, are provided for:

- the methods implemented by the company to identify relevant evidence (Section 4.1);
- the clinical efficacy of Respreeza (Section 4.2);
- the clinical efficacy of A1PIs as a class (Section 4.2.6);
- the safety profile of Respreeza (Section 4.3).

The ERG notes that RAPID[42] and RAPID-OLE[43] are the key studies informing the decision problem, with supporting data on clinical effectiveness of A1PIs derived from systematic reviews evaluating the effects of various augmentation therapies in A1PI deficiency.

4.1 Critique of the methods of review

4.1.1 Searches

The company sought to identify studies evaluating the clinical effectiveness of any intervention used to treat lung disease associated with A1PI deficiency, including Respreeza and other intravenous A1PIs belonging to the same class. The company did not explicitly provide a rationale for not restricting the intervention of interest to Respreeza. Other A1PIs given intravenously are commercially available but are not licensed in the UK, for example, Prolastin® (Grifols). Although there are differences in the manufacturing and purification processes for the various A1PIs, as highlighted by the company, given that the goal of augmentation therapy is to increase serum concentration of A1PI, as a class, the A1PIs are generally considered to be equally effective at achieving the target A1PI serum concentration of ≥11 μM. A biochemical comparison of four A1PIs given intravenously and commercially available in Europe suggests that there is a class effect for A1PIs (discussed in greater detail in Section 4.4). Although the ERG agrees with the company that a class effect can be considered for the A1PIs, in that the goal of treatment is to achieve a serum concentration of ≥11 μM A1PI, because of other potential sources of heterogeneity across studies, the ERG considers that there are issues that should be borne in mind when meta-analysing data from the identified studies (discussed in greater detail in Section 4.4).

In their submission, the company describes two systematic reviews of the literature on the clinical effectiveness of treatments for A1PI deficiency published in the past 2 years (Edgar 2017[44] and Gotzsche 2016[55]). The company's submission (CS) does not include a discussion of the methods

followed to identify the systematic reviews. Greater detail on the two systematic reviews identified by the company is available in Section 4.4.

Given the rarity of A1PI deficiency, the company decided against restricting the evidence base forming their submission to RCTs, and considered a systematic review including uncontrolled studies the more appropriate base for update.[44] The company utilised the search strategies created by the authors of the systematic review to update the search from 9 April 2015 to 11 April 2018. Search strategies of the original review are freely available in the Supplementary Information accompanying the full publication of the literature review,[44] and the company provided the search terms implemented in their literature review as an Appendix (Appendix 17.1.4 of the CS).

The company carried out searches in MEDLINE and EMBASE via ProQuest. The search strategies were based on a combination of Medical Subject Headings and free-text, and were limited to terms for the population, which was specified to be those with severe A1PI deficiency. A comprehensive set of free-text terms encompassing multiple variations of description of A1PI deficiency were applied in the searches, and the ERG is confident that the search strategies would retrieve relevant records. The ERG notes that terms for emphysema were not incorporated. Given the likely low volume of literature relevant to A1PI deficiency and augmentation therapy, the ERG considers non-inclusion of terms for interventions would not result in omission of relevant studies. The company supplemented the searches of the electronic databases with hand searches of the Centre for Reviews and Dissemination, the Cochrane library (Cochrane Database of Systematic Reviews [CDSR], conference websites and clinical trials registries. Details on the conference websites and clinical trial registries searched were not available in the CS.

In summary, the company conducted a search of the key electronic databases, including MEDLINE and EMBASE, for RCT and non-RCT evidence relevant to decision problem. The ERG considers that the company is likely to have identified all clinical evidence on the use of Respreeza and other intravenous A1PIs as augmentation therapy in the treatment of emphysema related to severe A1PI deficiency.

4.1.2 Inclusion criteria

Full eligibility criteria for the review of clinical effectiveness of Respreeza, and other A1PIs, are presented in Table 2. The CS also appropriately included a PRISMA diagram indicating the number of studies that were included and excluded at each stage of the systematic review (Figure 2).

As noted in Section 4.1.2, the systematic review commissioned by the company searched for evidence on clinical effectiveness of any treatment for lung disease related to A1PI deficiency, and was an update of a previously published systematic review.[44] Inclusion criterion specified the interventions of interest to be, “Treatment for A1PI-related lung disease, including any method of treatment that has been

accepted in peer-reviewed literature" (Table 2). The ERG appreciates that the inclusion criteria applied by the company are those specified by the authors of the original systematic review, but also considers that additional detail on interpretation of the term "accepted in peer-reviewed literature" would be required to replicate the appraisal process. In relation to the decision problem, given that Respreeza is given intravenously, the ERG considers, for the purposes of the submission, it would have been appropriate to specify an exclusion criterion of interventions other than intravenous A1PIs used in the management of COPD, for example, oral A1PIs and lung transplantation. Additionally, comparators of interest were not specified (Table 2). Considering the decision problem, the company reported that the most appropriate comparators for A1PIs would be placebo or no treatment, a comment with which the ERG and its clinical experts agree. Again, for the purposes of the evidence submitted in support of the application, the ERG considers that it would have been appropriate to limit comparators of interest to placebo or no treatment.

Overall, the ERG considers the inclusion criteria to reflect the final scope issued by NICE in terms of population and outcomes. However, the ERG deems that the submission has not provided a clear differentiation between the interventions and comparators to be included in the evidence base to inform decision making on use of Respreeza as an augmentation therapy in emphysema related to A1PI deficiency, and additional detail for these inclusion criteria would have been helpful.

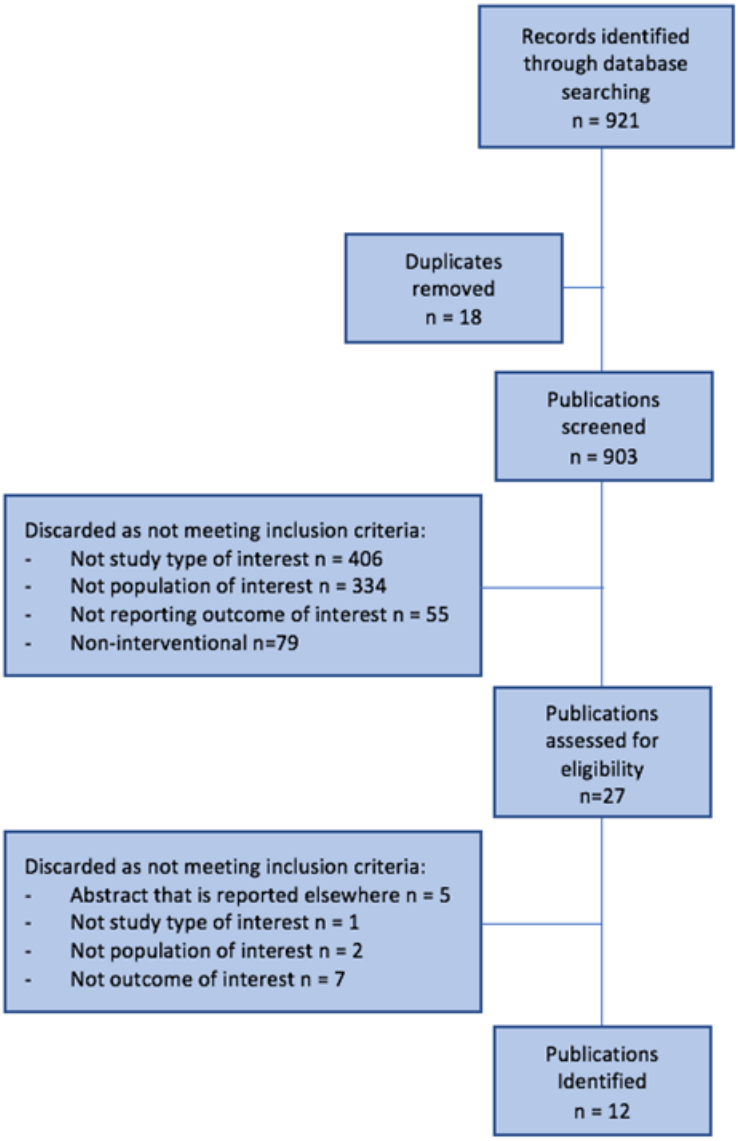
Table 2. Eligibility criteria for systematic review of the literature for interventions used to treat alpha-1 proteinase inhibitor deficiency (reproduced from CS, Table 5 [pg. 47])

	Inclusion criteria	**Exclusion criteria**
Population	Adults suffering from severe A1PI, circulating level of A1PI <11 μmol/L and/or a genotype consistent with such levels (e.g., PiZZ, PiZNull) with or without a diagnosis of COPD.	• Liver disease • Panniculitis • Children
Interventions	Treatment for A1PI-related lung disease, including any method of treatment that has been accepted in peer-reviewed literature.	None
Outcomes	Any outcome	Outcomes must have been reported <3 months after initiation of therapy
Study design	• Observational (i.e. registries); • Cohort studies; • RCTs.	• Animal; • Individual case study reports; • Letters; • Comment articles; • Reviews; • Epidemiology.
Language restrictions	None	
Search dates	Original search conducted by Edgar et al.[44]: search date of 9th April 2015.	

	Update SLR commissioned by CSL Behring: 9th April 2015 to 11th April 2018	

Abbreviations: A1PI, alpha-1 proteinase inhibitor; CS, company submission; pg, page; RCT, randomised controlled trial; SLR, systematic literature review.

Figure 2. PRISMA flow diagram illustrating results from company's systematic update of a previously published literature review (reproduced from CS, Figure 8 [pg. 49])



4.1.3 Critique of screening process and data extraction

Initial assessment of titles and abstracts of retrieved records was carried out by two independent reviewers. Disagreements on inclusion were resolved by discussion, with involvement of a third reviewer if consensus could not be reached. Print copies of potentially relevant articles were obtained

and the full text assessed against the inclusion criteria by two independent reviewers. Data extraction for studies deemed to be relevant was carried out by one reviewer, and the extraction subsequently validated by a second reviewer. Additional details on the data extraction process are not available within the CS, and so it is unclear whether all pre-specified data have been extracted from identified studies.

Based on the PRISMA flow diagram supplied as part of the CS (Figure 2), the search of the literature for the period 9 April 2015 to 11 April 2018, retrieved 903 non-duplicate records, of which 874 were excluded after assessment of titles and abstracts. Given that 874 studies were excluded, the ERG notes that only 27 full text publications were screened for inclusion, rather than 29 (Figure 2). Screening of the full-text publications against inclusion criteria (Table 2) led to the exclusion of a further 15 records. The company helpfully provided details for studies excluded during the appraisal of full-text publications.

In summary, the ERG considers it likely that the company has identified all studies relevant to the use of intravenous A1PIs as augmentation therapy in those with emphysema related to severe A1PI deficiency, and has extracted sufficient data to inform the decision problem.

4.1.4 Quality assessment

The company presented quality assessments for the RAPID RCT, and for the open-label extension phase, RAPID-OLE. Additionally, the company provided critiques of the quality of two other RCTs evaluating the effect of augmentation therapy in A1PI deficiency,[29, 56] and data from which, together with results from RAPID, were incorporated into meta-analyses that inform the discussion on the clinical effectiveness of Respreeza. The company's assessment of the quality of individual studies, together with the ERG's critique, are presented in Section 4.2.

The tool used by the company to appraise the RCTs forming the evidence base in the CS was based on the quality assessment criteria suggested by the NICE guideline template for companies. The ERG considers the domains appraised to be appropriate and aligned with the Cochrane risk-of-bias approach for RCTs.[57] Quality of RCTs was based on potential presence of:

- selection bias (random sequence generation and allocation concealment);
- performance bias (masking of participants and key trial personnel);
- detection bias (masking of outcome assessment);
- attrition bias (drop-out rate);
- reporting bias (selective reporting of outcomes or analyses).

From the reporting in the CS, it is unclear whether quality assessment was carried out in duplicate, either by two reviewers independently or by one reviewer and with a second reviewer validating the responses of the first reviewer. Therefore, there is potential for error and bias in assessments of study quality.

4.1.5 Evidence synthesis

In the CS, the company presents evidence from a systematic review (Edgar 2017[44]) that carried out meta-analyses of data from three RCTs, including the RAPID RCT, to generate effect estimates for augmentation therapy versus placebo or no treatment for five clinical outcomes: mean annual change in CT lung density (g/L); mean change FEV1 per cent predicted; standardised mean difference in D_{LCO}; annual patient-reported exacerbation episodes; and health status assessed using the SGRQ.[44] A second systematic review carried out meta-analyses of the same three RCTs, and reported results for similar outcomes.[55] Additionally, the company presents results from a third systematic review that synthesised data to evaluate the effect of augmentation therapy on rate of FEV1 decline and reported subgroup analyses based on baseline FEV1 per cent predicted.[45]

The two reviews synthesising data for the three RCTs reported similar analytical methods, with both reviews implementing a fixed effects model, unless heterogeneity was identified, in which case a random effects model was used.[44, 55] The ERG notes minor differences between the two systematic reviews, in terms of fixed versus random effects model and studies included in meta-analysis for one outcome. Despite the differences, the two reviews generated similar effect estimates and accompanying 95% confidence intervals (95% CIs) for three outcomes common to the two reviews. Results from the meta-analyses are discussed in greater detail in Section 4.4.

The systematic review reporting results for change in FEV1 per cent predicted by baseline FEV1 per cent predicted was published in 2009 (Chapman 2009).[45] The ERG notes that study types other than RCTs were eligible for inclusion in the review, and data from non-RCTs and RCTs were synthesised together. Due to anticipated heterogeneity across studies, the authors pre-specified that analyses would be carried out using the random effects model: statistically significant heterogeneity (p=0.012) was reported.[45] To help inform the discussion of clinical effectiveness and the economic model, as part of the clarification process, the ERG requested that the company carry out an update search for the review, and incorporate data from relevant studies as appropriate. In their clarification response, the company provides a detailed description of the methods used to conduct the meta-analysis. The ERG considers the methods followed by the company to be appropriate. However, the ERG notes that a measure of the level of heterogeneity is not reported, and potential sources of clinical heterogeneity are not discussed. The results of the analyses are discussed in more detail in Section 4.4.

4.1.6 Summary statement

The ERG considers that the company is likely to have identified all clinical evidence on the use of Respreeza and other intravenous A1PIs as augmentation therapy in the treatment of emphysema related to severe A1PI deficiency. To identify evidence on clinical effectiveness of A1PIs, the company carried out an update of a published systematic review evaluating the literature on any intervention used to treat lung disease associated with A1PI deficiency. Whether a systematic literature search was carried out to identify systematic reviews of A1PI augmentation therapy is unclear. In their update search, the company conducted a search of key electronic databases, using the search strategies implemented by the authors of the original review. Search strategies and inclusion criteria of the original review are freely available and the company provided the search terms implemented in their literature review

Inclusion criterion specified the interventions of interest to be, "*Treatment for A1PI-related lung disease, including any method of treatment that has been accepted in peer-reviewed literature*". The ERG appreciates that the inclusion criteria applied by the company are those specified by the authors of the original systematic review, but also considers that additional detail on interpretation of the term "accepted in peer-reviewed literature" would be required to replicate the appraisal process. Additionally, comparators of interest were not specified. From the context of the decision problem, only intravenous A1PIs are relevant interventions, and the most appropriate comparators of interest are placebo or no treatment. For the purposes of the evidence submitted in support of the application, the ERG considers that a more detailed description of inclusion criteria for interventions and comparators to be included in the evidence base on use of Respreeza as an augmentation therapy would have been helpful.

In terms of appraisal of titles, abstracts and full text publications, the ERG considers that the company has adhered to standard systematic review practices, with two people independently reviewing records at each appraisal stage. However, whether quality assessment of studies was carried out by two reviewers is unclear from the reporting in the CS, and, if not performed by two reviewers, there is potential for error or bias in evaluation of study quality.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Included studies on the clinical efficacy and safety of Respreeza

As discussed in Section 4.1, the company's systematic review of the literature on clinical effectiveness of A1PIs identified one full-text publication of an RCT, RAPID, comparing Respreeza versus placebo as an augmentation therapy in those with severe A1PI deficiency, together with an open-label extension phase of the study (RAPID-OLE). An overview of the design and conduct of RAPID and RAPID-OLE

is presented in Table 3: aspects of the design and conduct of RAPID and RAPID-OLE are discussed in greater detail in subsequent sections.

Table 3. Overview of the methodology of RAPID and RAPID-OLE (adapted from the CS, Table 9 [pg. 70])

Study details	Description
Location	28 centres in Australia (11.1%), Canada (16.1%), Czech Republic (1.1%), Denmark (20.6%), Estonia (1.1%), Finland (2.2%), Germany (10.6%), Ireland (12.2%), Poland (3.9%), Romania (0.6%), Russia (0.6%), Sweden (10.6%), United States of America (9.4%)
Design	Phase III/IV, randomised, double-blind, placebo controlled study followed by an open-label extension phase
Study duration	2 years randomised phase (RAPID) with subsequent 2 year extension stage, during which those initially receiving placebo went on to receive Respreeza, while those allocated Respreeza continued treatment.
Entry criteria	Key inclusion: • 18–65 years of age • Diagnosis of A1-PI deficiency (serum A1-PI levels <11 μM, or < 50 mg/dL [as determined by nephelometry]). This included newly diagnosed subjects, previously untreated subjects, currently treated subjects, and subjects currently not on treatment therapy but on treatment in the past. Genotypes were not restricted, >90% were PiZZ. • Diagnosed with emphysema resulting from A1PI deficiency and have a FEV1 of ≥35% and ≤70% predicted. Key exclusion: • Smoked tobacco within six months prior to recruitment • Undergone or were on a waiting list for lung transplantation, lobectomy or lung volume reduction surgery • A history of transfusion reactions
Method of randomisation	Subjects were randomised evenly, at a ratio of 1:1. The randomisation was stratified by centre. A randomisation list containing the assignment of subject numbers to treatment groups was reproducibly generated by a computerised pseudo-random number generator. A copy of the randomisation list was transferred to the drug supply and logistics group of the Clinical Operations Department at CSL Behring. Standard operating procedures were followed to ensure confidentiality of the randomisation list.
Method of blinding	This was a double-blind study. Respreeza and placebo were packaged identically. Individual packages were identified only by the subject number. The treatment groups randomised to the subject numbers were only known to the randomisation code administrator, and to the drug supply and logistics group of the Clinical Operations Department at CSL Behring.
Treatments, allocation and retention	After a screening period of 1 week to 1 month, each subject received, according to his or her subject number, weekly infusions of Respreeza at a dose of 60 mg/kg or an equivalent volume of placebo over 24 months. Respreeza and placebo were administered intravenously at a rate of 0.08 mL/kg/min, as determined by the response and comfort of the subject. The first dose and the doses given during the following quarterly visits at the study centre were administered by the investigator or designate. All other weekly doses could be given by the nurses of a home care service or by the family doctor. Where possible, all doses were given at the study centre.

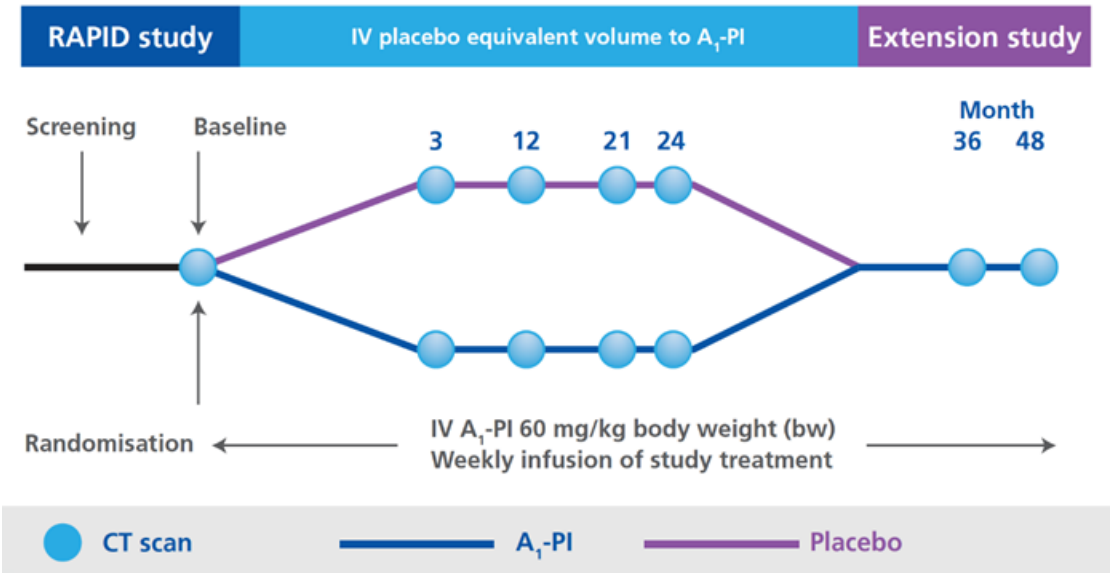
	In exceptional cases (e.g. holidays) a single weekly dose of 120 mg/kg bi-weekly was allowed to cover a 2-week time period.
Primary outcome objective	To investigate the effect of Respreeza on the progression of emphysema, assessed by the decline of lung density, measured by computed tomography (CT).
Secondary outcome objectives	To assess the effect of treatment with Respreeza on the following clinical assessments: Change in exercise capacity assessed by incremental shuttle walk test (ISWT) Change in symptoms assessed by the St George's Respiratory Questionnaire (SGRQ) Rate of pulmonary exacerbations (according to (Anthonisen et al., 1987)
Additional outcome objectives	A1PI levels Pulmonary function test parameters Other domains of the SGRQ
Safety outcomes	The incidence and nature of adverse events, viral serology, serum A1PI antibodies, laboratory parameter levels, and vital signs.
Duration of follow up	24 months followed by a further 24 month period in which all patients switched to Respreeza
Abbreviations: A1PI, alpha-1 proteinase inhibitor; CS, company submission; pg, page; RCT, randomised controlled trial; SLR, systematic literature review.	

4.2.2 Trial conduct

4.2.2.1 RAPID

RAPID is an international, randomised, double-blind, phase III/IV trial in which patients were screened between 1 March 2006 and 3 November 2010.[42] No study site was located in the UK: the ERG does not consider this a limitation in this case (discussed in further detail in Section 4.2.3). The primary objective of the study was to assess the change in lung density by CT on A1PI augmentation with Respreeza compared with placebo in people with emphysema secondary to severe A1PI deficiency. After 2 years of follow-up, all patients located outside the USA entered an open-label 2-year extension phase during which all patients received Respreeza: the design of RAPID and RAPID-OLE is depicted in Figure 3.

Figure 3. Design of Phase III/IV Respreeza RAPID RCT and extension phase, RAPID-OLE (reproduced from CS, Figure 9 [pg.69])



People were eligible for RAPID if they were aged between 18 and 65 years, and had emphysema secondary to severe A1PI deficiency, which was defined as a serum concentration of A1PI of <11 μM or <80 mg/dL, and a forced expiratory volume in 1 second (FEV1) of between 35% and 70% of predicted values.[42] People were ineligible for the study if they had smoked tobacco within the 6 months prior to recruitment. The ERG's clinical experts highlighted that those who had never smoked would have a better prognosis compared with those who were ex-smokers, and considered that subgroup analyses based on smoking status (never versus ex) would help inform the decision problem. During the clarification process, the company fed back that few people enrolled in RAPID had never smoked (13/93 [14.0%] in the Respreeza group *vs* 15/87 [17.2%] in the placebo group) and a subgroup analysis based on smoking status was not feasible.

After enrolment, people who completed a screening period of between 1 and 4 weeks were randomised in a 1:1 ratio to receive Respreeza or placebo. Randomisation was stratified by centre and was carried out by an external agency.[42] The Clinical Study Report (CSR) for RAPID states that, "*A randomization list containing the assignment of subject numbers to treatment groups (CE1226 [Respreeza] or placebo) was reproducibly generated by a computerised pseudo-random number generator. A copy of the randomization list was transferred to the drug supply and logistics group of the Clinical Operations Department at CSL Behring. Standard operating procedures were followed to ensure confidentiality of the randomization list*".[58] Participants and investigators were masked to allocated treatment. To maintain masking of key trial personnel, Respreeza and placebo were supplied as identical lyophilised preparations, with individual packages identified only by patient number. Once the allocated treatment had been prepared for intravenous infusion, a designated study nurse or pharmacist who did not interact with the patients covered the infusion bag with an opaque sleeve. Compliance with the masking

procedure was monitored by clinical trial associates. The ERG considers that the processes implemented are likely to maintain masking of treatment allocation.

RAPID involved 180 people, with 97 and 83 people allocated to Respreeza and placebo, respectively.[42] A considerably larger proportion of people from the placebo group withdrew from the study (9/97 [9.3%] in the Respreeza group vs 18/83 [21.7%] in the placebo group), with the predominant reason for discontinuation in each group being withdrawal of consent (5/97 [5.2%] in Respreeza group vs 7/83 [8.4%] in the placebo group). The company comments that the probability of withdrawal from the study was statistically significantly ($p = 0.04$) lower in the Respreeza group, and, in addition to a lower rate of withdrawal of consent in the active treatment group, fewer people in the group died, or withdrew as a result of an adverse effect. Moreover, the company noted that the pattern of withdrawal of patients over time was similar for each treatment group, and proposed that the timings of the withdrawals suggested that the decision to withdraw was not influenced by events related to study design issues.

Respreeza (60 mg/kg) or placebo was infused intravenously at a rate of 0.08 mL/kg/min (typical infusion time of about 15 mins) on a weekly basis for 2 years. In exceptional circumstances (e.g., holidays), a single weekly dose of 120 mg/kg was allowed to cover a 2-week time period. Where possible, the patient attended the study centre for administration of their allocated treatment. As a minimum, the first infusion, and infusions given during quarterly attendance at the study centre, were administered by the investigator or their designated member of staff. All other weekly doses could be given by nurses provided by a home care service or by the family physician. Treatment was continuous for the length of the study, unless a person experienced an adverse effect that necessitated cessation of treatment. Mean overall compliance during RAPID was 93.9% with Respreeza and 89.6% with placebo, and mean number of administrations of allocated intervention per person was 94.2 and 87.3 for Respreeza and placebo, respectively.[58]

The primary measure of clinical effectiveness in RAPID was annual change in lung density as measured by CT, with the value adjusted to account for lung volume: the advantages and disadvantages of using CT lung density as a clinical outcome are discussed in greater detail in Section 3.4. Spiral CT scans were taken at baseline and after 3, 12, 21, and 24 months of follow up.[42] CT scans were stored electronically and sent to an external laboratory for analysis (BioClinica, Leiden, Netherlands).[42] At the request of regulatory authorities, rather than capture lung density solely at total lung capacity (TLC), CT scans were taken at both TLC and functional residual capacity (FRC) and the primary outcome was a combined assessment of recordings at each inspiration state. Lung density was measured in Hounsfield units and subsequently transformed to a measure in g/L. Next, due to the variability across people, it is necessary to apply a physiological volume correction to the g/L measure to generate the 15th percentile CT lung density (PD15): the PD15 is the cut-off density at which 15% of all pixels have lower densities.[59]

The physiological adjustment applied was:

Adjusted PD15 = observed PD15 x (observed measured total lung volume / predicted TLC),

Where predicted TLC was derived as: 7.99 x (height in m) – 7.08 for males, and 6.60 x (height in m) – 5.79 for females.

In the CS, the company highlights that research indicates that CT scans captured at TLC provide optimal data for observing shifts in lung density over time.[60] Patients find it easier to replicate the TLC inhalation state than FRC over the duration of a study. Therefore, there is lower variability across TLC measures and TLC is more robust and associated with the optimum possibility to detect small differences in lung density. By contrast, FRC is the better inhalation state to assess changes in air trapping phenomena.[60] As noted by the company and in the European Public Assessment Report (EPAR) for Respreeza,[41] TLC is approved by the Committee for Medicinal Products for Human Use (CHMP) as the optimal method of monitoring disease progression in emphysema.

Various secondary outcomes were assessed in RAPID. The key secondary outcomes were deemed to be those that would help explain the clinical relevance of the primary objective of change in lung density as measured by CT scan and were listed in the EPAR as:[41]

- change in exercise capacity assessed by Incremental shuttle walking test (ISWT);
- change in symptoms score assessed by the St. George's Respiratory Questionnaire (SGRQ);
- risk of pulmonary exacerbation assessed by the annual rate of exacerbations.

Other secondary outcomes assessed included:[41, 42]

- adjusted PD15 change from baseline to month 24 (change in adjusted PD15 obtained by CT scans at baseline and at month 24);
- pulmonary function assessed using key spirometry variables (e.g., FEV1);
- characteristics of pulmonary exacerbations;
- single-breath diffusion capacity;
- baseline and achieved A1PI concentrations (functional and antigenic assays);
- body-mass index;
- mortality;

- safety.

Considering the assessment of FEV1 per cent predicted, the ERG considers it important to note that administration of a bronchodilator before assessment of FEV1, as is advised by GOLD for COPD,[30] was not compulsory in RAPID. The CSR states, "*If a bronchodilator was used, PFTs [pulmonary function tests] for pre-bronchodilator as well as post-bronchodilator were to be recorded*".[58] The ERG notes that the protocol for RAPID initially stipulated use of a bronchodilator 4 hours before CT scan, but was subsequently amended to use of bronchodilator only on interruption of treatment. The ERG considers that it is unclear whether results presented for FEV1 include results with and without pre-test use of bronchodilator. Neither the CS nor the CSR provides details on the proportion of assessments of FEV1 in which a bronchodilator was used prior to measurement, or whether the results of FEV1 have been adjusted to account for the difference in treatment. The ERG considers the direction of potential bias arising from variation in bronchodilator use prior to FEV1 measurement to be unclear. Although FEV1 is a secondary outcome in RAPID, and the study was not powered to detect a statistically significant change in this outcome, the ERG has reservations about the comparability of the results from RAPID with other RCTs assessing the effect of augmentation with A1PI in those with severe A1PI deficiency.

Six major protocol amendments were highlighted in the EPAR for Respreeza.[41] Most amendments involved addition of text to clarify study processes, for example, expansion of definition of severe A1PI deficiency to include the second unit of <80 mg/dL, clarification that the primary efficacy analysis is based on PD15 CT lung density adjusted for lung volume, and amendment of use of bronchodilator from compulsory to only when treatment for emphysema was interrupted.

In summary, RAPID represents the only available direct comparative evidence on the clinical effectiveness and safety of Respreeza versus placebo, and is the largest study reported to date enrolling those with emphysema secondary to severe A1PI deficiency. The ERG considers RAPID to be predominantly well-designed and well-conducted, with the caveat that the results for FEV1 are potentially biased and cannot be compared with results derived from other studies.

4.2.2.2 RAPID-OLE

The aim of RAPID-OLE was to investigate the prolonged treatment effect of A1PI on the progression of emphysema as assessed by the loss of lung density.[43] Everyone enrolled into RAPID-OLE received Respreeza (60 mg/kg) on a weekly basis for 2 years in an open label design.[43] Other than residents of the USA, those completing 2 years of their allocated treatment were eligible to progress from RAPID to RAPID-OLE.

Between 1 March 2006 and 13 October 2010, 140 patients from RAPID-RCT entered RAPID-OLE: 76 people allocated to Respreeza in RAPID became the early-start group and 64 allocated to placebo and receiving Respreeza for the first time in RAPID-OLE formed the delayed-start group. Of the 140 people enrolled, 9 people withdrew before the end of the study, with 6 (7.9%) and 3 (4.7%) people withdrawing from the early and delayed start groups, respectively. People were assessed at 22 hospitals in 11 countries. The patient's last visit of RAPID-RCT was their first visit of RAPID-OLE, with no washout period.[43]

As in RAPID, the primary prespecified outcome was adjusted change in lung density as assessed by CT scan (adjusted PD15). Spiral CT scans were carried out annually, and captured lung density at TLC and FRC. Lung volume variability was corrected using a physiological adjustment to derive the 15th percentile CT lung density (adjusted PD15). Secondary outcomes included spirometric pulmonary function, health-related quality of life (SGRQ), serum antigenic and functional A1PI concentrations, and safety.

4.2.3 Baseline characteristics

Baseline characteristics of people enrolled in RAPID were predominantly well balanced across the Respreeza and placebo groups (Table 4): baseline characteristics for people entering RAPID-OLE are available in Table 5. A key baseline imbalance between groups in RAPID is that in baseline CT lung density (adjusted PD15), with those receiving Respreeza having a baseline value of 46.6 g/L (standard deviation [SD] 15.6 g/L) for the combined measure of TLC and FRC compared with 49.8 g/L (SD 15.0 g/L) in those allocated to placebo. In the CS, the company presents research to support the proposal that those with a decrease in CT lung density of 2.0 g/L or greater annually are deemed to be in rapid decline, and likely to achieve a greater benefit from treatment with Respreeza compared with those who experiencing no or slow decline in lung density. Thus, the ERG considers that the difference of 3.2 g/L between groups at baseline could have an impact on the absolute difference between groups at the end of study follow-up, and it is unclear whether the difference at baseline is clinically meaningful.

The ERG notes that the thresholds proposed for rate of decline, at this time, have not been validated and could be considered arbitrary cut offs that are at risk of bias. The ERG is aware of research into the minimal clinically important difference in change in CT lung density that is yet to be published, and that is likely to contribute to understanding of the use of CT lung density to guide augmentation therapy in those with emphysema secondary to A1PI deficiency (personal communication).

Annual change in lung density was not monitored prior to start of allocated treatment in RAPID and so it is not possible to categorise those randomised as no, slow or rapid decliners were identified at baseline. If lung function decline had been evaluated prior to randomisation, following on from the company's initial proposal in the CS that evidence of "rapid" decline would indicate eligibility for

treatment, only those with "rapid" decline would have been randomised. Alternatively, should rate of decline not affect eligibility for treatment, to ensure balance across groups, stratified randomisation would have been appropriate. However, if the categories for decline are appropriate, due to small numbers randomised in RAPID, it is unlikely that the Respreeza and placebo groups are balanced in terms of rate of decline. Moreover, categorisation of rate of decline after randomisation is confounded by treatment received.

The ERG considers those receiving placebo in RAPID and moving to Respreeza in RAPID-OLE could form a relevant group for analysis of effect of Respreeza based on initial categorisation of rate of CT lung density decline. To obtain an estimate of the effect of Respreeza based on the proposed categories of rate of decline, during clarification, for those initially receiving placebo, the ERG asked the company to provide change in mean CT lung density (PD15) and in mean FEV1% predicted at 2 years' treatment with Respreeza, based on the categorisations of no decline, slow decline, and rapid decline as determined by the CT scans collected during receipt of placebo in RAPID. The company did not provide the requested analysis. Instead, the company provided a breakdown of the proportion of people in each class of CT lung density decline for the 2 years of treatment with Respreeza (information not presented in the ERG report).

The ERG considers that the direction of bias of the imbalance in lung density is unclear at this time. Those with a greater lung density at baseline could be at risk of losing a greater volume of lung density in a set period of time as they have more lung tissue to lose.

Given the rarity of A1PI deficiency, epidemiological data for the population are limited. Moreover, the ERG's clinical experts fed back that there is considerable variation across people with the condition in terms of their FEV1% predicted, age, and functional capacity at diagnosis. Moreover, no one has yet to receive Respreeza as a treatment in England. Taken together, the ERG considers that it is difficult to draw conclusions on the representativeness of the people enrolled in RAPID to people in England with emphysema secondary to severe A1PI deficiency. However, considering other RCTs of A1PI augmentation therapy, the baseline characteristics of those enrolled in RAPID are as generalisable as those enrolled in other trials to the population of interest in England. One of the ERG's clinical advisors commented that, based on the company's proposed criteria, all those with emphysema secondary to A1PI deficiency would be eligible for treatment with Respreeza. The EPAR for Respreeza outlines that an expert panel agreed that the appropriate target population in clinical practice for A1PI replacement would be patients presenting with a combination of risk factors, based on significant lung density decline, severity of emphysema, deficient level of A1PI (<11 μM), and phenotype or genotype at risk.[41]

Table 4. Baseline demographics and disease characteristics for RAPID (adapted from CS, Table 11 [pg. 81])

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
Race (Caucasian/Other)	100/0	100/0
Patients by region, %		
Australia	9.7	12.6
Europe	32.3	27.6
North America	25.8	25.3
Nordic	32.3	34.5
CT lung density, adjusted PD15 g/L, mean (SD)[a]		
TLC	45.5 (15.8)	48.8 (15.5)
FRC	47.6 (15.7)	50.7 (15.0)
Total	46.6 (15.6)	49.8 (15.0)
FEV1, % predicted, mean (SD)	47.5 (12.1)	47.2 (11.1)
FEV1/FVC ratio %, mean (SD)	45.2 (11.4)	43.2 (10.4)
D_{LCO}, mL/mmHg/min, mean (SD)	13.6 (5.3)	15.0 (5.6)
Antigenic A1PI level, mg/mL, mean (SD)	0.29 (0.21)	0.27 (0.11)
Distance walked, m, mean (SD)	424.5 (183.0)	435.1 (199.7)
SGRQ, symptoms score, mean (SD)	46.5 (22.7)	44.1 (24.8)
A1PI phenotype, n (%)		
ZZ	83 (89.2)	83 (95.4)
SZ	2 (2.2)	0 (0.0)
Z	2 (2.2)	1 (1.1)
Other	6 (6.5)	3 (3.4)
Prior medications (total frequency >3), n		
Vaccine (e.g., hepatitis/influenza)	7	11
Beta-2 agonist/corticosteroids	12	6
Nonsteroidal anti-inflammatory drugs	2	5
Antibiotics	10	11
Human A1PI (Prolastin)	3	1

[a] CT lung density values are from 90 subjects treated with Respreeza and 83 subjects who received placebo.

Abbreviations: A1PI, alpha-1 proteinase inhibitor; CS, company submission; CT, computed tomography; D_{LCO}, diffusing capacity of the lung for carbon monoxide; F, female; FEV1, forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; M, male; pg, page; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

Table 5. Baseline demographics and disease characteristics for RAPID-OLE[43, 61]

Characteristic	Early start (N=76)	Delayed start (N=64)
Mean age, years (SD)	53.8 (6.9)	52.4 (7.8)
Gender (M/F)	41/35	38/26
CT lung density, adjusted PD15 g/L, mean (SD)		
TLC	42.2 (15.2)	43.1 (14.0)
FRC	43.9 (14.8)	46.0 (14.0)
Total	43.1 (14.9)	44.8 (14.1)
FEV1, % predicted, mean (SD)	45.0 (12.6)	46.3 (12.0)
FEV1/FVC ratio, mean (SD)	0.429 (0.110)	0.423 (0.087)
D_{LCO}, mL/mmHg/min, mean (SD)	NR	NR
Antigenic A1PI level, μM, mean (SD)	15.9 (3.7)	5.9 (2.5)
Functional A1PI level, μM, mean (SD)	9.7 (2.7)	2.4 (1.4)
Distance walked, m, mean (SD)	NR	NR
SGRQ, symptoms score, mean (SD)	47.3 (18.2)	44.0 (16.9)
A1PI phenotype, n (%)		
ZZ	67 (88)	61 (95)
SZ	2 (3)	0 (0)
Z	1 (1)	0 (1)
Other	6 (8)	3 (5)

Abbreviations: A1PI, alpha-1 proteinase inhibitor; CS, company submission; CT, computed tomography; D_{LCO}, diffusing capacity of the lung for carbon monoxide; F, female; FEV1, forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; M, male; NR, not reported; pg, page; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

4.2.4 Description and critique of statistical approach used

Accounting for a dropout proportion of 25%, the sample size calculation for RAPID indicated that 180 people were required to have at least 80% power to detect a difference in CT lung density decline (primary outcome) between Respreeza and placebo of 1.07 g/L (SD 2.17 g/L) with two-sided α of 0·05. The estimate of treatment effect was based on results reported from an earlier RCT evaluating augmentation therapy in A1PI deficiency.[56] At a one-sided α of 0·025, with the same number of people, the study would have 92% power to detect a difference between Respreeza and placebo of 1 g/L (SD 2.5 g/L) in decline in CT lung density.

Those for whom at least one scan of CT lung density was available formed the modified intention-to-treat (mITT) population on which the primary analysis was based: mITT population comprised 92 people (out of 93 randomised) in the Respreeza group and 85 people (out of 87 randomised) in the placebo group. The primary analysis was based on a random regression model, and it was assumed that data were missing at random. As highlighted by the company, the random regression model utilises all

data contributed at each time point. In line with recommendations from the EMA,[62] the company also carried out sensitivity analyses in which missing data were accounted for by various methods to support the results from the primary analysis. The sensitivity analyses were pre-specified, and the rationale for choice of each method is outlined in the CSR, both of which are good practice processes and in line with guidance from the EMA.[62] The sensitivity analyses conducted by the company were:

- Complete-case analysis: included all those with valid CT scans at baseline and month 24. CT scans missing for follow-up assessments at months 3, 12, or 21 were not imputed. Missing values were assumed to be missing completely at random. Those completing treatment are anticipated to have a better treatment outcome compared with those that do not and, thus, the analysis is biased in favour of Respreeza;

- Pattern-mixture model with placebo-based pattern imputation: based on ITT population. All missing data were replaced by multiple imputation based on data from those randomised to placebo. The missing values were assumed to be missing not at random. Since the imputations were sampled from the placebo group, the analysis is considered biased in favour of placebo.

- Worst-case approach: based on ITT population. Missing scans were replaced by multiple imputations. Considered most conservative approach and associated with bias favouring placebo.

In summary, the ERG considers the statistical analysis plan followed by the company to be appropriate.

4.2.5 Quality assessment of studies

In the company's critique of the quality of RAPID (Table 6), the company indicated that the trial was appropriately randomised, with randomisation stratified by centre, and that treatment allocation was adequately concealed. The company also determined that groups were similar in terms of key baseline characteristics, key trial personnel were masked to treatment (double-blind design), there was no evidence of selective reporting bias, and that an intention-to-treat (ITT) analysis had been performed. A higher rate of withdrawal from the placebo group than the group receiving Respreeza was noted.

The ERG independently validated the company's assessment of the quality of RAPID and agrees with the company's assessments (Table 6), with the caveat that there is an imbalance between treatment groups in CT lung density, change in which over time is the primary outcome of RAPID. At this time, the ERG considers that the direction of any bias arising from the baseline imbalance in CT lung density is unclear. The ERG also notes that RAPID was sponsored by the company and several of the study authors are employees of the company. The role of the company and its employees in oversight and management of the trial is clearly outlined in the full publication: the funder had a role in oversight and

management of data collection, and employees of the funder participated in data analysis, data interpretation, and writing of the report.[42] In addition, it is stated that the corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.[42] In summary, the ERG considers RAPID to be a well-designed and well-conducted study at a low-risk of bias.

For completeness, the quality assessment carried out by the company for RAPID-OLE, together with that of the ERG, is presented in Table 7. As an open-label, non-randomised study in which everyone receives Respreeza, the ERG considers data from RAPID-OLE to inform on the maintenance of any effect of Respreeza in the longer term rather than on the comparative clinical effectiveness of the intervention. As an observational study, RAPID-OLE is associated with an inherently higher risk of bias than RAPID.

Table 6. Quality assessment for RAPID (adapted from CS, Table 13 [pg. 87])

Study question	**How is the question addressed in the study?**	
	Company's critique of RAPID	**ERG's critique of RAPID**
Was randomisation carried out appropriately?	Yes Subjects were randomised evenly, at a ratio of 1:1. A randomisation list containing the assignment of subject numbers to treatment groups was reproducibly generated by a computerised pseudo-random number generator. A copy of the randomisation list was transferred to the drug supply and logistics group of the Clinical Operations Department at CSL Behring. The randomisation was stratified by centre. Standard operating procedures were followed to ensure confidentiality of the randomisation list.	Yes The ERG agrees with the company that the randomisation process was robust.
Was the concealment of treatment allocation adequate?	Yes This was a double-blind study. Respreeza and placebo were packaged identically. Individual packages were identified only by the subject number. The treatment groups randomised to the subject numbers were only known to the randomisation code administrator, and to the drug supply and logistics group of the Clinical Operations Department at CSL Behring.	Yes The ERG agrees with the company that the methods implemented were adequate to conceal treatment allocation from those recruiting people to the study.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes There were no significant imbalances in clinically relevant baseline characteristics between the two study groups in RAPID.	Unclear The ERG agrees with the company that most baseline characteristics were balanced across groups but, as discussed in Section 4.2.3, there is a substantial difference between groups in baseline CT lung density, the change in which over

		time is the primary outcome.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes The study was double blinded so patients, caregivers, clinic staff, and other study personnel were blind to efficacy and safety data.	Yes The ERG considers that the processes implemented in RAPID mean that masking to treatment allocation is likely to be maintained throughout the study (described in greater detail in Section 4.2.1.1). In addition, CT lung density is determined by a computer programme, and is thus an objective measure at low risk of bias.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes A post-hoc Kaplan–Meier analysis and log rank test revealed a statistically significantly ($p = 0.04$) lower probability for withdrawal of subjects in the Respreeza group, although the pattern of withdrawals over time was similar for each treatment group. The timings of the withdrawals across the time period of the study suggest that differences present throughout the study influenced the probability of withdrawal rather than events at certain points in time that would be related to specific study design issues. The lower number of subjects who withdrew in the Respreeza arm is attributed to a lower number of subjects withdrawing due to an AE, fewer withdrawals of consent, fewer deaths and fewer "other reasons" (suspicion of pulmonary cancer and disinterest in spending time as a participant).	Yes The ERG agrees with the company's assessment of the imbalance in rate of withdrawal from the study.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No The study protocol is available and all outcomes have been reported.	No The ERG agrees with the company's assessment.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes The pre-specified ITT population included all randomised subjects with A1PI deficiency included in the study. In the ITT analysis, subjects were assigned to the treatment to which they were randomised. The number of subjects with major protocol deviations was comparable between the two treatment arms, including the number of subjects who were non-compliant with the investigational medicinal product regimen. The ITT population was the primary population for the analysis of the primary efficacy variable. ITT	Yes The ERG agrees with the company's assessment that an ITT population was defined. However, the ERG notes that the primary analysis for the primary outcome is based on a modified ITT population, which excludes those for whom no CT scan is available from any time point. However, the mITT excludes 1 person

	analyses were performed with and without (observed cases) imputation; some subjects were missing valid CT scans. In the primary analysis, the assumption was made that data were missing at random. Sensitivity analyses were conducted to verify the results of the primary analysis using multiple imputations to replace the missing data. The three sensitivity analyses indicated that the results of the primary analysis are robust with respect to the presence of missing CT data (Section 3.2.1). For endpoint analyses, observed cases were subjects with a baseline and at least 1 endpoint assessment available.	and 2 people from the Respreeza and placebo groups, respectively. Additionally, the company has carried out various sensitivity analyses to support the primary analysis.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.[63] Abbreviations: A1PI, alpha-1 proteinase inhibitor; AE, adverse effect; CRD, Centre for Reviews and Dissemination; CS, company submission; CT, computed tomography; ERG, Evidence Review Group; pg, page; ITT, intention-to-treat.		

Table 7. Quality assessment for RAPID-OLE (adapted from CS, Table 14 [pgs 88–89])

Study question	**How is the question addressed in the study?**	
	Company's critique of RAPID	**ERG's critique of RAPID**
Was the cohort recruited in an acceptable way?	Yes RAPID-OLE is an extension trial of RAPID-RCT study. This extension trial was designed as an open-label extension. To ensure that appropriate subjects were selected, eligibility requirements for RAPID-OLE were: patients recruited from RAPID-RCT, and who had either completed 2 years of A1PI treatment at a dose of 60 mg/kg weekly, or had received placebo for 2 years during RAPID-RCT. Further to this, inclusion criteria for RAPID-OLE included: serum A1PI concentrations of less than 11 μM and FEV_1 of 35-70% predicted at randomisation in RAPID-RCT. The entry criteria for both groups (early-start treatment group and delayed-start treatment group) were identical to allow for valid comparisons between the early-start treatment group, and delayed-start treatment group. The study was conducted in 11 countries in 22 hospitals outside of the USA, with the principle investigators considered specialists in the field of study.	Yes The ERG agrees with the company's rationale for recruitment of the cohort.
Was the concealment of treatment allocation adequate?	No This is an open-label study, and therefore patients and investigators are aware of the patient's treatment.	No The ERG agrees with the company's assessment but notes that everyone in RAPID-OLE receives Respreeza and so masking is not necessary.
Were the groups similar at the outset of the study in terms of prognostic	N/A The main difference between the enrolled groups was that the early-start treatment group had higher	Yes The ERG notes that baseline characteristics,

factors, for example, severity of disease?	antigenic and functional serum concentrations, as compared with the delayed-start treatment group. There were some differences in the AATD genotypes between the early-start treatment group and delayed-start treatment groups, where SZ genotype and Z/null genotypes were present in the early-start treatment group and absent in the delayed-start treatment group.	including CT lung density, were similar across groups.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No As this is an open-label study, patients and investigators are aware of the patient's treatment.	No The ERG agrees with the company's assessment but notes that everyone in RAPID-OLE receives Respreeza and so masking is not necessary. However, the primary outcome of change in CT lung density is determined by a computer programme based on CT scans and is, therefore, an objective outcome at a low risk of bias.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes 131 of the planned 140 patients recruited from the RAPID-RCT trial were enrolled. Of those that withdrew from the RAPID-OLE; 6 were from the early-start treatment cohort (1 death, 3 withdrew consent, 1 adverse event – drug abuse, 1 lung transplantation), and 3 were from the delayed-start treatment cohort (1 adverse event, 1 withdrew consent, 1 prolonged vacation).	Yes The ERG agrees with the company's assessment.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes All outcomes were reported *a priori* either in the article or in the appendices	Yes The ERG agrees with the company's assessment and notes that the CSR for the study is available.

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Since the duration of treatment received was different for patients in the delayed-treatment group who received placebo during RAPID-RCT, compared with the early-start treatment group who had received 60 mg/kg during RAPID-RCT, analyses were conducted accounting for the treatment duration for the full population. An ITT was included to assess the primary outcome on change in lung density (adjusted PD15) at different inspiration states. The RAPID-OLE intention-to-treat (ITT) population comprised all patients enrolled in RAPID-OLE. An analysis was also conducted in the completer population; a subset of the ITT population, comprised patients who had valid lung density values at day 1 in RAPID-RCT and at month 48 in RAPID-OLE.	Yes The ERG agrees with the company's assessment: the primary analysis is based on an ITT population.
Was the exposure accurately measured to minimise bias?	Yes RAPID-OLE was a prospective, interventional study with a planned treatment duration of 24 months. All patients received treatment for 24 months in this period. As this is an extension to RAPID-RCT, the early-start treatment group received A1PI for 48 months (the time point for analysis), and the delay-start treatment group received A1PI for 24 months.	Yes The ERG agrees with the company's assessment.
Was the outcome accurately measured to minimise bias?	A statistical analysis plan was created to test for disease modifying characteristics in RAPID-OLE. is an open-label, extension trial assessing sustained efficacy and longer-term safety and tolerability. The primary efficacy outcome was the annual rate of lung density loss assessed by adjusted PD15, which was the primary outcome in RAPID-RCT. Secondary outcomes included spirometric pulmonary function, health-related quality of life using the St George's Respiratory Questionnaire, serum antigenic and functional Q1PI concentrations, and safety (treatment-emergent adverse events, laboratory values, vital signs, and physical findings).	Yes The ERG agrees with the company's assessment.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	N/A
Was the follow-up of patients complete?	N/A	N/A
Abbreviations: A1PI, alpha-1 proteinase inhibitor; CT, computed tomography; ERG, Evidence Review Group; N/A, not applicable; pg, page; ITT, intention-to-treat.		

4.2.6 Clinical effectiveness results

4.2.6.1 CT lung density

In RAPID, Respreeza was associated with a lower rate of annual decline in CT lung density (adjusted PD15 for combined TLC and FRC) compared with placebo at 2 years of follow-up, but the difference did not reach statistical significance: quantitative data are presented in Table 8 and change in CT lung density over time is depicted graphically in Figure 4. Those receiving Respreeza had a decline in annual adjusted CT lung density of 1.50 g/L, whereas those allocated to placebo lost 2.12 g/L, giving an absolute difference between the two groups of 0.62 g/L per year (95% CI: –0.02 g/L to 1.26 g/L; p=0.06).

As discussed in Section 4.2.2.1, the CHMP recommends a focus on TLC alone, rather than the combined measure of TLC plus FRC, as there is greater consistency in measurement of the TLC inspiration state. Considering the individual components, Respreeza was associated with a statistically significantly lower annual decline in adjusted TLC compared with placebo (mean difference of 0.74; 95% CI: 0.06 to 1.42; p=0.03) but not annual loss in FRC (mean difference 0.48; 95% CI: –0.22 to 1.18; p=0.18; Table 8).

The ERG highlights that there was a difference of 3.2 g/L in baseline CT lung density (adjusted PD15) between treatment groups (46.6 g/L [SD 15.6 g/L] with Respreeza vs 49.8 g/L [SD 15.0 g/L]) with placebo). The direction of bias arising from the imbalance is unclear. The ERG also notes that the primary efficacy analysis for decline in CT lung density is based on 90 people in the Respreeza group, not 92 as expected based on the reported mITT population. The ERG considers this a minor discrepancy that is likely to have minimal impact on the results.

In the longer term, results from RAPID-OLE indicate that the effect of Respreeza in reducing rate of lung density decline is sustained.[64] Those initially receiving Respreeza, referred to as the early-start group, had a similar level of annual decline in CT lung density (TLC only) in the 2 years follow-up of RAPID-OLE (1.51 g/L [Standard error {SE} 0.25] for day 1 to month 24 versus 1.63 [SE 0.27] in months 24 to 48; Table 9).[64] By contrast, those who switched to Respreeza from placebo, referred to as the delayed start group, had a substantially lower rate of annual decline in the 2 years of active treatment compared with the 2 years prior to start of treatment (2.26 g/L [SE 0.27] for day 1 to month 24 versus 1.26 [SE 0.29] in months 24 to 48). The company reports that, in a mixed model that assessed lung density decline across RAPID and RAPID-OLE, the annual lung density decline rate was reduced by 0.52 g/L (p=0.001) when switching from placebo to Respreeza in the delayed-start group. The authors of the study concluded that those in the delayed-start group did not regain the lung tissue that had been lost during the previous 2 years of treatment with placebo, and that the result underscores the importance of early interventional treatment with an A1PI.[64]

In RAPID-OLE, absolute differences between the early and delayed start groups in adjusted CT lung density for TLC plus FRC and FRC alone are reported (Table 9), but the annual change for each group is not reported separately. The ERG is not concerned that data on measures for the TLC plus FRC and FRC alone assessments for RAPID-OLE are not available as it is acknowledged that the TLC state is the most reliable inspiration state (Table 9).

The ERG considers it important to reiterate that, although there is growing evidence that CT lung density is a robust technique for determining severity of emphysema, a minimally important clinical difference for decline in lung density has yet to be established. Moreover, there is uncertainty about the extent to which decline in CT lung density correlates with change in spirometric measures.

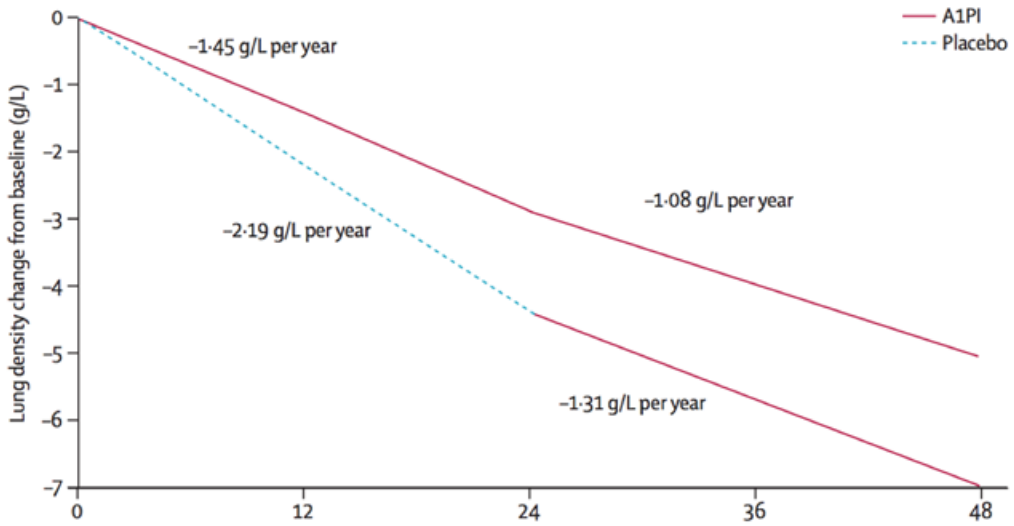
Table 8. Summary of changes in CT lung density (physiologically adjusted PD15) from RAPID[42]

	Respreeza (N=90)				**Placebo (N=83)**				**Respreeza versus placebo**
Mean adjusted PD15	Baseline	24 months	Change from baseline	Annual change[a]	Baseline	24 months	Change from baseline	Annual change[a]	Mean difference in annual change (95% CI)
TLC plus FRC, g/L (SD)	46·6 (15·6)	44.4 (15.5)	–-2.67 (4.30)	–1.50 (0.22)	49·8 (15·1)	45.5 (13.9)	–3.93 (4.02)	–2.12 (0.24)	0.62 (–0.02 to 1.26) p=0.06
TLC alone, g/L (SD)	45·5 (15·8)	43.6 (16.0)	–2.60 (4.44)	–1.45 (0.23)	48·9 (15·5)	43.9 (13.8)	–4.20 (4.50)	–2.19 (0.25)	0.74 (0.06 to 1.42) p=0.03
FRC alone, g/L (SD)	47·6 (15·7)	45.3 (15.3)	–2.74 (4.75)	–1.55 (0.24)	50·7 (15·0)	46.8 (13.8)	–3.73 (4.46)	–2.02 (0.26)	0.48 (–0.22 to 1.18) p=0.18

[a] Measure of variation is standard error rather than standard deviation.

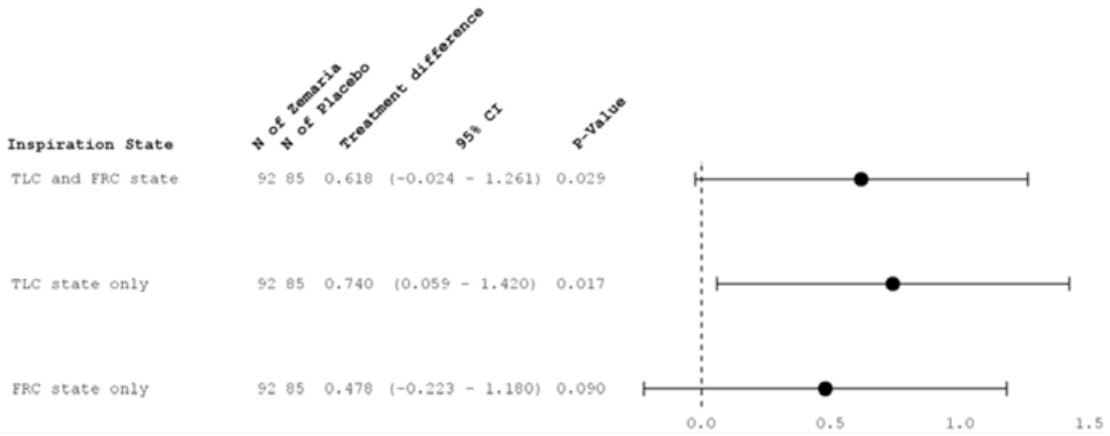
Abbreviations: CI, confidence interval; CT, computed tomography; FRC, functional residual capacity; SD, standard deviation; TLC, total lung capacity.

Figure 4. Rates of lung density decrease at TLC during 48 months of RAPID and RAPID-OLE (reproduced from CS, Figure 13 [pg. 109])



Abbreviations used in figure: A1PI, alpha-1 proteinase inhibitor; CS, company submission; pg, page; TLC, total lung capacity.

Figure 5. Comparison of RAPID results of lung density decline at combined TLC/FRC and FRC only, and the optimal measure of TLC only in RAPID (reproduced from CS, Figure 16 [pg. 111])



Abbreviations used in figure: CI, confidence interval; CS, company submission; FRC, functional residual capacity; ITT, intention to treat; pg, page; TLC, total lung capacity.

Table 9. Summary of changes in CT lung density (physiologically adjusted PD15) from RAPID-OLE[43]

	Early start group (N=76)[a]	**Delayed start group (N=62)**	**Early – delayed Mean difference (95% CI)**
Change in annual adjusted PD15			
Day 1 to month 24			
	Mean annual change	Mean annual change	
TLC plus FRC, g/L (SE)	N/R	N/R	0·60 (–0·09 to 1·30), p=0.0447[b]
TLC alone, g/L (SE)	–1.509 (0.2483)	–2.259 (0.2679)	0.750 (0.028 to 1.473), p=0.021[b]
FRC alone, g/L (SE)	N/R	N/R	0·45 (–0·31 to 1·21), p=0.1235[b]

Month 24 to month 48			
TLC plus FRC, g/L (SE)	N/R	N/R	–0·28 (–1·09 to 0·53), p=0.7519[b]
TLC alone, g/L (SE)	–1.627 (0.2743)	–1.256 (0.2891)	–0.371 (–1.159 to 0.417), p=0.823[b]
FRC alone, g/L (SD)	N/R	N/R	–0·18 (–1·09 to 0·74), p=0.6482[b]
[a] Analysis based on 73 people from the early-start group. [b] One-sided p value. Abbreviations: CI, confidence interval; CT, computed tomography; FRC, functional residual capacity; SE, standard error; TLC, total lung capacity.			

4.2.6.1.1 Sensitivity analyses

Sensitivity analyses carried out to account for missing CT lung density data (TLC and FRC combined) generated absolute differences in annual CT lung density between Respreeza and placebo that were comparable to the absolute difference of 0.62 g/L per year derived from the primary analysis (Table 10). The direction of effect in all three sensitivity analyses favoured Respreeza, and, as in the primary analysis, no difference reached statistical significance. The ERG agrees with the company that the sensitivity analyses indicate that the results of the primary analysis are robust.

As part of the clarification process, to assess the sensitivity of the results generated for decline in annual CT lung density at the TLC inspiration state, the ERG requested that the company carry out the three sensitivity analyses using data for that inspiration state alone. The company did not carry out the analyses and stated in their response, "*As stated in the CSR, none of the sensitivity analyses indicated a statistically significant difference between the treatment and placebo group, and so we expect that performing a sensitivity analysis for TLC alone would also provide non-significant differences between these groups*".

Table 10. Sensitivity analyses for the primary outcome of annual change in CT lung density based on data from RAPID (reproduced from CS, Table 21 [pg. 112])

Analysis	Respreeza		Placebo		Difference (95% CI)	1-sided p-value
	Number	Mean (SE)	Number	Mean (SE)		
Complete-case analysis[a]	80	–1.49 (0.22)	67	–2.08 (0.25)	0.59 (–0.07 to 1.25)	0.040
Pattern-mixture model[b]	93	–1.58 (0.22)	87	–2.13 (0.24)	0.54 (–0.09 to 1.17)	0.047
Worst-case approach[c]	93	–1.55 (0.33)	87	–2.26 (0.34)	0.71 (–0.23 to 1.64)	0.068
[a] Potential bias in favour of Respreeza. [b] Potential bias in favour of placebo. [c] Potential bias in favour of placebo. Abbreviations: CI, confidence interval; CS, company submission; pg, page; SE, standard error.						

4.2.6.2 Secondary outcomes deemed to be relevant to CT lung density

As noted in Section 4.2.2, the EMA identified key secondary outcomes as those that would help explain the clinical relevance of change in CT lung density:[41]

- change in exercise capacity assessed by the ISWT;
- change in symptoms score assessed by the SGRQ;
- risk of pulmonary exacerbation assessed by the annual rate of exacerbations.

No statistically significant differences were reported between Respreeza and placebo for the identified secondary outcomes, and, in the ISWT and rate of exacerbation, the direction of effect favoured placebo (Table 11). As noted by the company, RAPID was not powered to detect a difference in treatment effect on changes in secondary outcomes.

Considering the ISWT, the mean change from baseline to month 24 in the distance walked was lower with Respreeza (10.8 m [SD 139.8]) compared with placebo (16.1 m [SD 101.6]). The mean difference (least square) between Respreeza and placebo was 13.09 m, with the longer distance walked in the placebo group (p=0.48; Table 11)

In the SGRQ, a higher score reflects increased limitations in terms of overall health, daily life, and perceived well-being. Increases in mean change from baseline were noted for most components of the SGRQ. The only decrease noted was symptom score for those receiving Respreeza, with a mean change of –1.4 (SD 16.7; Table 11).

Surprisingly, the annual exposure-adjusted incidence rate of pulmonary exacerbations was higher with Respreeza than with placebo (1.70 exacerbations/subject year with Respreeza vs 1.42 exacerbations/subject year with placebo; Table 11), although the difference between groups did not reach statistical significance (adjusted risk ratio 1.26: 95% CI; 0.92 to 1.74). During clarification, the ERG requested additional information on pulmonary exacerbations, including the number of events, the number of people experiencing an exacerbation, and the number of exacerbations requiring healthcare intervention (including type of intervention). Based on the data helpfully provided by the company (summarised in Table 12), the ERG notes that the number of people [redacted] Respreeza group compared with the placebo group, although the [redacted]. COPD exacerbation was also captured as an adverse effect (discussed in Section 4.3.2).

Table 11. Key secondary endpoint results for Respreeza and placebo in the RAPID study (adapted from CS, Table 22 [pg. 114])

Outcome	Respreeza (N=93)		Placebo (N=87)		Respreeza versus placebo
	Baseline	24 months	Baseline	24 months	Least-square mean difference
SGRQ score					
Total	44.3 (17.1)	1.4 (11.1)	42.4 (18.0)	2.2 (11.7)	−0.19[a] (p=0.91)
Symptoms	46.5 (22.7)	−1.4 (16.7)	44.1 (24.8)	2.0 (20.1)	−1.11[a] (p=0.67)
Activity	62.1 (18.6)	1.7 (12.4)	60.1 (21.4)	2.6 (13.5)	−0.16[a] (p=0.94)
Impact	33.6 (18.4)	2.1 (14.8)	31.4 (17.6)	1.8 (12.5)	0.74[a] (p=0.72)
Shuttle walk distance (m)	424.5 (183.0)	10.8 (139.8)	435.1 (199.7)	16.1 (101.6)	−13.09[a] (p=0.48)
Exacerbations					
Annual number	1.70 (1.51 to 1.89)		1.42 (1.23 to 1.61)		1.26[b] (0.92 to 1.74)
Relative duration (days)	13.8 (15.0)		10.8 (11.6)		0.56 (p=0.18)

[a] Adjusted for country, treatment group, and baseline values.

[b] Presented as an adjusted risk ratio from a negative binomial regression model in which country and treatment were fixed effects, and adjustment was made for treatment duration.

Abbreviations: A1PI, alpha-1 proteinase inhibitor; CS, company submission; D_{LCO}=diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in one second; SGRQ=St George's Respiratory Questionnaire.

Table 12. Summary of pulmonary exacerbations reported in RAPID (adapted from company's response to clarification, question A8)

Outcome	Respreeza (N=93)	Placebo (N=87)	EAIR for Respreeza	EAIR for placebo	Difference in EAIR[c]
People experiencing ≥1 pulmonary exacerbation, n (%) (number of events)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 to 3 exacerbations	[redacted]	[redacted]	–	–	–
4 to 6 exacerbations	[redacted]	[redacted]	–	–	–
>6 exacerbations	[redacted]	[redacted]	–	–	–
People experiencing a moderate exacerbation[a], n (%) (number of events)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
People experiencing a severe exacerbation[b], n (%)(number of events)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of exacerbations requiring antibiotics	[redacted]	[redacted]	–	–	–
Number of exacerbations requiring oral corticosteroids	[redacted]	[redacted]	–	–	–
Hospitalisation	[redacted]	[redacted]			

Mean duration of hospitalisation due to exacerbations, years (SD)	[redacted]	[redacted]	–	–	–
Mean duration of hospitalisation due to exacerbations relative to total study duration, % (SD)	[redacted]	[redacted]	–	–	–
[a] Defined as [redacted].					
[b] Defined as [redacted].					
[c] Two-sided Mann-Whitney-Wilcoxon test.					
Abbreviations: EAIR, exposure-adjusted incidence rate; SD, standard deviation.					

4.2.6.3 Other secondary outcomes

Differences between Respreeza and placebo in FEV1 and D_{LCO} were not statistically significant, and the direction of effect favoured placebo in both outcomes (Table 13). The EPAR for Respreeza reports that a random regression analysis of the treatment effect for the overall rate of decline in FEV1 revealed a change of 0.003 L in favour of placebo, as compared with Respreeza, but the difference did not reach statistical significance.[41]

As expected, Respreeza was associated with a statistically significant increase in A1PI serum concentration, both antigenic (p=0.02) and functional (p=0.02), compared with placebo (Table 13).

Table 13. Other non-primary endpoint results for Respreeza and placebo in the RAPID study (adapted from CS, Table 22 [pg. 114])

Outcome	**Respreeza (N=93)**		**Placebo (N=87)**		**Respreeza versus placebo**
	Baseline	24 months	Baseline	24 months	Least-square mean difference
FEV1 % Predicted	47.4% (12.1)	−3.1% (10.7)	47.2% (11.1)	−2.3% (13.1)	−2.26%[a] (p=0.21)
D_{LCO} (mL/mm Hg per min; %)	13.6% (5.3)	−2.2% (18.2)	15.0% (5.6)	−1.5% (19.5)	−1.31%[a] (p=0.64)
A1PI concentration (μM)					
Antigenic	6.38 (4.62)	10.12 (3.52)	5·94 (2·42)	−0.07 (1.32)	10.05[b] (p=0.02)
Functional	2.88 (3.65)	7.30 (2.50)	2·30 (1·34)	0.12 (0.96)	7.18[b] (p=0.02)
[a] Adjusted for country, treatment group, and baseline values.					
[b] Based on a post-hoc analysis and are the results from t tests.					
Abbreviations: A1PI, alpha-1 proteinase inhibitor; CS, company submission; D_{LCO}=diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in one second; SGRQ=St George's Respiratory Questionnaire.					

4.2.7 Subgroup analyses

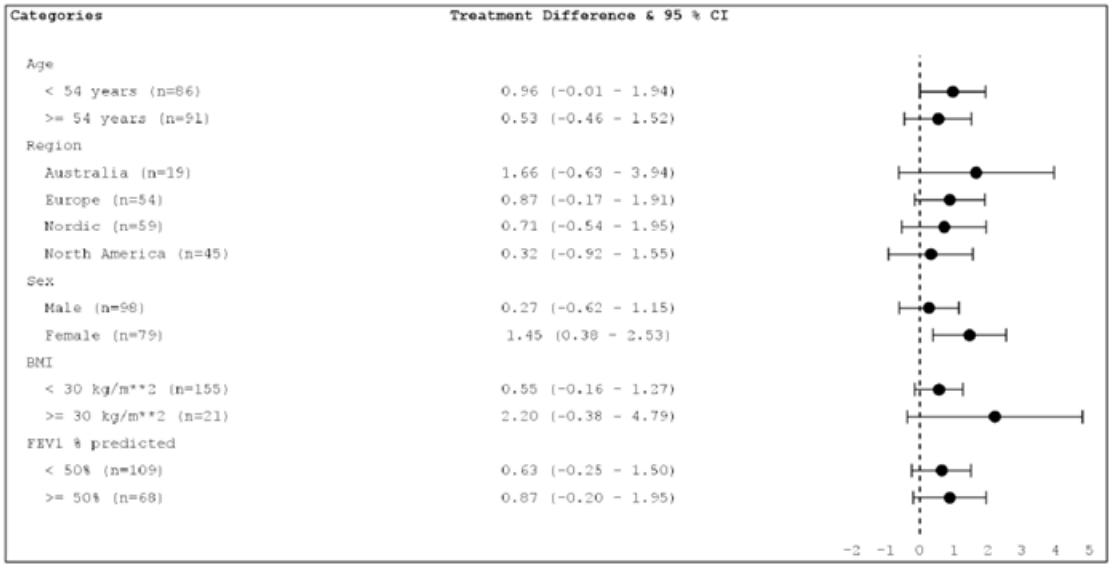
The final scope issued by NICE outlined that subgroup analyses based on the characteristics and progression of the disease (e.g., speed of decline, distribution of disease and frequency of exacerbations) would be of interest, should there be sufficient evidence available.[40]

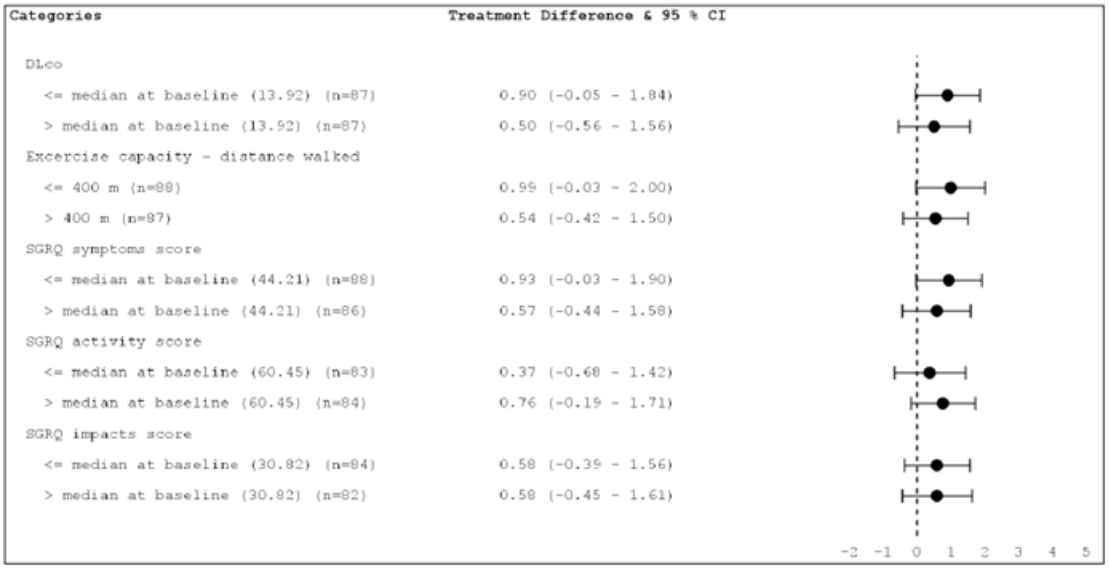
In the CS (pg. 112), the company presents forest plots for analysis of decline in adjusted CT lung density at the TLC inspiration state for various subgroups (Figure 6). As highlighted by the company, statistically significant differences favouring Respreeza were noted in the analysis of women only (1-sided p=0.004) and those with high baseline functional and antigenic A1PI levels (above the 66th percentile; p values not reported; Figure 6). All but one of the remaining subgroup analyses consistently showed a direction of effect favouring Respreeza in each category, although no difference reached statistical significance. Patients with low baseline functional or antigenic A1PI levels (<33rd percentile) experienced less treatment benefit compared with those with higher levels, with the direction of effect favouring placebo (Figure 6). There was insufficient evidence to carry out subgroup analyses based on disease characteristics, other than baseline serum A1PI concentrations.

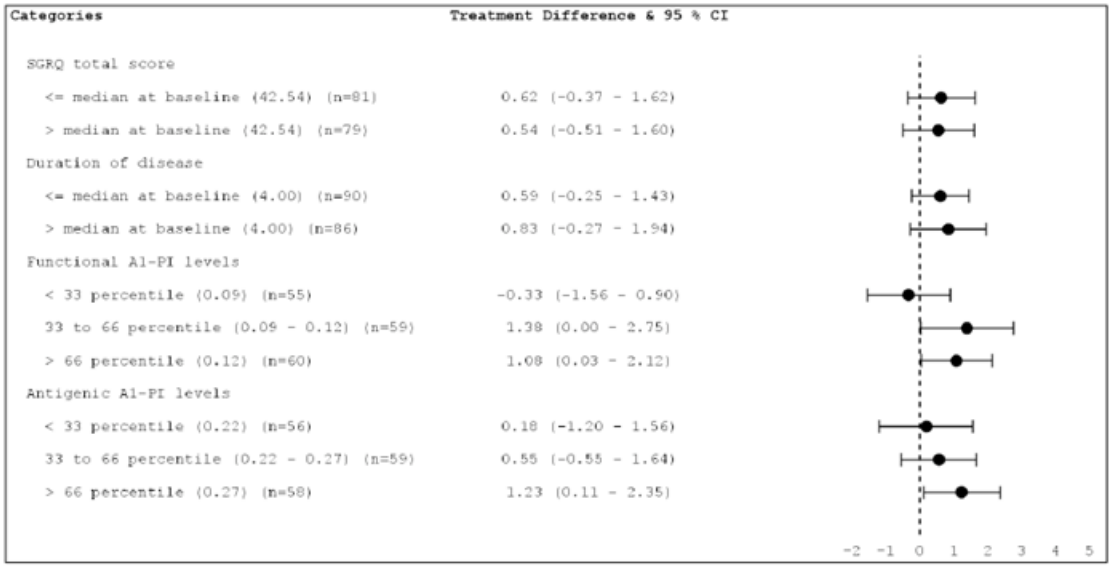
Based on feedback from its clinical experts, the ERG considered a subgroup analysis in those who have never smoked versus ex-smokers to be of clinical interest. The ERG requested subgroup analysis based on smoking status at clarification, but the company declined to provide the analysis, stating that too few people who had never smoked were enrolled in RAPID to facilitate the comparison.

The ERG notes that, given the large number of subgroup analyses carried out, it is possible that a statistically significant difference may have arisen by chance. Moreover, the subgroup analyses are not powered to detect a difference between treatments, should a true difference exist, and the ERG advises that the results are interpreted with caution.

Figure 6. Treatment differences in rate of decline in CT lung density (g/L) by various baseline parameters at the TLC state in RAPID study (reproduced from CS, Figure 17 [pg. 113])







4.2.8 Summary of critique

RAPID, and the subsequent open-label extension, represent the largest study to date evaluating the effects of A1PI augmentation therapy, specifically Respreeza, on slowing the progression of emphysema secondary to severe A1PI deficiency. The ERG considers RAPID to be predominantly well-designed and well-conducted and at a low risk of bias. In brief, RAPID is an international, randomised, double-blind, phase III/IV trial with a primary objective of assessing the change in lung density by CT on A1PI augmentation with Respreeza compared with placebo in people with emphysema secondary to severe A1PI deficiency. After 2 years of follow-up, all patients located outside the USA entered an open-label 2-year extension phase, RAPID-OLE.

The ERG notes that no study site for RAPID was located in the UK. However, the ERG does not consider this a limitation. The ERG determines that it is difficult to draw conclusions on the

representativeness of the people enrolled in RAPID to people in England with emphysema secondary to severe A1PI deficiency likely to be eligible for treatment with Respreeza. The ERG's clinical experts fed back that there is considerable variation across people with the condition in terms of their FEV1% predicted, age, and functional capacity at diagnosis. Also, because of the rarity of A1PI deficiency, epidemiological data for the population are limited. Considering other RCTs assessing clinical effectiveness of A1PI augmentation therapy in severe A1PI deficiency, the baseline characteristics of those enrolled in RAPID are as generalisable as those enrolled in other trials to the population of interest in England.

Baseline characteristics of people enrolled in RAPID were predominantly well balanced across the Respreeza and placebo groups, with the exception of baseline CT lung density (adjusted PD15). Those allocated to Respreeza had a baseline value of 46.6 g/L (SD 15.6 g/L) for the combined measure of TLC and FRC compared with 49.8 g/L (SD 15.0 g/L) in those receiving placebo. The company presents research to support the proposal that those with a decrease in CT lung density of 2.0 g/L or greater annually are deemed to be in rapid decline, and likely to achieve a greater benefit from treatment with Respreeza compared with those who experiencing no or slow decline in lung density. The ERG notes that the thresholds proposed for rate of decline, at this time, have not been validated and could be considered arbitrary cut offs that are at risk of bias. The ERG has concerns about the imbalance in CT lung density at baseline because the primary measure of clinical effectiveness in RAPID was annual change in lung density as measured by CT, with the value adjusted to account for lung volume. CT lung density was assessed at both the TLC and FRC inspiration states and the results combined to give a value for TLC plus FRC.

In RAPID, Respreeza was associated with a lower rate of annual decline in CT lung density (adjusted PD15 for combined TLC and FRC) compared with placebo at 2 years of follow-up, but the difference did not reach statistical significance. Those receiving Respreeza had a decline in annual adjusted CT lung density of 1.50 g/L, whereas those allocated to placebo lost 2.12 g/L, giving an absolute difference between the two groups of 0.62 g/L per year (95% CI: –0.02 g/L to 1.26 g/L; p=0.06).

As highlighted by the company, research indicates that CT scans captured at TLC provide optimal data for observing shifts in lung density over time as people find it easier to replicate the TLC inhalation state than FRC over the duration of a study. Therefore, there is lower variability across TLC measures and TLC is more robust and associated with the optimum possibility to detect small differences in lung density. Focusing on the TLC inspiration state, Respreeza was associated with a statistically significantly lower annual decline in adjusted TLC compared with placebo (mean difference of 0.74 g/L; 95% CI: 0.06 g/L to 1.42 g/L; p=0.03).

Various secondary outcomes were assessed in RAPID. The key secondary outcomes were deemed to be those that would help explain the clinical relevance of the primary objective of change in lung density as measured by CT scan and were specified to be:

- change in exercise capacity assessed by ISWT;
- change in symptoms score assessed by the SGRQ;
- risk of pulmonary exacerbation assessed by the annual rate of exacerbations.

No statistically significant differences were reported between Respreeza and placebo for the identified secondary outcomes, and, in the ISWT and rate of exacerbation, the direction of effect favoured placebo.

In terms of key spirometry measures, that is FEV1 and D_{LCO}, the difference between Respreeza and placebo in change in FEV1 and D_{LCO} did not reach statistical significance. Considering the assessment of FEV1 per cent predicted, the ERG considers it important to note that administration of a bronchodilator before assessment of FEV1, as is advised by GOLD for COPD, was not compulsory in RAPID. Neither the CS nor the CSR provides details on the frequency of use of bronchodilator, or whether the results have been adjusted to account for the disparity in use of FEV1. The ERG considers the direction of potential bias arising from variation in bronchodilator use prior to FEV1 measurement to be unclear.

4.3 Adverse effects

4.3.1 Administration

The Summary of Product Characteristics (SmPC) for Respreeza reports that the first infusion of the therapy should be administered under the supervision of a healthcare professional experienced in the treatment of A1PI deficiency at the recommended rate of infusion (about 0.08 ml/kg/ min).[48] During the first infusion, the patients should be monitored closely, and the rate of infusion decreased or stopped if the person experiences a reaction potentially related to the administration of Respreeza. Infusions may be resumed at a lower rate if symptoms subside immediately after decrease or cessation of infusion.

Subsequent infusions can be given by a caregiver or by the patient. As acknowledged by the company, limited data are available on the self-administration or home use of Respreeza.[48] Potential risks associated with home-treatment and self-administration highlighted in the SmPC arise from handling and administration of Respreeza, as well as occurrence of adverse reactions, particularly hypersensitivity.[48] The decision of whether a patient is suitable for home-treatment or self-administration should be made by the treating clinician, and appropriate training should be provided. Regular review of the use of Respreeza in the home setting is advised.

4.3.2 Reported adverse effects

In RAPID, any untoward medical event was deemed to be an adverse event, with events assessed by the investigators as being not related, possibly related, probably related, or related to the trial treatment.[42] Adverse events were categorised as mild, moderate or severe:[58]

- Mild: did not interfere with routine activities;
- Moderate: interfered with routine activities;
- Severe: impossible to perform routine activities.

Adverse events resulting in death or in admission to hospital, or that were judged to be life-threatening were categorised as serious events.

Overall, the total number of adverse events reported in RAPID was higher in those receiving Respreeza compared with placebo (1,298 with Respreeza versus 1,068 with placebo; Table 14). Most people (99%) forming the safety population experienced a treatment-emergent adverse event (TEAE), the largest proportion of which in each group were of moderate intensity (58% in Respreeza group vs 49% in placebo group). There were four deaths during the RAPID study (1 in the Respreeza group and 3 in the placebo group), and one additional death during RAPID-OLE (Table 15). During the conduct of RAPID, occurrence of a TEAE led to the withdrawal of one person from the Respreeza group (due to back pain), and of four people from the placebo group who experienced a total of 10 TEAEs.[42]

Based on preferred terms, the company noted that headache was the most common TEAE reported in RAPID (Table 16). Other TEAEs reported by ≥10% of people and occurring more frequently in the Respreeza group than in those receiving placebo included COPD (32% with Respreeza versus 23% with placebo), oropharyngeal pain (24% versus 12%), condition aggravated (22% versus 16%), and cough (22% versus 8%; Table 16). By contrast, more people in the placebo group developed pneumonia (12% with Respreeza vs 14% with placebo). For completeness, TEAEs reported by ≥10% of people in RAPID-OLE are presented (Table 17).

Following on from the discussion on exacerbation of COPD as a clinical efficacy measure in Section 4.2.6.2, the ERG considers it important to highlight capture of COPD exacerbation as a TEAE. As part of the application to the EMA for marketing authorisation, the company submitted safety data from 6 studies,[41] two of which were RAPID and RAPID-OLE. The European Public Assessment Report (EPAR) for Respreeza reported that, during the first 6 months of treatment, exacerbation of COPD was recorded in 40 people from a total pool of 221 people having taken Respreeza (18.1%). By contrast, 11 out of 149 people taking placebo experienced an exacerbation of COPD (12.6%).[41] The overall incidence rate for exacerbation of COPD was 0.59 and 0.36 events per patient year for Respreeza and

placebo, respectively, and the odds of experiencing the event were statistically significantly higher with Respreeza (odds ratio 1.66; 95% CI: 1.24 to 2.23). The EPAR reported that the definition of COPD exacerbation and serious COPD exacerbation differed for the safety and the efficacy components of the submission.[41] The company was asked to justify their assessment that there would be no increased risk of COPD exacerbations with Respreeza, and, in their response, the company presented data as "COPD composite" events, linking COPD as an adverse reaction with clinical exacerbations. The EMA concluded that the number of COPD exacerbations was not lowered following treatment, and commented that, as COPD is an end stage of lung disease, the statistically significant higher rate of COPD exacerbation recorded for Respreeza was unexpected.[41]

Table 14. Summary of TEAEs in the RAPID study (reproduced from CS, Table 23 [pg. 119])

	Respreeza[a] (N=93)		**Placebo[a] (N=87)**	
	Number of people (%)	**Number of events**	**Number of people (%)**	**Number of events**
Any TEAE	92 (99%)	1,298 (7.58)	86 (99%)	1,068 (7.23)
Mild	13 (14%)	–	16 (18%)	–
Moderate	54 (58%)	–	43 (49%)	–
Severe	25 (27%)	–	27 (31%)	–
Any related TEAE	21 (23%)	91 (0.53)	21 (24%)	50
Any serious TEAE	28 (30%)	57 (0.33)	28 (32%)	45
Any related serious TEAE	1 (1%)	1 (0.01)	1 (1%)	1
Any TEAE leading to withdrawal from study	1 (1%)	1 (0.01)	4 (5%)	10
Any related TEAE leading to withdrawal from study	1 (1%)	1 (0.01)	1 (1%)	4
Death due to TEAE	1 (1%)	1 (0.01)	3 (3%)	3

[a] Data are n (%) or n (annualised incidence rate).
Abbreviations: CS, company submission; pg, page; TEAE, treatment-emergent adverse event.

Table 15. Summary of TEAEs in the RAPID-OLE study (reproduced from CS, Table 24 [pg. 119])

	Early start[a] (N=76)		**Delayed start[a] (N=64)**	
	Number of people (%)	**Number of events**	**Number of people (%)**	**Number of events**
Any TEAE	76 (100%)	773 (5.28)	62 (96.9%)	620 (4.97%)
Mild	15 (19.7%)	–	10 (15.6%)	–
Moderate	38 (50%)	–	33 (51.6%)	–
Severe	23 (30.3%)	–	19 (29.7%)	–
Any related TEAE	11 (14.5%)	21 (0.14)	7 (10.9%)	7 (0.06%)
Any serious TEAE	28 (36.8%)	57 (0.39)	23 (35.9%)	56 (0.45%)
Any related serious TEAE	1 (1.3%)	1 (0.01)	3 (4.7%)	3 (0.02%)

Death due to TEAE	1 (1.3%)	1 (0.01)	0	0
Death due to related TEAE	0	0	0	0

[a] Data are n (%) or n (annualised incidence rate).

Abbreviations: CS, company submission; OLE, open label extension; pg, page; TEAE, treatment-emergent adverse event.

Table 16. Reported TEAEs and exposure-adjusted incidence rates organised by selected system organ classifications and preferred terms experienced by ≥10% of patients in either treatment group in RAPID (reproduced from CS, Table 25 [pg. 120])

	Respreeza[a] (N=93)		**Placebo[a] (N=87)**	
	Number of patients (%)	**Number of events**	**Number of patients (%)**	**Number of events**
Any event	92 (98.9)	1,298	86 (98.9)	1,068 (7.23)
Infections and infestations	**77 (83%)**	**334 (1.95)**	**76 (87%)**	**369 (2.50)**
Bronchitis	12 (13%)	26 (0.15)	11 (13%)	16 (0.11)
Influenza	14 (15%)	14 (0.08)	10 (11%)	12 (0.08)
Nasopharyngitis	30 (32%)	53 (0.31)	26 (30%)	58 (0.39)
Pneumonia	11 (12%)	15 (0.09)	12 (14%)	25 (0.17)
Sinusitis	12 (13%)	17 (0.10)	10 (11%)	18 (0.12)
Upper respiratory	14 (15%)	26 (0.15)	14 (16%)	25 (0.17)
Lower respiratory	18 (19%)	88 (0.51)	17 (20%)	72 (0.49)
Viral*	3 (3%)	5 (0.03)	4 (5%)	6 (0.04)
Respiratory disorders	**63 (68%)**	**249 (1.45)**	**49 (56%)**	**127 (0.86)**
Chronic obstructive pulmonary disease	30 (32%)	107 (0.63)	20 (23%)	53 (0.36)
Cough	20 (22%)	31 (0.18)	7 (8%)	7 (0.05)
Dyspnoea	17 (18%)	29 (0.17)	10 (11%)	11 (0.07)
Oropharyngeal pain	22 (24%)	36 (0.21)	10 (11%)	13 (0.09)
Gastrointestinal disorders	**46 (49%)**	**104 (0.61)**	**47 (54%)**	**92 (0.62)**
Nausea	15 (16%)	23 (0.13)	8 (9%)	11 (0.07)
General and administration site disorders	**48 (52%)**	**144 (0.84)**	**42 (48%)**	**101 (0.68)**
Condition aggravated	20 (22%)	62 (0.36)	14 (16%)	41 (0.28)
Fatigue	8 (9%)	14 (0.08)	10 (11%)	12 (0.08)
Pyrexia	13 (14%)	15 (0.09)	6 (7%)	8 (0.05)
Nervous system	**46 (49%)**	**194 (1.13)**	**43 (49%)**	**134 (0.91)**
Headache	37 (40%)	98 (0.57)	33 (38%)	105 (0.71)
Musculoskeletal and connective tissue disorders	**35 (38%)**	**68 (0.40)**	**37 (43%)**	**75 (0.51)**
Back pain	12 (13%)	12 (0.07)	10 (11%)	(0.08)

[a] Data are n (%) or n (annualised incidence rate).

Abbreviations: CS, company submission; pg, page; TEAE, treatment-emergent adverse event.

Table 17. TEAEs reported ≥10%of patients and exposure-adjusted incidence rates by MedDRA preferred term (safety population) in RAPID-OLE (reproduced from CS, Table 6 [pg. 121])

	Early start[a] (N=76)		Delayed start[a] (N=64)	
	Number of patients (%)	**Number of events**	**Number of patients (%)**	**Number of events**
Any event	**76 (100%)**	**773 (5.28%)**	**62 (96.9%)**	**620 (4.97%)**
Bronchitis	8 (10.5%)	15 (0.15)	4 (6.3%)	7 (0.06)
Influenza	6 (7.9%)	7 (0.05)	10 (15.6%)	11 (0.09)
Nasopharyngitis	24 (31.6%)	34 (0.23)	16 (25%)	38 (0.30)
Pneumonia	8 (10.5%)	13 (0.09)	7 (10.9%)	10 (0.08)
Oral Candidiasis	5 (6.6%)	16 (0.11)	8 (12.5%)	21 (0.17)
Upper respiratory	11 (14.5%)	23 (0.16)	6 (9.4%)	15 (0.12)
Lower respiratory	11 (14.5%)	66 (0.45)	6 (14.1%)	48 (0.38)
Chronic obstructive pulmonary disease	35 (46.1%)	105 (0.72)	21 (32.8%)	75 (0.60)
Cough	8 (10.5%)	16 (0.11)	7 (10.9%)	11 (0.09)
Dyspnoea	13 (17.1%)	36 (0.25)	5 (7.8%)	5 (0.04)
Oropharyngeal pain	12 (15.8%)	13 (0.09)	7 (10.9%)	8 (0.06)
Nausea	8 (10.5%)	9 (0.06)	3 (4.7%)	3 (0.02)
Diarrhoea	9 (11.8%)	9 (0.06)	3 (4.7%)	3 (0.02)
Oedema peripheral	5 (6.6%)	6 (0.04)	7 (10.9%)	7 (0.06)
Condition aggravated	16 (21.1%)	38 (0.26)	11 (17.2%)	37 (0.30)
Headache	15 (19.7%)	25 (0.17)	13 (20.3%)	33 (0.26)
Back pain	9 (11.8%)	12 (0.07)	10 (11%)	(0.08)

[a] Data are n (%) or n (annualised incidence rate).

Abbreviations: CS, company submission; OLE, open label extension; pg, page; TEAE, treatment-emergent adverse event.

4.4 Critique of the pairwise meta-analysis

As initially discussed in Section 4.1.5, rather than carry out their own meta-analyses, the company presents effect estimates from a systematic review by Edgar *et al*. 2017[44] that synthesised data from three RCTs, including the RAPID RCT, for various clinical outcomes. A second systematic review is available that presents meta-analyses of the same three RCTs for some clinical outcomes.[55] The ERG considers the company's approach to be appropriate. As reported by the company, one systematic review evaluated any treatment used for severe A1PI deficiency and additionally included cases series and uncontrolled studies, but with a focus on randomised controlled trials (RCTs),[44] whereas the second review limited study type to RCTs of A1PI augmentation therapy compared with placebo or no treatment.[55] Three RCTs were retrieved by each systematic review,[29, 42, 56] and the authors of both reviews carried out meta-analyses.

Given that the systematic reviews are published in peer-reviewed journals, the ERG has not carried out a detailed critique of the methods of the reviews.[44, 55] The reviews reported similar analytical methods, with both reviews specifying that a fixed effects model would be used, unless heterogeneity was identified, in which case, a random effects model would be preferred. The ERG presents results from both reviews, and highlights any differences between the reviews, in terms of studies included in the meta-analyses.

A description of the RCTs identified by the reviews is available in Table 69 (Appendix 10.1), together with an overview of the quality assessment for the studies as critiqued by the authors of the review by Edgar *et al*. 2017.[44] In brief, the inclusion criteria for the two RCTs additional to RAPID – Dirksen 1999[56] and Dirksen 2009[29] – were comparable to RAPID based on disease characteristics of A1PI deficiency, that is, either moderate to severe emphysema, or A1PI serum concentration <11 μM, or FEV1 per cent predicted lower than normal (FEV1% ≥25% and ≤80% in Dirksen 2009).[29] The ERG considers the baseline characteristics of the populations of the three studies to be comparable.

The ERG notes that Prolastin® was the A1PI assessed in Dirksen 1999[56] and Dirksen 2009[29], rather than Respreeza. As touched on in Section 4.2, data from a biochemical comparison of four A1PIs given intravenously support the company's proposal that A1PIs can be considered equivalent to each other.[65] Similar mean specific activities across the four formulations (range from 0.638 to 0.862) were identified, with Respreeza having the highest value:[65] specific activity calculated as mg of active A1PI divided by mg of total protein determined by Bradford assay. The authors of the report noted differences across the products in purity and protein structure, with Respreeza identified as being the highest purity formulation.[65] The four A1PIs compared were Alfalastin®, Prolastin®, Respreeza, and Trypsone®. The ERG notes that the study was carried out by employees of CSL Behring.

Additionally, whereas the Dirksen 2009[29] and RAPID[42] RCTs implemented a standard dose of A1PI of 60 mg/kg infused weekly, dose of A1PI in the Dirksen 1999[56] study was 250 mg/kg every 4 weeks, which may have resulted in a tailing off of A1PI serum levels towards the end of the treatment cycle. The comparator across all three RCTs was placebo, with human albumin forming the placebo in Dirksen 1999[56] and Dirksen 2009[29]. In terms of outcomes, the ERG highlights any differences in assessment across the studies in the relevant section below.

4.4.1 Change in CT lung density

Meta-analyses of results from three RCTs indicate that A1PI augmentation therapy is associated with a statistically significantly lower decline in mean annual CT lung density than placebo, with two systematic reviews reporting similar mean differences between A1PI and placebo (Table 18):

- Edgar 2017: mean difference 0.79 g/L (95% CI: 0.29 g/L to 1.29 g/L; p=0.02);[44]

- Gotzsche 2016: mean difference 0.86 g/L (95% CI: 0.31 g/L to 1.42 g/L; p=0.002).[55]

As noted by the company, deterioration in CT lung density was assessed as an experimental outcome in Dirksen 1999[56] and Dirksen 2009,[29] whereas it was the primary outcome in RAPID. Differences across the three RCTs were noted in capture of CT lung density. In Dirksen 1999,[56] CT lung density was recorded at 75% of the TLC inspiration state, whereas, in RAPID and Dirksen 2009,[29] CT lung density was captured at 100% TLC. Both meta-analyses use the CT lung density recorded at TLC for RAPID: primary outcome of RAPID was based on combination of TLC plus FRC. There was also disparity in the slice thickness of the CT scan, which was not reported for RAPID, but was 1 mm[56] and 8 mm[29] in the two remaining RCTs.

Reconstruction algorithms implemented also varied across the studies. Dirksen 1999[56] and RAPID applied regression analysis to analyse CT lung density, whereas Dirksen 2009[29] implemented four different analytical techniques to adjust for variation in inspiratory levels between scans. All four methods generated effect estimates in favour of A1PI, with three results not reaching statistical significance.[29] The meta-analysis carried out by Edgar 2017[44] incorporated change in CT lung density generated by the method most similar to that in the two other trials, whereas the meta-analysis by Gotzsche 2016[55] used the mean of the four estimates.

Despite the methodological differences highlighted by the ERG, I^2 values reported for the meta-analyses indicate the absence of statistical heterogeneity, with I^2 of 0% reported by both reviews (Table 18).

The ERG considers it important to reiterate that, as raised by the authors of the Edgar 2017[44] review, that a minimal clinically important difference for deterioration in CT lung density has yet to be established, and having such a value would aid in interpretation of the usefulness of CT lung density as a surrogate measure of emphysema.

Table 18. Summary of meta-analyses of mean annual change in lung density as reported in Gotzsche 2016[55] and Edgar 2017[44] (forest plot available in CS, Figure 20 [pg. 123])

Study	**A1PI**			**Placebo**			**Weight (%)**	**Mean difference (95% CI)**
	Mean	SD	N	Mean	SD	N		
Edgar 2017[44] (Fixed effect model)								
Dirksen 1999	–1.5	2.17	28	–2.57	2.17	28	19.4	1.07 (–0.07 to 2.21)
Dirksen 2009	–1.41	2.5	35	–2.1	1.72	32	24.1	0.69 (–0.33 to 1.71)
Chapman 2015	–1.45	2.21	92	–2.19	2.3	85	56.5	0.74 (0.07 to 1.41)
Total (95% CI)			**155**			**145**	**100**	**0.79 (0.29 to 1.29)[a]**

Gotzsche 2016[55] (Fixed effect model)								
Dirksen 1999	–1.5	2.17	28	–2.57	2.17	28	23.8	1.07 (–0.07 to 2.21)
Dirksen 2009	–2.87	4.91	35	–4.24	3.87	32	6.9	1.37 (–0.74 to 3.48)
Chapman 2015	–1.45	2.1	83	–2.19	2.05	67	69.2	0.74 (0.07 to 1.41)
Total (95% CI)			**146**			**127**	**100**	**0.86 (0.31 to 1.42)[b]**

[a] Heterogeneity: Chi^2=0.29, df=2, (p=0.86), I^2=0%. Test for overall effect: Z=3.10 (p=0.002)

[b] Heterogeneity: Chi^2=0.48, df=2, (p=0.79), I^2=0%. Test for overall effect: Z=3.05 (p=0.0023)

Abbreviations: CI, confidence interval; CS, company submission; CT, computed tomography; pg, page; SD, standard deviation.

4.4.2 FEV1

Meta-analyses indicate no statistically significant difference between A1PI and placebo in rate of decline of FEV1, either as FEV1 or FEV1 per cent predicted (Table 19):

- Edgar 2017: mean difference in FEV1 per cent predicted –0.56% (95% CI –1.41% to 0.29%; p=0.20);[44]
- Gotzsche 2016: standardised mean difference –0.19 (95% CI –0.42 to 0.05; p=0.012).[55]

The ERG notes that the direction of effect in both meta-analyses favours placebo.

As highlighted earlier, FEV1 was measured post-bronchodilator at baseline and follow-up assessments in both Dirksen 1999[56] and Dirksen 2009[29], but not in RAPID, in which use of bronchodilator was optional, and was required if optimal therapy for the person's emphysema was interrupted for any reason:[42]

Table 19. Summary of meta-analyses of mean change in FEV1 or FEV1 per cent predicted as reported in Gotzsche 2016[55] and Edgar 2017[44] (forest plot available in CS, Figure 21 [pg. 123])

Study	**A1PI**			**Placebo**			**Weight (%)**	**Mean difference (95% CI)**
	Mean	SD	N	Mean	SD	N		
Edgar 2017[44] (Fixed effect model): change in FEV1 per cent predicted								
Dirksen 1999	–2.11	1.85	28	–1.47	1.85	28	76.6	–0.64 (–1.61 to 0.33)
Chapman 2015	–1.55	5.35	93	–1.25	6.55	87	23.4	–0.30 (–2.05 to 1.45)
Total (95% CI)			**121**			**115**	**100**	**–0.56 (–1.41 to 0.29)[a]**
Gotzsche 2016[55] (Fixed effect model): change in FEV1 or FEV1 per cent predicted								
								Standardised mean difference (95% CI)
Dirksen 1999	–78.9	63.5	28	–59.1	63	28	19.8	–0.31 (–0.84 to 0.22)
Dirksen 2009	–43	60.1	38	–23	60.9	39	27.2	–0.33 (–0.78 to 0.12)
Chapman 2015	–3.1	10.7	83	–2.3	13.1	67	53.0	–0.07 (–0.39 to 0.25)
Total (95% CI)			**149**			**134**	**100**	**–0.19 (–0.42 to 0.05)[b]**

[a] Heterogeneity: Chi^2=0.11, df=1, (p=0.74), I^2=0%. Test for overall effect: Z=1.30 (p=0.20).

[b] Heterogeneity: Chi^2=1.11, df=2, (p=0.57), I^2=0%. Test for overall effect: Z=1.55 (p=0.12).

Abbreviations: CI, confidence interval; CS, company submission; FEV1, forced expiratory volume in 1 second; pg, page; SD, standard deviation.

4.4.2.1 Effect of A1PI based on baseline FEV1 per cent predicted

The company's economic model incorporates clinical effectiveness estimate for Respreeza based on CT lung density and various categories of FEV1 per cent predicted (Section 5.4.5). Effect estimates for A1PI augmentation by baseline FEV1 per cent predicted are derived from a systematic review carried out by Chapman *et al*. 2009.[45] The objective of the review was to assess whether A1PI therapy slows the deterioration in FEV1 in people with A1PI deficiency. Again, as the review has been subject to peer review, the ERG has not critiqued the methods in detail. In summary, the review included RCTs, observational controlled studies, and studies of a single-cohort pre-post design. Due to the expected heterogeneity across studies, meta-analysis was carried out using a random effects model.

The review presented results from a meta-analysis of five studies, one of which was the Dirksen 1999 RCT,[56] three were non-randomised observational studies[66-68] and one assessed FEV1 before and after augmentation.[69] Three of the studies evaluated A1PI at a dose of 60 mg/kg weekly, and the fourth study evaluated A1PI at 250 mg/kg given every 4 weeks: insufficient data are available on the fifth study for evaluation. Description and quality assessment of the studies included in the Chapman 2009[45] review are available in Table 69 (Appendix 10.1).

The ERG notes that the largest data set informing the analysis – data from the AATD registry[66] – included people who received A1PI on a part-time basis, which was defined as those who began therapy >3 months after enrolment in the registry or who discontinued therapy for >1 month after enrolment. Additionally, data are reported for subgroups by baseline FEV1 per cent categories that do not match those presented in Chapman 2009: the publication of results from the AATD registry presents data for FEV1 per cent predicted categories of <35%, 35 to 49%, 50 to 79%, and >80%.[66] Whether adjustments have been applied to data from the AATD registry to incorporate the results into the meta-analysis in Chapman 2009[45] is unclear from the details available in the full publication. Considering the quality of the studies, the ERG notes that two of the five studies are rated as unclear risk of bias,[56, 69] two are judged to be at high risk of bias,[66, 68] and the fifth study was reported only as a conference abstract.[67] Given the ERG's reservations about how data from the AATD registry have been incorporated into the meta-analysis, that only one of the included studies is an RCT and two of the studies have been deemed to be at high risk of bias, the ERG advises that results of the meta-analysis are interpreted with caution.

Meta-analysis of the five studies found that A1PI was associated with a statistically significant decrease in the decline in FEV1 by 23% (absolute difference 13.4 ml/year: 95% CI; 1.5 ml/year to 25.3 ml/year; Table 20) in all people receiving augmentation therapy.[45, 67] The authors also commented that the overall

effect predominantly reflected results in the subgroup of people with baseline FEV1 30 to 65% of predicted, for whom augmentation was associated with a 26% reduction in rate of FEV1 decline (absolute difference 17.9 ml/year: 95% CI; 9.6 ml/year to 26.1 ml/year).[45] Although subgroup analyses in people with baseline FEV1 percent of predicted <30% or >65% indicated an effect estimate favouring A1PI, the difference did not reach statistical significance (Table 20).

Table 20. Summary of meta-analyses of mean change in FEV1 by baseline FEV1 per cent predicted as reported in Chapman 2009[45]

Study	A1PI			Placebo			Weight (%)	Mean difference (95% CI)
	Mean	SE	N	Mean	SE	N		
<30% FEV1 predicted								
Seersholm 1997	–24.2	2.7	75	–30.9	7.0	27	32.0	6.7 (–8.0 to 21.4)
AATD 1998	–43.9	3.4	349	–46.5	6.2	99	34.0	2.6 (–11.3 to 16.5)
Wencker 2001	–19.0	3.65	25	–15.3	7.7	25	24.7	–3.7 (–22.8 to 15.4)
Chapman 2005	–57.8	27.1	5	–28.7	8.4	29	9.3	–29.1 (–79.6 to 21.4)
Total (95% CI)	**–30.6**	**12.0**	**454**	**–30.9**	**11.3**	**180**	**100**	**1.8 (–7.0 to 10.5)**
30% to 65% predicted FEV1								
Seersholm 1997	–61.8	2.4	112	–82.8	6.5	58	28.4	21.0 (7.5 to 34.5)
AATD 1998	–69.9	4.1	211	–83.5	7.6	66	22.6	13.6 (–3.3 to 30.5)
Wencker 2001	–37.8	3.2	60	–49.3	5.6	60	31.1	11.6 (–0.8 to 24.0)
Chapman 2005	–23.3	13.3	15	–57.0	7.5	79	17.9	33.8 (12.2 to 55.3)
Total (95% CI)	**–50.8**	**15.9**	**398**	**–67.9**	**17.0**	**263**	**100**	**17.9 (9.6 to 26.1)**
> 65% predicted FEV1								
Seersholm 1997	–162.0	8.7	11	–140.0	24.0	12	27.7	–22.0 (–72.0 to 28.0)
AATD 1998	–63.0	12.8	21	–39.2	5.6	152	50.4	–23.8 (–51.2 to 3.6)
Wencker 2001	–48.9	16.6	11	–122.5	32.7	11	21.9	73.6 (10.4 to 136.8)
Total (95% CI)	**–92.1**	**67.3**	**43**	**–97.2**	**63.5**	**175**	**100**	**3.5 (–49.0 to 55.9)**
All FEV1 per cent predicted								
Seersholm 1997	–53.0	2.7	198	–74.5	6.1	97	22.0	21.5 (8.5 to 34.5)
AATD 1998	–51.8	2.7	581	–56.0	3.8	317	31.2	4.2 (–4.9 to 13.3)
Dirksen 1999	–78.9	12.0	28	–59.1	11.9	28	8.6	–19.8 (–52.9 to 13.3)
Wencker 2001	–34.3	3.0	96	–49.2	6.2	96	23.3	14.9 (2.6 to 27.2)
Chapman 2005	–26.7	12.1	21	–59.0	7.0	143	15.0	32.4 (13.1 to 51.7)
Total (95% CI)	**–48.0**	**10.7**	**924**	**–59.4**	**7.3**	**681**	**100**	**13.4 (1.5 to 25.3)**

Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in 1 second; SE, standard error.

As data from the Chapman 2009 review inform the economic model, as part of the clarification process, the ERG asked the company to update the meta-analysis to include results from RAPID.[42] In their clarification response (Question A2), the company gave a detailed account of the methods followed to

identify the relevant studies, reasons for exclusion of studies, and methods followed to update the meta-analysis. The ERG considers the methods followed by the company to be appropriate.

In brief, the company's appraisal of previously retrieved records identified seven potentially relevant studies. As noted by the company, the outcome assessed in Chapman 2009 is change in FEV1 slope (ml/year). Of the seven potentially relevant studies, only three, including RAPID, reported data on FEV1 that could be incorporated into the meta-analysis.[42, 70, 71] The two studies additional to RAPID are both observational studies. One study[71] reported measurements of FEV1 for treated and untreated groups by baseline FEV1 categories mirroring those in Chapman 2009. The second study was of a before and after design and the FEV1 % predicted at baseline was not reported.[70] Given that people were diagnosed with severe A1PI deficiency and had been receiving continuous augmentation therapy for a minimum of 18 months before being included in the study, the company assumed that the FEV1 of 30% to 65% predicted was the most appropriate category. The ERG agrees with the company's assumption.

To update the meta-analysis and re-create the analysis as carried out in Chapman 2009, the company implemented a continuous data analysis with a random effects model. The company noted that their meta-analysis, although containing the correct slope differences from extracted data, allocated different weights to the studies from the Chapman 2009 analyses. The company attributed the differences in weighting, in part, to Chapman 2009 using individual patient data rather than extraction of the mean difference of the FEV1 slope for each study as was done by the company.

Additional details and quality assessments for the two observational studies included in the company's meta-analysis are available in Table 69 (Appendix 10.1).

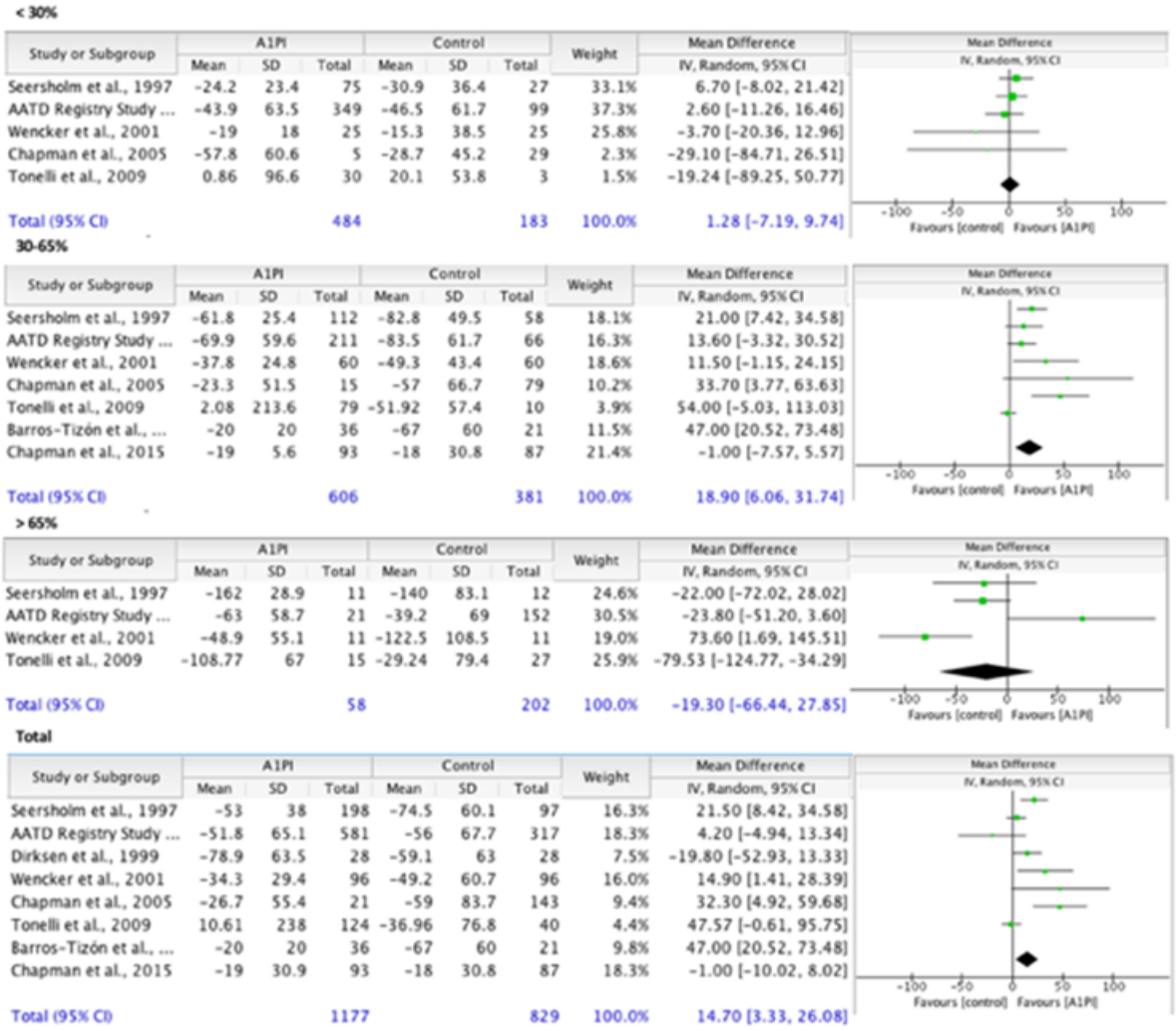
With the exception of FEV1 >65% predicted, incorporation of the three additional studies into the data set presented in Chapman 2009 generated similar effect estimates to those reported in the original analysis (Figure 7). Effect estimate in the overall population favoured A1PI augmentation and remained statistically significant, as did the result for the subgroup of those with baseline FEV1 of 30% to 65% predicted (Figure 7):

- FEV1 <30% predicted: mean difference 1.28 ml/year (95% CI: –7.19 ml/year to 9.74 ml/year);
- FEV1 30% to 65% predicted: mean difference 18.90 ml/year (95% CI: 6.06 ml/year to 31.74 ml/year);
- FEV1 >65% predicted: mean difference –19.30 ml/year (95% CI: –66.44 ml/year to 27.85 ml/year);

- All FEV1 per cent predicted: mean difference 14.70 ml/year (95% CI: 3.33 ml/year to 26.08 ml/year).

As noted by the company, the updated meta-analysis shows a change in direction of effect to favour placebo in FEV1 decline in the subgroup of people with FEV1 >65% predicted. In their response, the company highlights that the results from one study[71] are influencing the result, with the study reporting an increase in FEV1. The authors of the study comment that, "*It is unclear why we found an unusual increase in FEV1 instead of a reduction in the FEV1 decline as reported in previous studies. Possible explanations include anti-inflammatory effects of treatment with favorable effects over potential reversible processes such us bronchoconstriction and/or the use of different spirometry equipment*". Specifically, for results related to FEV1 >65% predicted, the authors of the study commented, "*augmented patients with an initial FEV1 >65% of predicted had a significant larger FEV1 decline than nonaugmented patients, probably due to selection bias, as it is more likely to provide augmentation treatment to patients who have FEV1 >65% and an accelerated FEV1 decline. Another possible explanation is based on the unusually low rate of FEV1 decline in patients with FEV1 >65% who did not receive augmentation therapy (Δ FEV1−29.24 mL/year)*".

Figure 7. Forest plot of the company's updated meta-analysis (reproduced from clarification response, Question A2)



4.4.3 Carbon monoxide diffusion

Meta-analyses indicate no statistically significant difference between A1PI and placebo in D_{LCO} (Table 21):

- Edgar 2017: standardised mean difference –0.11 (95% CI: –0.33 to 0.11; p=0.34);[44]
- Gotzsche 2016: standardised mean difference –0.11 (95% CI: –0.35 to 0.12; p=0.34).[55]

The ERG notes that the direction of effect in both meta-analyses favours placebo.

Table 21. Summary of meta-analyses of diffusion capacity for carbon monoxide as reported in Gotzsche 2016[55] and Edgar 2017[44] (forest plot available in CS, Figure 22 [pg. 123])

Study	A1PI			Placebo			Weight (%)	Standardised mean difference (95% CI)
	Mean	SD	N	Mean	SD	N		
Edgar 2017[44] (Fixed effect model)								
Dirksen 1999	–0.19	0.25	28	–0.16	0.25	28	17.9	–0.12 (–0.64 to 0.41)
Dirksen 2009	–0.46	0.44	38	–0.34	0.46	39	24.5	–0.26 (–0.71 to 0.18)
Chapman 2015	–2.2	18.2	93	–1.5	19.5	87	57.6	–0.04 (–0.33 to 0.26)
Total (95% CI)			**159**			**154**	**100**	**–0.11 (–0.33 to 0.11)[a]**
Gotzsche 2016[55] (Fixed effect model)								
Dirksen 1999	–0.19	0.25	28	–0.16	0.25	28	19.9	–0.12 (–0.64 to 0.41)
Dirksen 2009	–0.46	0.44	38	–0.34	0.46	39	27.2	–0.26 (–0.71 to 0.18)
Chapman 2015	–2.2	18.2	83	–1.5	19.5	67	52.9	–0.04 (–0.36 to 0.28)
Total (95% CI)			**149**			**134**	**100**	**–0.11 (–0.35 to 0.12)[b]**

[a] Heterogeneity: Chi^2=0.69, df=2, (p=0.71), I^2=0%. Test for overall effect: Z=0.95 (p=0.34).

[b] Heterogeneity: Chi^2=0.65, df=2, (p=0.72), I^2=0%. Test for overall effect: Z=0.96 (p=0.34).

Abbreviations: CI, confidence interval; CS, company submission; pg, page; SD, standard deviation.

4.4.4 Pulmonary exacerbation

Meta-analysis presented in Edgar 2017[44] indicates that A1PI therapy is associated with a statistically significantly higher risk of annual pulmonary exacerbation compared with placebo (mean difference 0.29: 95% CI; 0.04 to 0.54; p=0.02; Table 22). The ERG notes that the difference is statistically significant in favour of placebo both RCTs.

Table 22. Summary of meta-analyses of annual patient-reported exacerbation episodes as reported in Edgar 2017[44] (forest plot available in CS, Figure 23 [pg. 123])

Study	A1PI			Placebo			Weight (%)	Mean difference (95% CI)
	Mean	SD	N	Mean	SD	N		
Edgar 2017[44] (Fixed effect model)								
Dirksen 2009	2.55	2.14	38	2.19	1.33	39	9.9	0.36 (0.44 to 1.16)
Chapman 2015	1.7	0.92	93	1.42	0.89	87	90.1	0.28 (0.02 to 0.54)
Total (95% CI)			**131**			**126**	**100**	**0.29 (0.04 to 0.54)[a]**

[a] Heterogeneity: Chi^2=0.03, df=1, (p=0.85), I^2=0%. Test for overall effect: Z=2.25 (p=0.02).

Abbreviations: CI, confidence interval; CS, company submission; CT, computed tomography; pg, page; SD, standard deviation.

4.4.5 Health status

Meta-analysis presented in Edgar 2017[44] indicate no statistically significant difference between A1PI therapy and placebo in improvement in health status as assessed by the SGRQ (mean difference –0.83: 95% CI; –3.55 to 1.89; p=0.55; Table 23).

Table 23. Summary of meta-analyses of health status as reported in Edgar 2017[44] (forest plot available in CS, Figure 24 [pg. 123])

Study	A1PI			Placebo			Weight (%)	Mean difference (95% CI)
	Mean	SD	N	Mean	SD	N		
Edgar 2017[44] (Fixed effect model)								
Dirksen 2009	1.48	10.33	37	2.37	10.24	37	33.6	–0.89 (–5.58 to 3.80)
Chapman 2015	1.4	11.1	93	2.2	11.7	87	66.4	–0.80 (–4.14 to 2.54)
Total (95% CI)			**130**			**124**	**100**	**–0.83 (–3.55 to 1.89)[a]**

[a] Heterogeneity: Chi^2=0.00, df=1, (p=0.98), I^2=0%. Test for overall effect: Z=0.60 (p=0.55).
Abbreviations: CI, confidence interval; CS, company submission; pg, page; SD, standard deviation.

4.5 Conclusions of the clinical effectiveness section

The clinical effectiveness section in the CS was based on a systematic review of any intervention used in the treatment of A1PI deficiency. The ERG considers that the company is likely to have identified all clinical evidence on the use of Respreeza and other intravenous A1PIs as augmentation therapy in the treatment of emphysema related to severe A1PI deficiency, and the submitted evidence largely reflects the decision problem outlined in the final scope.

Enrolling 180 people, RAPID represents the largest RCT to date evaluating the clinical effectiveness of augmentation with intravenous A1PI, specifically Respreeza, in the management of emphysema secondary to severe A1PI deficiency: 97 and 83 people allocated to Respreeza and placebo, respectively. After 2 years of follow-up, all patients located outside the USA entered an open-label 2-year extension phase, RAPID-OLE, during which everyone received Respreeza.

The primary measure of clinical effectiveness in RAPID was annual change in lung density as measured by CT, with the value adjusted to account for lung volume. Respreeza was associated with a lower rate of annual decline in CT lung density (adjusted PD15 for combined TLC and FRC) compared with placebo at 2 years of follow-up, but the difference did not reach statistical significance. However, the difference between Respreeza and placebo in decline in CT lung density was statistically significant for the TLC inspiration state, and, again, favoured Respreeza:

- TLC plus FRC: mean difference of 0.62 g/L per year (95% CI: –0.02 g/L to 1.26 g/L; p=0.06);
- TLC alone: mean difference of 0.74 g/L (95% CI: 0.06 g/L to 1.42 g/L; p=0.03);

- FRC alone: mean difference 0.48 g/L (95% CI: –0.22 g/L to 1.18 g/L; p=0.18).

Meta-analyses of results from three RCTs, one of which was RAPID, evaluating intravenous A1PI augmentation therapy in severe A1PI deficiency support findings from RAPID in terms of effect on deterioration of CT lung density. Two systematic reviews analysing the same three RCTs reported statistically significant differences between A1PI and placebo in decline in CT lung density at the TLC inspiration state, with results favouring A1PI treatment:

- Edgar 2017: mean difference 0.79 g/L (95% CI: 0.29 g/L to 1.29 g/L; p=0.02);
- Gotzsche 2016: mean difference 0.86 g/L (95% CI: 0.31 g/L to 1.42 g/L; p=0.002).

In the longer term, results from RAPID-OLE indicate that the effect of Respreeza in reducing rate of lung density decline is sustained. Those initially receiving Respreeza, referred to as the early-start group, had a similar level of annual decline in CT lung density (TLC only) in the 2 years follow-up of RAPID-OLE (1.51 g/L [Standard error {SE} 0.25] for day 1 to month 24 versus 1.63 [SE 0.27] in months 24 to 48). By contrast, those who switched to Respreeza from placebo, referred to as the delayed start group, had a substantially lower rate of annual decline in the 2 years of active treatment compared with the 2 years prior to start of treatment (2.26 g/L [SE 0.27] for day 1 to month 24 versus 1.26 [SE 0.29] in months 24 to 48).

Various secondary outcomes were assessed in RAPID. The key secondary outcomes were deemed to be those that would help explain the clinical relevance of the primary objective of change in lung density as measured by CT scan:

- change in exercise capacity assessed by ISWT;
- change in symptoms score assessed by the SGRQ;
- risk of pulmonary exacerbation assessed by the annual rate of exacerbations.

Other secondary outcomes assessed included the key spirometry variables of FEV1 and gas transfer.

No statistically significant differences were reported between Respreeza and placebo for the identified secondary outcomes, with the direction of effect favouring Respreeza in some outcomes. However, for ISWT, FEV1, diffusion capacity of the lung for carbon monoxide (D_{LCO}) and, unexpectedly, rate of pulmonary exacerbation, the direction of effect favoured placebo:

Syntheses of data from three RCTs, including RAPID, generated similar results to those from RAPID, with meta-analyses reported by Edgar 2017 and Gotzsche 2016 indicating no statistically significant

differences between Respreeza and placebo for change in FEV1, D_{LCO}, and health status assessed by SGRQ. For FEV1 and D_{LCO}, direction of effect favoured placebo. By contrast, for health status, direction of effect favoured Respreeza. The ERG notes that a meta-analysis presented in one systematic review indicated a statistically significant difference between treatments in terms of annual patient-reported exacerbation episodes, with Respreeza associated with a significantly higher rate of exacerbation than placebo (2 RCTs, 257 people: mean difference: 0.29; 95% CI: 0.04 to 0.54).

Overall, the total number of adverse events reported in RAPID was higher in those receiving Respreeza compared with placebo (1,298 with Respreeza versus 1,068 with placebo). Most people (99%) forming the safety population experienced a treatment-emergent adverse event (TEAE). There were four deaths during the RAPID study (1 in the Respreeza group and 3 in the placebo group), and one additional death during RAPID-OLE. Based on preferred terms, the company noted that headache was the most common TEAE reported in RAPID.

COPD exacerbation was also captured as a TEAE. As part of the application to the EMA for marketing authorisation, the company submitted safety data from 6 studies, two of which were RAPID and RAPID-OLE. The EPAR for Respreeza reported that, during the first 6 months of treatment, exacerbation of COPD was recorded in 40 people from a total pool of 221 people having taken Respreeza (18.1%). By contrast, 11 out of 149 people taking placebo experienced an exacerbation of COPD (12.6%). The overall incidence rate for exacerbation of COPD was 0.59 and 0.36 events per patient year for Respreeza and placebo, respectively, and the odds of experiencing the event were statistically significantly higher with Respreeza (odds ratio 1.66; 95% CI: 1.24 to 2.23). The EPAR reported that the definition of COPD exacerbation and serious COPD exacerbation differed for the safety and the efficacy components of the submission. The EMA concluded that the number of COPD exacerbations was not lowered following treatment, and commented that, as COPD is an end stage of lung disease, the statistically significant higher rate of COPD exacerbation recorded for Respreeza was unexpected.

4.5.1 Clinical issues

Potential clinical issues and areas of uncertainty identified by the ERG are:

- The ERG notes that rate of deterioration in lung density or lung function pre-treatment are not available for RAPID, as RAPID did not include a "run in" period to establish that those potentially eligible for the trial were experiencing progressive decline in lung disease. Thus, it is not possible to categorise those randomised as no, slow or rapid decliners at baseline. The ERG considers those receiving placebo in RAPID and moving to Respreeza in RAPID-OLE could form a relevant group for analysis of effect of Respreeza based on initial categorisation of rate of CT lung density decline. However, the ERG emphasises that, at the time of writing,

the categorisation of no, slow and rapid decline are based on arbitrary thresholds that could be at risk of bias.

- Although inclusion criteria for RAPID are well-defined, the ERG has reservations about the lack of clearer definition of progressive lung disease, or eligibility criteria for treatment. Based on the eligibility criteria for RAPID, one of the ERG's clinical experts has fed back that everyone with emphysema secondary to A1PI deficiency will be eligible for treatment with Respreeza.

- At this time, no MCIDs have been established for CT lung density, FEV1 or gas transfer.

- There is currently no guidance for when it is appropriate to stop treatment with Respreeza. The company highlighted that, as the goal of treatment is to restore serum levels of A1PI to ≥11 μM, continuous treatment with Respreeza would be necessary. However, the ERG's clinical experts highlighted that, potentially, there could be people, for example, those whose CT lung density continues to deteriorate at the same rate or increases after treatment with Respreeza. Clinicians might want to consider stopping treatment for those who do not appear to be achieving a benefit from treatment.

- The primary outcome in RAPID of deterioration in lung density by CT is a surrogate outcome measure for progression of lung disease, as is change in FEV1. At this time, there is uncertainty around how changes in CT lung density correlate with spirometric measures, HRQoL and mortality. Thus, clinicians in England are likely to want to base decisions to treat people with Respreeza on CT densitometry, as was carried out in RAPID, as well as using CT lung density to monitor progression of emphysema.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and the *de novo* economic evaluation submitted by the company. Due to changes made to the company's model in reply to the clarification stage, the company provided an updated version of the Microsoft Excel®-based economic model. The focus of the ERG report is therefore on the second, updated, economic model.

5.2 Summary of the company's keys results

According to the company's updated base case analysis, the incremental cost-effectiveness ratio (ICER) for Respreeza and BSC, compared with BSC is £236,409 per QALY gained. The company's probabilistic sensitivity analysis ICER amounts to £181,879 per QALY gained. The discrepancy between the deterministic and probabilistic results is discussed in Section 5.5 of the ERG report.

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic literature review (SLR) to identify economic and quality of life evidence, in A1PI deficiency-related emphysema. As for cost and resource use evidence, the company searched the same sources identified for the economic evidence. The search was first run in April 2016 and updated in April 2018.

When conducting the SLR, the company searched the following electronic databases: MEDLINE, EMBASE, EMBASE Alert, the Cochrane Database of Systematic Reviews and the Centre for Reviews and Dissemination incorporating the: Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), and Health Technology Assessment Database (HTA). In addition to electronic databases, hand searches for grey literature in relevant conference websites, clinical trial registries and HTA agencies were conducted.

Search strategies for the original and updated searches are provided in Appendix 17.3.5 of the CS. In summary, search terms in MEDLINE, EMBASE and EMBASE Alert combined the population (patients with A1PI deficiency) with economic and health-related quality of life (HRQoL) outcome terms. Further searches were also conducted with the addition of brand names. Given the relatively low number of records included in the Cochrane and Centre for Reviews and Dissemination databases, only search terms related to the population were included. No date limits were imposed on either of the searches. The SLR identified 549 studies, following the removal of duplicates. Of those, 49 were evaluated for inclusion using the selection criteria provided in Table 30 of the CS. The company included a total of 17 studies. Two of those studies provided economic evidence in the UK (Gildea *et al*. 2003 and Sclar

et al. 2012), although neither compared against Respreeza specifically as an intervention.[72, 73] A summary of those two studies is provided in Section 11.2 of the CS.

The ERG considers the criteria reported in Table 30 of the CS to be too broad to have accurately identified all types of relevant evidence (economic, quality of life and cost and resource use), during the full-text screening stage. In response to the ERG's clarification question, the company explained that the criteria in Table 30 of the CS are an accurate representation of the search conducted, except that the search was not limited by intervention or country. Furthermore, many reasons for exclusion, provided by the company at clarification, were not clearly linked to the criteria reported in Table 30, suggesting that additional criteria were applied. For example, many economic and quality of life studies were excluded because they included a German population, although the company clarified that populations were not limited to the UK. As a result, the ERG is concerned the company excluded potentially relevant data.

With regards to the HRQoL search, a total of 13 studies were included. However, the company states that those studies did not provide adequate data that could be used to inform the economic model, either because utilities were not presented, could not be calculated, the data were not published by lung density decline rate, or because data were reported for the total population rather than by health state. Even so, the company identified additional studies to inform the economic model. The rationale for choosing those studies is provided in Section 5.4.9.1.

Finally, two studies (Stoller *et al.* 2000 and Mullins *et al.* 2001) reporting resource use data were identified.[74, 75] A summary of those two studies is provided in Section 12.13.2 of the CS. However, neither were deemed appropriate to inform the model as they were undertaken in the USA. Sources of resource and cost use data used to inform the model are provided in Section 5.4.10.

Overall, the ERG considers the searches (at 'first pass') to be inclusive and likely to identify all published studies for treatments of A1PI deficiency. However, the ERG is concerned that the inclusion criteria applied at full-text screening lacked transparency, and might have led the company to exclude important studies. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Finally, the ERG notes that the company provided an unpublished manuscript authored by Green *et al.*[76] The date of the study is unknown, and it is the basis of the published abstract by Green *et al.* 2014.[77] Hereafter, the ERG refers to the unpublished manuscript as Green *et al.*[76]

5.4 Overview and critique of company's economic evaluation

5.4.1 NICE reference case checklist

Table 24 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 3.

Table 24. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The final scope developed by NICE	Partially. Patients with an FEV1<30% were excluded from the trial population, and therefore not included as starting patients in the model (although patients can progress to this FEV1 category in the company's model). The ERG's clinical experts highlighted that there may be a rationale for initiating treatment with Respreeza in patients with a FEV1<30%, to salvage remaining the lung function of patients who are either ineligible, or on the waiting list for a lung transplant. One of the company's proposed eligibility criteria for treatment with Respreeza is a "rapidly declining lung function, measured by predicted values for FEV1 or gas transfer (D_{LCO}), or lung density decline". However, the marketing authorisation for Respreeza does not include any specifications on the rate of lung function decline for treatment initiation. Clinical expert opinion sought by the ERG confirmed that there would need to be demonstrable evidence of decline in patients' lung function for them to prescribe Respreeza, as they would not want to give it to patients with no decline in lung function. The experts added that, as the company is not proposing any definition of "rapid decline" in their eligibility criteria, if Respreeza is recommended, everyone with emphysema secondary to A1PI will be eligible for the treatment, as the former disease implies an inevitable decline in lung function. In reply to a clarification question, the company confirmed that there are no stopping rules for treatment with Respreeza. Nonetheless, the company applied a stopping rule in the model, as all patients progressing to an FEV1<30% state stop treatment.
Comparator(s)	Alternative therapies routinely used in the NHS	No. The NICE final scope sets the comparator as BSC (bronchodilators, corticosteroids, oxygen therapy, among others). Similar to the intervention arm, the company did not estimate any costs of BSC for the comparator arm. The company justifies not including BSC costs in either treatment arms as these would cancel out. The ERG disagrees with this statement because patients survive, and get lung transplants (hence stopping treatments) at different rates across treatment arms, therefore the BSC costs in both arms will not be exactly the same.
Perspective costs	NHS and Personal Social Services	Yes.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes.
Benefit valuation	Time-trade off or standard gamble	Yes.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	No. The company did not account for the correlation between lung density and lung function in their PSA, despite analysis of the endpoints in RAPID that showed higher CT lung density measurements correlated with FEV1 (Pearson correlation coefficient [PCC] 0.31, p <0.001), and similar findings in other recently published studies (Table 28 of the CS). Given the paramount uncertainty in the relationship between FEV1 and lung density decline outcomes in the company's model, the ERG considers that not correlating these parameters in PSA potentially renders the latter unreliable. This could explain the considerable difference between deterministic and probabilistic results.
Abbreviations used in the table: EQ-5D, EuroQoL 5-Dimension; HRQoL, health-related quality of life; HUI, health utility index; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SF-36, 36-Item Short Form Survey; TTO, time trade-off.		

5.4.2 Population

The population considered by the company comprises adults with severe alpha-1 proteinase inhibitor (A1PI) deficiency who have progressive lung disease. In the base case model, the baseline distribution of patients across FEV1 and lung density decline categories is based on RAPID data. In scenario analysis, the company used age and gender distribution reportedly from RAPID, however the mean age does not match that of RAPID patients. The company used different sources of clinical effectiveness data in the model, the majority of which were based on the UK registry dataset, ADAPT, looking at

patients with A1PI deficiency.[78] The ERG considers the modelled population broadly reflective of the NICE final scope, and with the exception of gender distribution, notes that the UK registry population and RAPID patients have similar baseline characteristics (54% males in RAPID, and 62% males in ADAPT).

Patients with an FEV1<30% were excluded from the trial population, and therefore not included as starting patients in the model (although patients can progress to this FEV1 category in the company's model). The ERG's clinical experts highlighted that there may be a rationale for initiating treatment with Respreeza in patients with a FEV1<30%, to salvage remaining lung function of patients who are either ineligible, or on the waiting list for a lung transplant. To note is that the US clinical practice guideline recommends treatment for patients whose FEV1 is less than, or equal to 65% of the predicted value,[34] and the Canadian Thoracic Society's recommendation is for patients with FEV1 between 30 and 80% of the predicted value.[35]

5.4.3 Interventions and comparators

The NICE final scope sets the intervention under consideration as human alpha 1-proteinase inhibitor in addition to BSC. In return, the company defined the intervention as Respreeza in addition to BSC; however, the company only included the cost of Respreeza in the model. This departs from the NICE scope, as it excludes BSC as a concomitant treatment to Respreeza.

The modelled intervention is Respreeza, formulated as 1,000 mg powder and indicated for intravenous infusion at a dose of 60 mg/kg once weekly. The company assumed that 75% of patients would receive treatment at home, with a nurse administering infusions, and 25% of patients would be treated at a clinic. The company's model assumes life-long treatment with Respreeza, which according to the ERG's clinical experts, is a likely scenario.

5.4.3.1 Treatment initiation and stopping rules for Respreeza

One of the company's proposed eligibility criteria for treatment with Respreeza is a, "*rapidly declining lung function, measured by predicted values for FEV1 or gas transfer (D_{LCO}), or lung density decline*". However, the marketing authorisation for Respreeza does not include any specifications on the rate of lung function decline for treatment initiation. Despite there being no clinically established definition of rapid lung function decline, the company has defined rapid decline as a deterioration in CT lung density of more than 2 g/L/year in their analysis of treatment effectiveness, within the economic model. Inconsistent with the former, the company did not apply their own "starting rule" in the economic model for the administration of Respreeza, as all patients in the intervention arm receive treatment, regardless of having no, slow, or, rapid baseline lung density decline.

Clinical expert opinion sought by the ERG confirmed that there would need to be demonstrable evidence of decline in patients' lung function for them to prescribe Respreeza, as they would not want to give it to patients with no decline in lung function. The experts added that, as the company is not proposing any definition of "rapid decline" in their eligibility criteria, if Respreeza is recommended, everyone with emphysema secondary to A1PI will be eligible for the treatment, as the former disease implies an inevitable decline in lung function. Furthermore, the EPAR expert panel recommend that the appropriate target population for Respreeza should have evidence of significant lung density decline.

Finally, the ERG notes that even though the company has defined rapid decline to measure treatment effectiveness, this was not based on a clinically defined threshold, and thus is an arbitrary categorisation of rate of decline. On the one hand, it would therefore, be inappropriate to suggest that the company matches its definition of rapid decline to a rule for initiating treatment with Respreeza. On the other hand, it is inconsistent that the company sets a threshold of rapid decline for assessing treatment effectiveness, but fails to do the same for treatment initiation.

In reply to a clarification question, the company confirmed that there are no stopping rules for treatment with Respreeza. Nonetheless, the company applied a stopping rule in the model, as all patients progressing to an FEV1<30% state stop treatment. This issue is further discussed in Section 5.4.10.

5.4.3.2 Best supportive care

The NICE final scope sets the comparator as BSC (bronchodilators, corticosteroids, oxygen therapy, among others). Similar to the intervention arm, the company did not estimate any costs of BSC for the comparator arm. The company justifies not including BSC costs in either treatment arms as these would cancel out. The ERG disagrees with this statement because patients survive, and get lung transplants (hence stopping treatments) at different rates across treatment arms, therefore the BSC costs in both arms will not be exactly the same. The ERG included the costs of BSC in both treatment arms and presents the results in Section 5.4.10.

5.4.4 Modelling approach and model structure

As a result of the clarification stage, the company updated the structure of their economic model, which is presented in Figure 8. The company developed a *de novo,* state transition, semi-Markov model in Microsoft Excel®. The model includes twelve health states: three FEV1 states, comprising of FEV1≥50%; 30%≤ FEV1%<50%; and FEV1<30%, each combined with three categories for lung density function decline: no decline (ND); slow decline (SD); and rapid decline (RD). The company defined lung density function decline as:

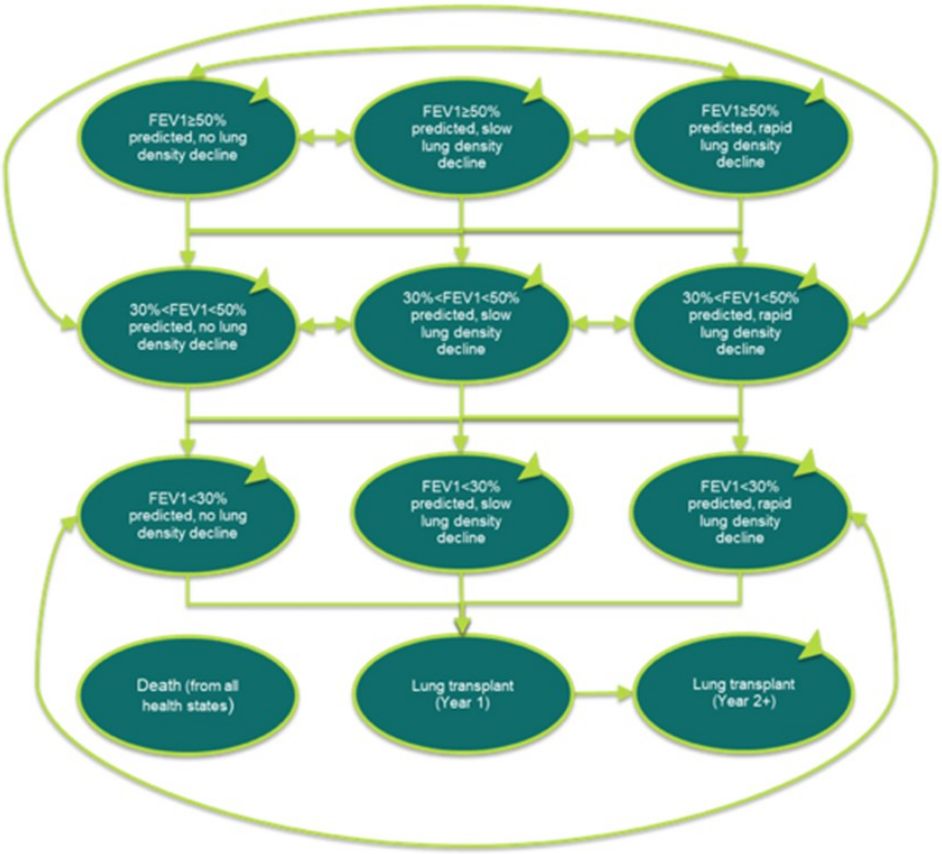
- No lung density decline: decline of <0 g/L/year in lung density measured by CT scan;

- Slow lung density decline: decline of 0-2 g/L/year in lung density measured by CT scan;
- Rapid lung density decline: decline of >2 g/L/year in lung density measured by CT scan.

The model also includes two lung transplant states, one of which is a tunnel state. Patients receive life-long treatment with Respreeza until they move to the FEV1<30% states, were they stop treatment. The cohort is allocated to the FEV1≥50% (ND, SD and RD) and to the 30%≤ FEV1%<50% (ND, SD and RD) states at the beginning of the model. Including lung density decline in all health states of the model implied that patients' baseline rate of decline had to be estimated. In order to estimate this, the company used the first year of data from the placebo arm of the RAPID trial, to inform patients' baseline lung density decline in the Respreeza and in the BSC arms of the economic model. Patients can then progress within FEV1 categories, across the different lung density declines states, and across FEV1 categories. Once patients reach the FEV1<30% category in the model, they cannot move within the category and across the different lung density states (regardless of Figure 8 indicating otherwise). If patients' FEV1 is below 30%, they are eligible for a lung transplant in the model. Patients can die at any point in the model.

A life time horizon of 49 years is adopted in the analysis and time is discretised into annual cycles. A half-cycle correction was applied in the model. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.[79]

Figure 8. Company's updated model structure



5.4.4.1 ERG critique

The ERG is concerned with the modelling approach taken by the company, particularly with the inclusion of health states based on a hybrid outcome of FEV1 and lung density decline. To aid the understanding of this issue, the ERG lists the purpose of each clinical outcome (i.e. FEV1 and CT lung density decline) in the economic model:

1. Lung density decline measured by CT:

    a. Patients' movement between these categories is a measure of Respreeza's effectiveness in the model, as it is uses RAPID data, more specifically, it uses the change in lung density, measured as g/L per year in the trial;

    b. The change in lung density in the model indirectly impacts survival, as survival differs by categories of lung density decline. Therefore, CT lung density decline is also indirectly used to estimate the impact of Respreeza on mortality.

2. Categories of FEV1 predicted:

    a. Patients' movement between FEV1 categories is also a measure of Respreeza's effectiveness in the model, albeit based on external data sources which assess the effectiveness of augmentation therapy (please see Section 5.4.5);

    b. The change in FEV1 categories in the model is used to estimate the impact of Respreeza on patients' quality of life, disease management costs, and when patients are eligible for a lung transplant (which happens when patients' FEV1 falls below 30%);

    c. The change in FEV1 is also indirectly used to estimate survival, as survival differs by categories of lung density decline as well as FEV1.

As acknowledged in the CS (Table 28, page 132), there is a considerable evidence base documenting the correlation between FEV1 and CT lung density measurements. However, there is no robust evidence to establish a predictive relationship between the two outcomes. This is problematic in this case, due to three issues:

1. The fact that in RAPID, changes in FEV1 outcomes were not statistically significant;

2. The implication of the latter, which led to changes in FEV1 in the model having to be estimated through different sources of evidence;

3. The fact that the definition of lung density decline in the model is not based on a clinically established threshold for assessing CT lung density decline.

The pillar of the economic model (patients' movement through the hybrid states of FEV1 and CT lung density decline) is therefore based on trial data for potentially clinically meaningless categories of lung density decline, and on two external sources of clinical evidence to estimate changes in FEV1 categories. This artificially decomposes the implicitly aggregated relationship in the evolution of FEV1 and CT lung density in the model. This is particularly concerning given the paucity of data on the predictive relationship between FEV1 and CT lung density measurements, which would allow some validation of the model clinical outcomes.

Had there been robust trial data, with a sufficiently long follow-up period and a sufficiently large sample size to capture statistically significant changes in FEV1, the ERG would be less concerned with implicitly modelling the relationship between FEV1 and lung density decline to estimate treatment effectiveness and ultimately the cost-effectiveness of Respreeza. Patients could move into the different FEV1 and lung density decline health states throughout the model, based on robust individual patient-

level data, and without having to resource to external sources of data to estimate movement between health states. The ERG also acknowledges that using such data would likely require building a discrete event simulation model, so every patient could be followed in order to appropriately capture the progression for the combined FEV1 and lung density outcome. Given this is not the case, the ERG is concerned that patients' transitions between health states in the model (and therefore the treatment effectiveness of Respreeza) is reduced to an artificially imposed, and impossible to validate, manipulation of clinical data.

Alternatively, the company could have taken a modelling approach based on either FEV1 or lung density decline outcomes. Given that most economic outcomes, such as disease management costs and eligibility for lung transplant are linked only to FEV1 status, and that quality of life and mortality are also easily linked to FEV1 outcomes, the ERG proposed, during the clarification stage, that the company built an alternative model based only on FEV1 outcomes. The company disagreed with the proposed approach, and stated that, "*FEV1 is considered an inappropriate outcome measure in A1PI as FEV1 has been shown to change slowly over time and is subject to a considerable degree of inter- and intra-patient variability* [...] *Additionally, intra-patient factors, such as the extent of airway obstruction, changes in bronchial tone and diurnal variations in FEV1, can contribute to further variability.*". The company added that, *"The most recently updated treatment guidelines (ERS guidelines) confirm that CT densitometry has been established as the most specific and sensitive surrogate end-point for the evaluation of therapeutic benefit of augmentation therapy* […] *Campos et al. also highlights that CT lung densitometry is more sensitive than other measurements of emphysema progression, and that the changes in CT lung density are related to changes in lung function, providing the foundation to use this imaging tool as an endpoint for therapeutic interventions in AATD. As COPD progresses slowly with high variability in FEV1 decline, detecting a significant decline in FEV1 would require the enrolment of hundreds to thousands of patients in a clinical trial and several years of follow-up (as presented by Schluchter, 2000). Campos et al concludes that instead of FEV1, investigators have used CT measures of emphysema as an endpoint in AATD clinical trials with relatively smaller sample sizes and shorter follow-up times."*

Other literature sources are in accordance with the superiority of CT measurements of lung decline function. Green *et al.* 2016 found that around half of patients in their study (UK ADAPT registry) who exhibited no significant decline in FEV1 (i.e. normal ageing), had whole lung CT density decline.[1] The authors concluded that use of serial spirometry to select patients most likely to benefit from augmentation, would miss many at risk individuals. Serial gas transfer would be a more reliable marker of the emphysema process detected by density change, but would still miss around 20% of patients with a declining CT scan. The authors added that even though some of the study patients did not decline at all, over the period when density was monitored, none of the standard measures taken in clinical practice

differentiated these patients clearly from decliners. The authors therefore, suggest that serial CT densitometry would be the most reliable way to identify progressing high risk A1PI patients for more aggressive treatment (i.e. augmentation), and lower risk A1PI patients, who could safely be monitored, therefore bringing A1PI management closer to a personalized, risk-based approach. The authors advise that if the NHS were to move to routine use of densitometry, hospitals/clinics would either need to buy software and train staff, or commission services from external providers of CT studies and analysis, to ensure consistency and accuracy.

The ERG acknowledges the fact that CT densitometry is a superior measurement of emphysema progression in A1PI deficiency, and of the therapeutic benefit of augmentation therapy. Nonetheless, it points to the contradiction in the company's approach of stating that FEV1 is an inappropriate outcome measure in A1PI, but still including it as a clinical outcome in their economic model. The ERG considered the feasibility of an economic model based on lung density decline outcomes only: treatment effectiveness measures would be available from RAPID; mortality and quality of life data would be available from Green *et al*.; the challenge would be to cost lung density decline outcomes and judge patients' suitability for lung transplant.[76] The ERG concluded that more research is needed to assess the feasibility, and surpass the initial barriers associated with such models.

From a current clinical practice perspective, the ERG is concerned that CT lung density is rarely measured in the clinical management of this condition, as explained by the ERG's clinical experts and discussed in Section 4. Consequently, the ERG is concerned that in order to prescribe, and monitor patients on Respreeza, clinicians would have to use CT scanning. The clinical experts advising the ERG have different views of this topic. While one of the experts stated that lack of access to CT scanning would not prevent the prescribing or monitoring of patients on Respreeza; the other explained that he would want to "replicate" the RAPID trial measurements, in order to be able to assess patients' response to the drug, therefore requiring CT scanning.

The company, in their reply to the ERG's clarification questions, state that it is not proposing that routine CT scanning is introduced in the NHS if Respreeza is recommended, as the latter is not necessary to initiate or monitor treatment. However, the ERG cannot fail to acknowledge the inconsistency in the company's need to have a CT lung density-based economic model to appropriately assess the cost-effectiveness of Respreeza, and the company's view that CT lung density assessments will not be necessary in clinical practice if the drug is recommended.

In response to the ERG's clarification request, the company has broken down the original health state of FEV1<50% into 30%≤ FEV1%<50% and FEV1<30% in their updated model, as to more appropriately capture the percentage of patients eligible for lung transplant. The ERG also requested that the company linked CT lung density decline with a need for lung transplant, given the company's

decision to include lung density decline in the economic model. The company replied that, "[…] *patients do not need declining lung function to be eligible for a lung transplant because a patient with an FEV1<30% is unlikely to be considered "stable" and therefore it is assumed that patients with an FEV1<30% with no decline within a one-year period would be eligible for a transplant.*" The ERG considers the reply from the company to be contradictory. Regardless, in the model all patients with an FEV1<30% are eligible for a lung transplant, independently of having no decline, slow or rapid decline after one year. Furthermore, patients are not allowed to transition between lung density decline status (ND, SD or RD) within the FEV1<30% category in the model, and are allocated to these based on their transition from the 30%≤ FEV1%<50% health states into the FEV1<30% ND, SD or RD states. The ERG is unclear why patients' lung density wouldn't change once patients reach the FEV1<30% threshold, and considers this to be clinically implausible. It is difficult to predict the impact of omitting this from the economic model, as this analysis would have to be based on the comparison of how patients progress from the 30%≤ FEV1%<50% into the FEV1<30% ND, SD and RD states, and how patients transition between the ND, SD and RD states within the FEV1<30% category (and there are no data available for the latter).

Including lung density decline in all health states of the model, implies that patients' baseline rate of decline had to be estimated. This creates problems, which are discussed in detail in Section 5.4.5. The use of a semi-Markov structure is acceptable in this case, given the nature of the underlying data (although as mentioned earlier, a discrete event simulation model would have its advantages), and the availability of survival data from Green *at al*.[76] The use of a tunnel state to model lung transplant is appropriate, however, the ERG proposed additional tunnels states to be included in the model during the clarification stage (see Section 5.4.7).

Patients enter the model with a mean age of 51 years. Twenty years into the model, when patients are 71 years, there are still 10% of patients alive in both treatment arms. At the end of the economic model, when patients are 100 years old, there is still 1% of patients alive in both treatment arms, which is implausible from a clinical point of view. This suggests an overestimation of survival tails in the long-term of the economic analysis. This issue is further discussed in Section 5.4.8.

5.4.5 Treatment effectiveness

Treatment effectiveness within the model was implemented with a semi-Markov method, which uses transitions probabilities to determine patients' flow through the different health states in the model. Transitions to death were estimated using RAPID trial data for the follow-up period of the trial (up to four years), and thereafter estimated with the analysis of survival in patients with A1PI deficiency undertaken by Green *et al*.[76] The company's approach to modelling mortality is explored in further detail in Section 5.4.7.

As discussed in Section 5.4.4, the company desegregated the relationship in the evolution of the hybrid FEV1 and lung density decline outcomes, by using different data sources to estimate transition probabilities between FEV1 and lung density decline, even though these outcomes are contained within the same health states in the model. The ERG reports how these probabilities were derived separately, in the two following subsections, and then proceeds to explain how these were combined to originate aggregated transition probabilities in the model.

5.4.5.1 Transition probabilities between FEV1 predicted states

The company used two different data sources to estimate FEV1 progression; one for the BSC arm, and another for the Respreeza arm of the model. In order to estimate FEV1 progression for BSC patients, the company used Stockley *et al*. 2014[80], who predicted the annual decline (by linear regression) in FEV1% predicted values in 406 patients with A1PI deficiency in a UK registry database (ADAPT), who had never received augmentation therapy and for whom at least 4 consecutive annual data points were available to determine FEV1 decline.[78] The study grouped patients into three FEV1 decline groups: no decline (< -0.1% predicted/year); mild (>-0.1and <-0.5%); moderate (>-0.5 and< -1.0%) and severe (>-1.0%) decline. The results of the analysis are reported in Table 25 below.

Table 25. Results from Stockley *et al*. 2014[80]

	Annual FEV1% decline	Equivalent ml/y	n
No FEV1% decline	0.00	0.00	88
Mild FEV1% decline	0.37	19.66	42
Moderate FEV1% decline	0.87	39.43	64
Rapid FEV1% decline	2.44	84.17	212
Average	**1.45**	**52.10**	**n/a**
Abbreviations: ml: millilitres; y: year; FEV1: forced expiratory volume in 1 second			

The company estimated a weighted average of 1.45% annual decline in FEV1 and used it to calculate BSC patients' transitions across FEV1 states in the model by taking the average baseline FEV1 for each FEV1 category in RAPID and calculating how many years it would take BSC patients to cross the threshold to the next category, with an annual decline of 1.45%. Patients in the FEV1≥50% category had a baseline FEV1 of 59.76% predicted in RAPID, therefore, at an annual decline of 1.45%, it would take these patients 6.7 years to transition to the 30%≤ FEV1%<50% category. Patients in the latter category had a baseline FEV1 of 39.60, thus it would take them 6.6 years to cross to the FEV1<30% category at a 1.45% annual decline. The company then converted these estimates into the annual probability of patients crossing the FEV1 thresholds in the model, using the following formula:

$$1 - EXP\left[LN\left(1 - \left(\frac{1}{number\ of\ years\ needed\ to\ cross\ FEV1\ thershold}\right)\right)\right]$$

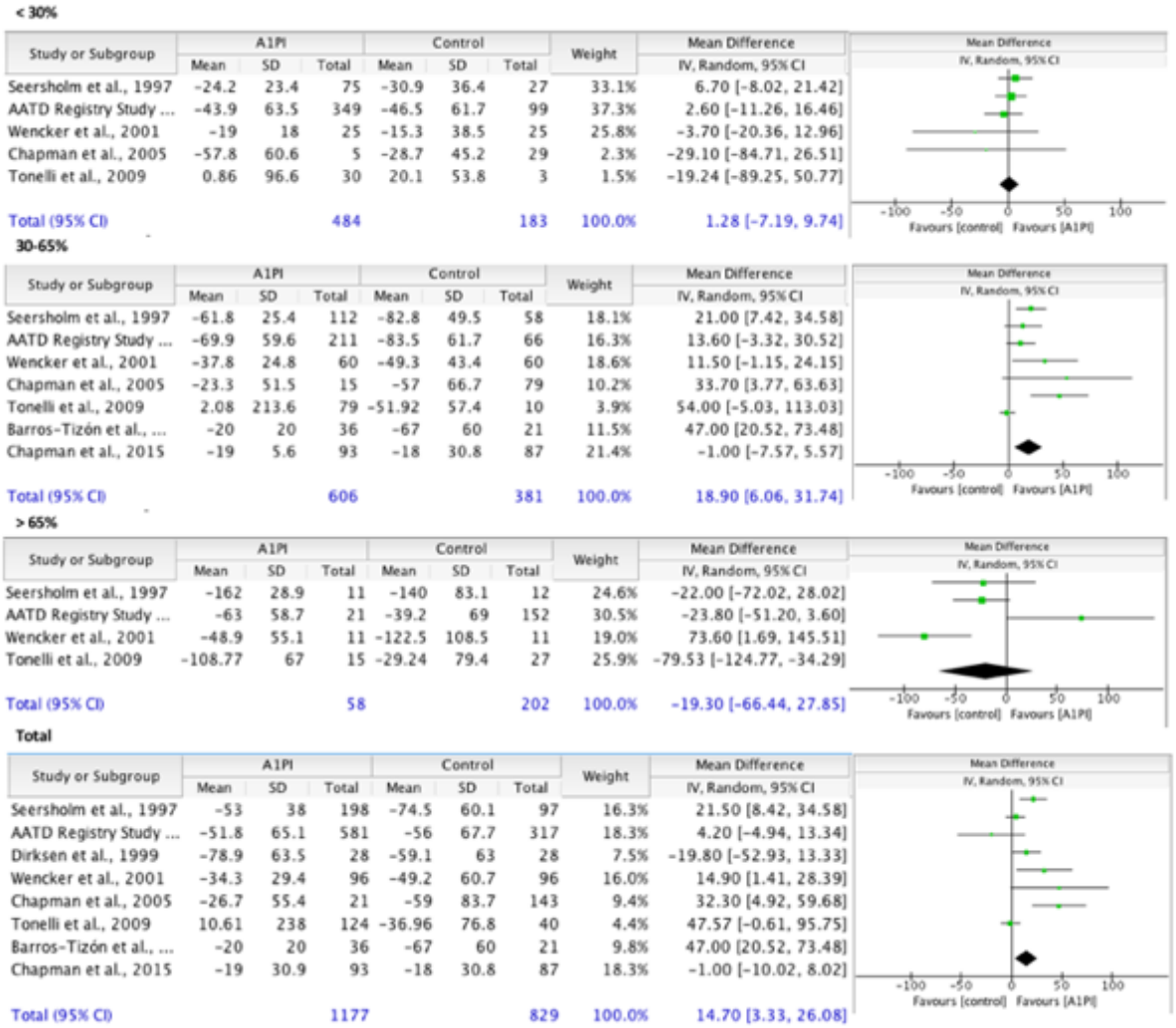
The company estimated that the annual probability of BSC patients transitioning from the FEV1≥50% category to the 30%≤ FEV1%<50% category is 14.82%, while the probability of patients in the latter category transitioning to the FEV1<30% category is 15.07%.

The company used the updated meta-analysis (described in Section 4.4) to estimate the treatment effectiveness of Respreeza in delaying FEV1 progression. The ERG replicates the results of the meta-analysis in Figure 9 below for clarity. After the clarification stage, the company used the 18.90 ml/y effect size and the 1.28 ml/y value to predict FEV1 progression in the Respreeza arm of the model, by applying these estimates of treatment effectiveness to the BSC annual probabilities of crossing the FEV1 thresholds in the model. The company used the average decline in ml/y reported by Stockley *et al*. 2014 (52.10 ml/y, Table 25) to be able to apply the meta-analysis results, also reported in ml/y, instead of annual decline in FEV1.[80] It then estimated the relative risk of FEV1 decline with Respreeza vs BSC, to then apply to the annual probability of BSC patients crossing between FEV1 thresholds. The ERG reports these calculations in Table 26. The company estimated that the annual probability of Respreeza patients transitioning from the FEV1≥50% category to the 30%≤ FEV1%<50% category is 9.44%, while the probability of patients in the latter category transitioning to the FEV1<30% category is 14.79%. The ERG disagrees with the implementation of the results of the meta-analysis to estimate transition probabilities for Respreeza, and discusses this in the next subsection.

Table 26. Company's estimation of Respreeza's transition probabilities across FEV1 thresholds

	Slope difference from updated meta-analysis used by the company (ml/y)	Annual probability of BSC patients crossing to the next FEV1 threshold	Relative risk of crossing to the next threshold	Annual probability of Respreeza patients crossing to the next FEV1 threshold
FEV1%≥50%	18.90	14.82%	(52.10-18.90)/52.10 = 64%	14.82%*64% = 9.44%
30%≤ FEV1%<50%	1.28	15.07%	(52.10-1.28)/52.10 = 98%	15.07%*98% = 14.79%
FEV1<30%	n/a	n/a	n/a	n/a
Abbreviations: ml: millilitres; y: year; FEV1: forced expiratory volume in 1 second				

Figure 9. Company's updated meta-analysis



5.4.5.2 ERG critique

The Stockley *et al*. 2014 source is an abstract, therefore, the ERG could not assess the full analysis.[80] The latter is based on the UK registry data for patients with A1PI deficiency, which has been the basis for several analyses (albeit from different sources) used in the company's submission. The registry population in the Stockley *et al*. 2014 analysis included 87 never smokers (21% of the total population).[80] This figure is not dissimilar from RAPID patients, who were mainly ex-smokers (about 74%), with only 14% and 17% patients being never-smokers in the Respreeza and placebo arms of the trial, respectively. Regardless, there is little detail on the method of the analysis provided in the abstract, thus the ERG cannot validate this. One clinical expert advising the ERG noted that the decline in FEV1 over time is unlikely to be linear, therefore the use of linear regression analysis to assess changes in this outcome might be inappropriate. Finally, using the Stockley *et al*. 2014 analysis assumes that patients

on BSC have the same probability of decline in FEV1 status, regardless of their current FEV1 value, which might be overly simplistic and clinically implausible.[80]

The company used their updated meta-analysis to estimate the probability of patients' decline in FEV1 status for the Respreeza arm of the model, compared with BSC patients. The ERG discusses the limitation of the meta-analysis in Section 4.4. of the report.

From a conceptual point of view, the ERG disagrees with the company's choice of treatment effect estimates from the meta-analysis, to be used in the economic model. The company used the 18.90 ml/y effect size and the 1.28 ml/y value (Figure 9) to predict the annual probability of Respreeza patients transitioning from the FEV1≥50% category to the 30%≤ FEV1%<50% category, and the probability of patients in the latter category transitioning to the FEV1<30%, respectively. However, given the outcome of the meta-analysis reflects the effect of augmentation therapy versus placebo on the annual change in FEV1 decline, measured by ml/y, for the specific FEV1 categories of FEV1>65%; 30%-65% and <30%, the ERG notes that the 18.90 ml/y, and the 1.28 ml/y effect sizes correspond to the effect of Respreeza on slowing patients' FEV1 decline within the 30%≤ FEV1%<50% category, and within the FEV1<30%, respectively. Therefore, in order to estimate the reduction in the probability of patients transitioning between FEV1 thresholds in the Respreeza arm of the model, the company should have used the corresponding effect sizes to apply to the annual decline of FEV1 of 52.10 ml/y experienced by BSC patients (Table 25). The ERG ran a scenario analysis using the appropriate effect sizes from the meta-analysis and summarises this information, together with its proposed approach in Table 27.

Given the effect size for the FEV1>65% group in the meta-analysis is, not only non-statistically significant, but also counterintuitive (as it is a negative value, suggesting augmentation therapy is detrimental compared to placebo), the ERG used a relative risk of 1, which suggests that augmentation therapy does not have an effect, compared with placebo, in the FEV1≥50% group in the model. The ERG used the 18.90 ml/y effect size (instead of 1.28 ml/y) to reflect the effect of augmentation therapy in reducing the decline in FEV1 in patients in the 30%≤ FEV1%<50% health states in the model. This results in the estimation of an annual transition probability of 9.60% for Respreeza patients, compared with 15.07% for BSC, for patients moving from the 30%≤ FEV1%<50% to the FEV1<30% states in the model.

The estimates used by the ERG translate into a clinical scenario where the benefit of Respreeza is in delaying patients' progression from the 30%≤ FEV1%<50% to the FEV1<30%, opposed to the company's analysis which suggests that the benefit of Respreeza is mainly in delaying patients' progression from the FEV≥50% to the 30%≤ FEV1%<50%. The ERG's correction increased the company's base case ICER from £236,409 to £316,685 per QALY gained.

Table 27. ERG's correction of company's estimation of Respreeza's transition probabilities across FEV1 thresholds

	Corresponding slope difference from updated meta-analysis (ml/y) (95% confidence interval)	Annual decline in FEV1 for BSC patients in ml/y (Stockley *et al*, 2014)	Annual probability of BSC patients crossing to the next FEV1 threshold (estimated)	ERG's proposed value to be used from meta-analysis	ERG's proposed relative risk of crossing to the next threshold	ERG's annual probability of Respreeza patients crossing to the next FEV1 threshold
FEV1%≥50% (FEV1>65% used as proxy in meta-analysis)	-19.30 (-66.44, 27.85)	52.10	14.82%	52.10	1	14.82%
30%≤ FEV1%<50% (30%<FEV1%<650% used as proxy in meta-analysis)	18.90 (6.06, 31.74)	52.10	15.07%	18.90	(52.10-18.90)/52.10 = 63.72	15.07%*63.72% = 9.60%
FEV1<30%	1.28 (-7.19, 9.74)	52.10	n/a	n/a	n/a	n/a
Abbreviations: ml: millilitres; y: year; FEV1: forced expiratory volume in 1 second; BSC: best supportive care						

5.4.5.3 Transition probabilities between lung density decline status

The company reports that *post-hoc* analysis of the RAPID data was conducted to generate patient counts in each lung density decline state, according to the company's definition of lung density decline:

- No lung density decline: decline of <0 g/L/year in lung density measured by CT scan;
- Slow lung density decline: decline of 0-2 g/L/year in lung density measured by CT scan;
- Rapid lung density decline: decline of >2 g/L/year in lung density measured by CT scan.

The company reports fitting a linear regression to data points at 0, 3 and 12 months for each patient, to obtain the proportion of patients in the ND, SD and RD heath states at the end of year 1. A further linear regression was fitted to the data points at 12, 21 and 24 months for each patient to track their transition in the second year. The company reports that the baseline characteristics of Respreeza and placebo patients were slightly different in RAPID thus the analysis used baseline covariate adjustment, which is reported to account for these differences.

In addition, the company reports using the RAPID extension study, RAPID-OLE, to estimate lung density decline for Respreeza patients. The company states that all of the extension data were analysed in the same way as the main RAPID study, using the data and time points available: 24 months, 36

months and 48 months. The company adds that in line with the Markovian assumption of the model, the data were then added to the 2-year analysis of RAPID data, for the Respreeza arm of the model.

The company ran the regression analysis for two patient groups in RAPID, the FEV1≥50% group and the FEV1<50% group. Therefore, transition probabilities were also derived for these two populations, and used in the model for the corresponding FEV1≥50% health states, while the FEV1<50% data were used for 30%≤ FEV1%<50% and the FEV1<30% health states in the model. The results of the regression analysis are reported in Table 28 and Table 30 below, for the FEV1≥50% and the FEV1<50% groups, respectively. The transition probabilities derived from the results of the regression analysis are presented in Table 29 and Table 31 for the FEV1≥50% and the FEV1<50% groups, respectively.

Table 28. Distribution of patients over lung density states from RAPID, for the FEV1≥50% category

		No decline	Slow decline	Rapid decline	Total
	Best supportive care arm	Year 1-2			
Year 0-1	No decline	0	6	0	6
	Slow decline	0	10	1	11
	Rapid decline	0	9	8	17
	Respreeza arm	Year 1-2			
Year 0-1	No decline	13	15	2	30
	Slow decline	1	27	4	32
	Rapid decline	0	15	4	19

Table 29. Transition probabilities between lung density decline states used for the FEV1≥50% health states

		No decline	Slow decline	Rapid decline	Total
	Best supportive care arm	Year 1-2			
Year 0-1	No decline	0%	100%	0%	100%
	Slow decline	0%	91%	9%	100%
	Rapid decline	0%	53%	47%	100%
	Respreeza arm	Year 1-2			
Year 0-1	No decline	43%	50%	7%	100%
	Slow decline	3%	84%	13%	100%
	Rapid decline	0%	79%	21%	100%

Table 30. Distribution of patients over lung density states from RAPID, for the FEV1<50% category

		No decline	Slow decline	Rapid decline	Total
	Best supportive care arm	Year 1-2			
Year 0-1	No decline	2	4	1	7
	Slow decline	0	17	12	29
	Rapid decline	0	3	12	15
	Respreeza arm	Year 1-2			
Year 0-1	No decline	6	15	1	22
	Slow decline	8	87	8	103
	Rapid decline	0	11	14	25

Table 31. Transition probabilities between lung density decline states used for the 30%≤ FEV1%<50% and the FEV1<30% categories

		No decline	Slow decline	Rapid decline	Total
	Best supportive care arm	Year 1-2			
Year 0-1	No decline	29%	57%	14%	100%
	Slow decline	0%	59%	41%	100%
	Rapid decline	0%	20%	80%	100%
	Respreeza arm	Year 1-2			
Year 0-1	No decline	27%	68%	5%	100%
	Slow decline	8%	84%	8%	100%
	Rapid decline	0%	44%	56%	100%

5.4.5.4 ERG critique

Overall, the ERG considers that there is a lack of transparency and detail in the CS regarding the estimation of lung density decline and the manipulation of RAPID data. Therefore, the ERG utilises these subsections to provide further details on the company's approach, together with its critique of the latter.

5.4.5.4.1 Baseline CT lung density decline

Including lung density decline in all health states of the model implied that patients' baseline rate of decline had to be estimated. The exceptions are the FEV1<30% health states, which have no patients at the beginning of the model, given the company's proposition that initiating treatment with Respreeza is not indicated for these patients. In order to estimate baseline decline, the company used the results of

their regression analysis and took the year 0 to year 1 estimates for the number of patients in the ND, SD and RD categories in the placebo arm of RAPID, in the FEV1≥50% (Table 28) and FEV1<50% (Table 30) populations in the trial. The ERG reports the company's calculations in Table 32 below.

Table 32. Company's calculation of baseline distribution of patients' lung density decline for both treatment arms

		No decline	Slow decline	Rapid decline	Total
	Best supportive care arm for FEV1≥50% patients	Year 1-2			
Year 0-1	No decline	0	6	0	6
	Slow decline	0	10	1	11
	Rapid decline	0	9	8	17
				Total	34
	Best supportive care arm for FEV1<50% patients	Year 1-2			
Year 0-1	No decline	2	4	1	7
	Slow decline	0	17	12	29
	Rapid decline	0	3	12	15
				Total	51
	Baseline distribution of patients in both treatment arms of the model for FEV1≥50% patients				
Year 0-1	No decline	6/(34+51)=7%			
	Slow decline	11/(34+51)=13%			
	Rapid decline	17/(34+51)=20%			
	Baseline distribution of patients in both treatment arms of the model for 30%≤ FEV1%<50% patients				
Year 0-1	No decline	7/(34+51)=8%			
	Slow decline	29/(34+51)=34%			
	Rapid decline	15/(34+51)=18%			

The company's decision to use data from the placebo arm in RAPID to model baseline lung density decline for both treatment arms in the model, implicitly assumes that the baseline lung density decline in placebo patients in RAPID is representative of the baseline decline in Respreeza patients, before they start treatment. This raises considerable concerns, given the company's acknowledgment of an imbalance in patients' baseline characteristics in the trial. The company does not provide more details on the baseline imbalance issue; however, the ERG is particularly concerned with the imbalance in baseline CT lung density, with Respreeza patients having a mean 46.6 g/L at baseline, and placebo patients having a lung density of 49.8 g/L. In the company's own definition of lung density decline, a

2 g/L annual decline is classified as rapid decline, thus, the difference and bias in baseline CT lung density across both treatment arms (3.2 g/L) should not be ignored. The direction of the bias is not clear to the ERG, as it could be argued that patients starting with a lower CT lung density are expected to have worse outcomes than patients with a higher lung density, but it could also be argued that the former are simply at a later stage of the disease and therefore might have "less room" for deteriorating, compared to the latter. Given that the real baseline CT lung density decline for the Respreeza group in RAPID is unknown, it is not possible to draw comparisons on baseline rate of decline, but only on absolute baseline lung density.

Worthy of note is also the fact that at the end of the 24-month follow-up period in RAPID, the mean lung density was still higher in the placebo group than in the Respreeza group (45.5 vs 44.4 g/L). Since the company's model is based on categories of lung density decline (i.e. ND, SD and RD), instead of lung density decline measurements in g/L, it is not possible to validate the model in this regard, to compare how absolute values of CT lung density evolved in both treatment arms of the model.

5.4.5.4.2 Estimation of treatment effectiveness on lung density decline using RAPID data

Subgroups of patients used in the analysis

Following the clarification stage, the company has included FEV1<30% health states in the model, to more accurately capture when patients would be eligible for a lung transplant in the model. Nonetheless, the RAPID data used to populate lung density decline in the FEV1<30% states, are the original data for the FEV1<50% patients in the trial. The ERG acknowledges that for the year 0-1 estimation of lung density decline, the broader aggregation of patients from the FEV1<50% was necessary, given that there were no patients with a baseline FEV1<30% in RAPID. Nonetheless, as time went by in the RAPID and in the RAPID extension studies, patients moved to the FEV1<30% category. Therefore, the company could have attempted an analysis of lung density decline data for patients in the FEV1<30% in RAPID. The company's approach implies that lung density decline is the same for patients in the 30%≤ FEV1%<50% and in the FEV1<30% categories of lung function. Given that mortality is a key driver of the economic model, the ERG considers that the company's simplification is potentially introducing bias into the cost-effectiveness results. The direction of the bias is unknown.

Covariate adjustment of treatment effectiveness

When estimating the effect of Respreeza in delaying lung density decline, the company states that in RAPID, "*The baseline characteristics of Respreeza and placebo were slightly different across arms thus the analysis is presented as a regression analysis using baseline covariate adjustment, which accounts for these slight differences*". The company did not provide any further detail on the adjustment

carried, or the covariates used. During the clarification stage, the ERG requested that the company provided, "*the equations used in the linear regression used to estimate transition probabilities between lung density states in the model using RAPID data (…), together with the covariates used to adjust these data, and with a clear description of the methods and data used in this process (including the results of the statistical process for selecting covariates)*". The company did not comply with the ERG's request, and instead confirmed that the covariates used in the RAPID analysis of change in CT lung density reported in the clinical study report (CSR), were used by the company in their assessment of CT lung density decline (defined with the 2 g/L threshold). The covariates listed in the CSR are [redacted].

To note is that the list referred by the company does not include baseline CT lung density, which the ERG considers to be the more obviously imbalanced baseline characteristic in RAPID, and an important prognostic factor as it has been linked with mortality, FEV1 decline and other important clinical outcomes (Green *et al*. 2016).[1] As the company's declined to provide the information requested by the ERG, this essentially renders the company's analysis of treatment effectiveness a "black box".

Furthermore, the company reports using a linear regression to estimate lung density decline and as mentioned in Section 5.4.5.2, the clinical expert advising the ERG noted that the decline in lung function outcomes over time is unlikely to be linear, therefore the use of linear regression analysis might be inappropriate. Finally, the ERG reinforces the issue that the thresholds used by the company to define lung density decline are not based on clinically standardised thresholds, and therefore are arbitrarily categorising Respreeza's measure of treatment effectiveness. The ERG is concerned that if the thresholds of lung density decline were defined differently, the measure of Respreeza's treatment effectiveness might also change considerably. This would have a direct impact on the final ICER, as the key model driver is mortality, which in its turn is driven by patient's change in lung density decline (i.e. ND, SD or RD).

Use of 4-year data for the Respreeza arm of the model

The ERG is concerned with the fact that the company is using the RAPID extension study data, which includes patients who crossed-over from the placebo arm of RAPID to treatment with Respreeza in the extension study. The company does not mention any data adjustments, and it reports that it is in line with the Markovian assumption of the model to add the data extension to the 2-year analysis of RAPID data, for the Respreeza arm of the model.

The ERG interprets the company's justification as a mention to the memoryless characteristic of the Markovian assumption. However, the ERG has not seen any evidence that patients whose disease has

progressed for two years longer (or put more simply, patients who have been diagnosed two years later) than other patients, are expected to have identical clinical outcomes as patients diagnosed earlier. The ERG's concern is further aggravated by the baseline imbalance in patients' characteristics across treatment arms, discussed in the previous subsection.

During the clarification stage, the ERG requested the company to provide the change in mean CT lung density per year, for Respreeza patients who received Respreeza in RAPID and carried on receiving Respreeza in RAPID-OLE (i.e. excluding the placebo patients from RAPID who crossed over to Respreeza in RAPID-OLE), over the 4-year follow-up period. The company instead provided the data for the placebo group in RAPID who went on to receive Respreeza during the open-label extension phase of RAPID.

The ERG also asked the company to use the requested Respreeza data (which the company did not provide) to calculate transition probabilities matrices estimating the probability of patients moving between the different lung density decline states in the model between year 0-1 and year 1-2; year 1-2 and year 2-3; and finally year 2-3 and year 3-4, using the 4-year Respreeza data (for the cohort of patients receiving Respreeza in RAPID and RAPID-OLE, excluding placebo patients from RAPID-OLE), for each FEV1% category included in the model. The company replied that, "*The transition probabilities already utilise this data: the Respreeza transition probabilities are based on transitions between years 0-1, 1-2, 2-3 and 3-4 which therefore includes those that switched from placebo*.", therefore ignoring the ERG's request to exclude placebo patients from the 4-year data analysis of Respreeza.

In summary, it is the ERG's opinion that there is too much uncertainty on how the treatment effectiveness for Respreeza was estimated in the model, therefore the current analysis of cost-effectiveness using RAPID data is associated with a high level of decision uncertainty.

5.4.5.5 Combined transition probabilities used in the model

The company combined the data reported in the previous sections to estimate the transition probabilities between the hybrid FEV1 and lung density decline health states in the economic model, which the ERG presents in Table 34 and in Table 35, for the BSC and Respreeza arms of the model, respectively. The calculations undertaken by the company are reported by the ERG in Table 33.

Table 33. Calculation of transition probabilities

		FEV1≥50%			30%≤ FEV1%<50%			FEV1<30%		
		ND	SD	RD	ND	SD	RD	ND	SD	RD
FEV1≥ 50%	ND	$P^{>50}_{ND/ND}$ - a	$P^{>50}_{ND/SD}$ - b	$P^{>50}_{ND/RD}$ - c	$P^{>50}_{ND/ND}$ * PC = a	$P^{>50}_{ND/SD}$ * PC = b	$P^{>50}_{ND/RD}$ * PC = c	-	-	-
	SD	$P^{>500}_{SD/ND}$ - d	$P^{>50}_{SD/SD}$ - e	$P^{>50}_{SD/RD}$ - f	$P^{>50}_{SD/ND}$ * PC = d	$P^{>50}_{SD/SD}$ * PC = e	$P^{>50}_{SD/RD}$ * PC = f	-	-	-

	RD	$P^{>50}_{RD/ND}$ - g	$P^{>50}_{RD/SD}$ - h	$P^{>50}_{RD/RD}$ - i	$P^{>50}_{RD/ND}$ * PC = g	$P^{>50}_{RD/SD}$ * PC = h	$P^{>50}_{RD/RD}$ * PC = i	-	-	-
30%≤ FEV1% <50%	ND	-	-	-	$P^{<50}_{ND/ND}$ - j	$P^{<50}_{ND/SD}$ - k	$P^{<50}_{ND/RD}$ - l	$P^{<50}_{ND/ND}$ * PC = j	$P^{<50}_{ND/SD}$ * PC = k	$P^{<50}_{ND/RD}$ * PC = l
	SD	-	-	-	$P^{<50}_{SD/ND}$ - m	$P^{<50}_{SD/SD}$ - n	$P^{<50}_{SD/RD}$ - o	$P^{<50}_{SD/ND}$ * PC = m	$P^{<50}_{SD/SD}$ * PC = n	$P^{<50}_{SD/RD}$ * PC = o
	RD	-	-	-	$P^{<50}_{RD/ND}$ - p	$P^{<50}_{RD/SD}$ - q	$P^{<50}_{RD/RD}$ - r	$P^{<50}_{RD/ND}$ * PC = p	$P^{<50}_{RD/SD}$ * PC = q	$P^{<50}_{RD/RD}$ * PC = r
Abbreviations: FEV1: forced expiratory volume in 1 second; ND: no decline; SD: slow decline; RD: rapid decline; PC: probability of crossing the FEV1 threshold; $P^{>50}$: probability of transitioning between lung density decline status in the FEV1≥50% category; $P^{<50}$: probability of transitioning between lung density decline status in the FEV<50% categories.										

Table 34. Transition probabilities used in the BSC arm

Best supportive care arm		**FEV1≥50%**			**30%≤ FEV1%<50%**			**FEV1<30%**		
		ND	**SD**	**RD**	**ND**	**SD**	**RD**	**ND**	**SD**	**RD**
FEV1≥50%	ND	0%	85%	0%	0%	15%	0%	-	-	-
	SD	0%	77%	8%	0%	13%	1%	-	-	-
	RD	0%	45%	40%	0%	8%	7%	-	-	-
30%≤ FEV1%<50%	ND	-	-	-	24%	49%	12%	4%	9%	2%
	SD	-	-	-	0%	50%	35%	0%	9%	6%
	RD	-	-	-	0%	17%	68%	0%	3%	12%
Abbreviations: FEV1: forced expiratory volume in 1 second; ND: no decline; SD: slow decline; RD: rapid decline.										

Table 35. Transition probabilities used in the Respreeza arm

Respreeza arm		**FEV1≥50%**			**30%≤ FEV1%<50%**			**FEV1<30%**		
		ND	**SD**	**RD**	**ND**	**SD**	**RD**	**ND**	**SD**	**RD**
FEV1≥50%	ND	39%	45%	6%	4%	5%	1%	-	-	-
	SD	3%	76%	11%	0%	8%	1%	-	-	-
	RD	0%	71%	19%	0%	7%	2%	-	-	-
30%≤ FEV1%<50%	ND	-	-	-	23%	58%	4%	4%	10%	1%
	SD	-	-	-	7%	72%	7%	1%	12%	1%
	RD	-	-	-	0%	38%	48%	0%	6%	8%
Abbreviations: FEV1: forced expiratory volume in 1 second; ND: no decline; SD: slow decline; RD: rapid decline.										

5.4.5.6 ERG critique

In terms of FEV1 decline, the company's estimated transition probabilities show that on average, patients on Respreeza are less likely than BSC patients to transition from the FEV1≥50% to the 30%≤ FEV1%<50% category, every year. Patients in the latter FEV1 category have a similar probability of transitioning to the FEV1<30% category across treatment arms, with patients on the 30%≤

FEV1%<50% ND state in the Respreeza and the BSC arms having the same probability of transitioning to the FEV1<30% state.

It is more difficult to analyse a pattern of Respreeza's effect on the transitions across lung density decline states. In general, it seems that Respreeza patients have a higher probability of remaining in the ND state than BSC patients in the FEV1≥50% state. However, Respreeza and BSC patients in the 30%≤ FEV1%<50% states have very similar probabilities of not having any reduction in their lung density decline, suggesting that Respreeza is not more effective than BSC at preserving lung density in these patients.

The transition probabilities resulting from the ERG's correction described in Section 5.4.5.2 (i.e. using different measures of effect for Respreeza from the meta-analysis) are reported in Table 36. The corrected transition probabilities show that patients on Respreeza are equally likely as BSC patients to transition from the FEV1≥50% to the 30%≤ FEV1%<50% category, every year. Conversely, Respreeza patients on the 30%≤ FEV1%<50% category have a lower probability of transitioning to the FEV1<30% category compared with BSC patients. From a clinical point of view, this is a more likely scenario than the one translated from the company's analysis given the ERG's clinical experts' opinion that most patients presenting in clinical practice with symptoms are in the 30%≤ FEV1%<50% category.

Furthermore, the transition probabilities estimated by the ERG are more consistent with the company's proposed benefit of Respreeza, which is to slow down patients' lung function decline and therefore, avoid the need for (or delay) lung transplant. Given that only patients with an FEV1<30% are eligible to receive a lung transplant in the model, it is by preventing them crossing from the 30%≤ FEV1%<50% to the FEV1<30% states that lung transplants can be avoided in the economic analysis.

Table 36. Transition probabilities estimated by the ERG for the Respreeza arm

Respreeza arm		FEV1≥50%			30%≤ FEV1%<50%			FEV1<30%		
		ND	SD	RD	ND	SD	RD	ND	SD	RD
FEV1≥50%	ND	37%	43%	6%	6%	7%	1%	-	-	-
	SD	3%	72%	11%	0%	13%	2%	-	-	-
	RD	0%	67%	18%	0%	12%	3%	-	-	-
30%≤ FEV1%<50%	ND	-	-	-	25%	62%	4%	3%	7%	0%
	SD	-	-	-	7%	76%	7%	1%	8%	1%
	RD	-	-	-	0%	40%	51%	0%	4%	5%

Abbreviations: FEV1: forced expiratory volume in 1 second; ND: no decline; SD: slow decline; RD: rapid decline.

Given the Markovian assumption in the company's model, transition matrices reported in Table 34 and in Table 35 do not change with time, which means that the probability of a patient progressing from a

certain state is independent of time spent in that state. For example, if there is one patient in the FEV1≥50% RD state for 1 year, and another patient in the same state for 3 years, they both have the same probability of moving to the 30%≤ FEV1%<50% state. Furthermore, the treatment effect of Respreeza is also maintained throughout that time.

As discussed in Section 5.4.4, the ERG is concerned that by estimating FEV1 progression and lung density decline separately, and then aggregating these in the model, the company is breaking an implicit relationship between clinical outcomes and artificially manipulating a relationship through the use of different assumptions and data sources, without any means of validating its approach nor its results. As a result, the ERG considers that there is a paramount degree of uncertainty in the cost-effectiveness results, which have not been appropriately accounted for through probabilistic sensitivity analysis (PSA). This issue is further discussed in Section 5.5.

5.4.6 Lung transplant

During the clarification stage, the ERG suggested that the FEV1<30% state was divided into tunnel states, to capture the change in probability of patients getting a lung transplant over time, after being enrolled in the lung transplant waiting list, according to the NHS Blood and Transplant (NHS BT) report for 2017.[81] The ERG also suggested the use of tunnels states to model mortality in the years following transplant, as the NHS BT reports survival data for years 1, 2 and 5 post-transplant.[81]

The company agreed with the ERG's proposed approach from a methodological point of view, however did not implement the tunnel states suggested as this was not considered practical. The company provided two reasons:

1. *"The ERGs proposed model structure only had one state for FEV1<30%. The updated model structure has three states for FEV1<30% (no, slow and rapid decline). Therefore, a higher number of tunnel states would be required which would make the model computationally complex*."

2. *"No data could be sought to provide transition probabilities for the proposed tunnel states. The NHS Blood and Transplant 2017 report provides some data to estimate some of these probabilities, but they are not specific to patients with A1PI deficiency. A literature search was undertaken but no studies have indicated what percentage of patients are ineligible for a lung transplant due to co-morbidities*."

Furthermore, the ERG requested that the company estimated what proportion of patients with an FEV1<30% would be ineligible for a lung transplant. The company reported that no data were found to inform this in the model. The company added that "*The only factor which could be applied in the model*

was the restriction that patients should not receive a transplant over the age of 65 years. This was implemented in the original model. In addition, in the original model, only patients with slow or rapid decline as well as an FEV1<50% were eligible for a transplant. Under the revised structure, all patients with an FEV1<30% are considered eligible, regardless of rate of lung density decline."

The ERG is unclear as to whether the company's intention was to cap lung transplants by age in the updated model. Nonetheless, this was not included in the economic analysis.

The company used the NHS BT data shown in Table 37 to estimate the probability of patients receiving a transplant, and assumed that patients have an equal probability of receiving a transplant regardless of how long they have been in the FEV_1<30% state.[81] After 3 years on the waiting list, 65 of 79 patients would have received a transplant, equating to an annual probability of 43.8%.

Table 37. Outcome of patients listed for lung transplantation in the UK (NHS BT, 2017, Figure 7.5, page 67)[81]

Outcomes by time since listing	6 months	1 year	2 years	3 years
Transplanted	12%	17%	20%	21%
Still waiting	1%	3%	5%	6%
Removed	48%	30%	14%	8%
Died	39%	50%	61%	65%
Post-progression outcome for 320 first lung only registrations made in the UK, from 1 April 2013 to 31 March 2014.				

The ERG requested that the company used the survival data from the NHS BT shown in Table 38, to model post-lung transplant survival in the model.[81] The company used the data for the 416 patients who received a transplant between 2009 and 2011, and for whom survival at year 1 was 82% (95% CI: 78% to 86%) and 59% (95% CI: 54% to 64%) at year 5. The company estimated that survival in year 1 equates to an annual probability of death of 16.47%, while the probability of death between one and two years equates to a probability of 9.8%. The company's estimated probability of death between three and five years equates to an annual probability of 7.3%. The company concluded that given the probability of death in the second year following a lung transplant was similar to the annualised probability of death between years 3 and 5, to reduce the number of health states, all patients entered one health state in the second year following a lung transplant. The annualised probability of death after year one equates to 7.9%.

The company added that the use of data from all lung transplantations, rather than those with A1PI deficiency, can be justified since recent published analysis has indicated that UK median survival after lung transplant is similar for A1PI deficiency and COPD patients.

Table 38. Patient survival after first lung transplant (NHS BT, 2017 – page 106) [81]

Year of transplant	Number at risk on day 0	% patient survival (95% confidence interval)			
		One year	Two years	Five years	Ten years
2003-2005	363	73 (68-78)	67 (62-72)	52 (47-57)	33 (28-38)
2006-2008	333	81 (76-85)	70 (65-75)	55 (49-60)	-
2009-2011	416	82 (78-86)	74 (69-78)	59 (54-64)	-
2012-2015	581	80 (77-83)	-	-	-

5.4.6.1 ERG critique

The ERG agrees with the company that introducing several tunnel states for time to lung transplant and mortality after lung transplant, for each FEV1<30%, subdivided by CT lung density, would make the model more computationally complex. Nonetheless, the company could have surpassed this difficulty by introducing survival curves to model mortality post-lung transplant, given these were available in the NHS BT report.[81] Furthermore, the ERG disagrees with the company's statement that no data were found to model transitional probabilities across the proposed tunnel states, as the NHS BT report provided all the necessary data.[81] Moreover, the company contradicts itself by saying that using NHS BT lung transplant data was not appropriate as these data are not specific to A1PI patients, and then concluding that the use of data from all lung transplantations in the NHS BT report can be justified since recent published analysis has indicated that UK median survival after lung transplant is similar for A1PI deficiency and COPD patients.[81]

Transition to lung transplant in the model

The ERG's clinical expert agreed with the company that there are no published data available to inform how many FEV1<30% patients would be eligible for lung transplant. However, the company could have sought clinical expert opinion to carry out scenario analysis. One of the clinical experts advising the ERG explained that in clinical practice, patients' symptoms and performance, as well as co-morbidities would be assessed for lung-transplant eligibility and that while it would be unusual to refer someone over the age of 65, largely because of co-morbidities, that is not always the case. The other clinical expert advising the ERG reported that, anecdotally 30% of patients would be expected to be turned down due to co-morbidities and another 30% due to age. Therefore, the ERG decided to run two separate scenarios regarding patients' eligibility for lung transplant: i) to cap the age at which patients can receive a transplant at 65 years, and ii) to decrease the FEV1<30% population eligible for transplant by 30%. These scenarios were run separately and combined.

When the ERG corrected the starting age in the model to reflect the mean baseline age in RAPID (i.e. from 51 to 53 years), and applied a lung transplant age cap of 65 years, the company's ICER increased

from £236,409 to £238,901 per QALY gained. When the ERG applied the 30% decrease in the FEV1<30% population eligible for lung transplant in the model, the ICER decreased from £236,409 to £228,865 per QALY gained. When both changes were applied, the ICER decreased to £231,403 per QALY gained.

The company assumed that patients have an equal annual probability of receiving a transplant regardless of how long they have been in the FEV_1<30% state. The company asserts that since this estimate is lower than the probability of transplantation in the first year in the NHS BT data, then the model effectively assumes an increased risk of death, since the probability of death is greater for patients with an FEV_1<30% than patients that have received a transplant.[81] The company concludes that, given Respreeza is expected to increase the proportion of patients that could receive a transplant, then assuming an equal probability in each year may be considered a conservative assumption.

The ERG notes that throughout the CS, the company states several times that one of the anticipated benefits of Respreeza is to delay, or obliviate the need for lung transplant, as exemplified below:

"*By delaying the loss of lung density and function, Respreeza is anticipated to prolong patient independence as well as prolonging the time to or obviating the need for lung transplant.*" (CS, page 19)

"A decrease in the rate of respiratory decline and delay in the need for lung transplantation is likely to have a positive impact on the psychological distress and reduce the health burden placed on patients, family members and caregivers." (CS, page 138)

"*Another indirect treatment effect found in the model was delayed time to lung transplant as a consequence of reduced disease progression.*" (CS, page 191)

"In addition, it is expected that Respreeza will delay disease progression, prolonging the time to or obviating the need for lung transplant, and therefore it is not expected that Respreeza will be cost saving." (CS, page 245)

Therefore, the ERG points to the inconsistency in the company's proposed value of Respreeza with regards to lung transplant. The impact of Respreeza on patients' need for lung transplant is one of the model key drivers. This, however, needs to be explained in the context of its interaction with the estimation of survival in the economic analysis. These issues are discussed in detail in Section 5.4.7.2.

Post-lung transplant survival

The ERG disagrees with the data manipulation undertaken by the company to estimate survival in the first year after lung transplant in the model. The company took the survival estimate at year 1 of 82%

(95% CI: 78% to 86%) and estimated the probability of death by doing 100% - 82%=18%. The ERG assumes the company interpreted the 18% estimate as a mortality rate, as it used the standard process for converting rates into probabilities, to derive the annualised estimate of 16.47%:

$$1 - EXP(-18\% * 1) = 16.47\%$$

Nonetheless, the ERG considers that the 18% estimate is the annual probability of patients dying at the end of year 1, and therefore the 18% estimate should have been used instead of the 16.47%. Therefore, the ERG replaced the 1-year mortality estimate in the economic model. The company's base case ICER went from £236,409 to £237,822 per QALY gained.

For the subsequent years after lung transplant, the company took the 59% survival at five years from the NHS BT report, and estimated an annual probability of death of 7.90%.[81] Clinical expert opinion provided to the ERG was consistent in reporting that survival after lung transplant is generally poor, with one clinical expert saying that the expected survival at year 5 is 50%, and the other clinical expert advising that on average, transplanted patients are expected to live between 5 and 10 years.

Furthermore, Anyanwu *et al.* 2002, an economic evaluation of lung transplantation in UK patients which used 15 years of data from the UK Cardiothoracic Transplant Audit, suggests that survival at year 5 is around 50%, while survival around year 10 is 37% for double lung transplants (Table 39).[82]

The 1-year survival estimate used by the company (82%) is quite different from the ones estimated in Anyanwu *et al.* 2002 (around 70%).[82] The 5-year survival estimate used by the company (59%), and that suggested by the ERG's clinical experts and Anyanwu *et al.* 2002 (50%) is not dissimilar.[82] However, given that this is one of the key drivers in the economic model, the difference in these estimates has a paramount effect on the final ICER. Given the need to explain the impact on lung density-related mortality in the context of its interaction with the estimation of overall survival in the economic analysis, a more detailed discussed is provided in Section 5.4.7.2.

Table 39. Survival estimates from Anyanwu *et al.* 2002[82]

Category	Survival with and without transplantation (%)				
	1 year	3 year	4 year	10 year	15 year
Waiting list					
KM (observed)	66	39	29	-	-
Weibull (extrapolated)	67	37	29	5	0
Single-lung transplantation					
KM (observed)	72	55	43	-	-
Weibull (extrapolated)	71	55	49	31	24
Double-lung transplantation					
KM (observed)	69	59	51	-	-

Weibull (extrapolated)	69	55	51	37	30
Heart-lung transplantation					
KM (observed)	69	57	54	-	-
Weibull (extrapolated)	71	57	53	41	34

5.4.7 Mortality

5.4.7.1 Lung function-related mortality

The ERG is concerned with the lack of transparency in the company's reporting of its modelling approach for mortality. Sufficient details were not provided in the CS and, more importantly, the ERG considers that data were presented in a potentially misleading way. Therefore, the ERG does not provide the standard initial description section of the company's approach, but instead proceeds to a combination of description and critique of the latter.

The company used RAPID and RAPID-OLE data to model mortality for the duration of the trial follow-up period. The data used by the company to model mortality in years 1, 2, 3 and 4 for Respreeza patients, and in years 1 and 2 for BSC patients are presented in Table 40. Thereafter, the company used the analysis by Green *et al.* to extrapolate mortality in the long-term economic analysis.[76] Green *et al.* analysed UK registry (ADAPT) data for patients with A1PI deficiency, and categorised lung function decline using the same thresholds as the company.[76, 78] Mortality data in the study were analysed in a multivariate Cox regression by lung function decline (ND, SD and RD) and FEV1 categories (>50%, ≥30%-≤50% and <30%).

The company didn't report how the "transition" from using the trial data to the registry data was modelled in their analysis. At year 4 in the Respreeza arm, and year 2 in the BSC arm, the company matched patients' cumulative survival from RAPID (Table 40) to its closest next value in the registry cumulative survival data (Table 41). The company then took the corresponding death hazard for the following year in the registry data (Table 41). From that year on, the company applied the registry hazards to model patients' survival in the economic analysis (Table 42 and Table 43).

The ERG has several concerns with the company's approach. Firstly, the ERG disagrees with using RAPID data given that only five events were observed over the 4-year follow-up period (two in the Respreeza arm and three in the BSC arm). The use of trial data is further compromised by the ERG's concerns around baseline imbalances, and placebo patients crossing over to the Respreeza arm of RAPID-OLE after 2 years, without any data adjustments.

Secondly, the company's approach to "transitioning" from the trial survival to the registry survival curve leads to a paramount overestimation of the survival benefit associated with Respreeza. In addition

to the survival gain derived from the trial data during the first 2 years of the model (where data for both Respreeza and BSC patients are available, Table 40), the company is artificially giving Respreeza patients extra years to "catch up" to BSC patients' death rate. This can be observed through comparison of Table 42 and Table 43, where it is shown that it takes Respreeza patients an additional 3 (or 2 depending on FEV1 category) years to "catch up" to the same mortality rate as BSC patients. This underestimates survival in the BSC arm, and overestimates survival in the Respreeza arm of the model. Given the ERG's consideration that RAPID data should not be used in the analysis, the ERG did not explore other transition methods from the RAPID to the registry survival data.

Thirdly, the company's approach assumes that survival in the RAPID, and in the ADAPT registry populations is the same, as patients simply join from RAPID survival curves into registry survival curves from ADAPT, without any data adjustments. Looking at the data in Table 40 and Table 41, the survival for placebo patients in RAPID for year 1 and 2 (97.70% and 96.55%) is much lower than the survival reported for the ADAPT registry patients, with the exception of rapid decline patients in the FEV<50% category. Therefore, survival data are not comparable in these sources, and thus cannot be used interchangeably, possibly because survival estimates from RAPID are unreliable, given the extremely small number of events.

The ERG asked the company to run a scenario analysis using only registry data to model survival. The company's scenario analysis increased the ICER from £236,409 to £280,942. However, the company implemented its scenario analysis incorrectly, as patients in the Respreeza and in the BSC arms of the model were still joining the registry survival data at different points in the curve, therefore implicitly assuming a survival benefit with Respreeza which was not linked to anything in the model, but simply a legacy calculation from the company's base case approach. When the ERG corrected the company's scenario analysis and applied only the registry survival data to the model, the company's base case ICER went from £236,409 to £940,650 per QALY gained. Using only the Green *et al.* data to model lung density-related survival in the model is consistent with the company's proposed value of Respreeza, which is that it delays lung density decline in patients, which in turn reduces patients' mortality.[76]

Nonetheless, the ERG also has several issues with the use of registry data by Green *et al*. and the company's reporting of the latter.[76] The ERG discusses these issues below.

Table 40. Deaths observed in RAPID and RAPID-OLE

Year	Respreeza				Placebo			
	Number of patients	Number of deaths	Annual probability of death	Cumulative survival	Number of patients	Number of deaths	Annual probability of death	Cumulative survival
1	93	1	1.08%	98.92%	87	2	2.30%	97.70%
2	92	0	0.00%	98.92%	85	1	1.18%	**96.55%**
3	140	1	0.71%	98.22%	-	-	-	-
4	139	0	0.00%	**98.22%**	-	-	-	-

Table 41. Mortality from UK registry data

t	FEV1>50%			FEV1<50%								
				No decline			Slow decline			Rapid decline		
	S(t)	h	Dif	S(t)	h	Dif	S(t)	h	Dif	S(t)	h	Dif
0	100.0%	0.00	0.33%	100.0%	0.00	0.01%	100.0%	0.00	0.77%	100.0%	0.00	1.62%
1	99.7%	0.00	0.49%	100.0%	0.00	0.15%	99.2%*	0.01	1.24%	98.4%*^	0.02	2.48%
2	99.2%	0.01	0.73%	99.8%	0.00	0.55%	98.0%^	0.02	1.98%*	95.9%	0.04	3.78%*^
3	98.5%*	0.02	1.08%	99.3%*	0.01	1.32%	96.1%	0.04	3.16%^	92.3%	0.08	5.74%
4	97.4%^	0.03	1.61%*	98.0%^	0.02	2.54%*	93.0%	0.07	5.02%	87.0%	0.14	8.68%
5	95.8%	0.04	2.39%^	95.5%	0.05	4.27%^	88.3%	0.12	7.94%	79.5%	0.23	13.02%

Abbreviations: FEV1: forced expiratory volume in 1 second; ND: no decline; SD: slow decline; RD: rapid decline.

* Point in registry survival data matched with Respreeza data from RAPID (previous table)

^ Point in registry survival data matched with BSC data from RAPID (previous table)

Table 42. Probability of death for Respreeza arm of the model

t	FEV1>50%	FEV1<50%		
		No decline	Slow decline	Rapid decline
1	1.08%	1.08%	1.08%	1.08%
2	0.00%	0.00%	0.00%	0.00%
3	0.71%	0.71%	0.71%	0.71%
4	0.00%	0.00%	0.00%	0.00%
5	1.61%	2.54%	1.98%	3.78%
6	**2.39%**	**4.27%**	**3.16%**	**5.74%**
7	3.54%	6.55%	5.02%	8.68%

Table 43. Probability of death for BSC arm of the model

t	FEV1>50%	FEV1<50%		
		No decline	Slow decline	Rapid decline
1	2.30%	2.30%	2.30%	2.30%
2	1.18%	1.18%	1.18%	1.18%
3	**2.39%**	**4.27%**	**3.16%**	3.78%
4	3.54%	6.55%	5.02%	**5.74%**
5	5.22%	9.41%	7.94%	8.68%

6	7.67%	12.85%	12.44%	13.02%

Relationship between lung density decline and survival

The company uses the Green *et al*. study to substantiate that rapid CT lung density decline is associated with death (p=0.026), while slow lung density decline and no decline have a similar impact on survival (p=0.065). [76] The company then points to [redacted], also provided in Green *et al.*, to demonstrate the latter analysis (CS, page 169).[76] The company also reported that since the FEV1>50% category showed counter-intuitive results ([redacted]).

Furthermore, in their original analysis, the company assumed that since [redacted] FEV1 30-50% survival was representative of FEV1<50% survival. Given the ERG's request, and the company's agreement, to disaggregate their original health state of FEV1<50% in the model into 30%≤ FEV1%<50% and FEV1<30%, the ERG expected the company to have updated their survival analysis accordingly, and used the respective population survival groups reported in Green *et al*. which are a perfect match to the company's modelled FEV1 groups.[76] Nonetheless, inspection of the economic model suggests that the company is using the FEV1 30-50% survival data from Green *et al*. to model survival for 30%≤ FEV1%<50% and FEV<30% states in the model.[76] The ERG disagrees with this simplification and considers that the company should have used the appropriate survival data to model each FEV1 category in the analysis.

Figure 10: [redacted]

(A)

Figure redacted - AIC

(B)

Figure redacted - AIC

(C)

Figure redacted - AIC

The company uses [redacted] to substantiate its descriptive analysis of the association between lung density decline and survival. However, the p-values reported by the company are from a different analysis reported in Green *et al*. and, therefore, do not corresponded to the survival analysis reported in [redacted].[76] Green *et al*. analysed [redacted]

The corresponding figure to this analysis is reported by the ERG in [redacted]. Therefore, the company's reported statistically significant association between rapid decline and death that was not based on desegregated FEV1 categories.

The analysis corresponding to [redacted], reported in Green *et al*. was based on [redacted]

[redacted]

In summary, the survival data used by the company are not statistically significantly associated with lung density decline. For FEV1>50% patients, the company used [redacted]. The authors of the latter analysis (Green *et al*.) concluded that in the [redacted].[76] With regards to 30%≤ FEV1%<50% and FEV1<30% patients, the company used the FEV1 30-50% survival data from Green *et al*., which again, the authors concluded did not show a statistically significant association with lung density decline.[76]

Contrarily to the company's view, the ERG concludes that the measure of the impact of declining CT lung function, by FEV1 group, on mortality is not well established, and neither is the impact of augmentation therapy on the latter.

Figure 11: [redacted]

Figure redacted - AIC

Green *et al*. 2016, used the same data and similar methods of analysis to Green *et al*., and aimed to determine whether changes in CT density related to survival.[1, 76] The study acknowledged that CT density has been the primary outcome measure for RCTs of augmentation therapy in A1PI, as it is more sensitive to change than other outcomes, despite densitometry having been considered an insufficiently validated outcome with reference to 'hard' outcomes like survival and QoL. The authors divided

patients into two groups for each measure of CT density: no decline and decline. This differs from Green *et al*. which defined categories of lung density decline using the 2 g/L threshold (the same categories as the company's analysis).[1, 76]

The authors' analysis showed that lower zone density decline was associated with subsequent death (p=0.048) (no stratification by FEV1 status). The authors explain that augmentation therapy typically results in a slowing of CT density change approaching 1 g/L/year in whole lung density, but the effect varies according to the region scanned, being most marked in the lower zone. The authors conclude that the magnitude of the difference in whole lung density decline between survivors and those who died (0.81g/L/year) was less than the difference in density that augmentation typically provides, suggesting that augmentation might improve survival, though this has not been confirmed in trials to date. The authors added that the latter was not surprising, given trial's typical follow-up periods of 3 years, and analysis of Kaplan-Meier (KM) plots reported in the study, which suggest deaths generally occur beyond this point in time.

Stratified analysis by FEV1 category undertaken by the authors, showed that for FEV1<30%, neither lower zone CT density (p=0.255), nor whole lung density (p=0.286) decline associated with survival. In patients with FEV1 30-50% lower zone decline in densitometry showed an apparent trend toward poor survival, at least visually, though this was not statistically significant for lower or whole lung density decline. In patients with FEV1 >50% lower zone CT density decline related to death (p=0.024) but whole lung density did not (p=0.198). The authors reinforced that the lack of statistically significance in their analysis could presumably be related to inadequate power, as the number of deaths per group was low, however, explained that the size of the primary cohort (n=76) was close in size to the placebo group of the RAPID trial, and equal to the number enrolled in EXACTLE (the two most recent RCTs of augmentation therapy for A1PI deficiency) [11].

In summary, the ERG considers that both Green *et al.* papers show a trend in the association between lung density decline and mortality, albeit failing to demonstrate a statistically significant predictive effect. The strongest association seems to be that of rapid lung density decline and increased mortality, in the entire A1PI deficiency population, without differentiating by FEV1 status. Even though the ERG acknowledges that the use of Green *et al*. data to model survival might reflect the best available data, caution is needed when interpreting the survival outcomes in the economic analysis.[76] Mortality gains associated with Respreeza in the model are linked to the drug's impact to slow patients' decline through lung density and FEV1 categories, which have not been shown to be statistically significantly associated with survival.

Extrapolation of survival data

The company digitised the Green *et al*. survival curves, in order to fit survival functions to these data and extrapolate survival into the long-term economic analysis.[76] During the clarification stage, the ERG asked the company to assess the goodness of fit (AIC, BIC, visual inspection and clinical plausibility) of the loglogistic, lognormal, exponential, Gompertz, Weibull and gamma distributions for the different survival curves used. The company replied that, "*based on the AIC values* […] *a Gompertz function was used for FEV1>50%, a Weibull function was used for patients with an FEV1<50% with no decline in lung density, and a Gompertz function was used for the two remaining health states."*

Despite the ERG's request, the company did not provide BIC statistics. The company's AIC statistics, provided in Table 44, show that the company's choices seem appropriate (albeit only based on AIC statistics), with the exception of the RD categories, which the company modelled with a Gompertz distribution, but for which the gamma seems to provide a better fit.

Despite the ERG's request for the company to include an option in the economic model to choose between the loglogistic, lognormal, exponential, Gompertz, Weibull and gamma distributions, the company decided to exclude the gamma distribution from the list of alternative curves to use in the model. Furthermore, the company has not provided the KM data used in the model from Green *et al*.[76]

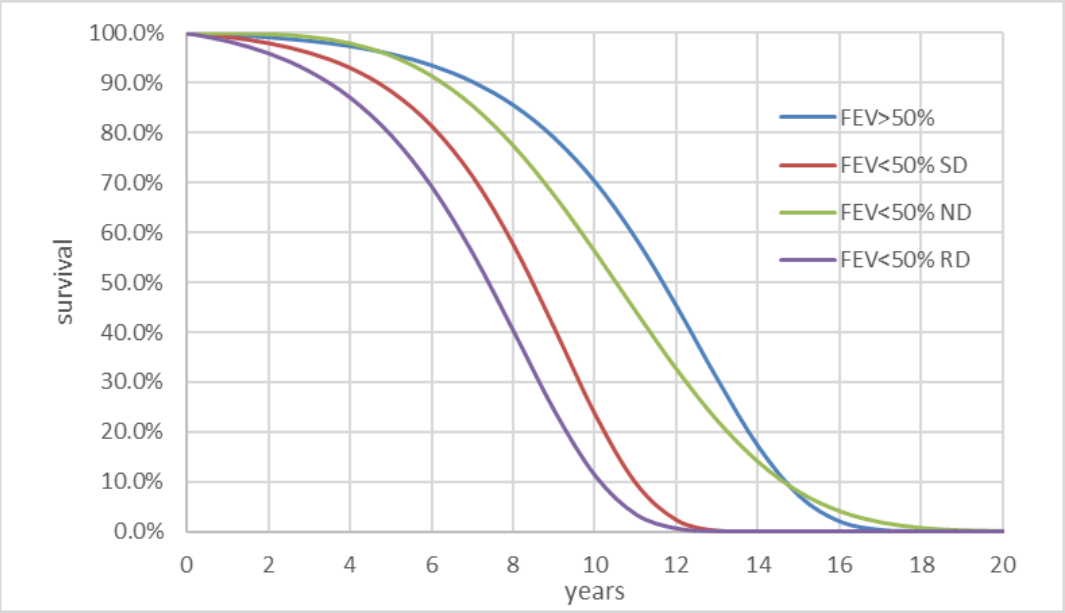
Table 44. Assessment of fit of parametric survival functions to the UK registry data (Table 36, CS)

	FEV_1 >50% predicted	**FEV_1 30-50% predicted**			**FEV_1 <30% predicted**		
		No decline	**Slow decline**	**Rapid decline**	**No decline**	**Slow decline**	**Rapid decline**
Weibull	88.756	17.818	65.074	48.995	33.695	56.473	65.013
Exponential	93.683	18.313	75.920	56.781	37.491	65.360	74.477
Lognormal	90.891	17.855	67.083	50.295	34.099	58.935	78.189
Generalised gamma	90.208	19.855	64.607	48.397	35.691	-	51.033
Gompertz	86.837	17.829	64.112	48.651	33.998	56.240	53.378
Loglogistic	89.297	17.937	66.967	50.687	33.877	58.336	71.948

This reinforces the ERG's concern with the lack of transparency in the company's approach, and with the exclusion of the gamma distribution from the economic model, without any justification. Furthermore, the ERG notes that the survival analysis is based on non-statistically significant data. The extrapolated survival curves used by the company are reported in Figure 12, which show a lower survival for RD patients, followed by SD patients. Survival curves for FEV1<50% ND and FEV1>50% patients cross, but separate substantially in the middle. This might be a reflection of the lack of statistical

significance of lung density decline as a predictor of survival, when patients are stratified by FEV1 status.

Figure 12. Extrapolated survival curves used in the model



5.4.7.2 Synergies in the economic model

In the company's base case, where RAPID survival data are included in the analysis, patients who receive Respreeza accrue incremental life years in all the FEV1 lung density decline states, as well as in the lung transplant states (Table 45).

Use of UK registry data in the analysis

When the ERG included only registry survival data in the model, the incremental life years gained decreased overall (as the company's base case overestimates survival with Respreeza and underestimates survival with BSC), and the incremental life-years in the FEV1<30% categories become close to zero (Table 46). Fewer Respreeza patients move to the 30%≤ FEV1%<50% category, compared to BSC patients, therefore, also accruing fewer life years in that state.

The biggest drop in life-years gained from the company's base case analysis, to the ERG's analysis, is in the lung transplant state, which decreased from 1.39 to 0.03 incremental life-years with Respreeza. Given that the ERG only changed the estimation of FEV1 lung density decline-related mortality, the change in life-years gained after lung transplant is a direct consequence of fewer Respreeza patients reaching the FEV1<30% state, where patients become eligible for transplant.

The life-years gained in this scenario are consistent with the company's base case transition probabilities, which suggest that patients on Respreeza are less likely than BSC patients to transition

from the FEV1≥50% to the 30%≤ FEV1%<50% category, but that patients on the latter FEV1 category have a similar probability of transitioning to the FEV1<30% category across treatment arms. Therefore, removing the RAPID survival data from the analysis, and more importantly, removing the company's approach of allocating Respreeza and BSC patients to different points in the registry survival curves, removes "noise" from the company's analysis and leads to a generation of incremental life-years consistent with the company's base case transition probabilities.

The change in ICER caused by the removal of RAPID survival data (from £236,409 to £940,650) also shows how, perhaps counterintuitively, avoiding lung transplants in the Respreeza arm of the model is detrimental to the company's ICER (i.e. the ICER increases). This is because lung transplant in the model is associated with a considerable improvement in quality of life and survival, and the total costs of lung transplant are not enough to offset this gain when considerably more patients in the Respreeza arm receive lung transplants than patients in the BSC arm.

Table 45. Undiscounted life years gained in company's base case analysis (ICER £236,409)

Health state	Undiscounted life years		
	BSC	Respreeza	Incremental
FEV1>50%: No decline	0.04	0.17	0.13
FEV1>50%: Slow decline	1.33	2.04	0.71
FEV1>50%: Rapid decline	0.39	0.44	0.05
Total	**1.76**	**2.65**	**0.89**
30%<FEV1<50%: No decline	0.07	0.33	0.26
30%<FEV1<50% Slow decline	1.46	2.92	1.47
30%<FEV1<50% Rapid decline	1.79	0.66	-1.13
Total	**3.32**	**3.91**	**0.60**
<30% ND	0.01	0.10	0.09
<30% SL	0.37	0.90	0.53
<30% RD	0.56	0.19	-0.37
Total	**0.93**	**1.18**	**0.25**
Lung transplant: first year	0.35	0.47	0.12
Lung transplant: subsequent years	3.59	4.85	1.27
Overall total	**9.94**	**13.07**	**3.13**

Table 46. Undiscounted life years gained in ERG's scenario using registry mortality data (ICER £940,650)

Health state	Undiscounted life years		
	BSC	Respreeza	Incremental
FEV1>50%: No decline	0.04	0.17	0.13
FEV1>50%: Slow decline	1.56	2.04	0.47
FEV1>50%: Rapid decline	0.43	0.43	0.01
Total	**2.03**	**2.64**	**0.62**

30%<FEV1<50%: No decline	0.07	0.29	0.23
30%<FEV1<50% Slow decline	1.57	2.57	1.00
30%<FEV1<50% Rapid decline	1.88	0.59	-1.29
Total	**3.52**	**3.45**	**-0.07**
<30% ND	0.01	0.09	0.08
<30% SL	0.40	0.74	0.34
<30% RD	0.58	0.15	-0.43
Total	**0.99**	**0.98**	**-0.01**
Lung transplant: first year	0.37	0.38	0.00
Lung transplant: subsequent years	3.84	3.87	0.03
Overall total	**10.75**	**11.32**	**0.57**

Use of different meta-analysis estimates

Using the ERG's proposed results from the meta-analysis, but maintaining the company's approach to using RAPID survival data, shows that Respreeza patients still accrue more life years in all the FEV1 states, including the lung transplant states (Table 47). However, the gain in life-years shifted from the FEV1≥50% to the 30%≤ FEV1%<50% category, compared with the company's base case (Table 45). This is broadly in line with the ERG's corrected transition probabilities (Table 36), which show that patients on Respreeza are equally likely to transition from the FEV1≥50% to the 30%≤ FEV1%<50% category as BSC patients, and that the latter have a lower probability of transitioning to the FEV1<30% compared with BSC patients. Nonetheless, the life-years gained in the economic analysis are not perfectly consistent with the ERG's transition probabilities, until the ERG included only registry mortality data in the model.

Use of UK registry data and different meta-analysis estimates

The combination of both changes to the company's model (Table 48, dominated ICER of -£5,898,567) decreased the overall survival benefit with Respreeza (overestimated in the company's base case analysis) and increased the survival benefit with BSC, and indeed generated no incremental life-year in the FEV1≥50% category as expected, given the ERG's use of a relative risk of 1 for Respreeza and BSC patients progressing from the FEV1≥50% to the 30%≤ FEV1%<50% category.

The biggest gain in survival with Respreeza is derived in the 30%≤ FEV1%<50% category, as more Respreeza patients stay in these states than BSC patients. More patients in the BSC arm of the model spend time in the FEV1<30% states, and therefore, there are more lung transplants in the BSC arm of the model, than in the Respreeza arm.

The utility associated with FEV1<30% is lower than the utility associated with 30%≤ FEV1%<50% category (0.63 vs 0.51); however, the utility associated with lung transplant after 2 years is higher than both (0.77). Moreover, survival in the lung transplant state is higher than in the FEV1<30% states, therefore, the treatment that allocates more patients to lung transplants, is the most likely to generate an additional clinical benefit in the economic analysis. Ironically, avoiding lung transplants is one of the outcomes that the company sets out to be Respreeza's biggest benefit (i.e. to slow down disease's progression and avoid lung transplants).

Use of UK registry data; different meta-analysis estimates, and reducing the proportion of patients eligible for lung transplant

Reducing the number of patients eligible for lung transplant by 30% (Table 49, dominated ICER) means that overall, more patients stay in the FEV<30% state, thus overall, fewer patients receive a lung transplant. Therefore, the negative incremental life-years and QALYs associated with Respreeza decrease from -0.15 to -0.07, but still generating a dominated ICER for Respreeza.

Use of UK registry data; different meta-analysis estimates; reducing the proportion of patients eligible for lung transplant, and reducing the survival benefit associated with lung transplant

When the survival benefit associated with lung transplant is reduced, the incremental QALYs become positive in the model (Table 50, ICER £10,468,323). The ERG replaced the company's survival estimates at year 1 and year 5 (82% and 59%, respectively), by an approximation of the Anyanwu *et al.* 2002 and ERG's clinical experts' estimates (around 70% for year 1 and 50% for year 2).[82] Reducing the survival benefit associated with lung transplant means that the benefit derived by Respreeza patients in the 30%≤ FEV1%<50% category is enough to offset the benefit derived by BSC patients in the lung transplant states.

It is therefore, crucial that the Committee discusses which health state – the 30%≤ FEV1%<50% or the post-lung transplant states – is likely to be associated with higher benefits in terms of quality of life and survival. It is also important to discuss if the goal of treatment with Respreeza is: i) to maintain patients in the 30%≤ FEV1%<50% state for the longest time possible, avoiding lung deterioration to FEV<30% and, thus, lung transplant (which the ERG's adapted model demonstrates); or ii) to allow more patients to transition to a lung transplant.

Given the small QALY gain generated with Respreeza in the 30%≤ FEV1%<50% state, and the very high costs associated with treatment, the ICERs generated in the ERG's analysis are unlikely to be considered cost-effective.

Table 47. Undiscounted life years gained in ERG's scenario using different meta-analysis results (ICER £316,685)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.33	1.54	0.20
FEV1>50%: Rapid decline	0.39	0.35	-0.03
Total	**1.76**	**2.03**	**0.27**
30%<FEV1<50%: No decline	0.07	0.43	0.37
30%<FEV1<50% Slow decline	1.46	3.92	2.46
30%<FEV1<50% Rapid decline	1.79	0.85	-0.94
Total	**3.32**	**5.20**	**1.88**
<30% ND	0.01	0.08	0.07
<30% SL	0.37	0.75	0.38
<30% RD	0.56	0.15	-0.41
Total	**0.93**	**0.98**	**0.05**
Lung transplant: first year	0.35	0.38	0.04
Lung transplant: subsequent years	3.59	3.95	0.36
Total	**9.94**	**12.54**	**2.60**

Table 48. Undiscounted life years gained in ERG's scenario using registry mortality data and different meta-analysis results (ICER -£5,898,567)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.07	0.06
<30% SL	0.40	0.60	0.19
<30% RD	0.58	0.12	-0.46
Total	**0.99**	**0.79**	**-0.21**
Lung transplant: first year	0.37	0.30	-0.08
Lung transplant: subsequent years	3.84	3.05	-0.79

Total	**10.75**	**10.60**	**-0.15**

Table 49. Undiscounted life years gained in ERG's scenario using registry mortality data, different meta-analysis results and reducing the proportion of patients eligible for lung trabsplant by 30% (ICER -£37,189,197)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.09	0.08
<30% SL	0.51	0.75	0.23
<30% RD	0.72	0.15	-0.57
Total	**1.24**	**0.99**	**-0.26**
Lung transplant: first year	0.32	0.26	-0.07
Lung transplant: subsequent years	3.31	2.64	-0.67
Total	**10.42**	**10.35**	**-0.07**

Table 50. Undiscounted life years gained in ERG's scenario using registry mortality data, different meta-analysis results, reducing the proportion of patients eligible for lung trabsplant by 30% and decreasing lung transplant-related survival (ICER £10,468,323)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.09	0.08
<30% SL	0.51	0.75	0.23
<30% RD	0.72	0.15	-0.57

Total	**1.24**	**0.99**	**-0.26**
Lung transplant: first year	0.32	0.26	-0.07
Lung transplant: subsequent years	2.88	2.30	-0.59
Total	**9.99**	**10.01**	**0.02**

5.4.8 Adverse events

In the RAPID study, 1% of the population in the Respreeza arm and 1% of the population in the placebo arm had a serious treatment-related adverse event. Therefore, the company assumed no additional costs due to adverse events in the model. Additionally, the small number of adverse events that occurred more frequently in the Respreeza arm of RAPID, were not expected to have a significant impact on HRQoL

5.4.8.1 ERG critique

The ERG consulted with its clinical experts who agreed that it was reasonable to exclude adverse events from the model as there are no relevant side effects of Respreeza that could affect the management of the condition, or patients' quality of life.

5.4.9 Health-related quality of life

5.4.9.1 Health-related quality of life data used in cost-effectiveness analysis

As no generic measures of HRQoL were captured in the RAPID trial, the quality of life analysis was informed by published utility data. However, as described in Section 5.3, the company did not identify any relevant utility data from the SLR to inform the model. As a result, the company obtained EQ-5D utility values from the ADAPT UK registry dataset (Ejiofor and Stockley 2015), which provides EQ-5D values by FEV1 predicted state, for patients with A1PI deficiency.[83] During the clarification stage, the company also added that Ejiofor and Stockley 2015 is the only study that has reported EQ-5D data for patients with A1PI deficiency, by disease severity in a UK population.[83] A description of the data included in the study, and used to inform the model, is provided in Table 51.

Table 51. Utilities by FEV1% predicted

FEV1% predicted	Mean utility (SD)	Number of patients
Data from the UK registry (Ejiofor and Stockley, 2015)[83]		
<30	0.51 (0.20)	26
30-35	0.53 (0.22)	15
35-40	0.59 (0.14)	12
40-45	0.61 (0.16)	13
45-50	0.73 (0.20)	20
>50	0.79 (0.18)	158
Values used in the model		
≥50	0.79 (0.18)	158

30-50*	0.63 (0.19)	60
≤30	0.51 (0.20)	26
*A weighted average of the utilities of patients with a predicted FEV1 30-35%, 35-40%, 40-45% and 45-50% was taken to derive the utility for the FEV1 30-50% predicted		

The company assumed no difference in HRQoL between patients in different lung density decline health states (no, slow and rapid decline). Therefore, the company assumed that HRQoL is driven only by FEV1 predicted in the model, but stated that this is unlikely to capture the full quality of life of patients with A1PI deficiency, and used the Green *et al*. to substantiate this.[76] This study used the UK registry data to perform a Cox regression analysis, including baseline density and decline in CT densitometry as covariates for assessing changes in quality of life. This study is discussed in detail in the next subsection of the ERG report.

After a clarification request from the ERG, the company used the Anyanwu *et al.* 2001 study to estimate the impact of lung transplant on patients' quality of life.[84] Anyanwu *et al.* 2001 collected EQ-5D data from 185 UK patients and reported utility values according to the type of lung transplant (single or bilateral) and further according to the number of months after transplantation, up to 36 months after transplantation.[84]

A description of the data included in Anyanwu *et al.* 2001, and used to inform the model, is provided in Table 52.[84] The utility value used for the first year after transplant was based on an average of the score from 0 to 6 months and 6 to 18 months, while the utility for subsequent years was based on an average of the utility from 19 to 36 months and >36 months. Following a review of lung transplants in end-stage COPD patients, the company found that 75% of patients with A1PI deficiency received a double lung transplant in 2005 (Aziz *et al*. 2010) and therefore, calculated a weighted average across single and double transplants to reflect this in their analysis.[85] The derived utilities were 0.76 in the first year of transplant, and 0.77 thereafter.

Table 52. Mean (SD) utility scores after lung transplantation reported by Anyanwu *et al*. 2001[84]

Months after transplant	Single LT utility (SD)	Bilateral LT utility (SD)
Data from Anyanwu *et al.* 2001		
0 to 6	0.69 (0.31)	0.75 (0.17)
7 to 18	0.66 (0.21)	0.83 (0.17)
19 to 36	0.65 (0.24)	0.81 (0.19)
>36	0.61 (0.31)	0.82 (0.19)
Values used in the model		
First year of LT (year 1)	0.76	
Subsequent years following LT (years 2+)	0.77	
Abbreviations: LT, lung transplant; SD, standard deviation		

In a scenario analysis, the company also adjusted utilities to incorporate the EQ-5D utilities reported by age and sex in the Kind *et al*. 1999 study.[86] However, the methods used to perform this scenario were not explained by the company in their clarification response. For completeness, the ERG investigated the economic model, and provides a description of the company's scenario analysis based on its interpretation of the former.

The company assumed that in the second and subsequent years after a lung transplant, patients would experience the same utility as the general UK population who were of the same age and gender (i.e. the company applied a decrement of zero to the Kind *et al*. 1999 utilities). For the remaining health states, including the FEV1 lung density decline states, the company used the second and subsequent years-related utility (0.77) as the reference utility, and calculated utility decrements by comparing the latter with the values used in the base case, as illustrated in Table 53. Those utility decrements were then subtracted from perfect health (utility value of one) to calculate a multiplier, described as a "relative difference" in the model (Table 54). Using a linear interpolation of the general UK population utilities reported by Kind *et al*. 1999[86], the company multiplied general UK population utilities in each cycle by the relative differences reported in Table 54. Following this, utilities declined with age.

Table 53. Calculation of utility decrements (scenario analysis)

Health state	HSUV	Source	Reference utility from Anyanwu *et al.* 2001 (LT: year 2+)	Decrement applied to general UK population estimate
FEV1 ≥50% predicted	0.79	Ejiofor and Stockley, 2015[83]	0.77	-0.02
FEV1 30-50% predicted	0.63			0.14
FEV1 ≤30% predicted	0.51			0.26
LT: year 1	0.76	Anyanwu *et al.* 2001[84]		0.01
LT: year 2+	0.77			0.00
Abbreviations: FEV, forced expiratory volume; HSUV, health state utility value; LT, lung transplant				

Table 54. Relative difference applied to population norms (scenario analysis)

Health state	Relative difference (1- utility decrement)
FEV1 ≥50% predicted	1.02
FEV1 30-50% predicted	0.86
FEV1 ≤30% predicted	0.74
LT: year 1	0.99
Abbreviations: FEV, forced expiratory volume; LT, lung transplant	

Finally, the ERG notes that in the decision problem pro-forma for this submission, it was reported that evidence from a European study including EQ-5D data was likely to become available during the evaluation. However, during the clarification stage the company explained that the study has been delayed and as such, the data is no longer anticipated within the timing of the NICE HST evaluation.

5.4.9.2 ERG critique

Overall, the ERG has three concerns regarding the company's analysis of quality of life in the model, including the generalisability of Ejiofor and Stockley 2015; the application of age-related utility decrements, and the company not attempting to model the impact of lung density decline on patients' quality of life.[83]

Ejiofor and Stockley 2015 was sent to the ERG as an abstract document, providing a limited description of the results and study population.[83] Based on the abstract, the proportion of male patients and body mass index (BMI) was similar between the populations in Ejiofor and Stockley 2015 and the RAPID trial (55% versus 54% and 26.04 versus 25.33). However, patients in Ejiofor and Stockley 2015 were older (58 years versus 53 years) and according to the total SGRQ score (50.9 versus 43.4), may have a slightly worse quality of life at baseline than RAPID patients. As such, the utility values implemented in the model could be underestimated, compared with the population in RAPID.

As requested by the ERG, the company used Anyanwu *et al.* 2001 to inform lung transplant-related utilities in the revised model.[84] However, in doing so, the company removed the age-related utility decrements applied in their original model. A scenario analysis was explored by the company to account for age-adjusted utilities, but the ERG is concerned that the company provided no justification as to why 0.77 (utility used for the second and subsequent years after a lung transplant) was chosen as the reference utility, or why the relative decrement was calculated from a utility of perfect health (with a value of 1). Ideally, the company should have implemented the published algorithm by Ara *et al.* 2010 to estimate age-adjusted utilities, which is based on a published, peer-reviewed methodology.[87] However, due to time constraints and limitations regarding the model structure, the ERG did not implement this in the model. The magnitude of the impact of adjusting utilities by age is unknown.

Finally, the company stated that the benefits of Respreeza may be underestimated by not capturing the effect of reducing lung density decline on HRQoL, however, it states that there were no data to allow such analysis. The company presented one of two analyses from the Green *et al.* looking at the impact of lung density decline in HRQoL.[76] The analysis reported by the company found [redacted] This is illustrated in Figure 13.

The second analysis in the manuscript, not reported by the company, showed [redacted]

[redacted] This is illustrated in Figure 14.

Although the second analysis is based on smaller patient numbers, and given that the definition of lung density in Green *et al.* is the same as the definition used by the company in its analysis of lung density decline, the ERG is concerned that the company did not use this source to model differences in HRQoL, according to baseline lung density and lung density decline.[76] Instead, the company states that there are no available data to conduct such analysis, and argues that the benefits of Respreeza may be underestimated in the analysis, without additional modelling to try and mitigate its concerns. The company's approach is also inconsistent with its overarching rationale for including lung density outcomes in the health states of the economic model, and in the overall economic analysis.

Figure 13. [redacted] (reproduced from Figure 39 of the CS)

Figure redacted - AIC

Figure 14. [redacted][76]

Figure redacted - AIC

5.4.10 Resources and costs

The costs included in the model are listed below and discussed in detail in this section:

- Acquisition and administration costs associated with the intervention (Section 5.4.10.1);
- Disease management costs (Section 5.4.10.2);
- Lung transplant costs (Section 0).

5.4.10.1 Acquisition and administration costs associated with the intervention

Respreeza is available based on a maximum NHS list price, which was agreed with the Department of Health and Social Care in 2016 (NHS Business Authority, 2018).[37] As for administration costs, unit costs were sourced from NHS Reference Costs 2016-17.[88] Drug acquisition and administration costs used in the model for Respreeza are presented in Table 55.

The dosing schedule modelled by the company was 60mg/kg once weekly, in line with RAPID and the SmPC.[48] The resulting number of vials per week modelled by the company (five), included vial wastage and was estimated using the mean weight of patients (75.9kg) in RAPID.

In the base case analysis, it was assumed that 75% of drug administration took place at home, with a nurse administering infusions, and 25% took place at a clinic. In sensitivity analysis, the company also explored 0% and 100% of administrations at a clinic.

In the model, Respreeza was administered to patients with an FEV1≥50% or 30%≤FEV1<50%, regardless of the rate of decline. Patients with an FEV1<30%, or receiving a lung transplant, did not receive Respreeza.

Table 55. Respreeza acquisition and administration costs (adapted form Tables 50 and 51 of the CS)

Treatment cost item	Value	Source
Acquisition costs		
Price of the technology	£220 per 1000mg vial	NA
Dose	60mg/kg once-weekly	Respreeza SmPC[48]
Patient weight	75.9kg	RAPID (Chapman *et al*. 2015)[42]
Vial size	1000mg	Respreeza SmPC[48]
Number of vials required per dose	4.55	Calculated
Actual vials used	5	Rounded up to account for wastage
Cost per administration	£1100	Calculated
Annual treatment cost per patient assuming weekly infusion (excludes cost of administering the infusion)	£57,200	Calculated
Administration costs		
Proportion of nurse-administered infusion at patient's home	75%	Assumption
Proportion of nurse administered infusion at clinic	25%	Assumption
Cost of nurse-administered infusion at patient's home	£36.93	NHS Reference Costs, 2016-17, N02AF, District Nurse, Adult, Face to face[88]
Cost of nurse administered infusion at clinic	£68.12	NHS Reference Costs, 2016-17, N29AF, Other Specialist Nursing, Adult, Face to face[88]
Cost per treatment administration per patient	£44.72	Calculated
Annual cost per patient assuming 52 administrations per year	£2,326	Calculated
Total costs		
Annual cost per patient assuming 52 administrations per year	£59,526	Calculated
Abbreviations: NA, not applicable; SmPC, summary of product characteristics		

5.4.10.2 Disease management costs

As noted in Section 5.3, the company's SLR did not identify resource or cost use evidence in the UK to manage patients with A1PI deficiency. As a result, the costs of managing patients with COPD were used as a proxy.

Disease management costs were sourced from Punekar *et al*. 2014 who undertook a retrospective analysis in 58,589 COPD patients identified from primary care in the UK.[89] Study outcomes included counts of GP interactions, moderate to severe COPD exacerbations and non-COPD hospitalisations. The authors then applied unit costs from NHS Reference Costs 2010/11, the PSSRU 2011 and BNF65 to the annual resource use counts to calculate the total annual cost for all patients, and patients with, no, one, and two or more moderate-to-severe exacerbations.[90-92] Costs were also summarised further in the study by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages. The company inflated the costs by Punekar *et al*. 2014 from 2010/11 to 2016/17 prices using the PSSRU pay and prices index.[89, 93]

The ERG was concerned that the rate of exacerbations in Punekar *et al*. 2014 might have differed from the rate observed in RAPID for each treatment arm.[89] During the clarification stage, the company replied that the annual number of exacerbations in the RAPID study was between 1.4 and 1.7 across the two treatment arms and that in the 58,589 patients with COPD in Punekar *et al*. 2014, the total number of moderate or severe exacerbations was 44,293 over a 12-month period, equating to an average annual number of exacerbations of 0.76.[89]

The company's attempt at addressing this issue was to weight the disease management costs (including moderate-to-severe exacerbations, non-COPD hospitalisations and GP surgery contacts) in the updated model by the number of patients with one, two or more exacerbations within Punekar *et al*. 2014 to try to reflect an average exacerbation rate of approximately 1.4 to 1.7.[89] Disease management costs were applied irrespective of treatment arm in the model.

Furthermore, to reflect the addition of the FEV1≤30% health state in the revised model, the company applied the disease management costs for GOLD stages 2, 3 and 4 from Punekar *et al*. 2014 to the health states relating to an FEV1% ≥50%, 30-50% and <30%, respectively.[89] Table 56 provides the data used in the company's calculations.

Table 56. Disease management costs estimated from Punekar *et al.* 2014

FEV1% predicted	GOLD stage	Exacerbation frequency	Patients included in Punekar *et al.* 2014	Cost per patient per year (2010/11 prices) reported by Punekar *et al.* 2014				Weighted cost calculated by the company (2016/17 prices)
				Exacerbations	Non-COPD hospitalisations	GP surgery contacts	Total	
≥50	2	One	7,324	£366	£739	£1,307	£2,412	£3,063[a]
		Two or more	5,693	£755	£1,002	£1,552	£3,308	
≤30-50	3	One	3,855	£348	£710	£1,332	£2,390	£3227[b]
		Two or more	4,629	£790	£1,019	£1,614	£3,423	
<30	4	One	814	£352	£682	£1,308	£2,342	£3,538[c]
		Two or more	1,411	£871	£1,137	£1,748	£3,756	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; FEV, forced expiratory volume; GOLD, Global Initiative for Obstructive Lung Disease; GP, general practitioner.

a inflation factor*((7324*2412.22+5693*3308.13)/(7324+5693))

b inflation factor*((3855*2390.06+4629*3422.57)/(3855+4629))

c inflation factor*((814*2341.71+1411*3756.23)/(814+1411))

Inflation factor = 302.3/276.7

During the clarification stage, the ERG also sought further explanation from the company as to why disease management costs were sourced from a study based on primary care (Punekar *et al.* 2014). Following this, the company agreed that patients with A1PI deficiency would also be managed in secondary care due to the complexity of their condition. To reflect this, the company added the cost of consultant-led appointments to the primary care costs obtained from Punekar *et al*. 2014.[89]

The cost of a consultation with an A1PI deficiency specialist in secondary care was estimated as £149 from NHS Reference Costs 2015-16 and it was assumed that patients with an FEV1≥50% would see a specialist twice per year, patients with a 30%≤FEV1<50% would see a specialist three times per year, while a patient with an FEV1<30% would see a specialist four times per year.[94] The total costs of disease management applied in the revised model are reported in Table 57.

Table 57. Total cost of disease management applied in the revised model

	FEV1≥50%	30%<FEV1<50%	FEV1≤30%
Disease management costs estimated from Punekar *et al*. 2014 (2016/17 prices) [89]	£3,063	£3,227	£3,538
Consultations with A1PI deficiency specialist (NHS Reference Costs 2015-16: average of WF01A and WF02A, non-admitted face to face, service code 340 and 341)[94]	£298	£447	£596
Total	£3,361	£3,674	£4,134

Abbreviations: A1PI, Alpha1-proteinase inhibitor; FEV, forced expiratory volume

Finally, no costs were identified to indicate how disease management varies by the rate of decline in lung density. Therefore, the company assumed disease management was driven by FEV1% predicted,

but explained that Respreeza is likely to be associated with lower disease management costs than BSC, given that Respreeza slows the rate of lung density decline.

5.4.10.3 Lung transplant costs

The company sourced lung transplant costs from an economic evaluation of lung transplantation in UK patients, using data from the UK Cardiothoracic Transplant Audit (Anyanwu *et al.* 2002).[82] First year costs consisted of the assessment, donor acquisition, transplant and inpatient follow-up care, while costs in subsequent years (year 3, years 4 to 10, and years 11 to 15) consisted of follow-up care based on a model developed by the Papworth unit for modelling post-transplantation costs.[95]

Costs for single and double lung transplants were reported in 1999 UK pounds, discounted at 6%. Therefore, the company estimated undiscounted costs and inflated those to 2017 costs using the PSSRU pay and prices index.[93] Costs occurring in years 3, 4 to 10, and 11 to 15 were averaged by the company to estimate the cost associated with the second and subsequent years after lung transplant. The company calculated a weighted average of single and double lung transplant costs based on the information on Aziz *et al*. 2010 from the International Thoracic Organ Transplant (ISHLT) registry, who found that 75% of patients with A1PI deficiency received a double lung transplant in 2005.[85] Following this, the company derived a cost of £76,698 in the first year after lung transplant, and a cost of £9,260 in subsequent years to inform the model (Table 58).

Table 58. Lung transplant costs (adapted from Table 54 of the CS)

Lung transplant cost item	Value	Source
Proportion of double lung transplants	75%	Aziz *et al*. 2010[85]
First year double lung transplant costs	£76,502	Anyanwu *et al*. 2002 inflated to 2017 costs[82, 93]
First year single lung transplant costs	£77,285	Anyanwu *et al*. 2002 inflated to 2017 costs[82, 93]
Subsequent years double lung transplant costs	£9,294	Anyanwu *et al*. 2002 inflated to 2017 costs[82, 93]
Subsequent years single lung transplant costs	£9,157	Anyanwu *et al*. 2002 inflated to 2017 costs[82, 93]
First year transplant costs	£76,698	Calculated
Subsequent year transplant costs	£9,260	Calculated
*Inflated to 2016/17 costs (inflation factor = 302.3/188.5)		

5.4.10.4 ERG critique

Costs are based on the 2016/17 prices, with unit costs obtained from published sources such as the NHS Reference Costs, and the PSSRU, which is in line with the NICE reference case.[88, 93, 96] The ERG validated all the costs from the sources cited, and checked that prices are correctly inflated when necessary, and that the formulae are generally correct and sound in the economic model. The ERG considers that, in the absence of resource and cost use data in patients with A1PI deficiency, using published sources in COPD patients, linked with FEV1 status, is reasonable.

Overall, the ERG has concerns regarding the impact of treatment initiation and stopping rules on Respreeza's costs; the omission of BSC costs from the model; the estimated cost of exacerbations; the omission of CT scans costs; the calculation of lung transplant costs; and the number of vials required for treatment with Respreeza. Each of these is described in turn below.

Treatment initiation and stopping rules for Respreeza

In the revised model, patients reaching the FEV1≤30% health states stop receiving Respreeza in the analysis. However, as part of the clarification process, the company reported that stopping rules for Respreeza have not been proposed and that such rules are not specified in the drug's marketing authorisation. For these reasons, the ERG considers that the costs of Respreeza are being underestimated in the company's base case and as such, ran a scenario where patients receive Respreeza until they receive a lung transplant or die. The impact of changing this assumption in the model increased the ICER from £236,409 to £275,698.

Furthermore, the ERG's clinical experts highlighted that there may be a rationale for starting treatment with Respreeza in patients with a baseline FEV1 below 30%, to salvage remaining lung function of patients who are either ineligible or on the waiting list for a lung transplant. Nonetheless, the entry criteria for RAPID limited the inclusion of these patients in the trial, meaning that there are no data available to assess the impact of Respreeza on this population.

Costs of BSC in the model

In the model, the company only costed treatment with Respreeza, based on the assumption that BSC is received in both treatment arms. However, because patients live for longer in the Respreeza arm of the model, the company is underestimating the additional costs associated with Respreeza treatment. In the CS, it clearly states, "*Respreeza is to be administered in conjunction with current symptomatic treatment (e.g. inhaled bronchodilators) where there is clear evidence of lung density decline*" (page 136 of the CS). Therefore, the ERG sought the literature to identify resource and cost use evidence for BSC in patients with COPD. Following this, the ERG identified Britton *et al.* 2003 from the NICE COPD guideline as a potential source to inform the costs of BSC in the model.[97, 98] The mean medication costs reported by Britton *et al*. 2003 from patients with COPD in the UK are provided in Table 59.[97] The ERG inflated those costs to 2016/17 prices and calculated a cost of £167.03 per year attributable to BSC. The impact of adding BSC costs to both treatment arms was minimal, increasing the ICER from £236,409 to £236,535.

Table 59. Medication costs reported by Britton *et al.* 2003[97]

Regular prescription medication	Cost year 2000/1	Cost year 2016/7*
	Estimated mean annual cost per patient	
Anticholinergics	£18.39	£28.29
Inhaled corticosteroids	£28.66	£44.09
Leukotriene receptor antagonist	£10.66	£16.40
Long-acting beta-2 agonists	£24.41	£37.55
Non-steroidal anti-inflammatory drugs	£1.79	£2.75
Short-acting beta- agonists	£23.59	£36.29
Systematic corticosteroids	£0.11	£0.17
Theophylline	£0.82	£1.26
Bupropion	£0.14	£0.22
Total	**£108.57**	**£167.03**
*Inflated using the PSSRU pay and prices index (302.3/196.5)[93]		

Cost of exacerbations in the model

During the clarification stage, the ERG requested the company to cost the exacerbations requiring oral steroids, antibiotics or hospitalisation, by treatment arm in RAPID. Instead, the company attempted to link the observed rate (EAIR) of all exacerbations in RAPID (1.4 to 1.7), irrespective of treatment arm, to the total disease management costs incurred by patients who had one, or two or more, moderate-to-severe exacerbations within Punekar *et al.* 2014.[89] The ERG has several issues with the company's approach:

1. Weighting the costs by the number of patients in the one, or two or more, categories of exacerbations in Punekar *et al.* 2014[89] does not match in the rates of exacerbations in RAPID (1.4 to 1.7), as the category two or more exacerbations could contain any possible range of number of exacerbations above one;

2. The company included all exacerbations (potentially including minor exacerbations) and costed these with the resource use associated with moderate-to-severe exacerbations;

3. The company based their analysis on exposure adjusted incidence rates (EAIR), instead of observed exacerbations in RAPID, without justification;

4. Disease management costs (including moderate-to-severe exacerbation costs) were equivalent in both treatment arms, despite the higher number of exacerbations in the Respreeza arm.

Nonetheless, the ERG conducted exploratory analysis, and found that the cost of managing exacerbations is not a key driver in the economic model.

Costs of CT scanning in the model

The company, in their reply to the ERG's clarification questions, state that it is not proposed that routine CT scanning is introduced in the NHS if Respreeza is recommended, as the latter is not necessary to initiate or monitor treatment, pointing to alternative measurements of lung density decline such as FEV1 and D_{LCO}. However, the ERG cannot fail to acknowledge the inconsistency in the company's need to have a CT lung density-based economic model to appropriately assess the cost-effectiveness of Respreeza, and the company's view that CT lung density assessments will not be necessary in clinical practice if the drug is recommended. Also, as mentioned in the EPAR: "*Respreeza is to be administered in conjunction with current symptomatic treatment (e.g. inhaled bronchodilators) where there is clear evidence of lung density decline*", suggesting the need to measure lung density decline through CT scanning.

The clinical experts advising the ERG have different views of this topic. While one of the experts stated that lack of access to CT scanning would not prevent the prescribing or monitoring of patients on Respreeza; the other explained that he would want to "replicate" the RAPID trial measurements and endpoints, in order to be able to assess patients' response to the drug, therefore requiring CT scanning.

Given the opposite views of the ERG's clinical experts on the subject, it is difficult to anticipate if the use of Respreeza in the NHS would have to be accompanied by routine use of CT lung density. If that is the case, then the company's analysis of cost-effectiveness is underestimating the costs associated with Respreeza.

Costs of lung transplant

In clinical practice, patients who are assessed but don't get a lung transplant also incur the respective assessment costs. However, the company explained that it was not possible to identify those who are eligible or ineligible for a lung transplant and therefore, only applied the costs of an assessment to patients who received a lung transplant. The ERG ran a scenario analysis looking at the impact of including assessment costs for all patients eligible for lung transplant. The impact on the final ICER was negligible.

Treatment costs with Respreeza

Patients in the Respreeza arm had a mean weight of 75.9kg however, which translates into 5 required vials per patient, per treatment (including wastage). However, the weight range in RAPID was quite broad (47.0 to 170.8kg) and, therefore, the number of vials of Respreeza required would change according to weight categories in RAPID. For example, for a patient with 88kg, 6 vials would be

required. Hence, the company should have looked at patients' weight categories in the trial, and assessed the proportion of patients requiring different number of vials.

Furthermore, the clinical experts advising the ERG noted that it could be challenging for patients to receive Respreeza at home. Therefore, the ERG a conducted scenario analysis to assess the impact of assuming 100% of patients receive treatment in a clinic. The ICER increased from £236,409 to £240,996.

5.5 Results included in company's submission

The company presented updated deterministic results but failed to report the updated probabilistic analysis, for the new economic model, resulting from the clarification stage. Nonetheless, the company's updated model appeared to include updated probabilistic results. Given that the ERG was uncertain about these results, it re-ran the probabilistic results in the company's updated model. The company also carried out a series of sensitivity analyses to test the robustness of model results to changes in model parameters and assumptions. Base case results are presented in Section 5.5.1, while the results of deterministic and probabilistic sensitivity analyses are presented in Section 5.5.2. and Section 5.5.3, respectively.

5.5.1 Base case results

The results of the company's updated base case analysis are presented in Table 60, using list prices. According to the company's analysis, Respreeza is expected to extend patients' lives by around 2.105 years compared to BSC. This translates to an incremental average QALY gain for Respreeza of 1.522 QALYs, and an incremental cost-effectiveness ratio (ICER) of £236,409 per QALY gained.

Table 60. Company's base case results

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£62,825	7.886	5.454	-	-	-	-
Respreeza	£422,681	9.991	6.977	£359,855	2.105	1.522	£236,409

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year

5.5.2 Deterministic sensitivity analysis

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying model parameters according their confidence intervals, or by 20% if no information on uncertainty around the mean was available. According to the company's updated OWSA, the results are most sensitive to the survival curve of patients with an FEV1<50% and rapid decline in lung density (Figure 15).

Table 61 reports the scenario analysis undertaken by the company in the revised model. In the initial model, the company carried out additional scenario analysis changing assumptions surrounding the baseline age and survival extrapolations, but these were omitted in the company's revised response, without justification.

Figure 15. Tornado diagram (updated model)

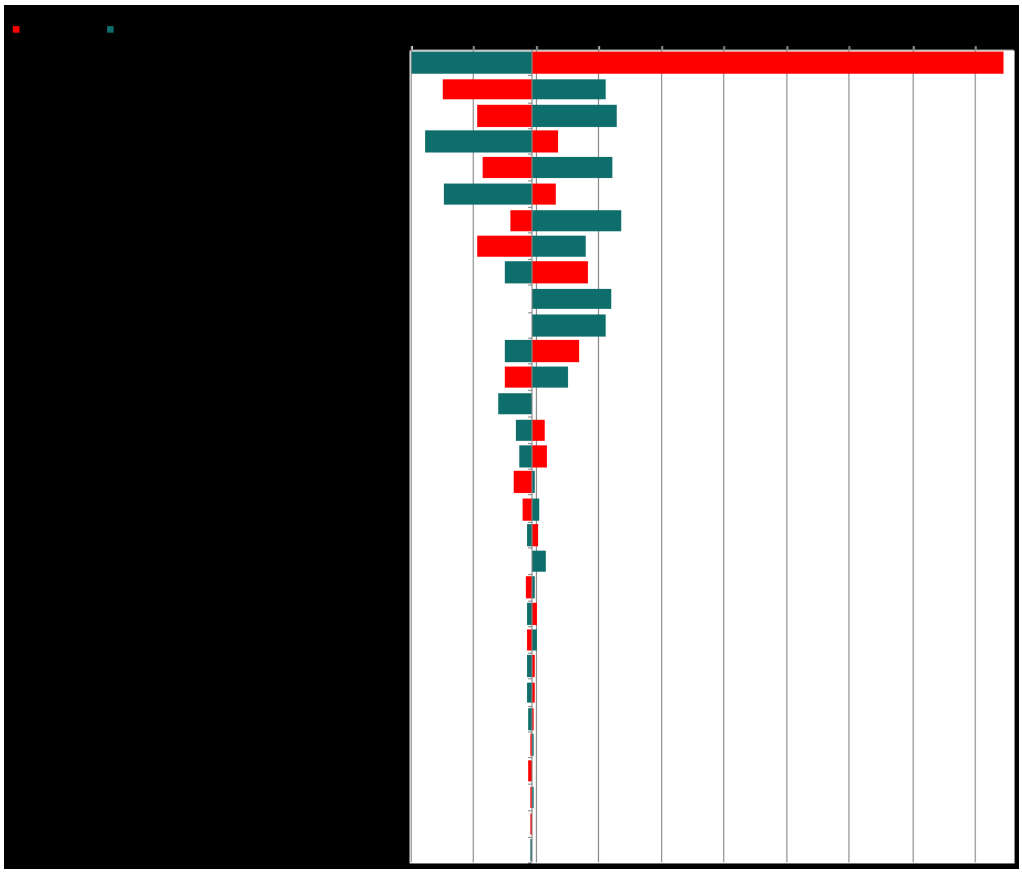


Table 61. Results of scenario analysis (updated model) (adapated from Table 7 of the company's clarification responses)

Analysis	Base case	Scenario	ICER
Structural scenario analyses			
Discount rate of 1.5% applied to benefits and 3.5% applied to costs	3.5% applied to both benefits and costs	Discount rate of 1.5% applied to benefits and 3.5% applied to costs	£189,946
Mortality data from RAPID excluded	4-year and 2-year survival from RAPID used, followed by UK registry survival curves	UK registry survival curves only	£280,942
Include carer disutility	No carer disutility applied	A five percent reduction in carer health related quality of life was applied to patients with FEV1%>50 and in lung transplant states (i.e. a QALY loss of -0.0425 per patient per year) and a ten percent reduction	£223,775

Analysis	Base case	Scenario	ICER
		was applied to all other health states including death (i.e. a QALY loss of -0.085 per patient per year).	
Adjust utilities to the general population	Use reported absolute utilities for health states	Use utility decrements derived from reported values and apply to population norms	£225,638
Scenario analyses			
Administration through infusion clinic rather than homecare.	25% infused administered at clinic	0% and 100% infused administered at clinic	£234,880 and £240,996 respectively
Scenario to explore additional cost and reduced utility as rate of lung density increases	As per base case inputs	20% increased utilities and 20% decreased costs from no lung density decline state and 20% decreased utilities and 20% increased costs from rapid lung density decline state	£207,109
Abbreviations: FEV, forced expiratory volume; ICER, incremental cost-effectiveness ratio QALY, quality-adjusted life year			

5.5.3 Probabilistic sensitivity analysis

The company's updated model included probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The results are based on 5,000 PSA iterations.

In summary, disease management costs (total cost for FEV1≥50%, 30%<FEV1<50% and FEV1<50%), lung transplant costs (total cost for year one and subsequent years), administration costs and patient weight were varied using a gamma distribution, while utilities, mortality rates and transition probabilities between FEV1 were varied using a beta distribution. For lung density decline, a Dirichlet distribution was applied using the expected distribution of patients moving between states. For reduction in FEV1 decline with Respreeza, the company applied a normal distribution. The dose per week (60mg/kg) and proportion of administrations in each setting were kept constant.

The ERG considers the parameters and respective distributions chosen for PSA, to appear reasonable. The PSA results in the revised model, generated by the ERG are presented in Table 62. Compared to the deterministic analysis, the ICER dropped from £236,409 to £181,879 per QALY gained. Moreover, both treatment arms accrue less costs, LYs and QALYs.

Furthermore, the company did not account for the correlation between lung density and lung function, despite analysis of the endpoints in RAPID that showed higher CT lung density measurements correlated with FEV1 (Pearson correlation coefficient [PCC] 0.31, p <0.001), and similar findings in other recently published studies (Table 28 of the CS). Given the paramount uncertainty in the relationship between FEV1 and lung density decline outcomes in the company's model, discussed throughout this report, the ERG considers that not correlating these parameters in PSA potentially

renders the PSA unreliable. This could explain the considerable difference between deterministic and probabilistic results. The ERG is unclear as to why the company stated it was not possible to account for the correlation of these outcomes in PSA, as there are several published measures of correlation for these.

To note is that in the initial model, the ERG produced substantially lower LYs than the company, when reproducing the PSA, which the company failed to explain during the clarification process. Overall, the ERG does not have sufficient confidence in the results produced by the company's PSA.

Table 62. Company's PSA results ran the the ERG

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£35,420	5.016	3.202	–	–	–	–
Respreeza	£332,913	7.488	4.838	£297,492	2.472	1.636	£181,879
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; PSA, probabilsitic sensitivty analysis; QALY, Quality-adjusted life year							

Figure 16. Cost-effectiveness plane in updated model, with PSA ran by the ERG

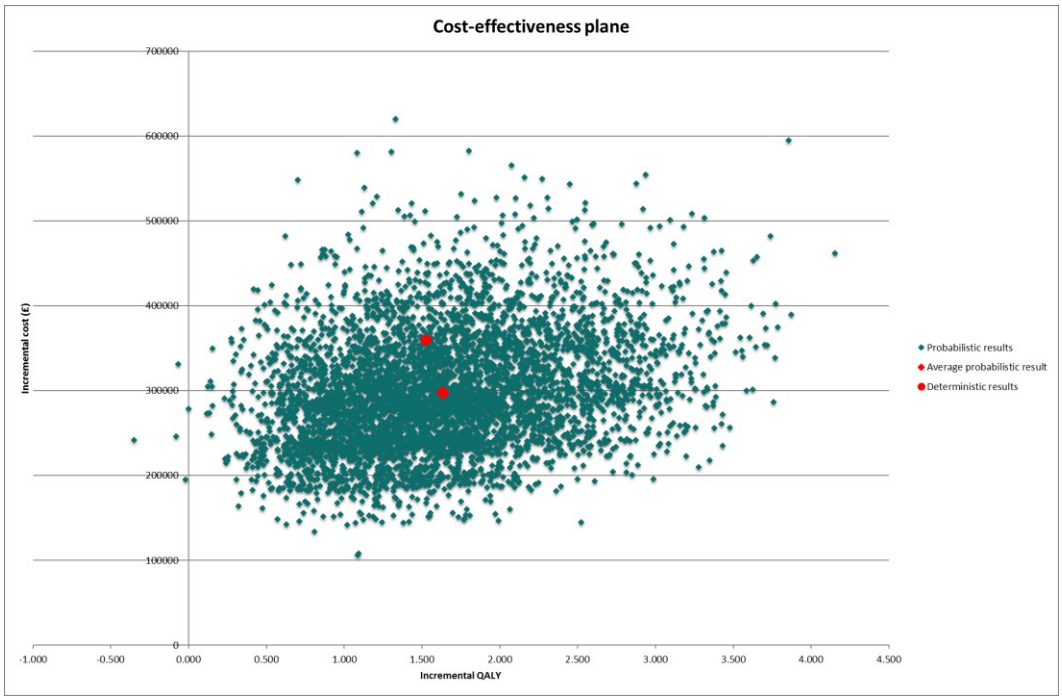
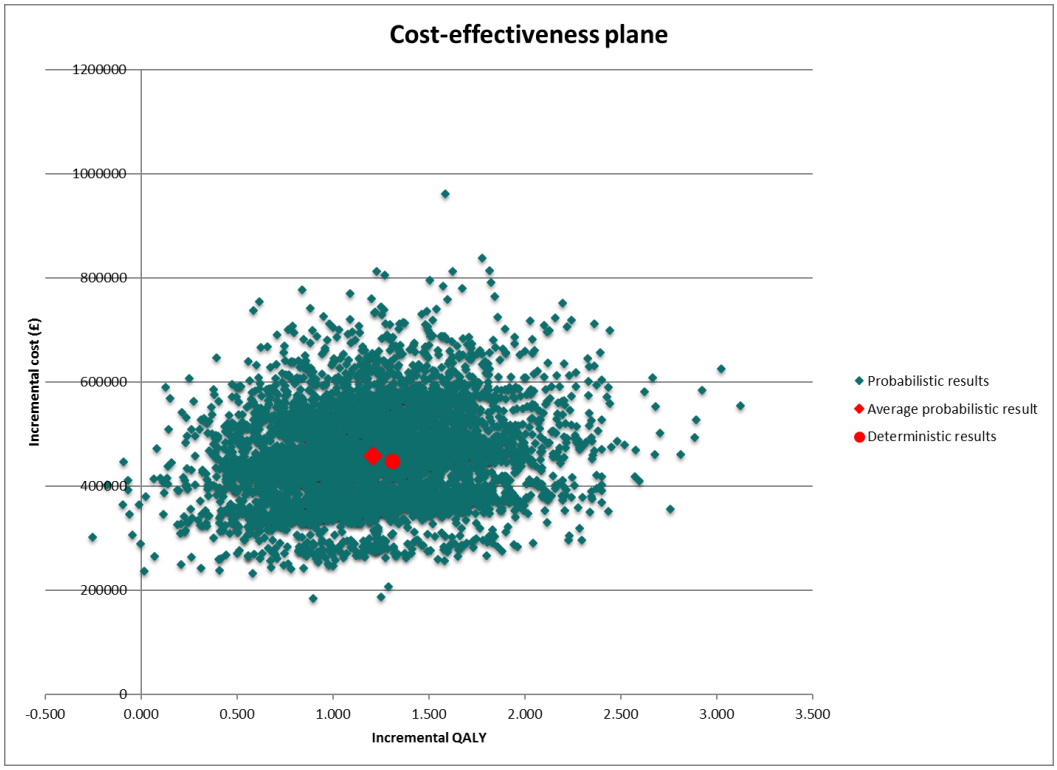


Figure 17. Cost-effectiveness plane in company's original model



6 COST TO THE NHS

The company submission (CS) includes an analysis of the estimated budget impact of Respreeza for the NHS in England. The budget impact analysis uses the assumptions and parameter estimates described in Section 5, together with the estimated prevalence of A1PI deficiency in England, and those eligible for treatment with Respreeza. The budget impact model estimates the total costs for England over five years.

6.1 Size of the eligible population

The budget impact model assumes that 549 people will be eligible for treatment in England. This was estimated using a 0.99 per 100,000 prevalence derived from NIHR 2014 and ONS 2014 data which was applied to 2016 English ONS population figures.[19, 20, 99] The company also assumed an English incident eligible population of 95 people per year, over the forthcoming 5 years. This was estimated from the company's clinical experts in Ireland who expected approximately 0.17 per 100,000 patients to be eligible for Respreeza (55,268,100*0.17*1000,000 = 95). Table 63 summaries the inputs applied in the budget impact model.

Table 63. Size of the eligible population

Eligible population	Value	Source
Number of patients with clinically significant A1PI deficiency in England 2014	540	NIHR report 2014[99]
English population 2014	54,316,600	ONS population estimates (mid 2014) (Office for National Statistics, 2015)[19]
English population 2016	55,268,100	ONS population estimates (mid 2016) (Office for National Statistics, 2017)[20]
Prevalence per 100,000	0.99	Calculated: English population 2014/ number of patients with clinically significant A1PI deficiency in England 2014*100,000
Number of patients with clinically significant A1PI deficiency in selected population	549	Calculated: English population 2016* prevalence per 100,000/100,000
Number of incident patients eligible for Respreeza in Ireland	8	Personal communication: Prof. McElvaney (department of medicine Beaumont Hospital, Ireland)
Irish population	4,635,400	CSO (Population and Migration Estimates April 2015)[100]
Incidence per 100,000	0.17	Calculated: Irish population/ number of incident patients eligible for Respreeza in Ireland*100,000
Incident population	95	Calculated: English population 2016*(Incidence per 100,000/100,000)

Abbreviations: A1PI, alpha-1 proteinase inhibitor; CSO, Central Statistics Office; ONS, Office for National Statistics; NIHR, National Institute for Health Research

As noted in Section 2.1.2, the ERG is unclear as to how the ADAPT registry was used to derive the size of the eligible population. At the clarification stage, the ERG asked the company to provide step-by-step methods of how it derived its estimates, and justify the reasoning for assuming incidence would remain stable over time should Respreeza be approved, but the company declined to provide this information. Nonetheless, the ERG is unaware of more reliable empirically derived incidence on which to base the size of the eligible population.

However, the ERG would like to comment that it is unclear if the eligible population considered in the budget impact model (estimated from the company's clinical experts) reflects the initiation criteria proposed by the company (patients with an FEV1% between 30 and 70% predicted). As described in Section 5, the ERG's clinical experts highlighted that there may be a rationale for giving Respreeza below the 30% FEV1% cut-off proposed, to salvage remaining lung function of patients who are either ineligible or on the waiting list for a lung transplant. Moreover, the ERG's clinical experts suggested the population under care for severe A1PI deficiency and progressive lung disease may be higher than the company have estimated (up to 600–700), and predicted that the number could rise substantially should Respreeza be approved. Furthermore, as described in Section 2.1.2 the ERG is concerned that eligibility for Respreeza may be underestimated because up to 1–2% of emphysema is thought to be related to A1PI deficiency, which remains unidentified in the majority of cases. For these reasons, the number of patients eligible for Respreeza may be substantially greater than the number suggested by the company.

6.2 Market share of the intervention

The budget impact model assumes that the proportion of patients who switch from BSC to Respreeza will gradually increase over time, up to a maximum of 90%, as the company reports it is unlikely that all patients will want to receive treatment with infusions. The budget impact model also assumes that only the incident population will be offered treatment, and once on Respreeza patients only stop treatment when they get a lung transplant or die. The number of people taking up Respreeza at the start of each year is estimated using the 95 patients in year 1, and thereafter considering the number of patients who are dead or in the lung transplant states in the model, and the market share, for the next 5 years. The expected uptake and number of people taking up Respreeza is shown in Table 64. The year 5 estimate of 357 patients includes the 90%*95= 86 patients initiating treatment at year 5, and the remaining patients who have been taking Respreeza since year 1, 2, 3 and 4.

Table 64. Summary of uptake and number of people taking up Respreeza (taken from the revised model).

Timepoint	Market share with Respreeza when imitating treatment	Number of people receiving Respreeza at the start of year
Year 1	50%	48
Year 2	70%	114
Year 3	90%	197
Year 4	90%	279
Year 5	90%	357

6.3 Base case budget impact

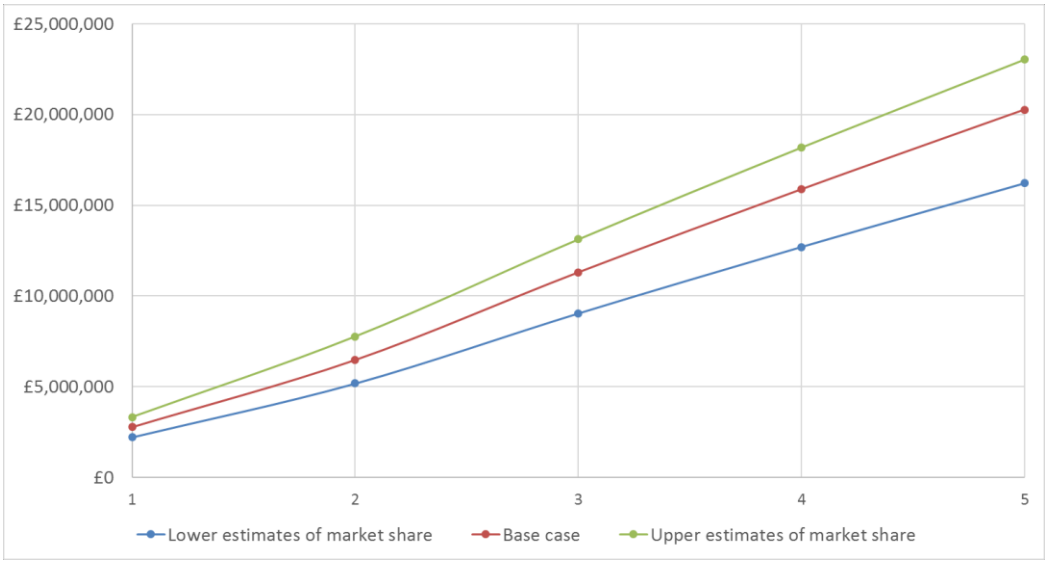
The base case budget impact of Respreeza for the NHS in England is estimated to be £2,839,911 in the first year, rising to £20,940,966 in year 5. Full budget impact results are presented in Table 65. The ERG amendments to the economic model had a relatively small impact on the budget impact results, with the 5 year incremental budget impact amounting to £21,015,391.

Table 65. Summary of the expected budget impact with the introduction of Respreeza (no half cycle) (taken from the revised model)

Timepoint	Respreeza plus BSC	BSC	New incremental budget impact
Year 1	£3,177,409	£338,499	£2,838,911
Year 2	£7,459,423	£674,823	£6,784,601
Year 3	£13,024,506	£1,277,109	£11,747,397
Year 4	£18,490,128	£2,007,652	£16,482,475
Year 5	£23,719,282	£2,778,316	£20,940,966
Abbreviations: BSC, best supportive care			

The company states that the future demand for Respreeza is uncertain and for this reason, provided a sensitivity analysis showing the expected incremental budget impact if market share is either 20% higher or 20% lower than the base case estimate (Figure 18).

Figure 18. Incremental budget impact using market share estimates which are 20% higher and 20% lower than the base case estimate (taken from the revised model)



7 ADDITIONAL WORK UNDERTAKEN BY THE ERG

7.1 Model corrections

The ERG replaced the company's estimated probability of death in the first year after lung transplant (16.47%) by 18% in the model. Results are provided in Table 66 and show an increase from the company's base case ICER of £236,409 to £237,822 per QALY gained.

Table 66. Results of company's base case analysis corrected by the ERG

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
BSC	£62,457	5.424	-	-	-
Respreeza	£422,198	6.936	£359,741	1.513	£237,822

7.2 ERG exploratory analysis

The scenario analyses undertaken by the ERG are explained throughout Section 5 of the report. The analyses consist on the following:

1. The ERG used the 18.90 ml/y effect size (instead of 1.28 ml/y) to reflect the effect of augmentation therapy in reducing the decline in FEV1 in patients in the 30%≤ FEV1 <50% health states in the model. This results in the estimation of an annual transition probability of 9.60% for Respreeza patients, compared with 15.07% for BSC, for patients moving from the 30%≤ FEV1 <50% to the FEV1<30% states in the model. Given the effect size for the FEV1>65% group in the meta-analysis is, not only non-statistically significant, but also counterintuitive (as it is a negative value, suggesting augmentation therapy is detrimental compared to placebo), the ERG used a relative risk of 1. This results in the estimation of an annual transition probability of 14.82% for Respreeza and BSC patients moving from the FEV1≥50% to the 30%≤ FEV1 <50% category;

2. The ERG removed the RAPID survival data from the analysis and replaced it with the UK registry survival data;

3. The ERG removed the treatment stopping rule applied in the model so that Respreeza patients who move to the FEV1<30% category continue to receive treatment, until they receive a lung transplant or die;

4. The ERG applied an age cap for lung transplant, so that patients above 65 years would not be eligible for a transplant in the model;

5. Clinical experts advising the ERG reported that 30% of patients would be expected to be ineligible for lung transplant due to co-morbidities. Therefore, the ERG decreased the population eligible for lung transplant in the model by 30%;

6. The ERG replaced the company's lung transplant survival estimates at year 1 and year 5 (82% and 59%, respectively), by an approximation of the Anyanwu *et al.* 2002 and ERG's clinical experts' estimates (70% for year 1 and 50% for year 2);[82]

7. The ERG assumed that 100% of drug administrations take place at a clinic.

Results from the ERG analysis are reported in Table 67. The two key drivers of the model are the source and method used to estimate FEV1, including the treatment effect on FEV1 progression taken from the meta-analysis, and lung density decline-related mortality. The change in the former increased the corrected base case ICER from £237,822 to £940,871, while changing the latter increased the corrected base case ICER to £317,053 per QALY gained.

Nonetheless, as discussed in Section 5.4.7.2, when all the changes are combined, there are synergies in the model which affect the final ICER. Therefore, even though the ERG is not presenting a preferred "ERG base case", the individual and cumulative ICERs (incorporating all the changes in Table 67), are reported in Table 68. The ERG's cumulative exploratory ICER amounts to £8,573,535 per QALY gained, with incremental QALYs of 0.046 and an incremental cost of £393,162.

The ERG ran the company's PSA on the ERG's cumulative analysis, and estimated a probabilistic ICER of approximately £3,000,000. The ERG notes that PSA results are unreliable, potentially due to the lack of correlating FEV1 and lung density declines in the analysis.

Table 67. Results of the ERG's exploratory analysis

Analysis from list	Results per patient	Respreeza (1)	Best supportive care (2)	Incremental value (1-2)
0	**Company's corrected base case**			
	Total costs (£)	£422,198	£62,457	£359,741
	QALYs	6.936	5.424	1.513
	ICER		**£237,822**	
1	**Using different results from the meta-analysis**			
	Total costs (£)	£446,278	£62,457	£383,821
	QALYs	6.634	5.424	1.211
	ICER		**£317,053**	
2	**Using the UK registry survival data**			
	Total costs (£)	£388,548	£66,733	£321,815
	QALYs	6.177	5.835	0.342

Analysis from list	Results per patient	Respreeza (1)	Best supportive care (2)	Incremental value (1-2)
	ICER		**£940,871**	
3	**Removing stopping rule for treatment with Respreeza**			
	Total costs (£)	£482,002	£62,457	£419,545
	QALYs	6.936	5.424	1.513
	ICER		**£277,359**	
4	**Applying an age cap for lung transplant (65 years)**			
	Total costs (£)	£421,764	£62,456	£359,308
	QALYs	6.919	5.424	1.495
	ICER		**£240,298**	
5	**Reducing the population eligible for lung transplant by 30%**			
	Total costs (£)	£417,047	£56,811	£360,236
	QALYs	6.804	5.239	1.565
	ICER		**£230,196**	
6	**Using alternative survival estimates for lung transplant**			
	Total costs (£)	£418,090	£59,324	£358,766
	QALYs	6.595	5.164	1.432
	ICER		**£250,584**	
7	**The ERG assumed that 100% of drug administrations took place at a clinic**			
	Total costs (£)	£429,180	£62,457	£366,723
	QALYs	6.936	5.424	1.513
	ICER		**£242,438**	
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.				

Table 68. Cumulative results of ERG's exploratory analysis

	Results per patient	Respreeza (1)	BSC (2)	Incremental value (1-2)
0	**Company's corrected base case**			
	Total costs (£)	£422,198	£62,457	£76,638
	QALYs	6.936	5.424	1.02
	ICER		£237,822	
1	**Using different results from the meta-analysis**			
	Total costs (£)	£446,278	£62,457	£383,821
	QALYs	6.634	5.424	1.211
	ICER (compared with base case)		£317,053	
	ICER with all changes incorporated		**£317,053**	
2	**Using the UK registry survival data**			
	Total costs (£)	£388,548	£66,733	£76,010
	QALYs	6.177	5.835	1.02
	ICER (compared with base case)		£940,871	

	Results per patient	Respreeza (1)	BSC (2)	Incremental value (1-2)
1+2	ICER with all changes incorporated	**Dominated (-£6,764,471)**		
3	**Removing stopping rule for treatment with Respreeza**			
	Total costs (£)	£482,002	£62,457	£75,929
	QALYs	6.936	5.424	0.95
	ICER (compared with base case)	£277,359		
1+2+3	ICER with all changes incorporated	**Dominated (-£7,580,023)**		
4	**Applying an age cap for lung transplant (65 years)**			
	Total costs (£)	£421,764	£62,456	£77,261
	QALYs	6.919	5.424	1.02
	ICER (compared with base case)	£240,298		
1+2+3+4	ICER with all changes incorporated	**Dominated (-£7,338,875)**		
5	**Reducing the population eligible for lung transplant by 30%**			
	Total costs (£)	£417,047	£56,811	£80,079
	QALYs	6.804	5.239	1.02
	ICER (compared with base case)	£230,196		
1+2+3+4+5	ICER with all changes incorporated	**Dominated (-£72,940,369)**		
6	**Using alternative survival estimates for lung transplant**			
	Total costs (£)	£418,090	£59,324	£358,766
	QALYs	6.595	5.164	1.432
	ICER (compared with base case)	£250,584		
1+2+3+4+5+6	ICER with all changes incorporated	**£8,399,246**		
7	**The ERG assumed that 100% of drug administrations took place at a clinic**			
	Total costs (£)	£429,180	£62,457	£366,723
	QALYs	6.936	5.424	1.513
	ICER (compared with base case)	£242,438		
1+2+3+4+5+6+7	ICER with all changes incorporated	**£8,573,535**		

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

8 SUBMISSIONS FROM PRACTITIONER AND PATIENT GROUPS

This section presents a summary of additional submissions received from patients, patient organisations, clinicians and NHS England.

8.1 Clinician and NHS England perspective

The first section presents a summary of the submissions from clinical experts from University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, University Hospitals Coventry and Warwickshire NHS Trust, Cambridge University Hospitals and the British Thoracic Society (BTS).

8.1.1 Patients eligible for human alpha1-proteinase inhibitor

BTS reported that approximately 200 to 250 of the 1,500 known cases of alpha-1 proteinase inhibitor (A1PI) deficiency associated with the PiZZ/Xnull genotypes are likely to be eligible for treatment with Respreeza. However, the BTS also highlighted that the estimate is dependent on criteria applied to determine patient eligibility, for example, the forced expiratory volume in 1 second (FEV1) threshold chosen or the definition of "decline" in computed tomography (CT) lung density.

8.1.2 Current management of A1PI deficiency

BTS reported that, in England, people with emphysema secondary to A1PI deficiency are usually seen in general respiratory clinics. Clinicians are available within the NIHR network who have specialist expertise in managing A1PI deficiency, but such specialists are typically commissioned via general respiratory clinics rather than a specialist service. Larger services may see up to 10 people with emphysema related to A1PI deficiency a week, with smaller centres seeing considerably fewer, if any, patients with this condition. In England, people with emphysema arising from A1PI deficiency are managed and treated equivalent to other people with chronic obstructive respiratory disease (COPD). Augmentation therapy with an intravenous A1PI is a treatment option in some countries for people meeting local eligibility criteria, but A1PI treatment is not currently available in England. Moreover, there is currently no alternative treatment to augmentation therapy for those with A1PI deficiency in England. Clinicians are, therefore, of the view that, if approved, Respreeza will be used to supplement the existing best supportive care (BSC) currently given to people with the condition.

8.1.3 A1PI

Clinicians and patients consider weekly A1PI augmentation therapy will be of benefit to reduce or delay progression of emphysema that is secondary to A1PI deficiency, and that there is clinical evidence in support of use of A1PI therapy.[44] Submissions highlight that use of A1PI therapy is global, including

in other European countries, the USA and Australia, with clinical benefits outweighing any harms. Where A1PI augmentation therapy is used in other countries, it is generally in patients with the PiZZ/Znull genotype who have emphysema and circulating levels of A1PI of <11 μM. In addition, some countries set eligibility criteria based on a patient's FEV1 status, with thresholds for eligibility varying across countries. Clinicians reported that there is now a European expert consensus statement recommending A1PI augmentation therapy in those with A1PI deficiency and that they, therefore, consider it important that the treatment is available on the NHS.[33]

In terms of clinical outcomes, the clinicians reported that they would expect to see a slowing in CT lung density decline in those treated with A1PI, which would, in turn, result in a reduction in mortality. Clinicians also suggested that a reduction in CT lung density decline translates into a predictable decrease in extent of deterioration of lung function, but clinicians also highlighted that clinical trials in those with A1PI deficiency are not usually adequately powered to detect differences between treatments in lung function.

8.1.3.1 Subgroups

The published subgroup data typically relates to FEV1 between 30% and 65% predicted, although the view of the BTS and respiratory clinicians is that FEV1 should not be the only criterion for determining eligibility for A1PI augmentation therapy. Clinicians highlighted that there are some patients with evidence of progressing lung disease as determined by assessment of gas transfer or CT lung density, but with a well-preserved FEV1 (e.g. >65% predicted), who are also likely to benefit from treatment with Respreeza. Clinicians also highlighted that those with a FEV1 <30% predicted may also benefit from treatment. Finally, clinicians reported evidence that those categorised as 'rapid decliners' may be a subgroup who experience more benefit from Respreeza.[69]

8.1.4 Changes to service delivery and resources required if A1PI is recommended

The BTS and clinical experts reported that changes to NHS service provision would be required if Respreeza is approved. Additional infrastructure would be needed to facilitate the provision of the specialised services required to identify patients suitable for treatment and to monitor those on treatment. In addition, in areas in which patients are unable to regularly access national centres, then additional staff training may be required to enable treatment at local centres or at the patient's home. CT scanning of lung density to assess extent of lung disease is not routinely performed in the NHS at present. Should implementation of CT scanning be required for patient selection or monitoring, then it would be necessary to invest in specialist software and staff training to enable analysis and interpretation of the CT scans.

8.1.5 Conclusion

Clinicians and the BTS widely support the approval of Respreeza for use in the NHS as a treatment option in line with its European marketing authorisation.[41] Moreover, clinicians consider it important that they have the freedom to exercise their clinical judgement in selecting appropriate patients for treatment, due to the difficultly in accurately selecting and predicting which patients would be most likely to benefit, rather than, for example, adhering to strict FEV1 thresholds.

8.2 Patient support group and patient submissions

Submissions were received from the Alpha-1 UK Support Group and two patients with the condition. The patient expert statements were in keeping with the patient support group submission, which is summarised below.

8.2.1 Summary of Alpha-1 UK Support Group submission

The Alpha-1 UK Support Group was founded in 1997 as a platform for patients with A1PI deficiency and their families and carers for advice, practical support and communication. The group is a Registered Charity in England, Wales and Scotland, and its main strategic objective is to improve patients' quality of life, and to improve access and equality of access to adequate healthcare services and effective therapies. The charity has approximately 600 members and they estimate that 70% to 80% of patients in England with symptomatic A1PI deficiency-associated emphysema are members.

The Alpha-1 UK Support Group submission provided a detailed overview of the challenges faced by people living with the condition, and the widespread impact the disease has on their physical, psychological and social well-being. The group welcomes the option of A1PI therapy and consider it will help slow disease progression and reduce the severity of acute exacerbations, which will also improve patient's quality of life. The Alpha-1 UK Support Group proposed that the benefits of A1PI therapy experienced by patients in the USA would also be expected to be achieved in UK patients. In the USA, reported benefits include:

- 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 dependency 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.

The charity reported that they considered the potential disadvantages of Respreeza were far-outweighed by the advantages. Disadvantages highlighted in the submission were localised infusion site reactions and the inconvenience or difficultly of attending hospital appointments to receive treatment.

In support of their opinion that Respreeza should be available in the UK, the Alpha-1 UK Support Group highlighted the recent publication of a consensus expert statement on the diagnosis and treatment of pulmonary disease in A1PI deficiency that recommends the use of human A1PI in patients with the ZZ phenotype or other rare phenotypes resulting in severe A1PI deficiency.[33] The Alpha-1 UK Support Group also reported that, although patients understand that Respreeza is not a cure, it would still be a welcomed treatment and provide a step-change in the current treatment pathway. In addition, similar to the clinical expert submissions, they reported that, while there is some evidence that particular subgroups of patients may benefit more from Respreeza, the evidence is mostly anecdotal.

The patient community also reported that they do not consider lung transplantation or lung volume reduction surgery to be suitable comparators for Respreeza, views that are in agreement with statements from clinicians and the opinions of the ERG's clinical experts. Patients consider BSC is the only suitable comparator. The Alpha-1 UK Support Group reported that they anticipated approximately 400 to 500 patients may be eligible for treatment with Respreeza, which is double the estimate put forward by clinicians. Depending on the criteria used to select patients for treatment, 500 is potentially an over-estimate.

8.2.2 Conclusion

Patients consider access to Respreeza would be life-changing as it has the potential to stabilise A1PI deficiency-related emphysema, slow its progression and reduce the rate and severity of exacerbations. Respreeza would, therefore, improve their quality of life, and also benefit their family members and carers.

9 OVERALL CONCLUSIONS

Treatment with Respreeza reduces rate of deterioration in annual CT lung density assessed at a combined measure of total lung capacity (TLC) and functional residual capacity (FRC), but the difference did not reach statistical significance. However, considering the more stable measure of deterioration in lung density at TLC alone, the difference between treatments does reach statistical significance and favours Respreeza.

Clinical experts consider change in CT lung density a validated outcome to assess progression of emphysema in RCTs but, in line with comments from the ERG's clinical experts, the technique is not currently routinely used in UK clinical practice to determine worsening lung disease. Many facilities likely to be involved in treating people with A1PI deficiency will not have access to the specialised software and personnel necessary for carrying out and interpreting CT densitometry, and adaptation of current infrastructure and processes would be required to introduce CT densitometry in routine clinical practice. Although the company is not advocating routine scanning of CT lung density to either diagnose eligible patients or monitor disease progression, the ERG's clinical experts fed back that they would prefer to determine eligibility for treatment with Respreeza as was done in RAPID, and thus would move to using assessing lung density with CT.

In terms of other measures of lung function, there were no statistically significant differences between Respreeza and placebo in key spirometric variables, such as FEV1 and D_{LCO}, and the direction of effect favoured placebo. Unexpectedly, meta-analyses indicated that A1PIs, including Respreeza, were associated with a statistically significant increase in risk of pulmonary exacerbations.

Additionally, as clarified by the company, there is currently no guidance when it is appropriate to stop treatment with Respreeza. The company highlighted that, as the goal of treatment is to restore serum levels of A1PI to ≥11 μM, continuous treatment with Respreeza would be necessary. However, the ERG's clinical experts highlighted that, potentially, there could be people, for example, those whose CT lung density continues to deteriorate at the same rate or increases after treatment with Respreeza. Clinicians might want to consider stopping treatment for those who do not appear to be achieving a benefit from treatment, and additional guidance in this area would be helpful.

Economic conclusions

The ERG's main concerns are related to the use of RAPID data to estimate baseline lung density decline and treatment effectiveness on CT lung density decline; the estimation of lung function-related mortality in the model; the benefits associated with lung transplant; the proposed value of Respreeza; and finally, the use of CT scanning in the NHS.

The ERG is concerned with the baseline imbalance in lung density across treatment arms in RAPID, and the use of unadjusted RAPID-OLE data including cross-over patients. The company's decision to not provide the information requested by the ERG related to these issues essentially renders the company's analysis of treatment effectiveness a "black box". In summary, it is the ERG's opinion that there is too much uncertainty on how the treatment effectiveness for Respreeza was estimated in the model, therefore the current analysis of cost-effectiveness using RAPID data is associated with a high level of decision uncertainty.

The ERG disagrees with the company's estimation of the mortality associated with lung function decline. Furthermore, the ERG notes that the data used by the company show that CT lung density decline, by FEV1 categories, is not statistically significantly related to patients' mortality.

Given that the utility value and the survival post-lung transplant are both higher than the respective estimates for the FEV1<30% and the 30%≤ FEV1<50% states in the model, the treatment that allocates more patients to lung transplants, is the most likely to generate an additional clinical benefit in the economic analysis. Ironically, avoiding lung transplants is one of the outcomes that the company proposes as Respreeza's biggest benefit (i.e. to slow down disease's progression and avoid lung transplants, which the company has contradicted during the clarification stage). It is therefore, crucial that the Committee discusses which health state – the 30%≤ FEV1<50% or the post-lung transplant states – is likely to be associated with higher benefits in terms of quality of life and survival. It is also important to discuss if the goal of treatment with Respreeza is: i) to maintain patients in the 30%≤ FEV1<50% state for the longest time possible, avoiding lung deterioration to FEV<30% and, thus, lung transplant (which the ERG's adapted model demonstrates); or ii) to allow more patients to transition to a lung transplant.

The company is proposing that routine CT scanning would not be necessary in the NHS, if Respreeza is recommended, as the latter is not needed to initiate or monitor treatment. From a current clinical practice perspective, the ERG is concerned that CT lung density is rarely measured in the clinical management of A1PI, as explained by the ERG's clinical experts and discussed in Section 4. Consequently, the ERG is concerned that in order to prescribe, and monitor patients on Respreeza, clinicians would have to use CT scanning. The clinical experts advising the ERG have different views of this topic. While one of the experts stated that lack of access to CT scanning would not prevent the prescribing or monitoring of patients on Respreeza; the other explained that he would want to "replicate" the RAPID trial measurements, in order to be able to assess patients' response to the drug, therefore requiring CT scanning.

Furthermore, the ERG cannot fail to acknowledge the inconsistency in the company's need to have a CT lung density-based economic model to appropriately assess the cost-effectiveness of Respreeza, and

the company's view that CT lung density assessments will not be necessary in clinical practice if the drug is recommended. Given the opposite views of the ERG's clinical experts on the subject, it is difficult to anticipate if the use of Respreeza in the NHS would have to be accompanied by routine use of CT lung density. If that is the case, then the company's analysis of cost-effectiveness is underestimating the costs associated with Respreeza.

Given the small QALY gain generated with Respreeza in the 30%≤ FEV1<50% state, and the very high costs associated with treatment, the ICERs generated in the ERG's analysis are unlikely to be considered cost-effective.

9.1 Implications for research

The ERG considers there is a need for further research into:

- the correlation between decline in CT lung density and spirometric variables, quality of life, and mortality;
- minimal clinically important differences in CT lung density, FEV1 and gas transfer;
- the number of people in the UK who would receive treatment with Respreeza, if recommended;
- health-related quality of life associated with treatment with Respreeza;
- feasibility of and barriers associated with building economic models based on CT lung density as a measure of clinical effectiveness.

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11 APPENDICES

11.1 Studies included in systematic reviews

Table 69. Characteristics of studies included in meta-analyses carried out by Gotzsche et al. 2016[55] and Edgar et al. 2017[44]

Author, year	Population inclusion criteria	Population characteristics	Intervention	Comparator	Outcomes	Overall risk of bias[44a]
Placebo-controlled RCTs of intravenous augmentation therapy						
Dirksen 1999[56]	PiZZ phenotype; moderate to severe emphysema; FEV1 30% to 80% of predicted.	N=58 Recruited from both the Danish and Dutch AATD Registries Mean FEV1% predicted (SD): Int: 50.0 (15.9) Cont: 46.2 (11.9)	AAT Augmentation (n=28) 250 mg/kg body weight intravenously infused every 4 weeks. Minimum treatment duration of 3 years.	Placebo (n=28) Human albumin in an isotonic solution 625 mg/kg body weight infused every 4 weeks. Minimum treatment duration of 3 years.	Lung Function: FEV1, SVC, K_{CO}, D_{LCO} and patient-administered serial spirometry. No differences between treatment groups Lung density: Annual rate of decrease in lung density measured by CT scan. Treatment significantly slowed lung density decline. Study underpowered for this outcome	**Unclear** Blinding of outcome assessments and selective outcome reporting deemed to be at low risk of bias. All other domains assigned unclear risk of bias.
Dirksen 2009[29]	AAT -serum concentrations <11 μM; ≥18 yrs; ≥1 exacerbation in past 2 years; post bronchodilator FEV1% ≥25% and ≤80% with FEV1/FVC ratio ≤0.70; Normal Spirometry could	N=82 77 randomised across 3 sites in Denmark, Sweden and the UK. Mean age (yrs.) (SD): Int: 54.7 (8.4) Cont: 55.3 (9.8) Sex (male) n (%):	AAT Augmentation (n=35) Prolastin: 60 mg/kg body weight intravenously infused weekly. 2 year treatment. Additional optional 6 month open label extension study.	Placebo (n=32) 2% human albumin infused weekly. 2 year treatment. Additional optional 6 month open label extension study.	Lung density: Trend for rate of lung density slower in treatment not significant. Pulmonary exacerbations: No difference in patient reported exacerbation frequency. Post hoc analysis showed proportionally fewer	**Unclear** Random sequence generation and masking of key personnel rated low risk of bias. Selective outcome reporting judged as high risk of bias. All other

	be included if K_{CO} was ≤80%; Weight 42 kg to 92 kg;	Int: 25 (65.8) Cont: 16 (41.0) Mean FEV1% predicted (SD): Int: 46.3 (19.6) Cont: 46.6 (21.0)			'severe' exacerbations in active treatment group. Lung function: FEV1, D_{LCO} and K_{CO} all demonstrated no significant differences between treatment groups. Mortality: Nil Quality of life: SGRQ no differences in groups Adverse events: Safe and well tolerated.	domains, assessed to be unclear risk of bias.
Chapman 2015[42]	Aged 18–65years; emphysema 2o AATD; serum AAT ≤11μM; FEV1 35 to 70% predicted.	N=180 180 randomised across 28 sites in 13 countries. Mean age (yrs) (SD): Int: 53.8 (6.9) Cont: 52.4 (7.8) Sex (male) n (%): Int: 48 (51.6) Cont: 50 (57.5) Mean FEV1% predicted (SD): Int: 47.4 (12.1) Cont: 47.2 (11.1)	AAT Augmentation (n=93) Zemaira: 60 mg/kg/week Investigational product: AAT 60 mg/kg body weight intravenously infused weekly. 2 year treatment. Additional optional 2 year open label extension study in non-US countries.	Placebo (n=87) Lyophilized preparation 60 mg/kg body weight intravenously infused weekly. 2 year treatment. Additional optional 2 year open label extension study in non-US countries.	Adverse events: Safe and well tolerated. Lung density: Annual rate of decrease in lung density measured by CT scan. Treatment group significantly slowed lung density decline. Mortality: 1death in treatment group, 3 deaths in control group. Pulmonary exacerbations: time to first exacerbation, rate, duration and severity of exacerbations. No differences. Lung function: FEV1, FEV1/FVC, FVC, D_{LCO} no significant or clinical differences.	**Low** With the exception of selective outcome reporting, all domains judged to be at low risk of bias: selective outcome reporting was assessed to be at unclear risk of bias.

					Quality of life: SGRQ showed no significant or clinical differences.	
Observational studies included in Chapman 2009[45] meta-analysis and update review carried out by the company						
Seersholm 1997[68] Observational controlled study. Retrospective	PiZZ or AAT serum level <12 µmol/L; either FEV1 <65% predicted or annual decline in FEV1 >120 mL; non/ex-smoking at enrolment; recipient of AAT augmentation therapy ≥1 yr; ≥2 spirometries ≥1 yr apart. performed during the treatment period; index cases; >25 yrs of age at entry.	N=295 Recruited from 25 centres across Germany and from the Danish AATD Registry Mean age (yrs) (SD): Int: 46 (8) Cont: 45 (10) Sex (male) n (%): Int: 142 (71.7) Cont: 55 (56.7) Mean FEV1% predicted (SD): Int: 37 (14) Cont: 42 (10)	AAT Augmentation (n=198) Prolastin: infused weekly at 60 mg/kg body weight Mean follow up duration 3.2±1.6 years.	Control (n=97) Normal clinical treatment with no AAT augmentation therapy Mean follow up duration 5.8±3.4 years.	Lung function: 22 ml/yr slower decline in FEV1 in treatment group across all patients (p=0·02). No significant difference in change in FEV1 between the treated group and the untreated group among the patients with the lowest and the highest FEV1% pred. In patients with initial FEV1 of 31 to 65% predicted, significantly lower rate of decline in FEV1 among the treated patients (p=0.04).	**High** High risk of selection, performance, and detection bias. Low risk of attrition and reporting bias.
AATD 1998[66] Observational uncontrolled study Retrospective	>18 yr of age; either AAT serum <11 mMol or PiZZ genotype.	N=1,129 Patients from NHLBI AATD Registry USA. 1,048 patients used in Survival analysis (no demographics) & 927 used for FEV1 slope analysis. Of the 927:	AAT Augmentation (n=747 in two groups: 1) 390 always received therapy, and 2) 357 partly receiving therapy while in the Registry)	Control (n=382) Normal care naive to AAT augmentation	Lung function: Overall change in FEV1 was not significantly different between groups. Subgroup into GOLD disease severity by FEV1 decline is slowest in those receiving augmentation p=0·03. Survival: Across all patients no changes.	**High** High risk of selection, performance, and reporting bias. Unclear risk of detection bias and low risk of attrition bias.

		Mean age (yrs) (SD): Int Grp 1: 46 (11) Int Grp 2: 47 (10) Cont: 43 (12) Sex (male) n (%): Int Grp 1: 227 (58.1) Int Grp 2: 206 (57.9) Cont: 187 (49.1) Mean FEV1% predicted (SD): Int Grp 1: 37 (18) Int Grp 2: 41 (21) Cont: 74 (35)	Prolastin 60 mg/kg body weight intravenously infused weekly. Up to 7 years follow up.		Those with FEV1 <50% saw significantly higher (p<0·001) mortality in subjects who never as opposed to sometimes or always received augmentation therapy.	
Wencker 2001[69] Observational controlled study Retrospective	AATD serum levels, 35% of normal regardless of phenotype; FEV1 ≤65% predicted or decline in FEV1 of 120 mL/yr; non-smokers or ex-smokers >3 months.	N=96 Data taken from the Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenkrankungen (WATL) Germany. Baseline demographics: Mean age (yrs) (SD): Int: 44.3 (8.6) Sex (male) n (%): Int: 62 (64.6) Mean FEV1% predicted (SD): Int: 41.0 (17.3)	AAT Augmentation (n=96) Prolastin: 60 mg/kg body weight intravenously infused weekly. Mean follow-up after start of augmentation was 50.2 (30.2) months.	Control (n=96) Control group was the same cohort with data taken from at least the year prior to commencement of treatment. Mean follow-up before augmentation was 47.5 (28.1) months.	Lung function: FEV1 declined significantly slower (p=0.019) after starting therapy -34.3±29.7 (SD) mL/yr than prior to therapy with AAT augmentation -49.2± 60.8 mL/yr.	**Unclear** High risk of selection bias. Unclear risk of detection and reporting bias. Low risk of performance and attrition bias.

Chapman 2005[67]	CONFERENCE ABSTRACT: ERG unable to obtain					
Tonelli 2009[71] Observational controlled study Retrospective	AATD PIZZ genotype; ≥2 post bronchodilator FEV1, ≥6 months apart.	N=164 The Alpha-1 Foundation DNA and Tissue Bank. Multiple sites across the USA Mean age (yrs.) (SE): Int: 61.3 (0.7) Cont: 65.1 (1.9) Sex (male) n (%): Int: 59 (47.6) Cont: 20 (50) Mean FEV1% predicted (SE): Int: 43 (2) Cont: 77 (5)	AAT Augmentation (n=124) The augmentation therapy used was predominantly weekly intravenous Prolastin 60 mg/kg/week (88% of patients) but also Aralast and Zemaira. Insufficient data on dosing and frequency. Patients were on their own Rx and study team had no input. Mean follow up of 41.7 months.	Control (n=40) Usual care no augmentation therapy	Lung function: statistical difference (p=0·05) in FEV1 decline between 2 groups, augmented group FEV1=10.61±21.4 mL/yr. non-augmented group FEV1 -36.96±12.1 mL/yr. Survival: No differences were observed in the 5-year mortality rate.	**Low** With the exception of detection bias, all domains judged to be at low risk of bias: study deemed to be at a high risk of detection bias.
Barros-Tizon 2012[70] Observational uncontrolled study Retrospective	>18 years; diagnosis of severe AATD (i.e. PI*ZZ genotypes and combinations of Z, rare and null alleles expressing AAT serum concentrations <11 µmol or 50 mg/dl); recipient of continuous augmentation	N=127 Multicentre study across Spain Mean age (yrs) (SD): Int: 51.7 (9.1) Sex (male) n (%): Int: 81 (63.8) Mean FEV1 L (SD): Int: 1.25 (0.5)	AAT Augmentation (n=127) Differing treatments and dosing regimes Prolastin: 68 patients (53.5%) Trypsone: 59 patients (46.5%). Weekly Therapy: 8 patients (6.3%) Bi-Weekly Therapy: 22 patients (17.3%)		Exacerbation rate: Reductions in administration of systemic antibiotics prior to and following commencement of augmentation therapy was observed, p<0.05. Reductions in exacerbations per patient (p<0.01). Lung function: Statistically significant	**High** High risk of selection, performance, and reporting bias. Unclear risk of detection bias and low risk of attrition bias.

	therapy with Trypsone or Prolastin ≥18 months prior to inclusion; available medical records of 18 months before starting augmentation therapy.		Every 3 weeks: 97 patients (76.4%) The average AAT concentrate dose administered was 60.7±3.8 mg/kg/week		decline FEV1 (L) for the total patient population $p<0.05$ were observed however this is within normal decline. Health care cost (Hospitalisation only): Saving of €416.76 per patient Adverse events: Safe and well tolerated.	

[a] Risk of bias as reported in systematic review carried out by Edgar 2017.[44]

Abbreviations: AAT, alpha-1 antitrypsin; CT, computed tomography; D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; K_{CO}, transfer coefficient for carbon monoxide; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; SVC, slow vital capacity.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

You are asked to check the ERG report from BMJ Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Wednesday 8 August 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Misspelling of transplant (page 8, 9, 38, 39 and 164).	Should be transplant and not trabsplant.	Correction of a typographical error.	The ERG thanks the company for highlighting this typographical error. All instances of "trabsplant" have been corrected.
"RAPID involved 180 people, with 97 and 83 people allocated to Respreeza and placebo, respectively" (page 14).	"RAPID involved 180 people, with **93** and **87** people allocated to Respreeza and placebo, respectively".	Correction of a typographical error.	The ERG thanks the company for highlighting this typographical error. The text has been amended as suggested by the company.
The least square mean difference of -13.9m is incorrect. (page 16).	The value should be -**13.09m** as stated in the CS.	Correction of a typographical error.	Text corrected as outlined by company.
"A considerably larger proportion of people from the placebo group withdrew from the study (9/97 [9.3%] in the Respreeza group vs 18/83 [21.7%] in the placebo group), with the predominant reason for discontinuation in each group being withdrawal of consent (5/97 [5.2%] in Respreeza group vs 7/83 [8.4%] in the placebo group)" (page 78).	"A considerably larger proportion of people from the placebo group withdrew from the study (9/**93** [**9.7%**] in the Respreeza group vs 18/**87** [**20.7%**] in the placebo group), with the predominant reason for discontinuation in each group being withdrawal of consent (5/**93** [**5.4%**] in Respreeza group vs 7/**87** [**8.1%**] in the placebo group)".	Correction of a typographical error.	The ERG thanks the company for highlighting this typographical error. The text has been amended as suggested by the company.
Table 5 (page 84) Mean age, years (SD) – Early start: 53.8 (6.9), Delayed start: 52.4 (7.8).	Mean age, years (SD) – Early start: **56.4** (6.9), Delayed start: **53.3** (7.8).	Correction of a typographical error.	Text corrected as outlined by company.

Table 8 (page 93) Respreeza (N=90), Placebo (N=83).	Respreeza (N=**93**), Placebo (N=**87**).	Correction of a typographical error.	No change required. The ERG notes that the reported data, and number of people in each treatment group, are taken directly from Table 9 of the Clinical Study Report (CSR) for RAPID.
(page 103) “oropharyngeal pain (24% versus 12%)”.	“oropharyngeal pain (24% versus **11**%)”.	Correction of a typographical error.	Text corrected as outlined by company.
Table 17 (page 106) “Table 17. TEAEs reported ≥10%of patients and exposure-adjusted incidence rates by MedDRA preferred term (safety population) in RAPID-OLE (reproduced from CS, Table 6 [pg. 121])”.	“Table 17. TEAEs reported ≥10%of patients and exposure-adjusted incidence rates by MedDRA preferred term (safety population) in RAPID-OLE (reproduced from CS, Table **26** [pg. 121])”.	Correction of a typographical error.	Text corrected as outlined by company.
(page 116) “Enrolling 180 people, RAPID represents the largest RCT to date evaluating the clinical effectiveness of augmentation with intravenous A1PI, specifically Respreeza, in the management of emphysema secondary to severe A1PI deficiency: 97 and 83 people allocated to Respreeza and placebo, respectively”.	“Enrolling 180 people, RAPID represents the largest RCT to date evaluating the clinical effectiveness of augmentation with intravenous A1PI, specifically Respreeza, in the management of emphysema secondary to severe A1PI deficiency: **93** and **87** people allocated to Respreeza and placebo, respectively”.	Correction of a typographical error.	Text corrected as outlined by company.
“By delaying the loss of lung density and function, Respreeza is anticipated to prolong patient independence as well as	“By delaying the loss of lung density and function, Respreeza is anticipated to prolong patient independence as well as prolonging the time to or obviating the need for lung transplant.	Correction of a typographical error.	Text corrected as outlined by company.

prolonging the time to or obviating the need for lung transplant. (CS, page 19)" (page 148).	(CS, page **18-19**)".		
"Table 44. Assessment of fit of parametric survival functions to the UK registry data (Table 36, CS)" (page 158).	"Table 44. Assessment of fit of parametric survival functions to the UK registry data (Table **173**, CS)".	Correction of a typographical error.	Not a factual inaccuracy – no change required. Data in Table 44 were taken from Table 36 of the CS.
"Table 61. Results of scenario analysis (updated model) (adapated from Table 7 of the company's clarification responses)" (page 179-180).	"Table 61. Results of scenario analysis (updated model) (adapated from Table **73** of the company's clarification responses)".	Correction of a typographical error.	Not a factual inaccuracy – no change required. Data in Table 61 were taken from Table 7 of the clarification response.

Issue 2 Treatment initiation

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Section 1.3 page 18. "The company presents research to support the proposal that those with a decrease in CT lung density of 2.0 g/L or greater annually are deemed to be in rapid decline, and likely to achieve a greater benefit from treatment with Respreeza compared with those who experiencing no or slow decline in lung density. The ERG notes that the thresholds	This statement should be removed.	The company has not presented an analysis showing that rapidly declining patients are most likely to benefit from treatment with Respreeza. Figure 1 on page 10 and figure 6 on page 39 of the CS proposes treatment initiation criteria based on rapid lung function (FEV_1 or DL_{co}) **OR** lung density decline. Lung density decline as the sole initiation criteria for treatment has not been proposed.	The ERG thanks the company for highlighting the error. Text deleted as outlined by the company.

proposed for rate of decline, at this time, have not been validated and could be considered arbitrary cut offs that are at risk of bias".			
Section 1.5.2 page 23. "the company proposes that those who are experiencing rapid deterioration in lung disease, which, based on reported research, the company proposed to be reached at an annual decline of ≥2.0 g/L in CT lung density, could potentially achieve greater benefit with Respreeza".	Please delete this statement.	The company is not proposing subgroups. The licensed indication specifies that patients must have "progressive lung disease (e.g. lower forced expiratory volume per second (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". No thresholds in terms of rate of lung density decline have been proposed by the company. Figure 1 and 6 of the submission indicated that, in addition to the licensed restrictions for Respreeza, treatment initiation could be limited to an FEV1 between 30% and 70% in line with the RAPID study.	Text highlighted by company deleted. Text now reads: However, the ERG considers that it would be appropriate to identify those whose lung density or lung function is declining. Alternatively, as people of any categorisation of rate of decline in CT lung density are eligible for treatment, it would be appropriate to stratify randomisation by the categories of rate of decline (none, slow or rapid) to ensure balanced groups at baseline for this characteristic.
Section 1.5.2, page 25. The ERG stated that the company did not apply their own "starting rule" in the economic model for the administration of Respreeza, as all patients in the intervention arm receive treatment, regardless of having no, slow, or, rapid baseline	Factual inaccuracy, please remove.	There is a difference between lung **density** and lung **function**. For the purposes of the model, we have stratified lung density decline rates as no, slow, or rapid. At no point have the company stated in the CS that treatment should be limited to patients with rapidly declining lung	Not a factual inaccuracy – no change required.

lung density decline.		density.	

Issue 3 Error in model regarding treatment in FEV1<30% states

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Section 1.4, page 20. "Patients receive life-long treatment with Respreeza until they move to the FEV1<30% states, where they stop treatment". Section 1.5.2, page 25. Nonetheless, the company applied a stopping rule in the model, as all patients progressing to an FEV1<30% state stop treatment, thus underestimating the costs associated with Respreeza.	Factual inaccuracy, please amend to read "patients receive life-long treatments with Respreeza, but the company introduced an error in the model in response to ERG clarification questions, whereby costs associated with Respreeza are not included in patients progressing to an FEV1<30% state, thus underestimating the costs associated with Respreeza".	This was not intentional. In the original model, patients were assumed to receive treatment throughout life. In the substantial revisions to the model that were conducted to address ERG clarification questions, an error was made in the model such that costs of treatment were not applied to patients in the FEV1<30% health states.	Not a factual inaccuracy – no change required.

Issue 4 MCID for CT lung density

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
No minimal clinically important differences (MCIDs) have been established for CT lung density.	Factual inaccuracy, please remove statement.	Recently, a study by Subramanian et al., 2018 has been published deriving a MCID for annual CT lung density decline in patients with A1P1 using the anchor and distribution method. The Birmingham A1PI cohort was used to validate the proposed MCID of	Not a factual inaccuracy – no change required. The ERG notes that the data reported by the company are taken from a conference abstract and the MCID for CT lung density has been

		-2.89g/l.	proposed but not established. Moreover, the ERG notes that, at a MCID of –2.89 g/L for annual CT lung density, in the CS, the company is likely to be over estimating the benefit of Respreeza.

Issue 5 The use of CT lung density in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Section 1.5.2, page 24. The ERG stated that clinicians in England are likely to want to base decisions to treat people with Respreeza on CT densitometry, as was carried out in RAPID, as well as using CT lung density to monitor progression of emphysema.	Please amend to include respiratory function (FEV_1 or DL_{CO}).	It is unclear if this is an evidence-based statement, or an opinion from the ERG. We believe that CT lung density scans alone are not mandated to initiate or monitor treatment but clinical expert feedback to the company suggest that this should be included as part of the NHS England highly specialised service specification.	Not a factual inaccuracy – no change required.
Section 1.5.2, page 27. The ERG is concerned that in order to prescribe, and monitor patients on Respreeza, clinicians would have to use CT scanning.			Not a factual inaccuracy – no change required.

References

SUBRAMANIAN, D., STOCKLEY, R. A. & TURNER, A. M. 2018. Proposal and Validation of a Minimal Clinically Important Difference (MCID) for Annual Pulmonary CT Density Decline. *B64. COPD: LUNG FUNCTION, IMAGING AND PATHOPHYSIOLOGY.*

Human alpha 1-proteinase inhibitor for treating emphysema

ERRATA

This report was commissioned by the NIHR HTA Programme as project number 15/121/01

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
8	Correction of typographical error: "trabsplant" amended to "transplant".
9	Correction of typographical error: "trabsplant" amended to "transplant".
14	Correction of number of people randomised to each group in RAPID: Text amended from "RAPID involved 180 people, with 97 and 83 people allocated to Respreeza and placebo, respectively" to "RAPID involved 180 people, with 93 and 87 people allocated to Respreeza and placebo, respectively".
16	ISWT least square mean difference amended from –13.9 to –13.09.
18	Text deleted: The company presents research to support the proposal that those with a decrease in CT lung density of 2.0 g/L or greater annually are deemed to be in rapid decline, and likely to achieve a greater benefit from treatment with Respreeza compared with those who experiencing no or slow decline in lung density. The ERG notes that the thresholds proposed for rate of decline, at this time, have not been validated and could be considered arbitrary cut offs that are at risk of bias.
23	Text deleted: the company proposes that those who are experiencing rapid deterioration in lung disease, which, based on reported research, the company proposed to be reached at an annual decline of ≥2.0 g/L in CT lung density, could potentially achieve greater benefit with Respreeza.
38	Correction of typographical error: "trabsplant" amended to "transplant".
39	Correction of typographical error: "trabsplant" amended to "transplant".
78	Correction of number of people randomised to each group in RAPID: Text amended from "RAPID involved 180 people, with 97 and 83 people allocated to Respreeza and placebo, respectively" to "RAPID involved 180 people, with 93 and 87 people allocated to Respreeza and placebo, respectively". Denominators in same paragraph amended as appropriate.
84	Mean ages corrected in each group.
103	Text corrected: "oropharyngeal pain (24% versus 12%)" amended to "oropharyngeal pain (24% versus 11%)".
106	Table 6 amended to Table 26 in caption accompanying Table 17 of the ERG report.
116	"97 and 83 people allocated to Respreeza and placebo, respectively" amended to "93 and 87 people allocated to Respreeza and placebo, respectively"
148	(CS, page 19) amended to (CS, pages 18–19)
164	Correction of typographical error: "trabsplant" amended to "transplant".

epidemiological data for the population are limited. Considering other RCTs assessing clinical effectiveness of A1PI augmentation therapy in severe A1PI deficiency, the baseline characteristics of those enrolled in RAPID are as generalisable as those enrolled in other trials to the population of interest in England. Therefore, the population in RAPID is considered to be relevant to the decision problem.

In RAPID and RAPID-OLE, Respreeza was infused intravenously at the licensed dose of 60 mg/kg body weight on a weekly basis, with infusion taking typically around 15 minutes (about 0.08 ml of solution per kg body weight each min). Evidence is available that suggests administration of Respreeza at a dose of 60 mg/kg per week could be a suboptimum augmentation dose for some people with A1PI deficiency. Two studies evaluating clinical effectiveness of A1PI at a dose of 120 mg/kg per week are ongoing. One study is an RCT (SPARTA) comparing A1PI 60 mg/kg versus 120 mg/kg given once weekly over 156 weeks. Results are not yet available for the study. Based on the licence for Respreeza, the ERG considers the evidence presented to be relevant to the decision problem.

The comparator in RAPID was placebo. In the final scope issued by NICE, various interventions given to ameliorate the symptoms of progressive lung disease were specified as comparators of interest to the decision problem. As highlighted by the company and the ERG's clinical experts, clinical management of progressive lung disease is dependent on the symptoms with which a person presents, and may involve administration of a single therapy or a more complex combination of interventions. The company highlights that the treatments listed as comparators are clinically equivalent to BSC in lung disease and that it would be more appropriate to view the interventions as a collective rather than individual comparators, an opinion with which the ERG's clinical experts agreed. Therefore, the ERG considers placebo to be an appropriate comparator.

All clinically relevant outcomes were reported in the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

RAPID is an international, randomised, double-blind, phase III/IV trial with a primary objective of assessing the change in lung density by CT on A1PI augmentation with Respreeza compared with placebo in people with emphysema secondary to severe A1PI deficiency. RAPID involved 180 people, with 93 and 87 people allocated to Respreeza and placebo, respectively. After 2 years of follow-up, all patients located outside the USA entered an open-label 2-year extension phase, RAPID-OLE, during which everyone received Respreeza. The ERG notes that RAPID did not include a "run in" period during which rate of deterioration in lung function could have been monitored.

The primary measure of clinical effectiveness in RAPID was annual change in lung density as measured by computed tomography (CT), with the value adjusted to account for lung volume. Spiral CT scans

lost during the previous 2 years of treatment with placebo, and that the result underscores the importance of early interventional treatment with an A1PI.

Various secondary outcomes were assessed in RAPID. The key secondary outcomes were deemed to be those that would help explain the clinical relevance of the primary objective of change in lung density as measured by CT scan and were listed in the European Public Assessment Report (EPAR) as:

- change in exercise capacity assessed by incremental shuttle walking test (ISWT);
- change in symptoms score assessed by the St. George's Respiratory Questionnaire (SGRQ);
- risk of pulmonary exacerbation assessed by the annual rate of exacerbations.

Other secondary outcomes assessed included the key spirometry variables of FEV1 and gas transfer.

No statistically significant differences were reported between Respreeza and placebo for the identified secondary outcomes, with the direction of effect favouring Respreeza in some outcomes. However, for ISWT, FEV1, diffusion capacity of the lung for carbon monoxide (DLCO) and, unexpectedly, rate of pulmonary exacerbation, the direction of effect favoured placebo:

- ISWT: change from baseline at 24 months: 10.8 m (SD 139.8) with Respreeza versus 16.1 m (SD 101.6) with placebo; least square mean difference of –13.09 m (p=0.48);
- total SGRQ score (higher score is less favourable): change from baseline at 24 months: 1.4 (11.1) with Respreeza versus 2.2 (11.7) with placebo; least square mean difference of –0.19 (p=0.91);
- annual number of exacerbations: risk ratio for Respreeza versus placebo of 1.26 (95% CI 0.92 to 1.74) (risk ratio greater than 1 indicates increased risk of exacerbation with Respreeza);
- FEV1% predicted: change from baseline at 24 months: –3.1% (SD 10.7) with Respreeza versus –2.3% (SD 13.1) with placebo; least square mean difference of –2.26% (p=0.21);
- D_{LCO}: change from baseline at 24 months: –2.2% (SD 18.2) with Respreeza versus –1.5% (SD 19.5) with placebo; least square mean difference of –1.31% (p=0.64).

Syntheses of data from three RCTs, including RAPID, generated similar results to those from RAPID, with meta-analyses reported by Edgar 2017 and Gotzsche 2016 indicating no statistically significant differences between Respreeza and placebo for change in FEV1, DLCO, and health status assessed by SGRQ. For FEV1 and DLCO, direction of effect favoured placebo. By contrast, for health status, direction of effect favoured Respreeza. The ERG notes that a meta-analysis presented in one systematic

RAPID, and the subsequent open-label extension, represent the largest study to date evaluating the effects of A1PI augmentation therapy, specifically Respreeza, on slowing the progression of emphysema secondary to severe A1PI deficiency. The ERG considers RAPID to be predominantly well-designed and well-conducted and at a low risk of bias.

Baseline characteristics of people enrolled in RAPID were predominantly well balanced across the Respreeza and placebo groups, with the exception of baseline CT lung density (adjusted PD15). Those allocated to Respreeza had a baseline value of 46.6 g/L (SD 15.6 g/L) for the combined measure of TLC and FRC compared with 49.8 g/L (SD 15.0 g/L) in those receiving placebo. The ERG has concerns about the imbalance in CT lung density at baseline because the primary measure of clinical effectiveness in RAPID was annual change in lung density as measured by CT, with the value adjusted to account for lung volume. CT lung density was assessed at both the TLC and FRC inspiration states and the results combined to give a value for TLC plus FRC.

Considering the assessment of FEV1 per cent predicted, the ERG considers it important to note that administration of a bronchodilator before assessment of FEV1, as is advised by GOLD for COPD, was not compulsory in RAPID: the protocol for RAPID initially stipulated use of a bronchodilator 4 hours before CT scan, but was subsequently amended to use of bronchodilator only on interruption of treatment for emphysema. The ERG considers that it is unclear whether results presented for FEV1 include results with and without pre-test use of bronchodilator. Neither the CS nor the Clinical Study Report (CSR) provides details on the frequency of use of bronchodilator, or whether the results have been adjusted to account for the disparity in use of FEV1. The ERG considers the direction of potential bias arising from variation in bronchodilator use prior to FEV1 measurement to be unclear.

1.3 Summary of cost effectiveness evidence submitted by the company

The population considered by the company comprises adults with severe alpha-1 proteinase inhibitor (A1PI) deficiency who have progressive lung disease. In the base case model, the baseline distribution of patients across FEV1 and lung density decline categories is based on RAPID data. In scenario analysis, the company used age and gender distribution reportedly from RAPID, however the mean age does not match that of RAPID patients. The company used different sources of clinical effectiveness data in the model, the majority of which were based on the UK registry dataset, ADAPT, looking at patients with A1PI deficiency. The ERG considers the modelled population broadly reflective of the

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

Clinical

The CS included a systematic review that used appropriate methodology to identify and appraise evidence relevant to the use of Respreeza in the management of emphysema secondary to severe A1PI deficiency. The ERG considers the evidence identified and included in the submission is appropriate to the decision problem and NICE scope. The ERG is confident that all relevant RCTs and relevant extensions were included in the submission.

The key findings were derived from a large, well-designed and well-conducted study, RAPID. Corroborative evidence on effect of A1PIs as a class was derived from two systematic reviews that included RAPID in their analyses. Results from the systematic reviews were consistent with the results reported from RAPID.

Economic

The formulae within the economic model are generally sound and the economic model is broadly well constructed.

1.5.2 Weaknesses and areas of uncertainty

Clinical

The ERG notes that data on rate of deterioration in lung density or lung function pre-treatment are not available for RAPID, as RAPID did not include a "run in" period to establish that those potentially eligible for the trial were experiencing progressive decline in lung disease. The ERG appreciates that monitoring lung function before treatment was not part of the design of other RCTs evaluating A1PI therapy. However, the ERG considers that it would be appropriate to identify those whose lung density or lung function is declining. Alternatively, as people of any categorisation of rate of decline in CT lung density are eligible for treatment, it would be appropriate to stratify randomisation by the categories of rate of decline (none, slow or rapid) to ensure balanced groups at baseline for this characteristic.

Although inclusion criteria for RAPID are well-defined, the ERG has reservations about the lack of clearer definition of progressive lung disease, or eligibility criteria for treatment. Based on the eligibility

Lung transplant: subsequent years	3.59	3.95	0.36
Total	**9.94**	**12.54**	**2.60**

Table D. Undiscounted life years gained in ERG's scenario using registry mortality data and different meta-analysis results (ICER -£5,898,567)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.07	0.06
<30% SL	0.40	0.60	0.19
<30% RD	0.58	0.12	-0.46
Total	**0.99**	**0.79**	**-0.21**
Lung transplant: first year	0.37	0.30	-0.08
Lung transplant: subsequent years	3.84	3.05	-0.79
Total	**10.75**	**10.60**	**-0.15**

Table E. Undiscounted life years gained in ERG's scenario using registry mortality data, different meta-analysis results and reducing the proportion of patients eligible for lung transplant by 30% (ICER -£37,189,197)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.09	0.08
<30% SL	0.51	0.75	0.23

<30% RD	0.72	0.15	-0.57
Total	**1.24**	**0.99**	**-0.26**
Lung transplant: first year	0.32	0.26	-0.07
Lung transplant: subsequent years	3.31	2.64	-0.67
Total	**10.42**	**10.35**	**-0.07**

Table F. Undiscounted life years gained in ERG's scenario using registry mortality data, different meta-analysis results, reducing the proportion of patients eligible for lung transplant by 30% and decreasing lung transplant-related survival (ICER £10,468,323)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.09	0.08
<30% SL	0.51	0.75	0.23
<30% RD	0.72	0.15	-0.57
Total	**1.24**	**0.99**	**-0.26**
Lung transplant: first year	0.32	0.26	-0.07
Lung transplant: subsequent years	2.88	2.30	-0.59
Total	**9.99**	**10.01**	**0.02**

12. Estimation of quality of life in the model: The company stated that the benefits of Respreeza may be underestimated by not capturing its effect of reducing lung density decline on patients' quality of life. The company presented one of two analyses from the Green et al. looking at the impact of lung density decline in HRQoL. The analysis reported by the company found [redacted] The second analysis in the manuscript, not reported by the company, showed [redacted]

procedure was monitored by clinical trial associates. The ERG considers that the processes implemented are likely to maintain masking of treatment allocation.

RAPID involved 180 people, with 93 and 87 people allocated to Respreeza and placebo, respectively.[42] A considerably larger proportion of people from the placebo group withdrew from the study (9/93 [9.7%] in the Respreeza group vs 18/87 [20.7%] in the placebo group), with the predominant reason for discontinuation in each group being withdrawal of consent (5/93 [5.4%] in Respreeza group vs 7/87 [8.1%] in the placebo group). The company comments that the probability of withdrawal from the study was statistically significantly ($p = 0.04$) lower in the Respreeza group, and, in addition to a lower rate of withdrawal of consent in the active treatment group, fewer people in the group died, or withdrew as a result of an adverse effect. Moreover, the company noted that the pattern of withdrawal of patients over time was similar for each treatment group, and proposed that the timings of the withdrawals suggested that the decision to withdraw was not influenced by events related to study design issues.

Respreeza (60 mg/kg) or placebo was infused intravenously at a rate of 0.08 mL/kg/min (typical infusion time of about 15 mins) on a weekly basis for 2 years. In exceptional circumstances (e.g., holidays), a single weekly dose of 120 mg/kg was allowed to cover a 2-week time period. Where possible, the patient attended the study centre for administration of their allocated treatment. As a minimum, the first infusion, and infusions given during quarterly attendance at the study centre, were administered by the investigator or their designated member of staff. All other weekly doses could be given by nurses provided by a home care service or by the family physician. Treatment was continuous for the length of the study, unless a person experienced an adverse effect that necessitated cessation of treatment. Mean overall compliance during RAPID was 93.9% with Respreeza and 89.6% with placebo, and mean number of administrations of allocated intervention per person was 94.2 and 87.3 for Respreeza and placebo, respectively.[58]

The primary measure of clinical effectiveness in RAPID was annual change in lung density as measured by CT, with the value adjusted to account for lung volume: the advantages and disadvantages of using CT lung density as a clinical outcome are discussed in greater detail in Section 3.4. Spiral CT scans were taken at baseline and after 3, 12, 21, and 24 months of follow up.[42] CT scans were stored electronically and sent to an external laboratory for analysis (BioClinica, Leiden, Netherlands).[42] At the request of regulatory authorities, rather than capture lung density solely at total lung capacity (TLC), CT scans were taken at both TLC and functional residual capacity (FRC) and the primary outcome was a combined assessment of recordings at each inspiration state. Lung density was measured in Hounsfield units and subsequently transformed to a measure in g/L. Next, due to the variability across people, it is necessary to apply a physiological volume correction to the g/L measure to generate the 15th percentile CT lung density (PD15): the PD15 is the cut-off density at which 15% of all pixels have lower densities.[59]

Table 5. Baseline demographics and disease characteristics for RAPID-OLE[43, 61]

Characteristic	Early start (N=76)	Delayed start (N=64)
Mean age, years (SD)	56.4 (6.9)	53.3 (7.8)
Gender (M/F)	41/35	38/26
CT lung density, adjusted PD15 g/L, mean (SD)		
TLC	42.2 (15.2)	43.1 (14.0)
FRC	43.9 (14.8)	46.0 (14.0)
Total	43.1 (14.9)	44.8 (14.1)
FEV1, % predicted, mean (SD)	45.0 (12.6)	46.3 (12.0)
FEV1/FVC ratio, mean (SD)	0.429 (0.110)	0.423 (0.087)
D_{LCO}, mL/mmHg/min, mean (SD)	NR	NR
Antigenic A1PI level, μM, mean (SD)	15.9 (3.7)	5.9 (2.5)
Functional A1PI level, μM, mean (SD)	9.7 (2.7)	2.4 (1.4)
Distance walked, m, mean (SD)	NR	NR
SGRQ, symptoms score, mean (SD)	47.3 (18.2)	44.0 (16.9)
A1PI phenotype, n (%)		
ZZ	67 (88)	61 (95)
SZ	2 (3)	0 (0)
Z	1 (1)	0 (1)
Other	6 (8)	3 (5)

Abbreviations: A1PI, alpha-1 proteinase inhibitor; CS, company submission; CT, computed tomography; D_{LCO}, diffusing capacity of the lung for carbon monoxide; F, female; FEV1, forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; M, male; NR, not reported; pg, page; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

4.2.4 Description and critique of statistical approach used

Accounting for a dropout proportion of 25%, the sample size calculation for RAPID indicated that 180 people were required to have at least 80% power to detect a difference in CT lung density decline (primary outcome) between Respreeza and placebo of 1.07 g/L (SD 2.17 g/L) with two-sided α of 0·05. The estimate of treatment effect was based on results reported from an earlier RCT evaluating augmentation therapy in A1PI deficiency.[56] At a one-sided α of 0·025, with the same number of people, the study would have 92% power to detect a difference between Respreeza and placebo of 1 g/L (SD 2.5 g/L) in decline in CT lung density.

Those for whom at least one scan of CT lung density was available formed the modified intention-to-treat (mITT) population on which the primary analysis was based: mITT population comprised 92 people (out of 93 randomised) in the Respreeza group and 85 people (out of 87 randomised) in the placebo group. The primary analysis was based on a random regression model, and it was assumed that data were missing at random. As highlighted by the company, the random regression model utilises all

4.3.2 Reported adverse effects

In RAPID, any untoward medical event was deemed to be an adverse event, with events assessed by the investigators as being not related, possibly related, probably related, or related to the trial treatment.[42] Adverse events were categorised as mild, moderate or severe:[58]

- Mild: did not interfere with routine activities;
- Moderate: interfered with routine activities;
- Severe: impossible to perform routine activities.

Adverse events resulting in death or in admission to hospital, or that were judged to be life-threatening were categorised as serious events.

Overall, the total number of adverse events reported in RAPID was higher in those receiving Respreeza compared with placebo (1,298 with Respreeza versus 1,068 with placebo; Table 14). Most people (99%) forming the safety population experienced a treatment-emergent adverse event (TEAE), the largest proportion of which in each group were of moderate intensity (58% in Respreeza group vs 49% in placebo group). There were four deaths during the RAPID study (1 in the Respreeza group and 3 in the placebo group), and one additional death during RAPID-OLE (Table 15). During the conduct of RAPID, occurrence of a TEAE led to the withdrawal of one person from the Respreeza group (due to back pain), and of four people from the placebo group who experienced a total of 10 TEAEs.[42]

Based on preferred terms, the company noted that headache was the most common TEAE reported in RAPID (Table 16). Other TEAEs reported by ≥10% of people and occurring more frequently in the Respreeza group than in those receiving placebo included COPD (32% with Respreeza versus 23% with placebo), oropharyngeal pain (24% versus 11%), condition aggravated (22% versus 16%), and cough (22% versus 8%; Table 16). By contrast, more people in the placebo group developed pneumonia (12% with Respreeza vs 14% with placebo). For completeness, TEAEs reported by ≥10% of people in RAPID-OLE are presented (Table 17).

Following on from the discussion on exacerbation of COPD as a clinical efficacy measure in Section 4.2.6.2, the ERG considers it important to highlight capture of COPD exacerbation as a TEAE. As part of the application to the EMA for marketing authorisation, the company submitted safety data from 6 studies,[41] two of which were RAPID and RAPID-OLE. The European Public Assessment Report (EPAR) for Respreeza reported that, during the first 6 months of treatment, exacerbation of COPD was recorded in 40 people from a total pool of 221 people having taken Respreeza (18.1%). By contrast, 11 out of 149 people taking placebo experienced an exacerbation of COPD (12.6%).[41] The overall incidence rate for exacerbation of COPD was 0.59 and 0.36 events per patient year for Respreeza and

Table 17. TEAEs reported ≥10%of patients and exposure-adjusted incidence rates by MedDRA preferred term (safety population) in RAPID-OLE (reproduced from CS, Table 26 [pg. 121])

	Early start[a] (N=76)		Delayed start[a] (N=64)	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Any event	**76 (100%)**	**773 (5.28%)**	**62 (96.9%)**	**620 (4.97%)**
Bronchitis	8 (10.5%)	15 (0.15)	4 (6.3%)	7 (0.06)
Influenza	6 (7.9%)	7 (0.05)	10 (15.6%)	11 (0.09)
Nasopharyngitis	24 (31.6%)	34 (0.23)	16 (25%)	38 (0.30)
Pneumonia	8 (10.5%)	13 (0.09)	7 (10.9%)	10 (0.08)
Oral Candidiasis	5 (6.6%)	16 (0.11)	8 (12.5%)	21 (0.17)
Upper respiratory	11 (14.5%)	23 (0.16)	6 (9.4%)	15 (0.12)
Lower respiratory	11 (14.5%)	66 (0.45)	6 (14.1%)	48 (0.38)
Chronic obstructive pulmonary disease	35 (46.1%)	105 (0.72)	21 (32.8%)	75 (0.60)
Cough	8 (10.5%)	16 (0.11)	7 (10.9%)	11 (0.09)
Dyspnoea	13 (17.1%)	36 (0.25)	5 (7.8%)	5 (0.04)
Oropharyngeal pain	12 (15.8%)	13 (0.09)	7 (10.9%)	8 (0.06)
Nausea	8 (10.5%)	9 (0.06)	3 (4.7%)	3 (0.02)
Diarrhoea	9 (11.8%)	9 (0.06)	3 (4.7%)	3 (0.02)
Oedema peripheral	5 (6.6%)	6 (0.04)	7 (10.9%)	7 (0.06)
Condition aggravated	16 (21.1%)	38 (0.26)	11 (17.2%)	37 (0.30)
Headache	15 (19.7%)	25 (0.17)	13 (20.3%)	33 (0.26)
Back pain	9 (11.8%)	12 (0.07)	10 (11%)	(0.08)

[a] Data are n (%) or n (annualised incidence rate).

Abbreviations: CS, company submission; OLE, open label extension; pg, page; TEAE, treatment-emergent adverse event.

4.4 Critique of the pairwise meta-analysis

As initially discussed in Section 4.1.5, rather than carry out their own meta-analyses, the company presents effect estimates from a systematic review by Edgar *et al*. 2017[44] that synthesised data from three RCTs, including the RAPID RCT, for various clinical outcomes. A second systematic review is available that presents meta-analyses of the same three RCTs for some clinical outcomes.[55] The ERG considers the company's approach to be appropriate. As reported by the company, one systematic review evaluated any treatment used for severe A1PI deficiency and additionally included cases series and uncontrolled studies, but with a focus on randomised controlled trials (RCTs),[44] whereas the second review limited study type to RCTs of A1PI augmentation therapy compared with placebo or no treatment.[55] Three RCTs were retrieved by each systematic review,[29, 42, 56] and the authors of both reviews carried out meta-analyses.

4.4.5 Health status

Meta-analysis presented in Edgar 2017[44] indicate no statistically significant difference between A1PI therapy and placebo in improvement in health status as assessed by the SGRQ (mean difference –0.83: 95% CI; –3.55 to 1.89; p=0.55; Table 23).

Table 23. Summary of meta-analyses of health status as reported in Edgar 201744 (forest plot available in CS, Figure 24 [pg. 123])

Study	A1PI			Placebo			Weight (%)	Mean difference (95% CI)
	Mean	SD	N	Mean	SD	N		
Edgar 2017[44] (Fixed effect model)								
Dirksen 2009	1.48	10.33	37	2.37	10.24	37	33.6	–0.89 (–5.58 to 3.80)
Chapman 2015	1.4	11.1	93	2.2	11.7	87	66.4	–0.80 (–4.14 to 2.54)
Total (95% CI)			**130**			**124**	**100**	**–0.83 (–3.55 to 1.89)[a]**

[a] Heterogeneity: Chi^2=0.00, df=1, (p=0.98), I^2=0%. Test for overall effect: Z=0.60 (p=0.55).

Abbreviations: CI, confidence interval; CS, company submission; pg, page; SD, standard deviation.

4.5 Conclusions of the clinical effectiveness section

The clinical effectiveness section in the CS was based on a systematic review of any intervention used in the treatment of A1PI deficiency. The ERG considers that the company is likely to have identified all clinical evidence on the use of Respreeza and other intravenous A1PIs as augmentation therapy in the treatment of emphysema related to severe A1PI deficiency, and the submitted evidence largely reflects the decision problem outlined in the final scope.

Enrolling 180 people, RAPID represents the largest RCT to date evaluating the clinical effectiveness of augmentation with intravenous A1PI, specifically Respreeza, in the management of emphysema secondary to severe A1PI deficiency: 93 and 87 people allocated to Respreeza and placebo, respectively. After 2 years of follow-up, all patients located outside the USA entered an open-label 2-year extension phase, RAPID-OLE, during which everyone received Respreeza.

The primary measure of clinical effectiveness in RAPID was annual change in lung density as measured by CT, with the value adjusted to account for lung volume. Respreeza was associated with a lower rate of annual decline in CT lung density (adjusted PD15 for combined TLC and FRC) compared with placebo at 2 years of follow-up, but the difference did not reach statistical significance. However, the difference between Respreeza and placebo in decline in CT lung density was statistically significant for the TLC inspiration state, and, again, favoured Respreeza:

- TLC plus FRC: mean difference of 0.62 g/L per year (95% CI: –0.02 g/L to 1.26 g/L; p=0.06);
- TLC alone: mean difference of 0.74 g/L (95% CI: 0.06 g/L to 1.42 g/L; p=0.03);

from £236,409 to £238,901 per QALY gained. When the ERG applied the 30% decrease in the FEV1<30% population eligible for lung transplant in the model, the ICER decreased from £236,409 to £228,865 per QALY gained. When both changes were applied, the ICER decreased to £231,403 per QALY gained.

The company assumed that patients have an equal annual probability of receiving a transplant regardless of how long they have been in the FEV_1<30% state. The company asserts that since this estimate is lower than the probability of transplantation in the first year in the NHS BT data, then the model effectively assumes an increased risk of death, since the probability of death is greater for patients with an FEV_1<30% than patients that have received a transplant.[81] The company concludes that, given Respreeza is expected to increase the proportion of patients that could receive a transplant, then assuming an equal probability in each year may be considered a conservative assumption.

The ERG notes that throughout the CS, the company states several times that one of the anticipated benefits of Respreeza is to delay, or obliviate the need for lung transplant, as exemplified below:

"*By delaying the loss of lung density and function, Respreeza is anticipated to prolong patient independence as well as prolonging the time to or obviating the need for lung transplant.*" (CS, pages 18–19)

"A decrease in the rate of respiratory decline and delay in the need for lung transplantation is likely to have a positive impact on the psychological distress and reduce the health burden placed on patients, family members and caregivers." (CS, page 138)

"*Another indirect treatment effect found in the model was delayed time to lung transplant as a consequence of reduced disease progression.*" (CS, page 191)

"In addition, it is expected that Respreeza will delay disease progression, prolonging the time to or obviating the need for lung transplant, and therefore it is not expected that Respreeza will be cost saving." (CS, page 245)

Therefore, the ERG points to the inconsistency in the company's proposed value of Respreeza with regards to lung transplant. The impact of Respreeza on patients' need for lung transplant is one of the model key drivers. This, however, needs to be explained in the context of its interaction with the estimation of survival in the economic analysis. These issues are discussed in detail in Section 5.4.7.2.

Post-lung transplant survival

The ERG disagrees with the data manipulation undertaken by the company to estimate survival in the first year after lung transplant in the model. The company took the survival estimate at year 1 of 82%

Total	**10.75**	**10.60**	**-0.15**

Table 49. Undiscounted life years gained in ERG's scenario using registry mortality data, different meta-analysis results and reducing the proportion of patients eligible for lung transplant by 30% (ICER -£37,189,197)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.09	0.08
<30% SL	0.51	0.75	0.23
<30% RD	0.72	0.15	-0.57
Total	**1.24**	**0.99**	**-0.26**
Lung transplant: first year	0.32	0.26	-0.07
Lung transplant: subsequent years	3.31	2.64	-0.67
Total	**10.42**	**10.35**	**-0.07**

Table 50. Undiscounted life years gained in ERG's scenario using registry mortality data, different meta-analysis results, reducing the proportion of patients eligible for lung transplant by 30% and decreasing lung transplant-related survival (ICER £10,468,323)

	Undiscounted life years		
	BSC	**Respreeza**	**Incremental**
Life years			
FEV1>50%: No decline	0.04	0.14	0.10
FEV1>50%: Slow decline	1.56	1.54	-0.03
FEV1>50%: Rapid decline	0.43	0.35	-0.07
Total	**2.03**	**2.03**	**0.00**
30%<FEV1<50%: No decline	0.07	0.38	0.31
30%<FEV1<50% Slow decline	1.57	3.34	1.77
30%<FEV1<50% Rapid decline	1.88	0.73	-1.15
Total	**3.52**	**4.44**	**0.92**
<30% ND	0.01	0.09	0.08
<30% SL	0.51	0.75	0.23
<30% RD	0.72	0.15	-0.57