NICE National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Contents:

9. Evidence Review Group additional analysis

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Human alpha-1 proteinase inhibitor for treating emphysema [ID856]

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
CSL Behring	CSL Behring are grateful for the opportunity to provide additional information and evidence to address the uncertainties the committee noted in the ECD. Human alpha-1 proteinase inhibitors have been used to treat A1PI deficiency for nearly three decades in the US, Canada and some European countries. Respreeza is the first maintenance therapy to be granted a licence in the UK to delay disease progression in A1PI deficient patients. We are pleased that, having considered the view of patients and clinical experts, the committee appreciates there is an unmet need for an effective treatment that protects people from the effects of infection and exposure to environmental toxins. We appreciate the long discussion during the committee meeting on defining a starting criteria for Respreeza. CSL Behring agree that the application of starting criteria would be appropriate if it were possible to define such criteria that would enable the identification of a patient population most likely to benefit from Respreeza. Our previous exploration of the RAPID data and engagement with the clinical community suggests that defining such criteria is not possible, but we welcome suggestions from clinical experts on what might be appropriate. During the committee meeting, clinicians stated that they felt a potential starting rule for treatment would be patients with a rapid decline in lung density, defined as >2 g/L/year. A post-hoc analysis of the RAPID study is presented in this response, which was conducted to ascertain whether this specific threshold might predict the patients most likely to benefit from treatment. [redacted]. However, intuitively, patients that are rapidly declining are the population presenting with the greatest unmet need as the time to respiratory failure will be quickest. CSL Behring anticipate that clinical experts' judgement may be the most effective measure in deciding to offer treatment with human A1PI, but welcome the view of the committee on alternative possible starting criteria to be explored. Whilst we are pleased that the committee recognised that A1PI could substantially increase survival, we are disappointed that the committee has considered the most plausible model scenario to be the ERGs analysis which results in a 7-month survival gain. Such a small increase in survival does not reflect the treatment effectiveness of Respreeza nor does it reflect the data from the US registry (NHLBI), which showed a near 30% reduced risk of death. Following the teleconference discussion on 11th September	Comment noted. The committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). Please see section 4 of the Evaluation Consultation Document (ECD) for the committee's consideration of the evidence.

Consultee	Comment	Response
	2018 with NICE, it has been agreed that additional mortality data will be provided as soon as it becomes available later this year. The additional data analysis and an update to the cost-effectiveness model is expected to reduce the uncertainty with regards to the overall survival gain associated with Respreeza. CSL Behring appreciates the approach from NICE to allow further evidence to be provided to support the submission. Within this response, we also present additional supportive evidence to reduce the committee's uncertainties regarding: • the potential effect of Respreeza on lung function and quality of life • the frequency of exacerbations compared to Respreeza • survival after lung transplantation in the economic analysis • the appropriate source of treatment effectiveness data with regards to FEV1 that is used in the economic analysis.	
CSL Behring	**Analysis of potential starting rules for treatment initiation** Section 4.4 of the ECD states that "the committee concluded that the most appropriate starting criteria for human A1PI have not been defined, and agreed that clearly defined starting criteria would help ensure that those most in need of treatment would have it". CSL Behring agree that the application of starting criteria would be appropriate if it were possible to define such criteria that would enable the identification of a patient population most likely to benefit from Respreeza. Our previous exploration of the RAPID data and engagement with the clinical community suggests that defining such criteria is not possible, but we welcome suggestions from clinical experts on what might be appropriate. During the committee meeting, clinicians stated that they felt a potential starting rule for treatment would be patients with a rapid decline in lung density (>2 g/L/year). A post-hoc analysis of the RAPID study has been undertaken to ascertain whether this specific threshold might predict the patients most likely to benefit from treatment. Since it is the rate of change in lung density, rather than the absolute value, longitudinal measurements of lung density are needed to analyse what happens prior to treatment. In future studies, this might be using a run-in period in which lung density decline had been analysed prior to the treatment being initiated. However, at the time of the RAPID study design, it was not known that a long-term run-in period would be required. Therefore, to understand whether such a starting rule would identify the patients most likely to benefit from treatment, an analysis of the placebo patients from the RAPID study has been undertaken. Patients who received placebo for 2 years in the double-blind study were switched to Respreeza (Delayed start group) for years 2 to 4, while those randomised to Respreeza remained on that treatment (Early start group). CSL Behring have analysed patients that were untreated in the 2 years of the RAPID trial to investigate whether there was a difference in treatment effects when the patients later switched to Respreeza in the extension study (RAPID-OLE).	Comment noted. The committee considered the additional evidence. The committee also heard concerns from patient experts about having to wait for treatment while suffering irreparable lung damage. It concluded that, although it may be valuable in clinical practice to agree appropriate starting criteria, it was not able to make recommendations that included specific starting criteria. Please see section 4.4 of the ECD.

Consultee	Comment	Response
	A detailed report of the methods and results is provided in Appendix 1. The estimated annual rate of change in lung density between 2 and 4 years is tabulated against the estimated rates between 0 and 2 years in **Error! Reference source not found.**. [redacted]	

Table 1. Categorisation of patients estimated annual rate of change 2 to 4 years, by annual rate in the first 2 years, ITT population

Estimated annual rate of change in lung density in the first 2 years	Estimated annual rate of change in lung density from 2 to 4 years			Total number
	No decline	Slow decline (0-2 /L/year)	Rapid decline (>2g/L/year)	
No decline	[redacted]	[redacted]	[redacted]	[redacted]
Slow (0-2 g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 2. Estimated change in lung density with treatment (2 to 4 years), stratified by rate in the first 2 years, ITT population

Lung density decline during placebo assignment	Number of patients with measurements	Mean change in lung density at TLC when treated in extension	Standard error	Lower 95% CI	Upper 95% CI
Not rapid (≤2 g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Consultee	Comment	Response
	[redacted] [redacted]. However, intuitively, patients that are rapidly declining are the population presenting with the greatest unmet need as the time to respiratory failure will be quickest in these patients. CSL Behring anticipate that clinical experts' judgement may be the most effective measure in deciding to offer treatment with human A1PI, but welcome the view of the committee on alternative possible starting criteria to be explored.	
CSL Behring	**Secondary Outcomes** Section 4.9 of the ECD states that "the committee concluded that the results from the secondary outcomes of lung function, quality of life and walking distance were inconclusive but there was no evidence that human A1PI provided benefits for these outcomes." Absolute effects to preserve lung function and QoL have not been established due to measurement sensitivities and the short period of time conducted for studies which are not indicative to the effects of the longer period of disease progression. Although no placebo controlled study has captured these effects to date, long-term correlations between lung density decline rates and declines in PFTs and QOL measurements have been established (**Error! Reference source not found.**). Stolk et al. identified the annual decline in lung density PD15 correlated moderately with the annual decline in FEV_1 (r=0.41; P = 0.003). The lung density PD15 annual decline rate was established in the first year of the trial from CT scans taken at Baseline, Month 6 and Month 12, whereas the mean annual decline in FEV_1 was 66 ml over 8 years thereafter in subjects with emphysema related to PiZZ A1PI **Error! Reference source not found.**. An analysis between annual lung density PD15 and DLco failed to establish a similar long-term correlation (r=0.21, p=0.165). Parr et al., 2006, identified a significant association in the rate of progression in FEV_1 with disease stage as characterised by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) **Error! Reference source not found.**. The EXACTLE study (Dirksen et al., 2009), identified a statistically significant relationship between the progression of CT densitometry and the rate of decline in FEV_1 **Error! Reference source not found.**. In the RAPID-OLE trial (McElvaney et al., 2017) modest and statistically significant 4 year correlations were consistently detected between change in lung density loss at TLC and spirometry values **Error! Reference source not found.**. An earlier study in 2003 by Stolk et al. established significant correlation between annual change in health status and lung density with A1PI **Error! Reference source not found.**. **Table 3. Outcome measures and treatment effects of identified studies**	Thank you for your comment. The committee considered the company's evidence and testimonies from patient and clinical experts. The committee recognised that it was biologically plausible that A1PI would improve secondary outcomes such as lung function but concluded that these benefits remain unproven. Please see section 4.11 and 4.12 of the ECD.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
<table>
<tr><th>Outcome Measure</th><th>Duration of follow-up</th><th>Number of centres</th><th>Sample size</th><th>Correlation coefficient with lung density</th><th>Reference</th></tr>
<tr><td>FEV_1</td><td>8 years</td><td>3</td><td>51</td><td>r=0.41 (p=0.003)</td><td>(Stolk et al., 2015)</td></tr>
<tr><td>FEV_1</td><td>3 years</td><td>1</td><td>34</td><td>r=0.52 (p=0.001)</td><td>(Parr et al., 2006)</td></tr>
<tr><td>FEV_1</td><td>2-2.5 years</td><td>3</td><td>77</td><td>r=0.32 (p=0.007)</td><td>(Dirksen et al., 2009)</td></tr>
<tr><td>FEV_1</td><td>4 years</td><td>22</td><td>118</td><td>r=0.286 (p=0.002)</td><td>(McElvaney et al., 2017)</td></tr>
<tr><td>FEV_1 % predicted</td><td>4 years</td><td>22</td><td>118</td><td>r=0.338 (p<0.001)</td><td>(McElvaney et al., 2017)</td></tr>
<tr><td>FVC</td><td>4 years</td><td>22</td><td>118</td><td>r=0.296 (p=0.001)</td><td>(McElvaney et al., 2017)</td></tr>
<tr><td>SGRQ</td><td>2.5 years</td><td>1</td><td>22</td><td>r=0.56 (p=0.007)</td><td>(Stolk et al., 2003)</td></tr>
</table>
</td><td></td></tr>
<tr><td>CSL Behring</td><td>Increased risk of pulmonary exacerbations
The ECD (section 4.10) stated that the committee expressed concern that human A1PI may be associated with an increased risk of pulmonary exacerbations. There is no clinical rationale for why human A1PI may be associated with an increased risk of pulmonary exacerbations and such an association would be at odds to beneficial effects of treatment seen on lung density. A critical analysis of exacerbation rates in the RAPID trial has been undertaken below to provide a potential justification for the unexpected results.
The RAPID study outcomes for the treated and untreated patients have been compared to other studies in A1PI deficiency (Appendix 2) and general COPD. Although numerical differences in favour of a lower annual number of exacerbations in the placebo arm were noted (1.70 vs 1.42 active:placebo) these rates are well within the 2.5-7 exacerbations/year in AATD patients (Dirksen et al., 2009, Needham and Stockley, 2005, Vijayasaratha and Stockley, 2008, Vijayasaratha and Stockley, 2012) or the 1-3 exacerbations/year expected in COPD patients (Wise, 2014).
A more striking disparity was noted in EAIRs for severe exacerbations. These were [redacted] for the Respreeza group and [redacted] for the placebo group. These rates are beneath the incidence rates for severe exacerbations of 0.26 in general COPD patients (Mullerova et al., 2015) and 0.14 in A1PI deficient subjects (Dirksen et al., 2009). Therefore, the incidence of exacerbations in RAPID was relatively low in both treatment groups, but particularly low in the placebo</td><td>Comment noted. Please see section 4.14 of the ECD.</td></tr>
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<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>group, compared to what would be expected in A1PI deficiency patients.
The incidence rate of severe exacerbations in the treated group was similar to the treated arm of the EXACTLE study (Dirksen et al., 2009). Of the 349 reported exacerbations, 13 (6.7%) and 21 (13.5%) were classified as severe in the human A1PI and placebo groups, respectively (p=0.013). Based on the published exposures of 127 and 108 weeks of therapy for Prolastin and placebo, CSL Behring has calculated the Exposure Adjusted Incidence Rates (EAIR) for severe exacerbations in both groups as 0.14 and 0.26 for Prolastin and placebo groups respectively (Table 4)

Table 4. Severe exacerbation rates in the EXACTLE study and RAPID study
<table>
<tr><td></td><td colspan="2">RAPID
(CSR, Table 14.2-2.3)</td><td colspan="2">EXACTLE
(Dirksen 2009)</td></tr>
<tr><td></td><td>Human A1PI (Respreeza)</td><td>Placebo</td><td>Human A1PI (Prolastin)</td><td>Placebo</td></tr>
<tr><td>Severe exacerbations</td><td>[redacted]</td><td>[redacted]</td><td>13</td><td>21</td></tr>
<tr><td>Subjects randomised</td><td>87</td><td>93</td><td>38</td><td>39</td></tr>
<tr><td>Subject years</td><td>[redacted]</td><td>[redacted]</td><td>96.2[a]</td><td>80.8[a]</td></tr>
<tr><td>Exposure adjusted incidence rate (EAIR)</td><td>[redacted]</td><td>[redacted]</td><td>0.14</td><td>0.26</td></tr>
</table>
[a]Based on the 127 and 108 weeks of therapy for the Prolastin and placebo groups, respectively

There is a significant difference between the rate of severe exacerbations in the placebo arms of the RAPID and EXACTLE studies where the baseline characteristics and study durations were comparable. There is no immediate explanation for this disparity; however comparisons between the RAPID active and placebo arms are clearly affected by the lower than expected severe exacerbation rate in the placebo arm.</td><td></td></tr>
<tr><td>CSL Behring</td><td>Transition Probabilities
In section 4.15 of the ECD, the committee concluded that the meta-analysis results had been incorrectly applied in the company's analysis and accepted the ERG's proposed amendment. CSL Behring partly agree with the approach applied by the ERG but would like to make a clarification.
For transition probabilities between FEV_1 states, two transitions are used:
1. from FEV_1 >50% to FEV_1 30-50%</td><td>Comment noted. Please see section 4.19 of the ECD.</td></tr>
</table>

Consultee	Comment	Response
	2. from FEV_1 30-50% to FEV_1 <30%. These transition probabilities are derived by estimating the time to which someone with an FEV_1 >50% would reach the FEV_1 value of exactly 50%, and similarly, by estimating the time to which someone with an FEV_1 30-50% would reach the FEV_1 value of exactly 30%. For the first transition state, CSL Behring had used the treatment effects in the FEV_1 30-65% group from the updated meta-analysis. The ERG felt that the treatment effects from the FEV_1 >65% group should have been used. We disagree with this because the majority of patients in the RAPID trial had a baseline FEV_1 of <65%, and therefore the patients being modelled typically have an FEV_1 of <65%. Applying treatment effects from the updated meta-analysis in a population with a baseline FEV_1 of >65% does not reflect the clinical trial population under consideration. Therefore, the updated meta-analysis results for patients in the group of FEV_1 30-65% should be used to generate both transition probabilities: the time to reaching the FEV_1 30-50% and the FEV_1 <30% health states. Since a statistically significant treatment effect of human A1PI was found in the FEV_1 30-65% group, whereas it was not in the FEV_1 >65% group, this correction will have a positive impact on the cost-effectiveness of Respreeza. Also, in section 4.15 of the ECD, the committee recognised that the evidence suggested FEV_1% and lung density decline were correlated, but these outcomes were implemented independently in the model and this would make the results uncertain. As part of amending the model with the pending mortality analysis, CSL Behring could be in the position to address this in the model later this year.	
CSL Behring	**Reduced Lung Transplant Survival** Section 4.16 of the ECD stated that the committee concluded that survival after transplant is uncertain and agreed with the ERGs survival estimates after lung transplantation. The ERGs survival estimates after lung transplantation were based on a study conducted 20 years ago and clinical expert opinion. The company's survival estimates after lung transplantation were based on survival data for all UK lung transplants published by the recent NHS Blood and Transplant Report from 2017 and are therefore the most robust evidence source. We acknowledge that this report does not report survival by indication but an alternative source has indicated that the survival of patients with A1PI deficiency is no different to the survival of all patients that have a lung transplantation, as discussed below. A presentation conducted by Dr Andrew Fisher, (Professor of Respiratory Transplant Medicine Institute of Transplantation, at the Freeman Hospital in Newcastle) illustrated survival after lung transplantation using a Kaplan-Meier curve from January 1990 to June 2011 by indication. For patients with A1PI deficiency, 1- and 5-year survival rates were 80% and 58%, further supporting the survival figures in the NHS Blood and Transplant Report for 2017 of 82% and 59% accordingly. A study published in 2015 by Stone et al., identified using a Kaplan-Meier curve, showed survival rates post-transplantation of UK patients with A1PI at 74.2% after 1 year and 52.9% after 5 years. The additional studies and	Comment noted. See sections 4.23–4.26 of the ECD. The committee acknowledged the new evidence provided by the company but noted the ERG's concerns about the modelling of survival after transplant. It concluded that survival after transplant is highly uncertain.

Consultee	Comment	Response
	presentation from Dr Andrew Fisher and Stone et al. show significant and robust evidence to support the survival figures used in the company submission.	
British Thoracic Society	**Has all of the relevant evidence been taken into account?** Yes, the major trials are included as is a meta-analysis of trial and cohort data which includes Respreeza and other AAT replacement products	Comment noted.
British Thoracic Society	**Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?** The report recognises unmet need in AATD and is supportive in terms of clinical effectiveness regarding emphysema progression (measured on CT scanning) and the effect that this would likely have on a range of other outcomes (eg FEV1, QOL, mortality) albeit noting that many of these have not been proven in trials. This is likely because effects occur over a longer period than trials could feasibly occur for. The economic model was viewed flawed in many ways, largely due to poor estimations around mortality in particular (and also QOL). This makes the cost estimate (ICER) uncertain and we anticipate a resubmission with new economic modelling. Regardless of whether this occurs, the committee's view that increasing numbers of AATD patients would be identified if screening occurred or if awareness of augmentation prompted more targeted testing and that this represents a risk to the NHS is sound. This is particularly so because the cost estimates are so uncertain.	Comment noted.
British Thoracic Society	**Are the provisional recommendations sound and a suitable basis for guidance to NHS England?** The NICE cost-effectiveness analysis used the current (higher) ICER threshold for highly specialised technology, and considered the potential magnitude of benefit. Based on the presented data, the recommendations are reasonable. However this case elegantly highlights common problems with this approach in rare conditions; limited data often leads to uncertainty about the estimate of benefit and financial modeling. The benefits of A1PI accrue over a long time period and may have been under-estimated in the current analysis. Issues around modelling of transplantation were also highlighted. To challenge the current decision, additional data on the likely survival benefit (bolstered by QoL data) will be required (work in progress).	Comment noted. The committee concluded that human A1PI could provide meaningful clinical benefits for patients and carers. But there are considerable uncertainties in the economic modelling. After considering the new evidence submitted during consultation, the committee concluded that a model which would allow it to consider the benefit of A1PI treatment with greater certainty, and which closely reflected clinical practice, would be preferred. It also agreed that collecting qualitative evidence systematically would allow it to further understand the benefits

Consultee	Comment	Response
		of A1PI treatment for people with the condition and their families, including its effects on quality of life. Please see sections 4.13, 4.26, 4.29 and 4.44 of the ECD
Royal College of Physicians	**Commentary on Respreeza ECD** The recognition by the Committee that A1PI deficiency has significant physical and emotional effects on people with the condition and their families, and that there is an unmet need for an effective treatment for A1PI deficiency in the NHS, is welcomed. Within the constraints of the limited extent of validated data provided by the company on the clinical effectiveness of A1PI (beyond the beneficial effects of treatment on the decline in CT measured lung density as a surrogate measure of emphysema), the committee appears to have reached a fair conclusion in its evaluation. However, the evaluation process may have been adversely affected by a number of factors.	Comment noted. The committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the ERG. Please see section 4 of the ECD for the committee's consideration of the evidence.
Royal College of Physicians	**Has all of the relevant evidence been taken into account?** Emphysema associated with AATD reduces life-expectancy to a much greater extent than emphysema associated with usual COPD because of the earlier onset and more rapid rate of progression in AATD-associated emphysema. In some patients, terminal respiratory failure significantly shortens life expectancy and lung transplantation may be the only alternative to death. However, lung transplantation does not represent a suitable comparator in the population being considered and this was highlighted by the patient experts at the HST committee meeting on the 23 August. The inclusion of lung transplantation in the company's model is not in keeping with the clinical utility of this treatment for AATD patients in the UK and does not appear to have taken account of patient perspective and patient choice. Lung transplantation is an option only for a small number of patients with end-stage disease and is limited by organ availability. 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 and, because a significant number of patients decline transplantation even when it is the only life-saving treatment available to them, it is likely to have been an unsuitable factor for the company to have included in its model. Furthermore, the criterion for transplantation that is employed in the company's model ('FEV1 <30%', which is presumed to be 30% predicted), is not representative of current clinical practice.	Comment noted. The committee noted that in clinical practice lung transplants are an integral part of the treatment pathway for a small proportion of the population but agreed that lung transplants had not been suitably modelled to appropriately capture costs and health effects. The committee concluded that a model which would allow the committee to consider the benefit of A1PI treatment with greater certainty, and which closely reflected clinical practice, would be preferred. Please see section 4.26 of the ECD.
Royal College of	Data relating to CT lung density decline and to mortality are critical to the evaluation. The data that have	Comments noted.

Consultee	Comment	Response
Physicians	been employed for the purposes of the company's submission are reported by the company to have originated from the Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT), which is stated by the company to be the UK registry of alpha-1 antitrypsin deficiency (page 28 of the committee papers; 'The Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) is the UK registry for A1PI deficiency patients, established in 1996'). Further reference is made to ADAPT as the UK registry throughout the company's submission (eg pages 306, 318, 320, 324, 325), in the ERG Report (pages 450, 454 etc) and in the ECD (section 4.24). Data employed in the company's model is reported to have come from the 'UK registry' (page 13 of the committee papers). The description of 'ADAPT' as the 'UK registry' is factually incorrect and the interchangeable use of the titles 'ADAPT' and 'UK registry' are potentially confusing and misleading. It should be noted that the ADAPT programme is a research programme funded principally by the pharmaceutical industry. Whilst the research programme has generated a significant quantity of peer-reviewed published manuscripts relating to AATD it does not provide outside access to raw data and is not synonymous with the UK Registry for AATD. The UK Registry for AATD is completely distinct from ADAPT, is a national registry rather than a research database, but contains only limited clinical information. Consequently, the UK Registry is unlikely to have provided the data referred to in the company submission or the ERG report. Clarification should be provided on which data (ie ADAPT or UK Registry) is being referred to by the company and the ERG.	References to data from ADAPT have been amended throughout the ECD. The committee recognised that ADAPT provided relevant observational evidence but concluded that it had potentially important limitations. See section 4.9 of the ECD for the committee's deliberations on the observational evidence.
Royal College of Physicians	It is stated in the ECD that 'the exact prevalence and incidence of emphysema associated with A1PI deficiency is unknown' and that there are 'about 670 people with emphysema caused by A1PI deficiency in England'. We believe that the UK Registry of AATD should be capable of providing a more realistic estimate of prevalence than the ADAPT database, and clarification should be sought on which of these sources was used to provide the estimate that was included in the ECD and the committee's evaluation	Comment noted.
Royal College of Physicians	**Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?** CT lung densitometry was developed as an outcome measure for use in studies of emphysema-modifying therapy in AATD as a direct response to the demonstration that it would be impractical and unethical to conduct a placebo-controlled study of augmentation therapy using traditional outcome measures, such as lung function. Subsequent studies, such as those in the RAPID Program, were powered to demonstrate a treatment effect using the more sensitive and specific measure of emphysema, CT lung densitometry, as the outcome measure. Consequently, it is illogical to draw any conclusions about the clinical effectiveness of A1PI on the basis of secondary outcomes, such as FEV1 or SGRQ, for which the studies were underpowered. The committee's approach to the interpretation of the published clinical trial data and meta-analyses does not always seem consistent and the conclusions drawn by the committee are, consequently, of questionable validity:	Comment noted. The ECD has been updated to reflect new evidence submissions in response to consultation, and to clarify the committee's interpretation of the evidence.

Consultee	Comment	Response
	• The data published in the RAPID trials demonstrate a treatment effect on lung density decline that is statistically significant but the ECD conclusion, that the clinical trial evidence 'suggests' that human A1PI slows decline in lung density more than placebo, implies doubt. • In contrast, the committee's interpretation of a treatment effect on lung function data that does not achieve a statistically significant difference is that 'there was a greater decline in lung function (FEV1% and diffusing capacity of the lungs for carbon monoxide [DLCO]) for people who had human A1PI than for those who had placebo'. This difference was not statistically significant, yet the statement implies certainty that treatment with Respreeza worsens lung function. The conclusion is, therefore, misleading. • Later, in section 4.8, the ECD states, 'The committee concluded that human A1PI slows the rate of lung density decline, and agreed that this was an important clinical benefit.' These three statements taken together do not demonstrate a consistent approach to data interpretation and a clear, evidence-based conclusion. The use of clinical terminology is, at times, either incorrect or confusing; for example, on page 14 of the ECD, 'In particular the committee was concerned that the evidence suggested FEV1% and lung density decline were correlated, but these outcomes were implemented independently in the model and this would make the results uncertain.' Clarification is required over the term 'FEV1%', since FEV1% actually refers to the ratio of FEV1/FVC, whereas it is assumed that the intended meaning here is 'FEV1% predicted'. It is unclear from the company submission which data is published and which data is unpublished because data from published manuscripts has also been highlighted in yellow eg Figure 3 Green et al 2014a. All data that has been published should be made publicly available rather than restricted by confidentiality.	
Royal College of Physicians	**Are the provisional recommendations sound and a suitable basis for guidance to NHS England?** The short notice period and the allocation of a meeting date during the summer holiday period may have significantly limited the availability of clinical experts to attend the NICE Committee meeting and, consequently, reduced the potential spectrum of clinical perspective. The submitted written statements and the clinical expert advice provided to the ERG appear only to have originated from a total of four clinical experts. As a consequence, a single clinical expert provided advice to the ERG, contributed to statements on behalf of the BTS and RCP and attended the Committee meeting as one of two clinical experts. It is therefore possible that a consensus view on fundamental issues relating to the evaluation (for example, the criteria for commencing and stopping treatment) would more likely have been reached had the number of clinical experts providing input and the breadth of expert opinion been greater. In a rare disease for which it will be hard to define evidence-based treatment criteria, an expert consensus view may be all that can be obtained (as evidenced by the large proportion of NICE clinical guidance	Comment noted. The committee considered that it had adopted a wide view in considering the evidence and factored in a range of analyses (both quantitative and testimonial) in its decision-making. It recognised concerns from stakeholders raised during consultation about variation in clinical expert opinion and sought clarification on both the AATD network and

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	recommendations that are based on expert opinion). The NICE evaluation process did not fully facilitate a consensus view due to the restricted number of experts employed, in combination with the need to adhere to a strictly confidential approach to the HST process. Furthermore, confusion regarding a consensus view of clinical experts may have been obtained by the Committee from written statements. In particular, references were made to the existence of an NIHR AATD Network. It should be acknowledged that the NIHR AATD Network, whilst existing as a defined research project for a finite period between 2014 and 2016, does not have any continuing formal mandate from the NIHR or a formal mandate with respect to providing a consensus view on AATD. It also included clinicians and researchers without significant specialist clinical expertise in AATD nor expertise in the technology under evaluation. In the context of the discussion on AATD at the HST meeting, reference was made to the existence of a British Thoracic Society Specialist Advisory Group (BTS SAG). However, it should be appreciated that the BTS SAG relates to COPD and does not specifically cover AATD - although its members are asked for open comment to inform the BTS submission. As emphasised at the committee meeting, usual COPD and AATD-associated lung disease are distinct clinical entities with only limited common features.	the BTS SAG. The committee considered that it had received the necessary expert advice for this evaluation. Please see section 4 of the ECD for the committee's consideration of the evidence.
Royal College of Physicians	**Could the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology?** Not to our knowledge. **Could the preliminary recommendations have any adverse impact on people with a particular disability or disabilities?** Not to our knowledge.	Comment noted.
Alpha-1 UK Support Group	The Alpha-1 UK Support Group is disappointed that NICE's draft guidance does not recommend Human alpha1-proteinase inhibitor (A1PI) as maintenance treatment to slow the progression of emphysema in adults with severe alpha1-proteinase inhibitor deficiency. Our charity has been supporting patients with alpha-1 antitrypsin deficiency (AATD) in the UK for 21 years and has been instrumental in systematically capturing and describing both the burden that patients with AATD-associated lung disease, their families and carers experience, as well as the high level of unmet medical need arising from this burden and the lack of effective treatment options for AATD-associated emphysema. We have been working with AATD expert clinicians across the UK and internationally for many years and are very active members of European and global patient-driven initiatives aimed at improving the lives of AATD patients and their families. As such, we are well informed about past, ongoing and planned clinical research into new treatments for AATD, and we are well connected in the national and international multi-stakeholder AATD landscape. We consider that the evidence submitted during this technology appraisal has, in many parts, been	Comment noted.

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	adequately and fairly reflected and interpreted in NICE's draft guidance. However, we disagree with several of the committee's assumptions. We also wish to highlight our concern about some of the information submitted as part of this evaluation that we consider is factually incorrect and believe may have adversely influenced the process. This consultation response has been prepared by the Board of Trustees of the Alpha-1 UK Support Group and reflects contributions from our members, i.e. AATD patients and carers of AATD patients, our trustees, and committee members and several individual AATD patients who are not formally members of our group.	
Alpha-1 UK Support Group	**1. Has all of the relevant evidence been taken into account?** We consider that the committee failed to recognise the full impact of AATD on patients' and their families' economic situation. Patients have a significantly reduced earning potential due to the limitations the disease places on their ability to maintain full-time work and progress their careers. This is particularly pertinent in younger patients, patients who are the main bread winners in their family, for single parents and for patients with more physical jobs. We know of many patients who have had to take early retirement due to ill-health and at an age where they would otherwise be in the prime of their career, thereby significantly impacting the family income. We know of families who, following early retirement of the parent with AATD, became reliant on financial support from the wider family or dependent on state support, had to down-size and significantly restrict the life-style they had been accustomed to. This has a negative downstream effect on the entire family, particularly patients' children. The direct and indirect impact on patients' economic situations frequently has a severe psychological impact. Mental health problems consequent to patients' loss of their career and the ability to provide for the family are common.	Comment noted. The committee recognised that A1PI deficiency is often diagnosed in mid adulthood, at a time when financial and family responsibilities can be particularly important. Please see sections 4.1 and 4.38 of the ECD.
Alpha-1 UK Support Group	We consider that the patient and clinical perspectives on the role of lung transplantation as a current treatment option has not been adequately reflected in the company submission, the ERG report and the committee's conclusions. All fail to acknowledge that, in addition to considerations around lung transplantation (such as eligibility, post-transplant survival etc.), the key determinants for the ability to even receive a lung transplantation are the shortage of donor organs and, very importantly, patient choice. A significant proportion of AATD patients who are technically eligible for lung transplantation either die before they receive a transplant or choose not to undergo this very invasive and risky procedure for a variety of reasons (detailed in our original submission). It can therefore not be assumed that lung transplantation is an option that is available for all or even the majority of patients once their disease has progressed sufficiently for them to meet the formal eligibility criteria for transplantation.	Comment noted. See sections 4.23–4.27 of the ECD for the committee's considerations around lung transplants. The committee noted that lung transplants are an integral part of the treatment pathway for a small proportion of the population, and that a model which would allow it to consider the impact of lung transplant with greater certainty, and which more closely reflected clinical practice, would be

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		preferred.
Alpha-1 UK Support Group	We consider that the structure of the cost-effective model presented by the company is unsuitable and some assumptions underlying transition probabilities are not feasible, and we would like to add several points to the committee's observations and conclusions about the model. The different health states in the model do not represent the natural disease progression of AATD-associated emphysema and are unnecessarily complicated. The combination of FEV1 % predicted and lung density decline to define a health state is illogical, given that the primary outcome of the RAPID trial was based only on measures of lung density, which has been shown to be the most sensitive and most specific measure of emphysema in AATD. It is also not clear why the health states in the model are based on the rate of lung density decline, rather than on absolute measures of lung density. The choice of health states based on FEV1 % predicted values above and below 30% and 50% seems arbitrary, and the clinical rationale of these model states is non-transparent. In the transition probabilities, both the rate of lung density decline and the change of FEV1 % predicted are assumed to be linear throughout emphysema progression. This is unrealistic, as the rate of decline over time levels off at very low absolute lung density and FEV1 % predicted values. The transition options to lung transplantation are illogical. The model suggests that patients with FEV1<50% predicted and no lung density decline cannot transition to lung transplantation directly but, instead, have to first transition to the health states of FEV1<50% predicted and slow lung density decline or FEV1<50% predicted and rapid lung density decline, respectively. This assumption is unrealistic and lacks validation. In clinical practice, patients do not loose eligibility for lung transplantation if their lung density decline were to stabilise after they have reached a level that would qualify them to be accepted for transplantation.	Comments noted. The committee recognised that it was challenging to accurately model the course of A1PI deficiency but heard from clinical experts that the modelled health states captured important and recognisable points in the progression of A1PI deficiency. Please see sections 4.16–4.18 of the ECD. The ECD has been revised to reflect the updated evidence on transition probabilities presented during consultation. See section 4.19 of the ECD.
Alpha-1 UK Support Group	We are concerned that, throughout the submissions from the company, the BTS, and one clinical expert as well as in the ERG report, reference is made to data from the "Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT)" and the "UK registry for A1PI deficiency patients" synonymously, implying that ADAPT and the UK registry for AATD are one and the same, when they are not. In addition, the company explicitly and repeatedly stated in their submission "The Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) is the UK registry for A1PI deficiency patients,..." (e.g. pages 28, 133, 144). We would like to advise the committee that ADAPT and the National UK AATD Registry are not	Comment noted. References to data from ADAPT have been amended throughout the ECD. See section 4.9 of the ECD for the committee's deliberations on the observational evidence. It recognised that ADAPT provided relevant observational

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	synonymous, and that clarity and transparency about the correct data sources, erroneously referred to synonymously as ADAPT and the National UK AATD Registry throughout, is required. A clear distinction between these two sources is important and relevant for this evaluation for the reasons detailed below. ADAPT is a locally run non-NHS research programme based in Birmingham that was established and, since its inception in 1996, has been predominantly funded by industry. Data originating from the ADAPT programme will be subject to bias arising from a number of factors, including: • Patient self-selection (participation into the research programme required informed consent), • Ability to regularly travel to Birmingham (which is extremely likely to exclude the most severely affected patients, patients in full-time employment, patients with young families, patients living at a distance from Birmingham), • Patients drop-out due to worsening health or other reasons, • Patients not interested to participate in research or very mildly affected patients who may not see the benefit in participation, • Patients lacking awareness of the existence of the research programme. In addition, access to raw data generated in the ADAPT research programme and the opportunity to mine data sets held in ADAPT is not granted to any party outside the programme, but could historically be requested by third parties, typically in exchange for research funding. In contrast, the National UK AATD Registry, also held in Birmingham, is a conventional disease registry into which NHS centres from across the UK contribute data and to which a broad range of parties can gain access. Historically, and as indicated by the lack of an extensive publication record, the National UK AATD Registry has held little data. It is stated in the company submission that some of the key inputs of the cost-effectiveness model (incl. the data used to model transitions between disease states, mortality for the remainder of the modelled time horizon beyond the clinical trials, health-state specific EQ-5D utility values) have been obtained from the “UK Registry”. However, the company also stated that it had no access to the raw data underlying these data analyses, and that the analyses were conducted by the “ADAPT Registry team”. Some of the data the company stated to have obtained from the UK Registry were marked as confidential and are presumably unpublished. We therefore assume that the company was, in fact, referring to data from the ADAPT research programme, rather than the UK Registry.	evidence but concluded that it had potentially important limitations.

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	It is unknown from the company submission which inclusion and exclusion criteria were applied to the patient cohorts selected for the different analyses "performed by the ADAPT team", whether the patient characteristics of these selected cohorts from the ADAPT database were comparable with the patient cohorts in the RAPID and the RAPID-OLE studies and, given the intrinsic bias of the data from the ADAPT programme detailed above, whether the ADAPT data was representative of the AATD population in England. We consider that the data from the ADAPT research programme might have excluded original data from more severely affected patients. Data from the UK registry (not ADAPT) or from other UK expert centres that have generated their own longitudinal databases from their NHS practice, might therefore have been more relevant for the analysis. Given that a significant proportion of the data that informed key parameters of the health economic model and the outcomes of the cost-effectiveness analysis was apparently not available to the company, its validity could not have been tested by the company, the ERG or the committee. In the interest of accuracy and full transparency, we ask the committee to seek clarification of the source of all data referred to in the company submission as originating from the "UK Registry" and/or "ADAPT", i.e. an accurate attribution of the data to either source.	
Alpha-1 UK Support Group	The committee concluded that there was no evidence that human A1PI provides benefits to patients' quality of life. We acknowledge that the lack of direct HRQoL outcome measures in the RAPID trial and the limitations of mapping SGRQ data to EQ-5D have not resulted in adequately capturing and demonstrating quality of life improvements in patients receiving the therapy. However, over the years, most patients who have been receiving human A1PI in countries where it is available have reported significant and life-changing benefits. Unfortunately, these benefits have not yet been systematically and quantitatively captured in relevant prospective clinical trials or retrospective studies. We have therefore recently undertaken telephone interviews with three patients in the U.S. who have been receiving human A1PI. The results of these interviews indicate that these patients have been experiencing significant beneficial effect with the treatment. We ask the committee to take the reports from the patient interviews, summarised below, into consideration.	Comment noted. The committee carefully considered the comments received from experts, consultees, commentators and the public in response to the draft guidance. It recognised the value of this evidence along with the testimonies from clinical and patient experts. The committee considered that although the clinical trial results were inconclusive, testimonies from clinical and patient experts showed that it was likely that A1PI would improve quality of life. Please see sections 4.12

Consultee	Comment	Response
	PATIENT 1 ***General information and diagnosis:*** • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] ***Family history:*** • [redacted] ***Clinical presentation at diagnosis / burden of illness:*** • Breathlessness • At diagnosis, FEV1 42% predicted and rapidly declining • Frequent infective exacerbations, requiring hospital admissions 2-3 times a year • No longer able to pursue any sports • Reduced working hours and frequent periods of sick-leave ***Human A1PI therapy treatment and reported benefits:*** • Initiated on Respreeza in [redacted] → [redacted] years on weekly augmentation therapy • Lung function stabilised • Significantly reduced breathlessness and exacerbation frequency - only one hospital admission since commencement of therapy with Respreeza • Returned to full-time work as an administrator in hospital – stable financial situation • Able to participate fully in family, social and community life • Significantly improved quality of life **PATIENT 2** ***General information and diagnosis:*** • [redacted] • [redacted] • [redacted]	and 4.13 of the ECD.

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	• [redacted] • [redacted] ***Family history:*** • [redacted] • [redacted] ***Clinical presentation at diagnosis / burden of illness:*** • Severe breathlessness • At diagnosis, 30% FEV1 predicted and rapidly declining • Had to stop working on [redacted] farm • Unable to carry things, walk anywhere or play with [redacted] children • Frequent respiratory infections • Major burden of housework and childcare was placed on [redacted] • Limited ability to participate in family and social life; relationship with [redacted] suffered due to inability to have sex due to breathlessness ***Human A1PI therapy treatment and reported benefits:*** • Started on Respreeza in [redacted] → [redacted] years on weekly therapy; self-infuses therapy at home • Lung function stabilised and even increased upon taking up regular exercise • Significantly reduced breathlessness • Able to stop taking supplementary oxygen • Significantly reduced infection frequency • Returned to working part-time work on [redacted] ranch – improved financial situation • Currently performs regular physical exercise 3 times weekly (karate, shooting, horse riding) • Took up volunteer work at local church 7 years ago • Improved family, social and sex life due to higher energy levels and less breathlessness • Significantly improved quality of life • Describes Respreeza as a “game changer that gave me my life back” **PATIENT 3** ***General information and diagnosis:*** • [redacted]	

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	• [redacted] • [redacted] • [redacted] • [redacted] ***Family history:*** • [redacted] ***Clinical presentation at diagnosis / burden of illness:*** • Breathlessness • At diagnosis: 41% FEV1 predicted • Regular respiratory exacerbations • Difficulties performing everyday tasks such as shopping, cleaning, walking short distances and being physically active with [redacted] small children • Supplementary oxygen therapy at night • Negative impact on social life and ability to exercise ***Human A1PI therapy treatment and reported benefits:*** • Started on augmentation therapy in late [redacted] → more than [redacted] years on weekly therapy • Lung function stabilised • Reduced breathlessness; supplementary oxygen treatment was stopped • Regained ability to socialise • Significantly improved quality of life	
Alpha-1 UK Support Group	During the committee meeting, one of the clinical experts gave the impression that several of their statements represented or were endorsed by the "Special Advisory Group (SAG)" of the British Thoracic Society (BTS), implying that this SAG is specifically concerned with AATD and/or represents the consensus opinion of a group of AATD experts. We advise the committee that the BTS confirmed to us that it has no SAG specifically for AATD, and that the clinical expert who referred to the SAG is in fact a member of the COPD SAG (and it has been specifically highlighted that usual COPD and AATD are distinct diseases). We therefore conclude that the statements made with reference to the SAG refers to the personal opinion of the clinical expert rather than a consensus opinion of a group of AATD specialists at the BTS. We ask the committee to seek clarification on this issue and weight the clinical expert's statements	Comment noted. The committee recognised the concerns of stakeholders raised during consultation and sought clarification on the role of the BTS SAG. It considered that it had received the necessary expert advice for this evaluation. Please see section 4 of the ECD for the committee's consideration of the evidence.

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	accordingly	
Alpha-1 UK Support Group	Frequent reference is made in the consultee submission by the BTS to the “NIHR AATD Network”, particularly in relation to this being a network through which AATD specialist NHS services are currently being provided throughout the UK (e.g. pages 2, 3, 4, 5 of the BTS submission). It is also implied that this “network” has some formal mandate or remit by the NIHR, and that this “network” includes all relevant AATD expert centres in England. We advise the committee that no such formal “NIHR AATD Network” exists. Several years ago, a number of UK centres undertook a joint, NIHR-funded research project under the lead of Birmingham, with a specific research objective and a defined duration of 3 years. NIHR funding for this multi-centre project stopped in 2016 as planned in the research protocol, when the project came to an end. Since then, the clinical expert who has authored the BTS consultee submission has repeatedly referred to the “NIHR AATD Network” and its alleged role in providing specialist NHS care for AATD. We have previously and repeatedly sought clarification from Dr Alice Turner (who leads the ADAPT research programme) and her colleagues at Birmingham about the precise nature and remit of this “network” in relation to providing specialist NHS care for AATD, as reference to the “NIHR AATD Network” has been made repeatedly in publications, at conferences, in presentations etc. since the formal conclusion of the initial NIHR research project. In the absence of an answer to our enquiry, our charity eventually obtained the study protocol from the NIHR and a list of all participating centres through a public request under the Freedom of Information Act 2000. This confirmed that the original “network” of participating study centres never had a formal (or informal) remit or accreditation from the NIHR to provide specialist NHS services, and that the NIHR has no formal role of any nature beyond the limited and defined remit of the NIHR research project (principally to provide data and biological samples from AATD patients to Birmingham for the purposes of a biomarker development/validation) that finished in 2016. In 2016, our charity also conducted a survey of the centres that had been listed in the study protocol as participants of the NIHR research project in order to understand which of these centres had relevant expertise in clinical management of AATD or were running/ planning to run a specialist NHS service for AATD. Our key finding was that only a small number of all collaborating centres in the NIHR research project had special expertise in AATD, or were running or planning to establish a specialist service. In contrast, centres with recognised AATD expertise that were already providing specialist AATD NHS services had not participated in the NIHR research project. (Please see outcomes of this survey in our charity newsletter 2016 at	Comment noted. The committee recognised the concerns of stakeholders raised during consultation and sought clarification on the role of the AATD network. It considered that it had received the necessary expert advice for this evaluation. Please see section 4 of the ECD for the committee’s consideration of the evidence.

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	http://www.alpha1.org.uk/attachments/article/51/A1UK_NEWSLETTER%20ISSUE%2015%20AUTUMN%202016.pdf.pdf, page 9). We repeatedly sought clarification from Dr Turner as to the remit of the "NIHR AATD Network" for the provision of NHS clinical AATD services. Dr Turner finally responded in writing in September 2018, "The Network is a research group and, as such, has no "remit" for the provision of NHS clinical AATD services. However, the member centres of the Network do provide NHS clinical AATD services, which are funded through their provider contracts." Notably, many of the centres listed in the original NIHR research protocol are no longer members of the current "NIHR AATD Network" described in the BTS consultee submission We therefore consider that the repeated references to and the representation of the "NIHR AATD Network" in the context of provision of care for AATD given in the BTS statement is grossly misleading. The statements in relation to the "NIHR AATD Network" also wrongly imply that, if human A1PI was recommended for use in the NHS, it would be made available principally through this "network" which would also develop national guidelines for AATD. Given that this evaluation process should be conducted transparently and in accordance with high standards of accuracy, we ask the committee to seek clarification from the author of the BTS statement as to the exact nature and role of "NIHR AATD Network" in the context of provision of NHS-based clinical care for AATD.	
Alpha-1 UK Support Group	On page 5 of the BTS consultee statement, it is stated that "This response has the support of the NIHR AATD Group." Given that this group does not formally exist according to Dr Turner's own account (see 1.7 above), we ask the committee to seek clarification on: • which experts have formally supported this submission, • how this support was obtained given the confidential nature of the process, and • whether, prior to the submission being made by the BTS, approval from the NIHR had been sought in order to confirm that the "NIHR AATD Network" had in fact formally supported the submission. We ask the committee to weight the statements submitted by the BTS in the light of whether or not they truly reflect a formal consensus opinion of a group of AATD experts or are just those of the author of the BTS submission.	Comment noted.
Alpha-1 UK	Data from the ADAPT research programme appears to have constituted a significant role in informing	Comment noted.

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Support Group	the cost-effectiveness model submitted by the company. Dr Alice Turner, one of the two clinical advisors to the ERG and a clinical expert in the evaluation, declared a personal specific financial interest for receiving personal fees for consultancy with CSL Behring. However, we ask the committee to seek clarification from Dr Turner, as the lead for the ADAPT programme, as to her and her research group's involvement in the provision of any data or analyses for the direct or indirect purpose of the company submission, and whether this potential interest had been declared.	
Alpha-1 UK Support Group	**2. Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?** The committee concluded that there was no evidence that human A1PI provided benefits for secondary outcomes such as lung function, quality of life and walking distance. This is not surprising, given that the RAPID study was not sufficiently powered to demonstrate a statistically significant effect in any of the secondary functional outcome parameters. Any non-statistically significant trend is therefore merely a chance finding and cannot be interpreted as the presence or the absence of a treatment effect.	Comment noted. The committee acknowledged that the clinical trials were not powered to detect changes in lung function or walking distance. It concluded that it was biologically plausible that A1PI would improve secondary outcomes such as lung function but this was unproven. Please see section 4.11 of the ECD.
Alpha-1 UK Support Group	**3. Are the provisional recommendations sound and a suitable basis for guidance to NHS England?** The Alpha-1 UK Support Group considers that, given our comments above, the provisional recommendations have not been based on and interpreted in view of all the relevant information. **4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We are not aware of any.	Comments noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Professor David Parr	I welcome the Committee's recognition that human alpha1-proteinase inhibitor (A1PI) deficiency has significant physical and emotional effects on people with the condition and on their families. Furthermore, the recognition by the Committee that there is an unmet need for an effective treatment for alpha-1 antitrypsin deficiency (AATD) in the NHS represents a significant step towards the institution of appropriate specialist NHS clinics for this group of patients. However, it will be extremely disappointing to AATD specialists who have contributed for many years towards generating a body of scientific evidence sufficient to obtain an EMA license for A1PI therapy that the initial response of the NICE Committee is not to recommend this treatment. More importantly, this decision will result in a much deeper sense of disappointment for patients in England who will still be unable to receive AIPI augmentation therapy, at the same time as they are aware of the patients in other European countries and around the world who have funded access to treatment with this therapy. Nevertheless, I recognise that the committee's decision reflects a fair evaluation of the available evidence and that, beyond the beneficial effects of treatment on the progression of emphysema as assessed on computed tomography imaging, there was only limited validated data on the clinical effectiveness of A1PI provided in the company's submission. However, I consider that there are some factors which may have adversely affected the evaluation process, as detailed below.	Comment noted. The committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). Please see section 4 of the ECD for the committee's consideration of the evidence.
Professor David Parr	**1. Has all of the relevant evidence been taken into account?** The role of lung transplantation in the patient 'journey' has been exaggerated in the company submission and, consequently, in the evaluation process: since the majority of patients approaching 'end-stage' disease do not undergo lung transplantation, the characterisation of the role of transplantation is not representative of UK practice. Patients with AATD-related emphysema tend to experience earlier onset emphysema and more rapidly progressive emphysema than patients with usual COPD so that they reach terminal respiratory failure at a lower age. However, lung transplantation is only an option for a minority of patients due, in part, to limited organ availability. In addition, for the reasons described by the expert patients in the committee meeting, patient choice is often to decline this treatment even when it is the only life-saving option left to them. The transplantation criterion of FEV1 <30% predicted that the company has chosen for use in its model seems too early in the natural history of the disease process and does not reflect UK clinical practice. It is not clear from where this clinical information originated but, as a consequence, the company has relied on a model that appears to be flawed from a clinical perspective.	Comment noted. The committee acknowledged that in clinical practice lung transplants are an integral part of the treatment pathway for a small proportion of the population. Please see section 4.23–4.27 of the ECD for the committee's considerations on lung transplants in the economic modelling.
Professor David Parr	The company's model and the committee's evaluation is heavily reliant on data relating to differential rates of decline in CT lung density and mortality. It is reported by the company that the data used in	Comment noted. References to data from

Nominating organisation	Comment	Response
	its submission was provided by the Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT). However, at several points in the submission the company states that ADAPT is the UK registry for AATD patients, which is incorrect. The same incorrect information is included on a number of occasions in the ERG Report and, as a consequence of these statements, it is also included in the ECD. The UK Registry and the ADAPT programme are not synonymous but there appears to be interchangeable reference to these two distinct entities throughout the company's submission, leading to confusion and, potentially, misleading conclusions. The UK Registry is a national register of patients with AATD that is sourced from clinicians across the UK, but contains only limited clinical information. In contrast, ADAPT is a research programme that has been funded primarily by industry and, whilst it may provide data analyses to interested parties, does not offer any access to the raw data. It is important that the distinction is made between ADAPT and the UK Registry, not least, because it is stated in the submission of one of the clinical experts that they lead the ADAPT programme and, if ADAPT did provide data to the company, this represents a potential conflict of interest that has not been declared. It is also important to clarify whether it was the ADAPT Programme or the UK Registry data that was used to estimate prevalence, since the UK Registry should, in theory, represent a more comprehensive record of AATD patients across England	ADAPT have been amended throughout the ECD. See section 4.9 of the ECD for the committee's deliberations on the observational evidence. It recognised that ADAPT provided relevant observational evidence but concluded that it had potentially important limitations.
Professor David Parr	**2. Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?** The summaries of clinical effectiveness are, at some points, confusing and give the appearance of some inconsistencies in the approach adopted by the committee to data interpretation. In section 4.8 of the ECD it is documented; 'The committee concluded that human A1PI slows the rate of lung density decline, and agreed that this was an important clinical benefit.' It is not logical to state that treatment with human A1PI provides an 'important clinical benefit' when the committee does not also report a beneficial treatment effect on lung function or health status (and without any data to show beneficial effects on mortality). Indeed, the committee's actual interpretation of the treatment effect on lung function data is that 'there was a greater decline in lung function (FEV1% and diffusing capacity of the lungs for carbon monoxide [DLCO]) for people who had human A1PI than for those who had placebo'. This difference was not statistically significant, yet the statement misleadingly implies certainty that treatment with Respreeza worsens lung function. In contrast, the committee concludes that the clinical trial evidence only 'suggests' that human A1PI slows decline in lung density more than placebo, even though this beneficial treatment effect is statistically significant. It should be recognised that CT lung densitometry was specifically developed for use as an outcome measure in studies of A1PI augmentation therapy because it had been recognised that a placebo-controlled study using traditional outcome measures, such as lung function, would be impractical and unethical. The studies that were designed subsequently were not statistically powered to identify a treatment effect on lung function or health status indices but were specifically powered to show a	Comment noted. The committee acknowledged that the clinical trials were not powered to detect changes in lung function or walking distance. It concluded that it was biologically plausible that A1PI would improve secondary outcomes such as lung function but this was unproven. Please see section 4.11 of the ECD.

Nominating organisation	Comment	Response
	treatment effect when assessed using CT lung densitometry. Under these circumstances, any apparent treatment effects on lung function or health status indices are likely to arise by chance and it is potentially misleading to draw conclusions about the clinical effectiveness of A1PI on the basis of these 'underpowered' secondary outcomes.	
Professor David Parr	**3. Are the provisional recommendations sound and a suitable basis for guidance to NHS England?** Clinical expertise in rare diseases is usually rare and access to suitably experienced clinicians is therefore likely to be limited. Consequently, the short notice period provided by NICE and the allocation of a meeting date during the summer holiday period may have significantly impacted on the ability to identify a good range of available clinical opinion to inform the evaluation process. This situation may have been compounded by the fact that the same clinical expert has provided advice to the ERG, has written statements on behalf of the BTS and RCP and attended the HST committee meeting as one of two clinical experts. I am concerned that the NICE Committee may have been given the impression at the committee meeting that they were being presented with a consensus view of clinical experts from some of the content of the written statements and from the content of the discussion at the committee meeting. In the written statements of one of the clinical experts, reference was made on many occasions to the 'NIHR AATD Network' and it was stated in the statement written on behalf of the BTS that the BTS response was supported by this 'network'. Whilst the NIHR AATD Network did exist as a defined research project for a fixed two-year period until 2016, it does not have any continuing formal mandate from the NIHR and was not given a formal mandate with respect to providing a consensus view on AATD. It is not evident whether the support of the 'NIHR AATD Network' referred to in the statement on behalf of the BTS received the endorsement of the BTS nor, if the response on behalf of the BTS had received the informed support of other experts, how the response could have been shared with them within the process of confidentiality. One of the clinical experts referred during the discussion at the HST committee meeting to the existence of a British Thoracic Society Specialist Advisory Group (BTS SAG) and their membership of the group. It is possible that this reference may have given the committee the impression that the BTS SAG referred to was a specialist group advising on AATD since this was the subject under discussion at the time. There is no BTS SAG for AATD and I can, therefore, only assume that the reference related to a BTS SAG for usual COPD. Nevertheless, I am concerned that the committee may have drawn the false conclusion that the clinical expert's comments represented a consensus view of a group of experts in AATD when, at best, they may have represented the views of experts in usual COPD: as acknowledged during the committee meeting, usual COPD and AATD-associated lung disease are distinct clinical entities with only limited common features. Consequently, the views of the BTS SAG for COPD, if this was the intended reference, would have only limited relevance to the evaluation.	Comment noted. The committee considered that it had adopted a wide view in considering the evidence and factored in a range of analyses (both quantitative and testimonial) in its decision-making. It recognised concerns from stakeholders raised during consultation about variation in clinical expert opinion and sought clarification on both the AATD network and the BTS SAG. The committee considered that it had received the necessary expert advice. Please see section 4 of the ECD for the committee's consideration of the evidence.

Nominating organisation	Comment	Response
	The committee may, consequent to the above factors, have been left with the impression that the content of the discussion at the meeting represented the consensus view of UK AATD experts and that, despite representations from a wide range of expert opinion across the UK, there remained uncertainty in relation to critical issues such as, but not limited to, criteria for starting and stopping A1PI therapy. Irrespective of whether this impression was obtained, it seems unfortunate that the NICE evaluation process did not fully facilitate a consensus view due to the restricted number of experts employed, and that the need to adhere to a strictly confidential approach to the HST process may present obstacles that limit access to a wider range of opinion and the opportunity to identify a consensus opinion on issues for which there is no scientific data to support an evidence-based decision. In a rare disease for which it will be particularly difficult to define evidence-based treatment criteria, an expert consensus view may be all that can be obtained (as evidenced by the large proportion of recommendations in NICE Clinical Guidelines that are graded on the basis of expert opinion). The restriction on the number of experts, combined with the circumstances of the same single expert contributing to the evaluation process as described above, may have adversely influenced a fair outcome.	
Professor David Parr	**4) Could the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology?** Not to my knowledge. **5) Could the preliminary recommendations have any adverse impact on people with a particular disability or disabilities?** Not to my knowledge.	Comments noted.
Dr Ravi Mahadeva	This therapy is the only disease modifying therapy for severe alpha 1 antitrypsin deficiency. PiZZ individuals will experience development of emphysema due to severe lack of circulating antitrypsin which progresses at different rates. Some of whom will experience rapid decline and development of disability and death at a young age. Many will not be suitable for lung transplantation and even after lung transplantation there may be significant morbidity and premature death. It is clearly rational to augment the very low levels of antitrypsin in those with progressive emphysema.	Comment noted.

Nominating organisation	Comment	Response
Dr Ravi Mahadeva	**Has all the relevant evidence been taken into account?** References 33, 46 are useful. It is not clear whether this reference has been considered Int J Chron Obstruct Pulmon Dis. 2016 Aug 1;11:1745-56. doi: 10.2147/COPD.S111508. eCollection 2016. This details rates of lung function decline from the National registry. I would recommend analysis of this data and most recent data from the National registry ADAPT.	Comment noted. The committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). Please see section 4 of the ECD for the committee's consideration of the evidence.
Dr Ravi Mahadeva	**Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** The objective of the therapy is to slow the rate of decline of emphysema and therefore disability and death. CT densitometry will best show the rate of decline in emphysema. Lung function, health quality of life are less sensitive and will need longer studies and larger number of patients to clearly show the rate of decline therefore I do not agree with the statement that augmentation therapy does not show a signal in these parameters. The clinical criteria could be more specific for example. Only PiZZ or PiZnull individuals with and FEV1 > 40% with documented evidence of emphysema on CT, documented decline in an accredited centre of more than 2% per year for 3 years and/or loss of lung density by > 2g/year (or corrected for the initial density- see comment below). I agree with the comment that the starting densitometry is likely to influence the absolute rate of decline. More detailed analysis of the RAPID data should be able to clarify this. The antitrypsin NIHR network could be consulted for an opinion and existing centres of expertise can be used to manage selection of patients. The above criteria will influence the economic model; some comments regarding this model. Starting the therapy before the onset of sever disability will lead to reduced health care costs, medications, need for long term oxygen therapy, domiciliary NIV, admissions, primary care consultations, need to consider lung transplantation and LVR. IN addition to ability to work and retirement age. Furthermore, some individuals will experience severe disease after a transplantable age and therefore will have premature mortality.	Comment noted. The committee considered the additional evidence around starting criteria submitted by the company, clinical experts and patient experts at the second evaluation committee meeting. The committee concluded that, although it may be valuable in clinical practice to agree appropriate starting criteria, it was not able to recommend specific starting criteria. Please see section 4.4 of the ECD.

Nominating organisation	Comment	Response
Dr Ravi Mahadeva	**Are the provisional recommendations sound and a suitable basis for guidance on the use of alpha1-proteinase inhibitor in the context of national commissioning by NHS England?** No- the analysis needs to be reassessed with specific groups of patients informed by analysis of RAPID data and ADAPT.	Comment noted. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). This included updated analyses using both the ADAPT and RAPID cohorts. Please see section 4 of the ECD for the committee's consideration of the evidence.
Dr Ravi Mahadeva	**Equality** This is a disease of Caucasians. I can see no equality issues related to gender etc. However, patients in this country are currently disadvantaged in comparison to many other countries where augmentation therapy is available.	Comment noted. The committee recognise that human A1PI is available in other European countries and stakeholders concerns that there is a disparity in access to treatment. The committee concluded this is not an equality issue that can be addressed in a highly specialised technologies evaluation. Please see section 4.38 of the ECD for further information on equality issues.

Comments received from commentators

Commentator	Comment	Response
NA	NA	NA

Comments received from members of the public

Role*	Section	Comment	Response
Health professional (within NHS)	4.4	Thank you for your recent advice on adding a response to the current NICE report on augmentation therapy for patients with Alpha-1-antitrypsin deficiency. In 2016 the NIHR funded an Alpha-1-antitrypsin network as part of its Rare diseases call with the express aim of enabling collaboration between centres actively involved in managing patients and facilitating research and the development and delivery of appropriate clinical trials. The funding brought together centres coordinated by Birmingham ([redacted]) and involving Cambridge ([redacted]), Royal Free Hospital London ([redacted]), The Royal Brompton London ([redacted]), Leicester ([redacted]), Nottingham ([redacted]) and Southampton ([redacted]). These clinicians have experience in the study and management of over 2000 deficient patients and several contributed widely to the literature of Chronic obstructive pulmonary Disease as well as the European Respiratory Strategy for management of the condition published in 2017 (1) and the European Union statement on the disease. With extensive background knowledge of the disease and its progression the group now referred to as the “AATD collaborative” have seen and discussed the NICE preliminary report and the Royal College of Physicians response. As a group we acknowledge the published literature showing that augmentation therapy can reduce the progression of the central emphysematous process in the disease. The rarity of the condition has made it extremely difficult to undertake trials based on conventional outcome measures of physiology and health status (2). However we believe that very careful patient assessment and characteristics are a necessary pre-requisite to consideration, implementation and monitoring of the efficacy of augmentation therapy. This includes several key elements in decision making that need to be considered with implications for health care cost modelling.	Comment noted. The committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the ERG on potential starting criteria. It concluded that, although it may be valuable in clinical practice to agree appropriate starting criteria, it was not able to recommend specific starting criteria. Please see section 4.4 of the ECD.

* When comments are submitted via the Institute’s web site, individuals are asked to identify their role by choosing from a list as follows: ‘patent’, ‘carer’, ‘general public’, ‘health professional (within NHS)’, ‘health professional (private sector)’, ‘healthcare industry (pharmaceutical)’, ‘healthcare industry’(other)’, ‘local government professional’ or, if none of these categories apply, ‘other’ with a separate box to enter a description.

Role*	Section	Comment	Response
		1. Only patients (ZZ or Znull) who are never or ex-smokers (at least 6 months after stopping) should be considered for treatment 2. They must have a diagnosis of Emphysema 3. They must have evidence of ongoing decline in lung function despite optimal use of current therapy. **4.** This decline should be 2% of the predicted value (for age, sex, height and race) or more per year as documented over at least 4 annual assessments obtained with stringent standard operating procedures. This decline for an individual is essentially linear (3). **Members of the collaborative will actively search their current patient data bases to determine the number of patients who currently have this documented rate of decline.** 5. Following commencement of therapy there should be also a documented reduction in the decline of lung function again over 4 consecutive annual assessments to determine the evidence of efficacy before deciding on continuation. **6. All the steps and decision should be undertaken in designated expert centres providing comprehensive care for the condition.** **References** **1.** M.Miravitlles, A.Dirksen, I.Ferrarotti, V.Koblizek, P.Lange, R.Mahadeva, N.G.McElvaney, D.Parr, E.Piitulainen, N.Roche, J.Stolk, G.Thabut, A.Turner, C.Vogelmeier, R.A.Stockley (2017). European Respiratory Society statement: diagnosis and treatment of pulmonary disease in a1-antitrypsin deficiency. *Eur Respir J*. 50(5): **2.** R.A.Stockley, R.G.Edgar, S.Starkey, A.M.Turner (2018) Health status decline in a-1 antitrypsin deficiency: a feasible outcome for disease modifying therapies? *Respir Res* 19(1):137 **3. R.A.Stockley**, R.G.Edgar, A.Pillai, A.M.Turner (2016) Individualized lung function trends in alpha-1-antitrypsin deficiency: a need for patience in order to provide patient centered management? *Int J*	

Role*	Section	Comment	Response
		COPD, 11: 1745-1756	

Summary of comments received from members of the public

Theme	Response
NA	NA

Highly Specialised Technology Evaluation

Human alpha-1 proteinase inhibitor for treating emphysema [ID 856]

Manufacturer's Response to the Evaluation Consultation Document (ECD)

CSL Behring are grateful for the opportunity to provide additional information and evidence to address the uncertainties the committee noted in the ECD. Human alpha-1 proteinase inhibitors have been used to treat A1PI deficiency for nearly three decades in the US, Canada and some European countries. Respreeza is the first maintenance therapy to be granted a licence in the UK to delay disease progression in A1PI deficient patients. We are pleased that, having considered the view of patients and clinical experts, the committee appreciates there is an unmet need for an effective treatment that protects people from the effects of infection and exposure to environmental toxins.

We appreciate the long discussion during the committee meeting on defining a starting criteria for Respreeza. CSL Behring agree that the application of starting criteria would be appropriate if it were possible to define such criteria that would enable the identification of a patient population most likely to benefit from Respreeza. Our previous exploration of the RAPID data and engagement with the clinical community suggests that defining such criteria is not possible, but we welcome suggestions from clinical experts on what might be appropriate. During the committee meeting, clinicians stated that they felt a potential starting rule for treatment would be patients with a rapid decline in lung density, defined as >2 g/L/year. A post-hoc analysis of the RAPID study is presented in this response, which was conducted to ascertain whether this specific threshold might predict the patients most likely to benefit from treatment.

[redacted]. However, intuitively, patients that are rapidly declining are the population presenting with the greatest unmet need as the time to respiratory failure will be quickest. CSL Behring anticipate that clinical experts' judgement may be the most effective measure in deciding to offer treatment with human A1PI, but welcome the view of the committee on alternative possible starting criteria to be explored.

Whilst we are pleased that the committee recognised that A1PI could substantially increase survival, we are disappointed that the committee has considered the most plausible model scenario to be the ERGs analysis which results in a 7-month survival gain. Such a small increase in survival does not reflect the treatment effectiveness of Respreeza nor does it reflect the data from the US registry (NHLBI), which showed a near 30% reduced risk of death. Following the teleconference discussion on 11th September 2018 with NICE, it has been agreed that additional mortality data will be provided as soon as it becomes available later this

year. The additional data analysis and an update to the cost-effectiveness model is expected to reduce the uncertainty with regards to the overall survival gain associated with Respreeza. CSL Behring appreciates the approach from NICE to allow further evidence to be provided to support the submission.

Within this response, we also present additional supportive evidence to reduce the committee's uncertainties regarding:

- the potential effect of Respreeza on lung function and quality of life
- the frequency of exacerbations compared to Respreeza
- survival after lung transplantation in the economic analysis
- the appropriate source of treatment effectiveness data with regards to FEV_1 that is used in the economic analysis.

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Analysis of potential starting rules for treatment initiation

Section 4.4 of the ECD states that "the committee concluded that the most appropriate starting criteria for human A1PI have not been defined, and agreed that clearly defined starting criteria would help ensure that those most in need of treatment would have it". CSL Behring agree that the application of starting criteria would be appropriate if it were possible to define such criteria that would enable the identification of a patient population most likely to benefit from Respreeza. Our previous exploration of the RAPID data and engagement with the clinical community suggests that defining such criteria is not possible, but we welcome suggestions from clinical experts on what might be appropriate.

During the committee meeting, clinicians stated that they felt a potential starting rule for treatment would be patients with a rapid decline in lung density (>2 g/L/year). A post-hoc analysis of the RAPID study has been undertaken to ascertain whether this specific threshold might predict the patients most likely to benefit from treatment.

Since it is the rate of change in lung density, rather than the absolute value, longitudinal measurements of lung density are needed to analyse what happens prior to treatment. In future studies, this might be using a run-in period in which lung density decline had been analysed prior to the treatment being initiated. However, at the time of the RAPID study design, it was not known that a long-term run-in period would be required. Therefore, to understand whether such a starting rule would identify the patients most likely to benefit from treatment, an analysis of the placebo patients from the RAPID study has been undertaken. Patients who received placebo for 2 years in the double-blind study were switched to Respreeza (Delayed start group) for years 2 to 4, while those randomised to Respreeza remained on that treatment (Early start group). CSL Behring have analysed patients that were untreated in the 2 years of the RAPID trial to investigate whether there was a difference in treatment effects when the patients later switched to Respreeza in the extension study (RAPID-OLE).

A detailed report of the methods and results is provided in Appendix 1.

The estimated annual rate of change in lung density between 2 and 4 years is tabulated against the estimated rates between 0 and 2 years in Table 1. [redacted]

Table 1. Categorisation of patients estimated annual rate of change 2 to 4 years, by annual rate in the first 2 years, ITT population

Estimated annual rate of change in lung density in the first 2 years	Estimated annual rate of change in lung density from 2 to 4 years			Total number
	No decline	Slow decline (0-2 /L/year)	Rapid decline (>2g/L/year)	
No decline	[redacted]	[redacted]	[redacted]	[redacted]

Slow (0-2 g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 2. Estimated change in lung density with treatment (2 to 4 years), stratified by rate in the first 2 years, ITT population

Lung density decline during placebo assignment	Number of patients with measurements	Mean change in lung density at TLC when treated in extension	Standard error	Lower 95% CI	Upper 95% CI
Not rapid (≤2 g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]. However, intuitively, patients that are rapidly declining are the population presenting with the greatest unmet need as the time to respiratory failure will be quickest in these patients.

CSL Behring anticipate that clinical experts' judgement may be the most effective measure in deciding to offer treatment with human A1PI, but welcome the view of the committee on alternative possible starting criteria to be explored.

Secondary Outcomes

Section 4.9 of the ECD states that "the committee concluded that the results from the secondary outcomes of lung function, quality of life and walking distance were inconclusive but there was no evidence that human A1PI provided benefits for these outcomes." Absolute effects to preserve lung function and QoL have not been established due to measurement sensitivities and the short period of time conducted for studies which are not indicative to the effects of the longer period of disease progression. Although no placebo controlled study has captured these effects to date, long-term correlations between lung density decline rates and declines in PFTs and QOL measurements have been established (Table 3).

Stolk et al. identified the annual decline in lung density PD15 correlated moderately with the annual decline in FEV_1 (r=0.41; P = 0.003). The lung density PD15 annual decline rate was established in the first year of the trial from CT scans taken at Baseline, Month 6 and Month 12, whereas the mean annual decline in FEV_1 was 66 ml over 8 years thereafter in subjects with emphysema related to PiZZ A1PI Table 3. An analysis between annual lung density PD15 and DLco failed to establish a similar long-term correlation (r=0.21, p=0.165).

Parr et al., 2006, identified a significant association in the rate of progression in FEV_1 with disease stage as characterised by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Table 3.

The EXACTLE study (Dirksen et al., 2009), identified a statistically significant relationship between the progression of CT densitometry and the rate of decline in FEV_1 Table 3.

In the RAPID-OLE trial (McElvaney et al., 2017) modest and statistically significant 4 year correlations were consistently detected between change in lung density loss at TLC and spirometry values Table 3.

An earlier study in 2003 by Stolk et al. established significant correlation between annual change in health status and lung density with A1PI Table 3.

Table 3. Outcome measures and treatment effects of identified studies

Outcome Measure	Duration of follow-up	Number of centres	Sample size	Correlation coefficient with lung density	Reference
FEV_1	8 years	3	51	r=0.41 (p=0.003)	(Stolk et al., 2015)
FEV_1	3 years	1	34	r=0.52 (p=0.001)	(Parr et al., 2006)
FEV_1	2-2.5 years	3	77	r=0.32 (p=0.007)	(Dirksen et al., 2009)
FEV_1	4 years	22	118	r=0.286 (p=0.002)	(McElvaney et al., 2017)
FEV_1 % predicted	4 years	22	118	r=0.338 (p<0.001)	(McElvaney et al., 2017)

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

Increased risk of pulmonary exacerbations

The ECD (section 4.10) stated that the committee expressed concern that human A1PI may be associated with an increased risk of pulmonary exacerbations. There is no clinical rationale for why human A1PI may be associated with an increased risk of pulmonary exacerbations and such an association would be at odds to beneficial effects of treatment seen on lung density. A critical analysis of exacerbation rates in the RAPID trial has been undertaken below to provide a potential justification for the unexpected results.

The RAPID study outcomes for the treated and untreated patients have been compared to other studies in A1PI deficiency (Appendix 2) and general COPD. Although numerical differences in favour of a lower annual number of exacerbations in the placebo arm were noted (1.70 vs 1.42 active:placebo) these rates are well within the 2.5-7 exacerbations/year in AATD patients (Dirksen et al., 2009, Needham and Stockley, 2005, Vijayasaratha and Stockley, 2008, Vijayasaratha and Stockley, 2012) or the 1-3 exacerbations/year expected in COPD patients (Wise, 2014).

A more striking disparity was noted in EAIRs for severe exacerbations. These were [redacted] for the Respreeza group and [redacted] for the placebo group. These rates are beneath the incidence rates for severe exacerbations of 0.26 in general COPD patients (Mullerova et al., 2015) and 0.14 in A1PI deficient subjects (Dirksen et al., 2009). Therefore, the incidence of exacerbations in RAPID was relatively low in both treatment groups, but particularly low in the placebo group, compared to what would be expected in A1PI deficiency patients.

The incidence rate of severe exacerbations in the treated group was similar to the treated arm of the EXACTLE study (Dirksen et al., 2009). Of the 349 reported exacerbations, 13 (6.7%) and 21 (13.5%) were classified as severe in the human A1PI and placebo groups, respectively (p=0.013). Based on the published exposures of 127 and 108 weeks of therapy for Prolastin and placebo, CSL Behring has calculated the Exposure Adjusted Incidence Rates (EAIR) for severe exacerbations in both groups as 0.14 and 0.26 for Prolastin and placebo groups respectively (Table 4)

Table 4. Severe exacerbation rates in the EXACTLE study and RAPID study

	RAPID (CSR, Table 14.2-2.3)		EXACTLE (Dirksen 2009)	
	Human A1PI (Respreeza)	Placebo	Human A1PI (Prolastin)	Placebo
Severe exacerbations	[redacted]	[redacted]	13	21
Subjects randomised	87	93	38	39
Subject years	[redacted]	[redacted]	96.2[a]	80.8[a]
Exposure adjusted incidence rate (EAIR)	[redacted]	[redacted]	0.14	0.26

[a]Based on the 127 and 108 weeks of therapy for the Prolastin and placebo groups, respectively

There is a significant difference between the rate of severe exacerbations in the placebo arms of the RAPID and EXACTLE studies where the baseline characteristics and study durations were comparable. There is no immediate explanation for this disparity; however comparisons between the RAPID active and placebo arms are clearly affected by the lower than expected severe exacerbation rate in the placebo arm.

Transition Probabilities

In section 4.15 of the ECD, the committee concluded that the meta-analysis results had been incorrectly applied in the company's analysis and accepted the ERG's proposed amendment. CSL Behring partly agree with the approach applied by the ERG but would like to make a clarification.

For transition probabilities between FEV_1 states, two transitions are used:

1. from FEV_1 >50% to FEV_1 30-50%
2. from FEV_1 30-50% to FEV_1 <30%.

These transition probabilities are derived by estimating the time to which someone with an FEV_1 >50% would reach the FEV_1 value of exactly 50%, and similarly, by estimating the time to which someone with an FEV_1 30-50% would reach the FEV_1 value of exactly 30%.

For the first transition state, CSL Behring had used the treatment effects in the FEV_1 30-65% group from the updated meta-analysis. The ERG felt that the treatment effects from the FEV_1 >65% group should have been used. We disagree with this because the majority of patients in the RAPID trial had a baseline FEV_1 of <65%, and therefore the patients being modelled typically have an FEV_1 of <65%. Applying treatment effects from the updated meta-analysis in a population with a baseline FEV_1 of >65% does not reflect the clinical trial population under consideration. Therefore, the updated meta-analysis results for patients in the group of FEV_1

30-65% should be used to generate both transition probabilities: the time to reaching the FEV_1 30-50% and the FEV_1 <30% health states.

Since a statistically significant treatment effect of human A1PI was found in the FEV_1 30-65% group, whereas it was not in the FEV_1 >65% group, this correction will have a positive impact on the cost-effectiveness of Respreeza.

Also, in section 4.15 of the ECD, the committee recognised that the evidence suggested FEV_1% and lung density decline were correlated, but these outcomes were implemented independently in the model and this would make the results uncertain. As part of amending the model with the pending mortality analysis, CSL Behring could be in the position to address this in the model later this year.

Reduced Lung Transplant Survival

Section 4.16 of the ECD stated that the committee concluded that survival after transplant is uncertain and agreed with the ERGs survival estimates after lung transplantation.

The ERGs survival estimates after lung transplantation were based on a study conducted 20 years ago and clinical expert opinion. The company's survival estimates after lung transplantation were based on survival data for all UK lung transplants published by the recent NHS Blood and Transplant Report from 2017 and are therefore the most robust evidence source. We acknowledge that this report does not report survival by indication but an alternative source has indicated that the survival of patients with A1PI deficiency is no different to the survival of all patients that have a lung transplantation, as discussed below.

A presentation conducted by Dr Andrew Fisher, (Professor of Respiratory Transplant Medicine Institute of Transplantation, at the Freeman Hospital in Newcastle) illustrated survival after lung transplantation using a Kaplan-Meier curve from January 1990 to June 2011 by indication. For patients with A1PI deficiency, 1- and 5-year survival rates were 80% and 58%, further supporting the survival figures in the NHS Blood and Transplant Report for 2017 of 82% and 59% accordingly. A study published in 2015 by Stone et al., identified using a Kaplan-Meier curve, showed survival rates post-transplantation of UK patients with A1PI at 74.2% after 1 year and 52.9% after 5 years. The additional studies and presentation from Dr Andrew Fisher and Stone et al. show significant and robust evidence to support the survival figures used in the company submission.

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Appendix 1: Analysis of Patients with Rapidly Declining Lung Function

Introduction

[redacted]

Methods

a. *Original analysis*

[redacted]

b. Current analysis

[redacted]

Results

a. Classification of rates of change

[redacted]

[redacted]

[redacted]

b. *Estimated mean change in lung density and %FEV$_1$*

[redacted]

Table 5. Estimated mean change in lung density and FEV$_1$ 2-4 years by estimated rate of decline (0-2 years), ITT (N=64)

	Lung density (g/L) (N=61)				% predicted FEV$_1$ (N=58)			
	Mean	Standard error	Lower 95% CI	Upper 95% CI	Mean	Standard error	Lower 95% CI	Upper 95% CI
No decline (N=2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slow (0-2 g/L/year) (TLC: N=25) (FEV: N=26)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year) (TLC:N=34) (FEV:N=30)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6. Estimated mean change in lung density and FEV_1 2-4 years by estimated rate of decline (0-2 years), Completers (N=58)

	Lung density (g/L) (N=57)				% predicted FEV_1 (N=52)			
	Mean	Standard error	Lower 95% CI	Upper 95% CI	Mean	Standard error	Lower 95% CI	Upper 95% CI
No decline (N=2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slow (0-2 g/L/year) (TLC: N=23) (FEV: N=22)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year) (TLC:N=32) (FEV:N=28)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 7. Estimated change in lung density and FEV_1 2-4 years by estimated rate of decline (0-2 years); no decline and slow decline categories combined; ITT (N=64)

	Lung density (g/L) (N=61)				% predicted FEV_1 (N=58)			
	Mean	Standard error	Lower 95% CI	Upper 95% CI	Mean	Standard error	Lower 95% CI	Upper 95% CI
Not rapid (≤2 g/L/year) (TLC: N=27) (FEV: N=28)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Rapid (>2g/L/year) (TLC:N=34) (FEV:N=30)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8. Estimated change in lung density and FEV_1 2-4 years by estimated rate of decline (0-2 years); no decline and slow decline categories combined; Completers (N=58)

	Lung density (g/L) (N=57)				% predicted FEV_1 (N=52)			
	Mean	Standard error	Lower 95% CI	Upper 95% CI	Mean	Standard error	Lower 95% CI	Upper 95% CI
Not rapid (≤2 g/L/year) (TLC: N=25) (FEV: N=24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year) (TLC:N=32) (FEV:N=28)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 9. Observed mean change in lung density and FEV(%) from 2 to 4 years by observed annual rate of change in lung density 0 to 2 years; ITT

Last observed	Last observed lung density change from Year 2 (g/L)				Last observed FEV_1 change from Year 2 (%)			
	Mean	s.d.	n	No data	Mean	s.d.	n	No data
Observed decline in TLC (3 gp)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Last observed	Last observed lung density change from Year 2 (g/L)				Last observed FEV_1 change from Year 2 (%)			
	Mean	s.d.	n	No data	Mean	s.d.	n	No data
No data								
No decline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slow (0-2 g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10. Observed mean change in lung density and FEV(%) from 2 to 4 years by observed annual rate of change in lung density 0 to 2 years; completers

Last observed (Year 4)	Last observed lung density change from Year 2 (g/L)				Last observed FEV_1 change from Year 2 (%)			
	Mean	s.d.	n	No data	Mean	s.d.	n	No data
Observed decline in TLC (3 gp)								
No data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No decline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slow (0-2 g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11. Observed mean change in lung density and FEV(%) from 2 to 4 years by observed annual rate of change in lung density 0 to 2 years Slow/No decline groups combined; ITT

Last observed	Last observed lung density change from Year 2 (g/L)				Last observed FEV_1 change from Year 2 (%)			
	Mean	s.d.	n	No data	Mean	s.d.	n	No data
Observed decline in TLC (2 gp)								
No data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not rapid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 12. Observed mean change in lung density and FEV(%) from 2 to 4 years by observed annual rate of change in lung density 0 to 2 years Slow/No decline groups combined; Completers

Last observed (Year 4)	Last observed lung density change from Year 2 (g/L)				Last observed FEV_1 change from Year 2 (%)			
	Mean	s.d.	n	No data	Mean	s.d.	n	No data
Observed decline in TLC (2 gp)								
No data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not rapid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

c. *Rates of change in lung density from 2 to 4 years*

[redacted]

Table 13. Estimated annual rate of change 2 to 4 years by annual rate in years 0-2; ITT

Estimated 0-2 years	Annual rate of change from Y2 to Y4 in lung density (estimated, g/L/year)			
	No decline	Slow (0-2 /L/year)	Rapid (>2g/L/year)	Total No.
Estimated decline in lung density				
No decline	[redacted]	[redacted]	[redacted]	[redacted]
Slow (0-2 g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Table 14. Estimated annual rate of change 2 to 4 years by annual rate in years 0-2; ITT

Estimated 0-2 years	Annual rate of change from Y2 to Y4 in lung density (observed, g/L/year)				
	No data	No decline	Slow (0-2 /L/year)	Rapid (>2g/L/year)	Total No.
Estimated decline in lung density					
No decline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slow (0-2 g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15. Observed annual rate of change 2 to 4 years by observed annual rate in years 0-2; ITT

Observed 0-2 years	Annual rate of change from Y2 to Y4 in lung density (observed, g/L/ year)				
	No data	No decline	Slow (0-2g/L/year)	Rapid (>2g/L/ year)	Total No.
Observed decline in lung density					
No data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No decline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slow (0-2 g/L/ year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rapid (>2g/L/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Observed 0-2 years	Annual rate of change from Y2 to Y4 in lung density (observed, g/L/ year)				
	No data	No decline	Slow (0-2g/L/year)	Rapid (>2g/L/ year)	Total No.
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

alpha-1 uk support group

Supporting alphas, their families, carers and friends since 1997

20th October 2018

NICE
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

Uploaded to: NICE Docs/Appraisals
Cc: email hst@nice.org.uk

RE: Human alpha1-proteinase inhibitor for treating emphysema [ID856]
Evaluation consultation document Response from Alpha-1 UK Support Group

The Alpha-1 UK Support Group is disappointed that NICE's draft guidance does not recommend Human alpha1-proteinase inhibitor (A1PI) as maintenance treatment to slow the progression of emphysema in adults with severe alpha1-proteinase inhibitor deficiency.

Our charity has been supporting patients with alpha-1 antitrypsin deficiency (AATD) in the UK for 21 years and has been instrumental in systematically capturing and describing both the burden that patients with AATD-associated lung disease, their families and carers experience, as well as the high level of unmet medical need arising from this burden and the lack of effective treatment options for AATD-associated emphysema.

We have been working with AATD expert clinicians across the UK and internationally for many years and are very active members of European and global patient-driven initiatives aimed at improving the lives of AATD patients and their families. As such, we are well informed about past, ongoing and planned clinical research into new treatments for AATD, and we are well connected in the national and international multi-stakeholder AATD landscape.

We consider that the evidence submitted during this technology appraisal has, in many parts, been adequately and fairly reflected and interpreted in NICE's draft guidance. However, we disagree with several of the committee's assumptions. We also wish to highlight our concern about some of the information submitted as part of this evaluation that we consider is factually incorrect and believe may have adversely influenced the process.

This consultation response has been prepared by the Board of Trustees of the Alpha-1 UK Support Group and reflects contributions from our members, i.e. AATD patients and carers of AATD patients, our trustees, and committee members and several individual AATD patients who are not formally members of our group.

1. Has all of the relevant evidence been taken into account?

1.1 We consider that the committee failed to recognise the full impact of AATD on patients' and their families' economic situation. Patients have a significantly reduced earning potential due to the limitations the disease places on their ability to maintain full-time work and progress their careers. This is particularly pertinent in younger patients, patients who are the main bread winners in their family, for single parents and for patients with more physical jobs. We know of many patients who have had to take early retirement due to ill-health and at an age where they would otherwise be in the prime of their career, thereby significantly impacting the family income. We know of families who, following early retirement of the parent with AATD, became reliant on financial support from the wider family or dependent on state support, had to down-size and significantly restrict the life-style they had been accustomed to. This has a negative downstream effect on the entire family, particularly patients' children. The direct and indirect impact on patients' economic situations frequently has a severe psychological impact. Mental health problems consequent to patients' loss of their career and the ability to provide for the family are common.

1.2 We consider that the patient and clinical perspectives on the role of lung transplantation as a current treatment option has not been adequately reflected in the company submission, the ERG report and the committee's conclusions. All fail to acknowledge that, in addition to considerations around lung transplantation (such as eligibility, post-transplant survival etc.), the key determinants for the ability to even receive a lung transplantation are the shortage of donor organs and, very importantly, patient choice. A significant proportion of AATD patients who are technically eligible for lung transplantation either die before they receive a transplant or choose not to undergo this very invasive and risky procedure for a variety of reasons (detailed in our original submission).

It can therefore not be assumed that lung transplantation is an option that is available for all or even the majority of patients once their disease has progressed sufficiently for them to meet the formal eligibility criteria for transplantation.

1.3 We consider that the structure of the cost-effective model presented by the company is unsuitable and some assumptions underlying transition probabilities are not feasible, and we would like to add several points to the committee's observations and conclusions about the model.

The different health states in the model do not represent the natural disease progression of AATD-associated emphysema and are unnecessarily complicated. The combination of FEV1 % predicted and lung density decline to define a health state is illogical, given that the primary outcome of the RAPID trial was based only on measures of lung density, which has been shown to be the most sensitive and most specific measure of emphysema in AATD. It is also not clear why the health states in the model are based on the rate of lung density decline, rather than on absolute measures of lung density.

The choice of health states based on FEV1 % predicted values above and below 30% and 50% seems arbitrary, and the clinical rationale of these model states is non-transparent.

In the transition probabilities, both the rate of lung density decline and the change of FEV1 % predicted are assumed to be linear throughout emphysema progression. This is unrealistic, as the rate of decline over time levels off at very low absolute lung density and FEV1 % predicted values.

The transition options to lung transplantation are illogical. The model suggests that patients with FEV1<50% predicted and no lung density decline cannot transition to lung transplantation directly but, instead, have to first transition to the health states of FEV1<50% predicted and slow lung density decline or FEV1<50% predicted and rapid lung density decline, respectively. This assumption is unrealistic and lacks validation. In clinical practice, patients do not loose eligibility for lung transplantation if their lung density decline were to stabilise after they have reached a level that would qualify them to be accepted for transplantation.

1.4 We are concerned that, throughout the submissions from the company, the BTS, and one clinical expert as well as in the ERG report, reference is made to data from the "Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT)" and the "UK registry for A1PI deficiency patients" synonymously, implying that ADAPT and the UK registry for AATD are one and the same, when they are not. In addition, the company explicitly and repeatedly stated in their submission "The Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) is the UK registry for A1PI deficiency patients,..." (e.g. pages 28, 133, 144).

We would like to advise the committee that ADAPT and the National UK AATD Registry are not synonymous, and that clarity and transparency about the correct data sources, erroneously referred to synonymously as ADAPT and the National UK AATD Registry throughout, is required. A clear distinction between these two sources is important and relevant for this evaluation for the reasons detailed below.

ADAPT is a locally run non-NHS research programme based in Birmingham that was established and, since its inception in 1996, has been predominantly funded by industry. Data originating from the ADAPT programme will be subject to bias arising from a number of factors, including:

- Patient self-selection (participation into the research programme required informed consent),
- Ability to regularly travel to Birmingham (which is extremely likely to exclude the most severely affected patients, patients in full-time employment, patients with young families, patients living at a distance from Birmingham),
- Patients drop-out due to worsening health or other reasons,
- Patients not interested to participate in research or very mildly affected patients who may not see the benefit in participation,
- Patients lacking awareness of the existence of the research programme.

In addition, access to raw data generated in the ADAPT research programme and the opportunity to mine data sets held in ADAPT is not granted to any party outside the programme, but could historically be requested by third parties, typically in exchange for research funding.

In contrast, the National UK AATD Registry, also held in Birmingham, is a conventional disease registry into which NHS centres from across the UK contribute data and to which a broad range of parties can gain access. Historically, and as indicated by the lack of an extensive publication record, the National UK AATD Registry has held little data.

It is stated in the company submission that some of the key inputs of the cost-effectiveness model (incl. the data used to model transitions between disease states, mortality for the remainder of the modelled time horizon beyond the clinical trials, health-state specific EQ-5D utility values) have been obtained from the "UK Registry". However, the company also stated that it had no access to the raw data underlying these data analyses, and that the analyses were conducted by the "ADAPT Registry team". Some of the data the company stated to have obtained from the UK Registry were marked as confidential and are presumably unpublished. We therefore assume that the company was, in fact, referring to data from the ADAPT research programme, rather than the UK Registry.

It is unknown from the company submission which inclusion and exclusion criteria were applied to the patient cohorts selected for the different analyses "performed by the ADAPT team", whether the patient characteristics of these selected cohorts from the ADAPT database were comparable with the patient cohorts in the RAPID and the RAPID-OLE studies and, given the intrinsic bias of the data from the ADAPT programme detailed above, whether the ADAPT data was representative of the AATD population in England.

We consider that the data from the ADAPT research programme might have excluded original data from more severely affected patients. Data from the UK registry (not ADAPT) or from other UK expert centres that have generated their own longitudinal databases from their NHS practice, might therefore have been more relevant for the analysis.

Given that a significant proportion of the data that informed key parameters of the health economic model and the outcomes of the cost-effectiveness analysis was apparently not

available to the company, its validity could not have been tested by the company, the ERG or the committee.

In the interest of accuracy and full transparency, we ask the committee to seek clarification of the source of all data referred to in the company submission as originating from the "UK Registry" and/or "ADAPT", i.e. an accurate attribution of the data to either source.

1.5 The committee concluded that there was no evidence that human A1PI provides benefits to patients' quality of life. We acknowledge that the lack of direct HRQoL outcome measures in the RAPID trial and the limitations of mapping SGRQ data to EQ-5D have not resulted in adequately capturing and demonstrating quality of life improvements in patients receiving the therapy.

However, over the years, most patients who have been receiving human A1PI in countries where it is available have reported significant and life-changing benefits. Unfortunately, these benefits have not yet been systematically and quantitatively captured in relevant prospective clinical trials or retrospective studies.

We have therefore recently undertaken telephone interviews with three patients in the U.S. who have been receiving human A1PI. The results of these interviews indicate that these patients have been experiencing significant beneficial effect with the treatment. We ask the committee to take the reports from the patient interviews, summarised below, into consideration.

PATIENT 1

General information and diagnosis:

[redacted]

Family history:

[redacted]

Clinical presentation at diagnosis / burden of illness:

- Breathlessness
- At diagnosis, FEV1 42% predicted and rapidly declining
- Frequent infective exacerbations, requiring hospital admissions 2-3 times a year
- No longer able to pursue any sports
- Reduced working hours and frequent periods of sick-leave

Human A1PI therapy treatment and reported benefits:

- Initiated on Respreeza in [redacted] → [redacted] years on weekly augmentation therapy
- Lung function stabilised

- Significantly reduced breathlessness and exacerbation frequency - only one hospital admission since commencement of therapy with Respreeza
- Returned to full-time work as an administrator in hospital – stable financial situation
- Able to participate fully in family, social and community life
- Significantly improved quality of life

PATIENT 2

General information and diagnosis:

[redacted]

Family history:

[redacted]

Clinical presentation at diagnosis / burden of illness:

- Severe breathlessness
- At diagnosis, 30% FEV1 predicted and rapidly declining
- Had to stop working on [redacted] farm
- Unable to carry things, walk anywhere or play with [redacted] children
- Frequent respiratory infections
- Major burden of housework and childcare was placed on [redacted]
- Limited ability to participate in family and social life; relationship with [redacted] suffered due to inability to have sex due to breathlessness

Human A1PI therapy treatment and reported benefits:

- Started on Respreeza in [redacted] → [redacted] years on weekly therapy; self-infuses therapy at home
- Lung function stabilised and even increased upon taking up regular exercise
- Significantly reduced breathlessness
- Able to stop taking supplementary oxygen
- Significantly reduced infection frequency
- Returned to working part-time work on [redacted] ranch – improved financial situation
- Currently performs regular physical exercise 3 times weekly (karate, shooting, horse riding)
- Took up volunteer work at local church 7 years ago
- Improved family, social and sex life due to higher energy levels and less breathlessness
- Significantly improved quality of life
- Describes Respreeza as a “game changer that gave me my life back”

PATIENT 3

General information and diagnosis:

[redacted]

Family history:

[redacted]

Clinical presentation at diagnosis / burden of illness:

- Breathlessness
- At diagnosis: 41% FEV1 predicted
- Regular respiratory exacerbations
- Difficulties performing everyday tasks such as shopping, cleaning, walking short distances and being physically active with [redacted] small children
- Supplementary oxygen therapy at night
- Negative impact on social life and ability to exercise

Human A1PI therapy treatment and reported benefits:

- Started on augmentation therapy in late [redacted] → more than [redacted] years on weekly therapy
- Lung function stabilised
- Reduced breathlessness; supplementary oxygen treatment was stopped
- Regained ability to socialise
- Significantly improved quality of life

1.6 During the committee meeting, one of the clinical experts gave the impression that several of their statements represented or were endorsed by the "Special Advisory Group (SAG)" of the British Thoracic Society (BTS), implying that this SAG is specifically concerned with AATD and/or represents the consensus opinion of a group of AATD experts.

We advise the committee that the BTS confirmed to us that it has no SAG specifically for AATD, and that the clinical expert who referred to the SAG is in fact a member of the COPD SAG (and it has been specifically highlighted that usual COPD and AATD are distinct diseases). We therefore conclude that the statements made with reference to the SAG refers to the personal opinion of the clinical expert rather than a consensus opinion of a group of AATD specialists at the BTS.

We ask the committee to seek clarification on this issue and weight the clinical expert's statements accordingly.

1.7 Frequent reference is made in the consultee submission by the BTS to the "NIHR AATD Network", particularly in relation to this being a network through which AATD

specialist NHS services are currently being provided throughout the UK (e.g. pages 2, 3, 4, 5 of the BTS submission). It is also implied that this "network" has some formal mandate or remit by the NIHR, and that this "network" includes all relevant AATD expert centres in England.

We advise the committee that no such formal "NIHR AATD Network" exists. Several years ago, a number of UK centres undertook a joint, NIHR-funded research project under the lead of Birmingham, with a specific research objective and a defined duration of 3 years. NIHR funding for this multi-centre project stopped in 2016 as planned in the research protocol, when the project came to an end.

Since then, the clinical expert who has authored the BTS consultee submission has repeatedly referred to the "NIHR AATD Network" and its alleged role in providing specialist NHS care for AATD. We have previously and repeatedly sought clarification from Dr Alice Turner (who leads the ADAPT research programme) and her colleagues at Birmingham about the precise nature and remit of this "network" in relation to providing specialist NHS care for AATD, as reference to the "NIHR AATD Network" has been made repeatedly in publications, at conferences, in presentations etc. since the formal conclusion of the initial NIHR research project.

In the absence of an answer to our enquiry, our charity eventually obtained the study protocol from the NIHR and a list of all participating centres through a public request under the Freedom of Information Act 2000. This confirmed that the original "network" of participating study centres never had a formal (or informal) remit or accreditation from the NIHR to provide specialist NHS services, and that the NIHR has no formal role of any nature beyond the limited and defined remit of the NIHR research project (principally to provide data and biological samples from AATD patients to Birmingham for the purposes of a biomarker development/validation) that finished in 2016.

In 2016, our charity also conducted a survey of the centres that had been listed in the study protocol as participants of the NIHR research project in order to understand which of these centres had relevant expertise in clinical management of AATD or were running/ planning to run a specialist NHS service for AATD. Our key finding was that only a small number of all collaborating centres in the NIHR research project had special expertise in AATD, or were running or planning to establish a specialist service. In contrast, centres with recognised AATD expertise that were already providing specialist AATD NHS services had not participated in the NIHR research project. (Please see outcomes of this survey in our charity newsletter 2016 at http://www.alpha1.org.uk/attachments/article/51/A1UK_NEWSLETTER%20ISSUE%2015%20AUTUMN%202016.pdf.pdf, page 9).

We repeatedly sought clarification from Dr Turner as to the remit of the "NIHR AATD Network" for the provision of NHS clinical AATD services. Dr Turner finally responded in writing in September 2018, "The Network is a research group and, as such, has no "remit" for the provision of NHS clinical AATD services. However, the member centres of the Network do provide NHS clinical AATD services, which are funded through their provider contracts." Notably, many of the centres listed in the original NIHR research

protocol are no longer members of the current “NIHR AATD Network” described in the BTS consultee submission

We therefore consider that the repeated references to and the representation of the “NIHR AATD Network” in the context of provision of care for AATD given in the BTS statement is grossly misleading. The statements in relation to the “NIHR AATD Network” also wrongly imply that, if human A1PI was recommended for use in the NHS, it would be made available principally through this “network” which would also develop national guidelines for AATD.

Given that this evaluation process should be conducted transparently and in accordance with high standards of accuracy, we ask the committee to seek clarification from the author of the BTS statement as to the exact nature and role of “NIHR AATD Network” in the context of provision of NHS-based clinical care for AATD.

1.8 On page 5 of the BTS consultee statement, it is stated that “This response has the support of the NIHR AATD Group.” Given that this group does not formally exist according to Dr Turner’s own account (see 1.7 above), we ask the committee to seek clarification on:

- which experts have formally supported this submission,
- how this support was obtained given the confidential nature of the process, and
- whether, prior to the submission being made by the BTS, approval from the NIHR had been sought in order to confirm that the “NIHR AATD Network” had in fact formally supported the submission.

We ask the committee to weight the statements submitted by the BTS in the light of whether or not they truly reflect a formal consensus opinion of a group of AATD experts or are just those of the author of the BTS submission.

1.9 Data from the ADAPT research programme appears to have constituted a significant role in informing the cost-effectiveness model submitted by the company. Dr Alice Turner, one of the two clinical advisors to the ERG and a clinical expert in the evaluation, declared a personal specific financial interest for receiving personal fees for consultancy with CSL Behring.

However, we ask the committee to seek clarification from Dr Turner, as the lead for the ADAPT programme, as to her and her research group’s involvement in the provision of any data or analyses for the direct or indirect purpose of the company submission, and whether this potential interest had been declared.

2. Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?

2.1 The committee concluded that there was no evidence that human A1PI provided benefits for secondary outcomes such as lung function, quality of life and walking distance.

This is not surprising, given that the RAPID study was not sufficiently powered to demonstrate a statistically significant effect in any of the secondary functional outcome parameters. Any non-statistically significant trend is therefore merely a chance finding and cannot be interpreted as the presence or the absence of a treatment effect.

3. Are the provisional recommendations sound and a suitable basis for guidance to NHS England?

The Alpha-1 UK Support Group considers that, given our comments above, the provisional recommendations have not been based on and interpreted in view of all the relevant information.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We are not aware of any.

Signed:

[redacted]

[redacted], on behalf of the Alpha-1 UK Support Group

NICE

10 October 2018

Dear Sir,

Highly Specialised Technology
Human alpha1-proteinase inhibitor for treating emphysema [ID856]
Evaluation consultation document

Thank you for inviting comments on this Evaluation consultation document.

- Has all of the relevant evidence been taken into account?
  Yes, the major trials are included as is a meta-analysis of trial and cohort data which includes Respreeza and other AAT replacement products.
- Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?
  The report recognises unmet need in AATD and is supportive in terms of clinical effectiveness regarding emphysema progression (measured on CT scanning) and the effect that this would likely have on a range of other outcomes (eg FEV1, QOL, mortality) albeit noting that many of these have not been proven in trials. This is likely because effects occur over a longer period than trials could feasibly occur for. The economic model was viewed flawed in many ways, largely due to poor estimations around mortality in particular (and also QOL). This makes the cost estimate (ICER) uncertain and we anticipate a resubmission with new economic modelling. Regardless of whether this occurs, the committee's view that increasing numbers of AATD patients would be identified if screening occurred or if awareness of augmentation prompted more targeted testing and that this represents a risk to the NHS is sound. This is particularly so because the cost estimates are so uncertain.
- Are the provisional recommendations sound and a suitable basis for guidance to NHS England?
  The NICE cost-effectiveness analysis used the current (higher) ICER threshold for highly specialised technology, and considered the potential magnitude of benefit. Based on the presented data, the recommendations are reasonable. However this case elegantly highlights common problems with this approach in rare conditions; limited data often leads to uncertainty about the estimate of benefit and financial modeling.

  The benefits of A1PI accrue over a long time period and may have been under-estimated in the current analysis. Issues around modelling of transplantation were also highlighted. To challenge the current decision, additional data on the likely survival benefit (bolstered by QoL data) will be required (work in progress).

Yours sincerely,

[redacted]

[redacted]

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From [redacted]

19 October 2018

Dear Sir or Madam

Re: Human alpha1-proteinase inhibitor for treating emphysema [ID856]

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 35,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The RCP is grateful for the opportunity to respond to the above consultation and would like to make the following comments.

Commentary on Respreeza ECD
The recognition by the Committee that A1PI deficiency has significant physical and emotional effects on people with the condition and their families, and that there is an unmet need for an effective treatment for A1PI deficiency in the NHS, is welcomed. Within the constraints of the limited extent of validated data provided by the company on the clinical effectiveness of A1PI (beyond the beneficial effects of treatment on the decline in CT measured lung density as a surrogate measure of emphysema), the committee appears to have reached a fair conclusion in its evaluation. However, the evaluation process may have been adversely affected by a number of factors.

Has all of the relevant evidence been taken into account?
Emphysema associated with AATD reduces life-expectancy to a much greater extent than emphysema associated with usual COPD because of the earlier onset and more rapid rate of progression in AATD-associated emphysema. In some patients, terminal respiratory failure significantly shortens life expectancy and lung transplantation may be the only alternative to death. However, lung transplantation does not represent a suitable comparator in the population being considered and this was highlighted by the patient experts at the HST committee meeting on the 23 August. The inclusion of lung transplantation in the company's model is not in keeping with the clinical utility of this treatment for AATD patients in the UK and does not appear to have taken account of patient perspective and patient choice.

Lung transplantation is an option only for a small number of patients with end-stage disease and is limited by organ availability. 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 and, because a significant number of patients decline transplantation even when it is the only life-saving treatment available to them, it is likely to have been an unsuitable factor for the company to have included in its model. Furthermore, the criterion for transplantation that is employed in the company's model ('FEV1 <30%', which is presumed to be 30% predicted), is not representative of current clinical practice.

Data relating to CT lung density decline and to mortality are critical to the evaluation. The data that have been employed for the purposes of the company's submission are reported by the company to have originated from the Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT), which is stated by the company to be the UK registry of alpha-1 antitrypsin deficiency (page 28 of the committee papers; 'The Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) is the UK registry for A1PI deficiency patients, established in 1996'). Further reference is made to ADAPT as the UK registry throughout the company's submission (eg pages 306, 318, 320, 324, 325), in the ERG Report (pages 450, 454 etc) and in the ECD (section 4.24). Data employed in the company's model is reported to have come from the 'UK registry' (page 13 of the committee papers). The description of 'ADAPT' as the 'UK registry' is factually incorrect and the interchangeable use of the titles 'ADAPT' and 'UK registry' are potentially confusing and misleading.

It should be noted that the ADAPT programme is a research programme funded principally by the pharmaceutical industry. Whilst the research programme has generated a significant quantity of peer-reviewed published manuscripts relating to AATD it does not provide outside access to raw data and is not synonymous with the UK Registry for AATD. The UK Registry for AATD is completely distinct from ADAPT, is a national registry rather than a research database, but contains only limited clinical information. Consequently, the UK Registry is unlikely to have provided the data referred to in the company submission or the ERG report. Clarification should be provided on which data (ie ADAPT or UK Registry) is being referred to by the company and the ERG.

It is stated in the ECD that 'the exact prevalence and incidence of emphysema associated with A1PI deficiency is unknown' and that there are 'about 670 people with emphysema caused by A1PI deficiency in England'. We believe that the UK Registry of AATD should be capable of providing a more realistic estimate of prevalence than the ADAPT database, and clarification should be sought on which of these sources was used to provide the estimate that was included in the ECD and the committee's evaluation.

Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?

CT lung densitometry was developed as an outcome measure for use in studies of emphysema-modifying therapy in AATD as a direct response to the demonstration that it would be impractical and unethical to conduct a placebo-controlled study of augmentation therapy using traditional outcome measures, such as lung function. Subsequent studies, such as those in the RAPID Program, were powered to demonstrate a treatment effect using the more sensitive and specific measure of emphysema, CT lung densitometry, as the outcome measure. Consequently, it is illogical to draw any conclusions about the clinical effectiveness of A1PI on the basis of secondary outcomes, such as FEV1 or SGRQ, for which the studies were underpowered.

The committee's approach to the interpretation of the published clinical trial data and meta-analyses does not always seem consistent and the conclusions drawn by the committee are, consequently, of questionable validity:

- The data published in the RAPID trials demonstrate a treatment effect on lung density decline that is statistically significant but the ECD conclusion, that the clinical trial evidence *'suggests'* that human A1PI slows decline in lung density more than placebo, implies doubt.

- In contrast, the committee's interpretation of a treatment effect on lung function data that does not achieve a statistically significant difference is that 'there was a greater decline in lung function (FEV1% and diffusing capacity of the lungs for carbon monoxide [DLCO]) for people who had human A1PI than for those who had placebo'. This difference was not statistically significant, yet the statement implies

certainty that treatment with Respreeza worsens lung function. The conclusion is, therefore, misleading.

- Later, in section 4.8, the ECD states, 'The committee concluded that human A1PI slows the rate of lung density decline, and agreed that this was an important clinical benefit.'

These three statements taken together do not demonstrate a consistent approach to data interpretation and a clear, evidence-based conclusion.

The use of clinical terminology is, at times, either incorrect or confusing; for example, on page 14 of the ECD, 'In particular the committee was concerned that the evidence suggested FEV1% and lung density decline were correlated, but these outcomes were implemented independently in the model and this would make the results uncertain.' Clarification is required over the term 'FEV1%', since FEV1% actually refers to the ratio of FEV1/FVC, whereas it is assumed that the intended meaning here is 'FEV1% predicted'.

It is unclear from the company submission which data is published and which data is unpublished because data from published manuscripts has also been highlighted in yellow eg Figure 3 Green et al 2014a. All data that has been published should be made publicly available rather than restricted by confidentiality.

Are the provisional recommendations sound and a suitable basis for guidance to NHS England?
The short notice period and the allocation of a meeting date during the summer holiday period may have significantly limited the availability of clinical experts to attend the NICE Committee meeting and, consequently, reduced the potential spectrum of clinical perspective. The submitted written statements and the clinical expert advice provided to the ERG appear only to have originated from a total of four clinical experts. As a consequence, a single clinical expert provided advice to the ERG, contributed to statements on behalf of the BTS and RCP and attended the Committee meeting as one of two clinical experts.

It is therefore possible that a consensus view on fundamental issues relating to the evaluation (for example, the criteria for commencing and stopping treatment) would more likely have been reached had the number of clinical experts providing input and the breadth of expert opinion been greater. In a rare disease for which it will be hard to define evidence-based treatment criteria, an expert consensus view may be all that can be obtained (as evidenced by the large proportion of NICE clinical guidance recommendations that are based on expert opinion). The NICE evaluation process did not fully facilitate a consensus view due to the restricted number of experts employed, in combination with the need to adhere to a strictly confidential approach to the HST process.

Furthermore, confusion regarding a consensus view of clinical experts may have been obtained by the Committee from written statements. In particular, references were made to the existence of an NIHR AATD Network. It should be acknowledged that the NIHR AATD Network, whilst existing as a defined research project for a finite period between 2014 and 2016, does not have any continuing formal mandate from the NIHR or a formal mandate with respect to providing a consensus view on AATD. It also included clinicians and researchers without significant specialist clinical expertise in AATD nor expertise in the technology under evaluation. In the context of the discussion on AATD at the HST meeting, reference was made to the existence of a British Thoracic Society Specialist Advisory Group (BTS SAG). However, it should be appreciated that the BTS SAG relates to COPD and does not specifically cover AATD - although its members are asked for open comment to inform the BTS submission. As emphasised at the committee meeting, usual COPD and AATD-associated lung disease are distinct clinical entities with only limited common features.

Could the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology?
Not to our knowledge.

Could the preliminary recommendations have any adverse impact on people with a particular disability or disabilities?
Not to our knowledge.

Yours faithfully

[redacted]

[redacted]

Sent By email 17 October 2018

Dr Ravi Mahadeva ECD response: Human alpha1-proteinase inhibitor for treating emphysema [ID856]

This therapy is the only disease modifying therapy for severe alpha 1 antitrypsin deficiency. PiZZ individuals will experience development of emphysema due to severe lack of circulating antitrypsin which progresses at different rates. Some of whom will experience rapid decline and development of disability and death at a young age. Many will not be suitable for lung transplantation and even after lung transplantation there may be significant morbidity and premature death.

It is clearly rational to augment the very low levels of antitrypsin in those with progressive emphysema.

In response to the specific queries

1. Has all of the relevant evidence been taken into account?

references 33, 46 are useful. It is not clear whether this reference has been considered Int J Chron Obstruct Pulmon Dis. 2016 Aug 1;11:1745-56. doi: 10.2147/COPD.S111508. eCollection 2016.

this details rates of lung function decline from the National registry. I would recommend analysis of this data and most recent data from the National registry ADAPT.

2. Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?

The objective of the therapy is to slow the rate of decline of emphysema and therefore disability and death. CT densitometry will best show the rate of decline in emphysema. Lung function, health quality of life are less sensitive and will need longer studies and larger number of patients to clearly show the rate of decline therefore I do not agree with the statement that augmentation therapy does not show a signal in these parameters.

The clinical criteria could be more specific

for example. Only PiZZ or PiZnull individuals with and FEV1 > 40% with documented evidence of emphysema on CT, documented decline in an accredited centre of more than 2% per year for 3 years and/or loss of lung density by > 2g/year (or corrected for the initial density- see comment below). I agree with the comment that the starting densitometry is likely to influence the absolute rate of decline. More detailed analysis of the RAPID data should be able to clarify this.

The antitrypsin NIHR network could be consulted for an opinion and existing centres of expertise can be used to manage selection of patients.

The above criteria will influence the economic model; some comments regarding this model.

Starting the therapy before the onset of sever disability will lead to reduced health care costs, medications, need for long term oxygen therapy, domiciliary NIV, admissions, primary care consultations, need to consider lung transplantation and LVR. IN addition to ability to work and retirement age.

Furthermore, some individuals will experience severe disease after a transplantable age and therefore will have premature mortality.

3. Are the provisional recommendations sound and a suitable basis for guidance on the use of alpha1-proteinase inhibitor in the context of national commissioning by NHS England?

No- the analysis needs to be reassessed with specific groups of patients informed by analysis of RAPID data and ADAPT.

4. Equality- this is a disease of Caucasians. I can see no equality issues related to gender etc. However, patients in this country are currently disadvantaged in comparison to many other countries where augmentation therapy is available.

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16 October 2018

Dear Sir or Madam

Re: Human alpha1-proteinase inhibitor for treating emphysema [ID856]

I welcome the Committee's recognition that human alpha1-proteinase inhibitor (A1PI) deficiency has significant physical and emotional effects on people with the condition and on their families. Furthermore, the recognition by the Committee that there is an unmet need for an effective treatment for alpha-1 antitrypsin deficiency (AATD) in the NHS represents a significant step towards the institution of appropriate specialist NHS clinics for this group of patients. However, it will be extremely disappointing to AATD specialists who have contributed for many years towards generating a body of scientific evidence sufficient to obtain an EMA license for A1PI therapy that the initial response of the NICE Committee is not to recommend this treatment. More importantly, this decision will result in a much deeper sense of disappointment for patients in England who will still be unable to receive AIPI augmentation therapy, at the same time as they are aware of the patients in other European countries and around the world who have funded access to treatment with this therapy.

Nevertheless, I recognise that the committee's decision reflects a fair evaluation of the available evidence and that, beyond the beneficial effects of treatment on the progression of emphysema as assessed on computed tomography imaging, there was only limited validated data on the clinical effectiveness of A1PI provided in the company's submission.

However, I consider that there are some factors which may have adversely affected the evaluation process, as detailed below.

1) Has all of the relevant evidence been taken into account?

The role of lung transplantation in the patient 'journey' has been exaggerated in the company submission and, consequently, in the evaluation process: since the majority of patients approaching 'end-stage' disease do not undergo lung transplantation, the characterisation of the role of transplantation is not representative of UK practice. Patients with AATD-related emphysema tend to experience earlier onset emphysema and more rapidly progressive emphysema than patients with usual

COPD so that they reach terminal respiratory failure at a lower age. However, lung transplantation is only an option for a minority of patients due, in part, to limited organ availability. In addition, for the reasons described by the expert patients in the committee meeting, patient choice is often to decline this treatment even when it is the only life-saving option left to them. The transplantation criterion of FEV_1 <30% predicted that the company has chosen for use in its model seems too early in the natural history of the disease process and does not reflect UK clinical practice. It is not clear from where this clinical information originated but, as a consequence, the company has relied on a model that appears to be flawed from a clinical perspective.

The company's model and the committee's evaluation is heavily reliant on data relating to differential rates of decline in CT lung density and mortality. It is reported by the company that the data used in its submission was provided by the Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT). However, at several points in the submission the company states that ADAPT is the UK registry for AATD patients, which is incorrect. The same incorrect information is included on a number of occasions in the ERG Report and, as a consequence of these statements, it is also included in the ECD. The UK Registry and the ADAPT programme are not synonymous but there appears to be interchangeable reference to these two distinct entities throughout the company's submission, leading to confusion and, potentially, misleading conclusions. The UK Registry is a national register of patients with AATD that is sourced from clinicians across the UK, but contains only limited clinical information. In contrast, ADAPT is a research programme that has been funded primarily by industry and, whilst it may provide data analyses to interested parties, does not offer any access to the raw data. It is important that the distinction is made between ADAPT and the UK Registry, not least, because it is stated in the submission of one of the clinical experts that they lead the ADAPT programme and, if ADAPT did provide data to the company, this represents a potential conflict of interest that has not been declared. It is also important to clarify whether it was the ADAPT Programme or the UK Registry data that was used to estimate prevalence, since the UK Registry should, in theory, represent a more comprehensive record of AATD patients across England.

2) Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?

The summaries of clinical effectiveness are, at some points, confusing and give the appearance of some inconsistencies in the approach adopted by the committee to data interpretation.

In section 4.8 of the ECD it is documented; 'The committee concluded that human A1PI slows the rate of lung density decline, and agreed that this was an important clinical benefit.' It is not logical to state that treatment with human A1PI provides an 'important clinical benefit' when the committee does not also report a beneficial treatment effect on lung function or health status (and without any data to show beneficial effects on mortality). Indeed, the committee's actual interpretation of the treatment effect on lung function data is that 'there was a greater decline in lung function (FEV1% and diffusing capacity of the lungs for carbon monoxide [DLCO]) for people who had human A1PI than for those who had placebo'. This difference was not statistically significant, yet the statement misleadingly implies certainty that treatment with Respreeza worsens lung function. In contrast, the committee concludes that the clinical trial evidence only *'suggests'* that human A1PI slows decline in lung density more than placebo, even though this beneficial treatment effect is statistically significant.

It should be recognised that CT lung densitometry was specifically developed for use as an outcome measure in studies of A1PI augmentation therapy because it had been recognised that a placebo-controlled study using traditional outcome measures, such as lung function, would be impractical and unethical. The studies that were designed subsequently were not statistically powered to identify a treatment effect on lung function or health status indices but were specifically powered to show a treatment effect when assessed using CT lung densitometry. Under these circumstances, any apparent

treatment effects on lung function or health status indices are likely to arise by chance and it is potentially misleading to draw conclusions about the clinical effectiveness of A1PI on the basis of these 'underpowered' secondary outcomes.

3) *Are the provisional recommendations sound and a suitable basis for guidance to NHS England?*

Clinical expertise in rare diseases is usually rare and access to suitably experienced clinicians is therefore likely to be limited. Consequently, the short notice period provided by NICE and the allocation of a meeting date during the summer holiday period may have significantly impacted on the ability to identify a good range of available clinical opinion to inform the evaluation process. This situation may have been compounded by the fact that the same clinical expert has provided advice to the ERG, has written statements on behalf of the BTS and RCP and attended the HST committee meeting as one of two clinical experts.

I am concerned that the NICE Committee may have been given the impression at the committee meeting that they were being presented with a consensus view of clinical experts from some of the content of the written statements and from the content of the discussion at the committee meeting. In the written statements of one of the clinical experts, reference was made on many occasions to the 'NIHR AATD Network' and it was stated in the statement written on behalf of the BTS that the BTS response was supported by this 'network'. Whilst the NIHR AATD Network did exist as a defined research project for a fixed two-year period until 2016, it does not have any continuing formal mandate from the NIHR and was not given a formal mandate with respect to providing a consensus view on AATD. It is not evident whether the support of the 'NIHR AATD Network' referred to in the statement on behalf of the BTS received the endorsement of the BTS nor, if the response on behalf of the BTS had received the informed support of other experts, how the response could have been shared with them within the process of confidentiality.

One of the clinical experts referred during the discussion at the HST committee meeting to the existence of a British Thoracic Society Specialist Advisory Group (BTS SAG) and their membership of the group. It is possible that this reference may have given the committee the impression that the BTS SAG referred to was a specialist group advising on AATD since this was the subject under discussion at the time. There is no BTS SAG for AATD and I can, therefore, only assume that the reference related to a BTS SAG for usual COPD. Nevertheless, I am concerned that the committee may have drawn the false conclusion that the clinical expert's comments represented a consensus view of a group of experts in AATD when, at best, they may have represented the views of experts in usual COPD: as acknowledged during the committee meeting, usual COPD and AATD-associated lung disease are distinct clinical entities with only limited common features. Consequently, the views of the BTS SAG for COPD, if this was the intended reference, would have only limited relevance to the evaluation.

The committee may, consequent to the above factors, have been left with the impression that the content of the discussion at the meeting represented the consensus view of UK AATD experts and that, despite representations from a wide range of expert opinion across the UK, there remained uncertainty in relation to critical issues such as, but not limited to, criteria for starting and stopping A1PI therapy. Irrespective of whether this impression was obtained, it seems unfortunate that the NICE evaluation process did not fully facilitate a consensus view due to the restricted number of experts employed, and that the need to adhere to a strictly confidential approach to the HST process may present obstacles that

limit access to a wider range of opinion and the opportunity to identify a consensus opinion on issues for which there is no scientific data to support an evidence-based decision. In a rare disease for which it will be particularly difficult to define evidence-based treatment criteria, an expert consensus view may be all that can be obtained (as evidenced by the large proportion of recommendations in NICE Clinical Guidelines that are graded on the basis of expert opinion). The restriction on the number of experts, combined with the circumstances of the same single expert contributing to the evaluation process as described above, may have adversely influenced a fair outcome.

4) ***Could the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology?***

Not to my knowledge.

5) ***Could the preliminary recommendations have any adverse impact on people with a particular disability or disabilities?***

Not to my knowledge.

Yours faithfully

Professor David Parr

Comment prepared for NICE following publication of preliminary report on Alpha-1-antitrypsin augmentation therapy

Prepared by [redacted] and with input from the NIHR AATD collaborative:-

[redacted] University Hospital Birmingham

[redacted] University Hospital Birmingham

[redacted] Addenbrooke's Hospital Cambridge

[redacted] Royal Free Hospital London

[redacted] The Royal Brompton Hospital London

[redacted] Glenfield Hospital Leicester

[redacted] City Hospital Nottingham

[redacted] Southampton

Dear Jo,

Thank you for your recent advice on adding a response to the current NICE report on augmentation therapy for patients with Alpha-1-antitrypsin deficiency.

In 2016 the NIHR funded an Alpha-1-antitrypsin network as part of its Rare diseases call with the express aim of enabling collaboration between centres actively involved in managing patients and facilitating research and the development and delivery of appropriate clinical trials.

The funding brought together centres coordinated by Birmingham ([redacted] and [redacted]) and involving Cambridge ([redacted]), Royal Free Hospital London ([redacted]), The Royal Brompton London ([redacted]), Leicester ([redacted]), Nottingham ([redacted]) and Southampton ([redacted]). These clinicians have experience in the study and management of over 2000 deficient patients and several contributed widely to the literature of Chronic obstructive pulmonary Disease as well as the European Respiratory Strategy for management of the condition published in 2017 (1) and the European Union statement on the disease.

With extensive background knowledge of the disease and its progression the group now referred to as the "AATD collaborative" have seen and discussed the NICE preliminary report and the Royal College of Physicians response. As a group we acknowledge the published literature showing that augmentation therapy can reduce the progression of the central emphysematous process in the disease. The rarity of the condition has made it extremely difficult to undertake trials based on conventional outcome measures of physiology and health status (2). However we believe that very

careful patient assessment and characteristics are a necessary pre-requisite to consideration, implementation and monitoring of the efficacy of augmentation therapy. This includes several key elements in decision making that need to be considered with implications for health care cost modelling.

1. Only patients (ZZ or Znull) who are never or ex-smokers (at least 6 months after stopping) should be considered for treatment
2. They must have a diagnosis of Emphysema
3. They must have evidence of ongoing decline in lung function despite optimal use of current therapy.
4. This decline should be 2% of the predicted value (for age, sex, height and race) or more per year as documented over at least 4 annual assessments obtained with stringent standard operating procedures. This decline for an individual is essentially linear (3). **Members of the collaborative will actively search their current patient data bases to determine the number of patients who currently have this documented rate of decline.**
5. Following commencement of therapy there should be also a documented reduction in the decline of lung function again over 4 consecutive annual assessments to determine the evidence of efficacy before deciding on continuation.
6. **All the steps and decision should be undertaken in designated expert centres providing comprehensive care for the condition.**

References

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2. R.A.Stockley, R.G.Edgar, S.Starkey, A.M.Turner (2018)
Health status decline in a-1 antitrypsin deficiency: a feasible outcome for disease modifying therapies? *Respir Res* 19(1):137

3. R.A.Stockley, R.G.Edgar, A.Pillai, A.M.Turner (2016)
Individualized lung function trends in alpha-1-antitrypsin deficiency: a need for patience in order to provide patient centered management? *Int J COPD*, 11: 1745-1756

[redacted]

Human alpha-1 proteinase inhibitor for treating emphysema [ID 856]

Additional evidence for consideration at the second committee meeting

CSL Behring are grateful for the opportunity to provide additional information and evidence to address the uncertainties noted by the committee.

A1PI therapy has been available outside of the UK for many years, including the United States, where it has been used for many decades. Clinical experts in A1PI deficiency have been gathering real-world evidence in both the US and the UK to enable a comparison of outcomes between treated patients in the US and untreated patients in the UK, with adjustments for differences in characteristics of the two populations.

[redacted]

To incorporate the mortality analysis as well as addressing comments made in the ECD, a revised model has been developed. The following amendments were assessed:

- The committee's preferred assumptions regarding lung transplantation were factored into the analysis. We appreciate the uncertainty surrounding transplantation, so we present a scenario excluding lung transplantation altogether, which has a relatively small impact on the ICER, indicating that lung transplantation assumptions are not a major driver of the model results.
- The impact of treatment on FEV_1 has been revised to reflect the cohort from the RAPID trial, rather than the ERGs proposals. With this amendment, patients are less likely to

transition from $FEV_1 \geq 50\%$ to $30\% \leq FEV_1 < 50\%$ with Respreeza compared to BSC. The ERGs proposals had assumed that patients would transition between these states at the same rate regardless of treatment received.

- A [redacted] was applied to Respreeza patients based on the UK-AlphaNet report. Since the model already indirectly captures A1PI impact on mortality through transition probabilities, including an additional HR may run the risk of double counting. [redacted]
    - It should be noted that the ERG proposed removing the mortality data from the first four years of the analysis due to the methodological limitations of the approach. However, in doing so, the model predicted survival gain would only be [redacted] years (when excluding lung transplant) which would not reflect the evidence presented. Therefore, the four year mortality data from the RAPID study should be retained in order for the model to reflect the available evidence, despite the methodological approach being sub-optimal.

In addition, the model was amended such that a utility weight could be applied to better reflect the expected relationship between lung density decline and quality of life, as per the committee's request. Additional scenarios are also presented to demonstrate the likely effect of modelling the correlation between FEV_1 and lung density. All cost-effectiveness analyses are presented using prior discount rates as well as the differential discount rate of 3.5% for costs and 1.5% for health outcomes as per recent recommendations from the HM Treasury Green Book.

Further detail regarding the economic analysis are presented in Appendix B.

Respreeza is the first human plasma derived medicine to go through the NICE HTA process. It is important to clarify the difference between Plasma Protein Therapeutics (PPTs) and traditional pharmaceuticals, with the costs of manufacturing and raw materials being approximately 4 times higher for PPTs compared with traditional pharmaceuticals. This is a result of the nature of the plasma collection process and complex manufacturing steps involved. It takes around 600 plasma donations to treat one person for one year with A1PI deficiency. Human plasma-derived medicines are manufactured and purified using complex fractionation, viral inactivation, filtration and lyophilisation processes. As a result, Respreeza has higher fixed production costs compared to the traditional pharmaceuticals. Patients in other European countries already have access to Respreeza. The NHS list price is considerably lower than in these other European markets.

Within the UK, there are two pricing arrangements for branded medicines made between pharmaceutical companies and the Department of Health and Social Care. CSL Behring is part of the Statutory Scheme and recent changes to the scheme, made after entering the NICE HST process, have meant that the company is now subject to rebate payments for the first time. These changes will mean any Respreeza sales will be liable to a rebate of 9.9% in 2019 rising to 20.5% in 2021. The ICER using the net price of Respreeza (accounting for these discounts) is presented in Appendix B.

Finally, to provide the context for this new mortality analysis, we have also included a summary of the evidence for A1PI to date in Appendix C.

Appendix A – Mortality Analysis of augmented patients in the US vs. un-augmented patients in the UK

[redacted]

Table 1. Baseline demographic data for patients receiving augmentation therapy and control for whole cohort and from 2007 onwards

		Augmentation		Control		p value
Whole Cohort [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Male (%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years) baseline		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years) start augmentation		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Smoking status (%) baseline						
Smoking status (%) Start augmentation						
AATD variant (%)						
2007 onwards		**Augmentation**		**Control**		
Male (%)						
Age (years) baseline						
Age (years) Start augmentation						
Smoking status (%) Baseline						
Smoking status (%) Start augmentation						
AATD variant						
Lung transplant						
FEV_1% predicted						
COPD severity (%)						
MRC score						
Values are given as either percentage (%), mean ±SD or median (IQR)						

Table 2. Survival (years) for patients receiving augmentation vs control for whole cohort and 2007 onwards

Survival (years)	Augmentation	Control	p value
Whole cohort			
Mortality (%)			

Survival (years) **mean** **median**	[redacted]	[redacted]	[redacted]
2007 onwards			
Mortality (%)	[redacted]	[redacted]	[redacted]
Survival (years)	[redacted]	[redacted]	[redacted]

Cox regression for whole cohort: survival augmented v not

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Cox regression for matched whole cohort: augmented v not

[redacted]

[redacted]

[redacted]

[redacted]

Post 2007 cox regressions

[redacted]

Future work

[redacted]

Appendix B – Revised CEA

A revised model has been developed to incorporate the mortality analysis and comments from the ECD.

Lung Transplantation

As per the committee's preferences expressed in the ECD, it has been assumed that 30% of patients eligible for a transplant do not receive one and also that there is no upper age limit on lung transplantation. As per the company response to the ECD, there are additional studies showing significant and robust evidence to support the survival figures used in the company submission, therefore, the ERGs proposed assumed survival figures have not been used.

The ECD also expresses that it would be reasonable to include pre-transplant anxiety in the model, noting that this could be done using utility estimates for people who had been on the transplant waiting list. Consequently, the utility of patients with an FEV_1<30% who would be eligible for a lung transplant has been set to reflect the utility pre-transplant from Anyanwu et al (2002) of 0.31. This was the same study that was used to generate post-transplant utilities. As mentioned above, it is assumed that only 70% of patients are eligible for a lung transplant. Therefore, a weighted average utility in the FEV_1<30% state has been calculated as 0.37, based on 70% of patients having a utility of 0.31 and 30% of patients retaining the earlier utility of 0.51.

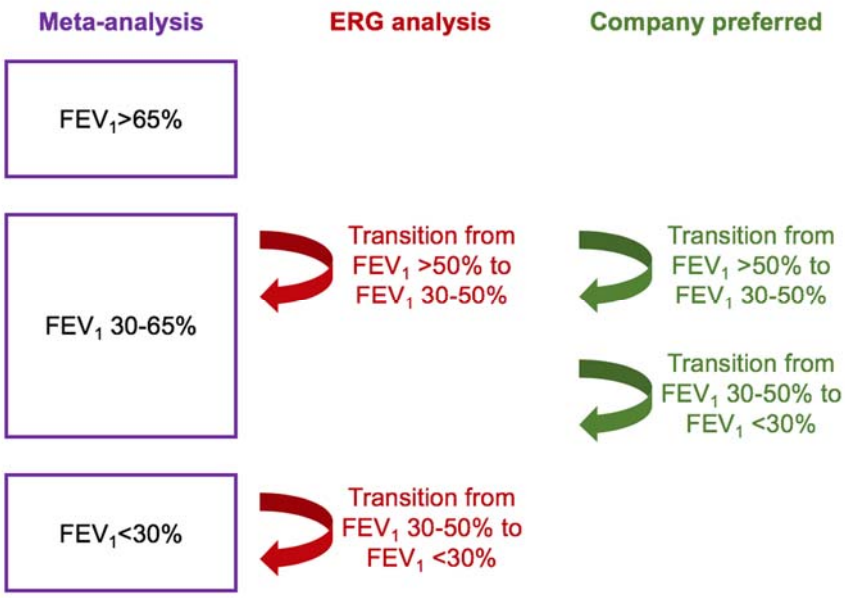
Furthermore, to demonstrate the sensitivity of the model results to all parameters relating to lung transplantation, a scenario has also been presented in which lung transplantation has been excluded altogether. With the removal of lung transplantation from the model, the ICER increased by 11% from £278,615 to £310,480 (Table 6).

Impact of treatment on FEV_1

As detailed in our consultation response to the ECD, CSL disagrees with the approach taken by the ERG with regards to modelling the effects of treatment on FEV_1. The ERG's exploratory analysis suggested that patients receiving Respreeza has the same probability as BSC patients in transitioning from FEV_1≥50% to 30%≤ FEV_1<50%. To reflect the patient cohort included in the RAPID study, we believe that the transition from FEV_1>50% should be based on the treatment effects in FEV_1 30-65% as majority of patients in RAPID were <65% at baseline. Therefore, the health state we were looking to model is mostly 50-65%, which falls in the category of 30-65% rather than >65%. When using this data in the revised model, patients on Respreeza are less likely to transition from FEV_1≥50% to FEV_1 30-65% compared to patients on BSC.

The proposed use of treatment effects is illustrated below (Figure 1). In the revised analysis, we utilise the treatment effects for the FEV_1 30-65% group to model both sets of transitions in the model.

Figure 1. Proposed treatment effects on FEV_1



Correlation between FEV_1 and lung density decline

The ECD states that the ERG considered FEV_1% predicted and lung density decline were artificially separated in the transition estimates and thus clinically implausible transitions were possible in the model. Whilst it is correct that the transition probabilities between the FEV_1% predicted categories and the lung density decline categories were derived separately, the rates of lung density decline from the RAPID study were analysed separately by those with an FEV_1>50% and those with an FEV_1<50%. On this basis, the model does already account for some correlation between the estimates, but we appreciate that there are further improvements that could be included if data permits.

As presented in Appendix C, there are several studies that have demonstrated the correlation between lung density decline and FEV_1. Across the 4-year data from the RAPID study including the extension study, there was a moderate statistically significant correlation ($r=0.338$, $p<0.001$). A 1 g/L/y loss in CT lung density was associated with a 3.33% loss in FEV_1% in one year. Since the model does not explicitly track FEV_1 but rather the time between three FEV_1 health states, it was not possible to identify how this correlation could be accounted for, given the different sources of treatment effect data (RAPID study for lung density, meta-analysis for FEV_1).

However, in order to explore the sensitivity of the model to this correlation, we have explored a scenario in which the probability of transitioning in FEV_1 was reduced by 50% for those in the no-decline health states and increased by 50% in the rapid-decline health states. When lung transplant is included in the analysis, the impact of including the correlation is that patients receiving BSC progress more quickly and more are therefore transplanted, than with Respreeza patients, resulting in an increase in the ICER.

Survival analysis

The committee raised that mortality was uncertain in the model. Following the new mortality data from the UK-AlphaNet report (Appendix A), a hazard ratio (HR) was included in the model to reflect the mortality gain with Respreeza. From the Cox regression for the whole cohort, (matched for cohort year, age, gender and smoking status) the treatment was associated with a HR of [redacted]. This HR was applied to the hazard used to generate each of the survival curves for Respreeza.

Since the model already indirectly captures A1PI impact on mortality through the transition probabilities, including an additional HR may run the risk of double counting. However, when the HR is incorporated, the estimated survival gain from the model is still only [redacted] years so reflects the UK-AlphaNet analysis.

The ERG proposed removing the mortality data from the first 4 years of the analysis due to the methodological limitations of the approach. However, in doing so, the model predicted survival gain would only be [redacted] years which would not reflect the evidence presented, therefore the data up to 4 years should be retained in order for the model to reflect the available evidence, despite the methodological approach being sub-optimal.

Utility Weight

The committee concluded that it was not convinced that the approach to modelling quality of life appropriately reflected the course of the disease and would have liked to consider the effect of lung density decline on utility values. There is some indication from the published UK registry that patients with lower decline in lung density would have higher utilities. However, sufficient data are not available to be able to model the exact relationship between SGRQ and lung density decline, so we have provided additional scenario analysis to explore the impact. We explored different scenarios where patients with no decline in lung density have greater utilities than patients with slow lung density decline and patients with a rapid decline in lung density have lower utilities than patients with a slow decline in lung density. The factors considered were 5%, 10%, 15%, 20% and 25%.

Costs

In the ECD, the committee expressed that it would prefer best supportive care and CT densitometry costs to be included. The costs of conducting one CT scan per year have therefore been included in the analysis. The costs of best supportive care remain unchanged from the base case.

Discounting

A differential discount rate approach has been incorporated, applying an annualised 3.5% discount rate to costs and 1.5% discount rate to QALYs. This model approach of using the differential rate is aligned with the most recent UK HM Treasury Green Book, which specifies its use for all health outcomes, specifically for QALYs (HM Treasury, 2018):

> *"…the recommended discount rate for risk to health and life values is 1.5%. This is because the 'wealth effect', or real per capita consumption growth element of the discount rate, is excluded. … health and life effects are expressed using welfare or utility values, such as Quality Adjusted Life Years (QALYs), as opposed to monetary values. The diminishing marginal utility associated with higher incomes does not apply as the welfare or utility associated with additional years of life will not decline as real income rise."*

With a discount rate of 1.5% for outcomes and 3.5% for costs, the ICER was £230,810 (Table 4). With a discount rate of 3.5% for both costs and health outcomes, the ICER increased by 20.7% to £278,615 (Table 5).

Statutory scheme rebate payments

Recent changes to the Statutory Scheme for 2019, of which CSL Behring are members, has meant that the company is now subject to rebate payments for the first time. This change was made after CSL entered the NICE HST process. Sales of Respreeza will now be liable to rebate payments of 9.9% in 2019, rising to 14.9% in 2020 and 20.5% in 2021.

As CSL Behring is one of the few companies in the Statutory Scheme, this generates an additional cost burden and positions CSL Behring at a disadvantage not reflected elsewhere in the pharmaceutical market. In order to reflect net cost of Respreeza, we have modelled a scenario whereby a statutory scheme rebate payment of 9.9% in the first year, 14.7% in the second year, and 20.5% in the third year is deducted from the unit cost of Respreeza (Table 6). Although the rebates are likely to continue in the longer term, predicted percentages are only available for the first 3 years.

Revised Model Results

The base case model includes the parameters and assumptions outlined in

Table ***3***.

Table 3. Overview of changes to model base case

Transition probabilities	• The treatment effect derived from the meta-analysis for patients with an FEV_1 30-65% is applied to patients transitioning from FEV_1>50% to FEV_1 30-50% as well as to patients transitioning from FEV_1 30-50% to FEV_1<30% • Correlation between FEV_1 and lung density transition probabilities are not included in the base case; this is considered in scenario analysis only
Lung transplantation	• 30% of eligible patients do not receive a transplant

	• No age limit applied to lung transplantation
Mortality	• Hazard ratio from new analysis presented in Appendix A is incorporated to all survival curves for Respreeza
Utilities	• The utility in the FEV_1<30% state is based on a weighted average of the utility for those with an FEV_1<30% and the utility of patients on a lung transplant waiting list • Utilities are not assumed to vary based on lung density decline status in the base case; this is considered in scenario analysis only
Costs	• The costs of CT densitometry are included, assuming 1 scan is needed per year

Base-case results

When incorporating all of the assumptions discussed above, the ICER becomes £278,615. The revised base-case results with and without a 1.5% discount rate are presented in Table 4 and Table 5.

Table 4. Base-case results (with 3.5% discount on costs and 1.5% discount on outcomes)

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
Respreeza and BSC	£524,220	12.790	8.320	£468,991	3.247	2.032	£230,810
BSC	£55,230	9.543	6.289				

Table 5. Base-case results (with 3.5% discount on costs and outcomes)

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
Respreeza and BSC	£524,220	12.790	7.277	£468,991	3.247	1.683	£278,615
BSC	£55,230	9.543	5.594				

Scenario Analysis

Table 6 outlines the expected survival gain and ICERs expected with various scenarios discussed above.

Table 6. Scenario analysis

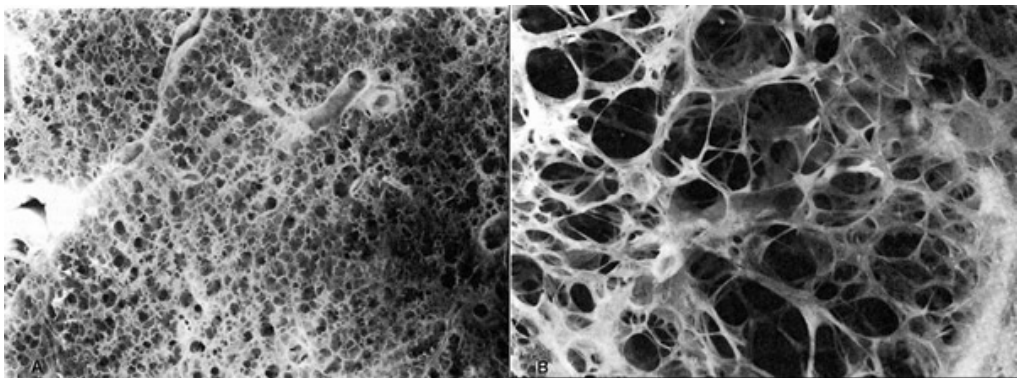
Scenario		**Life years**	**ICER with 1.5% discount rate**	**ICER with 3.5% discount rate**
Revised base case		3.247	£230,810	£278,615
Exclude lung transplantation		3.426	£265,287	£310,480
Assume correlation between FEV1 and lung density: reduce the probability of transitioning in FEV1 by 50% for no decline patients, and increase it by 50% for rapidly declining patients		2.937	£246,380	£293,298
Increased utility for patients with no decline in lung density and decreased utility for patients with rapid decline in lung density	5%	3.247	£224,447	£269,393
	10%	3.247	£217,668	£260,763
	15%	3.247	£211,643	£252,668
	20%	3.247	£205,943	£245,060
	25%	3.247	£200,541	£237,898
Use of ERGs preferred meta-analysis results		3.317	£233,797	£285,357
Incorporating statutory scheme rebate payments of 9.9% for 2019, 14.7% for 2020, and 20.5% for 2021 for Respreeza		3.247	£218,979	£264,334

Appendix C – Totality of the Evidence to Date

Assessment of emphysema

Emphysema is a histopathologically defined disease of airspace enlargement (Figure 2). Gough and Wentworth first standardised the measurement of emphysema in the 1950s using macroscopic evaluation of thin slices of excised lungs, fixed in inflation (Gough and Wentworth, 1960).

Figure 2. Electron micrograph image of normal (left) and emphysemic lung tissue (right)



Source: (Snell, 2006)

However, analysis of excised lung tissue is impractical within the clinical setting, and non-invasive measures have been developed to quantify the degree of emphysema. CT scans have been used to this effect for decades.

The measurements of emphysema on excised lung tissue that were first correlated with CT lung density measures used matched inflationary states to facilitate analogous measurement. Specifically, the *ex vivo* tissue for evaluation using macroscopic and microscopic techniques was fixed at a state calculated to equate to full inspiration *in vivo* and, likewise, inspiratory CT scans at full total lung capacity (TLC) were used for the parallel evaluations. The results demonstrated a high degree of correlation between the measures as shown in Table 7.

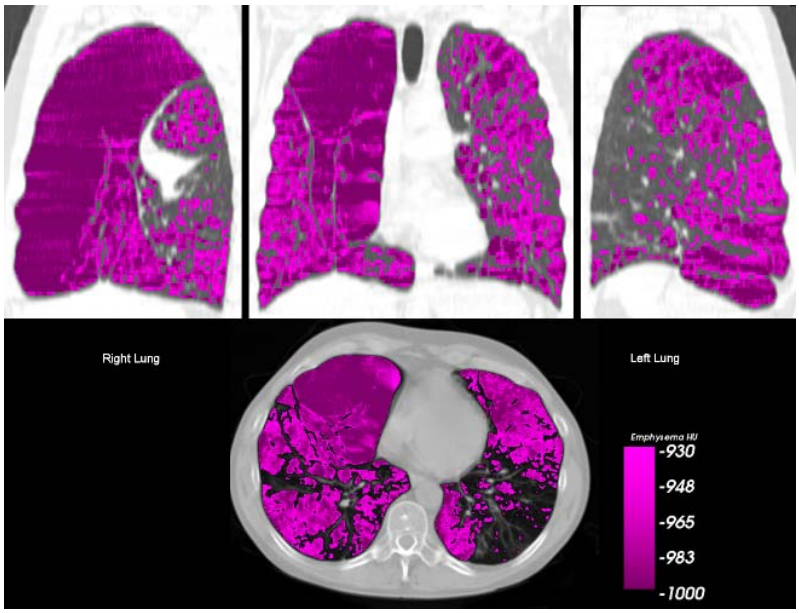
Table 7. Correlations between excised lung tissue samples and CT scans

Parameter	Description	Correlation (p-value)	Reference
Pathologic score	Picture grading system	0.94 (<0.001)	(Muller et al., 1988)
AWUV	Alveolar wall surface area per unit volume (mm2/mm3)	0.77 (<0.001)	(Gould et al., 1988)
Gough-Wentworth	Relative area of macroscopic emphysema	0.93 (<0.001)	(Gevenois et al., 1995)
MIWD	Mean interval distance (mm)	0.70 (<0.001)	(Gevenois et al., 1995)

AWUV = Alveolar wall surface area per unit volume; CT = Computed tomography; MIWD = .Mean interval distance.

CT lung density measurements are also capable of quantifying emphysema in the lung, as shown in Figure 3 (areas of low lung density highlighted in pink).

Figure 3. CT scan of emphysemic lungs



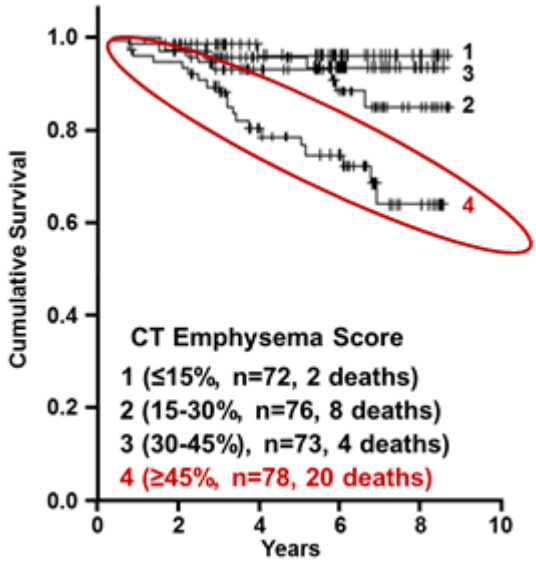
CT = Computed tomography.
Screenshot from Pulmo CMS, courtesy of BioClinica

Consequently, CT-measured lung density is an established, direct, reproducible, quantitative parameter that has been used effectively in clinical studies of emphysema, including A1PI deficiency. Clinicians use CT scans to assess patients with chronic COPD and emphysema due to A1PI deficiency.

CT lung density decline rates as a predictor of mortality

Dawkins 2009 demonstrated that CT scans can be predictive of mortality outcomes in a study involving 299 A1PI deficiency patients. Sub-groups were characterised at baseline by the percent of emphysema on CT scans, termed “emphysema score”, with higher values representing more extensive disease. Patients with an emphysema score of greater than 45% had a significantly higher mortality rate than those with lower emphysema scores (Dawkins et al., 2009) (Figure 4).

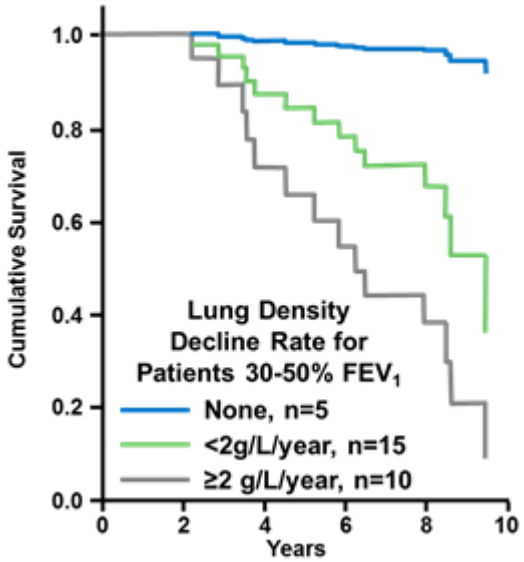
Figure 4. CT emphysema score as a predictor of mortality



CT = Computed tomography; n = number of subjects.
Source: (Dawkins et al., 2009)

Dawkin's findings are corroborated with currently unpublished data from the University of Birmingham, United Kingdom (UK). Turner and Stockley 2013 evaluated mortality in a group of untreated A1-PI subjects followed longitudinally for up to 10 years in the ADAPT registry in the UK. Based on the annual rate of lung density decline, the subjects were allocated into 3 groups: no decline, annual decline rate <2 g/L, and annual decline rate ≥2 g/L. A Cox proportional hazards model was applied to assess the risk of death, and the results strongly supported lung density loss as a predictor of mortality.

Figure 5. Lung Density Decline as a Predictor of Mortality in a Cohort of Untreated A1-PI subjects



A_1-PI = Alpha$_1$-proteinase inhibitor; FEV_1 = Forced expiratory volume in 1 second; n = number of subjects.
Source: Unpublished data from the ADAPT registry in the UK

Thus, both absolute CT lung density and its annual rate of decline have been demonstrated to be significant predictors of mortality, thereby establishing sequential evaluations of CT lung density as a valuable and clinically relevant measure in the study A1PI disease and treatments designed to slow its progression.

Correlations between CT lung density decline and other clinical measurements of emphysema

Other clinical parameters have been evaluated in a series of studies focusing on the cross-sectional and longitudinal correlations between CT lung density measures, and clinical parameters of emphysema.

Table 8 lists the cross-sectional correlations for seven clinically relevant endpoints, including functional and physiological health outcomes. Moderate-to-strong, statistically significant cross-sectional correlations were demonstrated in all of the evaluated parameters supporting the use of CT lung density as an appropriate measure of disease severity and progression.

Table 8. Cross-sectional correlations between CT lung density and functional/physiological endpoints

Parameter	Correlation (p-value)	Reference
FEV_1 % predicted	0.44 (<0.001)	(Kinsella et al., 1990)
	0.74 (<0.001)	(Parr, 2004 #277)
FEV_1/FVC	0.85 (<0.001)	(Kinsella et al., 1990)
	0.44 (0.002)	(D'Anna et al., 2012)
DL_{CO}/VA % predicted	0.63 (<0.001)	(Parr, 2004 #277)
DL_{CO} % predicted	0.64 (0.003)	(D'Anna et al., 2012)
SGRQ activity	0.37 (<0.05)	(Dowson et al., 2001)
ISWT	0.63 (<0.001)	(Dowson et al., 2001)
A-a gradient	0.70 (<0.001)	(Schwaiblmair and Vogelmeier, 1998)

A-a = Alveolar-arterial; CT = Computed tomography; DLCO = Diffusion capacity of the lung for carbon monoxide; FEV1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity, ISWT = Incremental shuttle walking test; SGRQ = St. George's Respiratory Questionnaire; VA = Alveolar volume.

In the following sections the longitudinal outcomes of three randomised, placebo-controlled studies in patients with A1PI deficiency along with the results from an observational study in untreated patients with A1PI deficiency in the UK are reviewed in further detail.

UK non-interventional study outcomes

Seventy-four untreated patients with A1PI deficiency in a single site in the UK contributed 2-year CT and PFT data, a sub-set of 34 patients with A1PI deficiency contributed 4 consecutive, complete annual assessments. Baseline characteristics for all subjects are given in Table 9 (Parr et al., 2006).

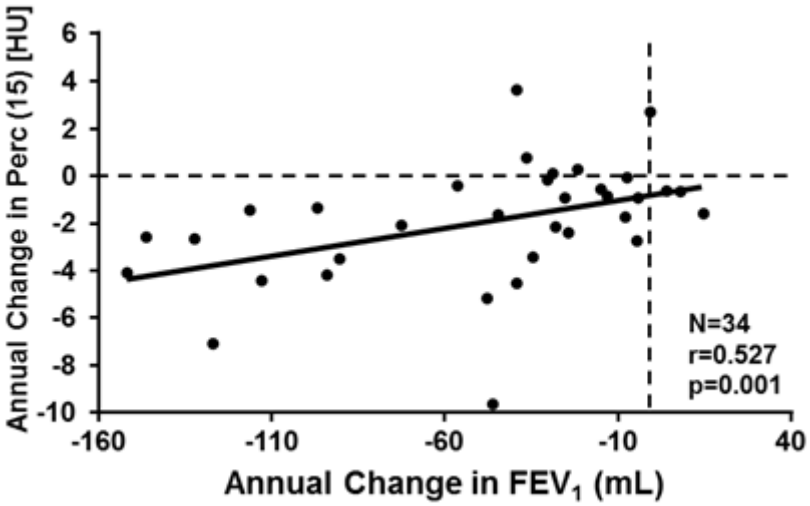
Table 9. UK non-interventional study, median baseline patient characteristics (IQR)

Baseline characteristic	Untreated subjects (n=74) Median (IQR)
Age (years)	51 (46-56)
Pack-years	15 (0-28)
FEV_1 (L)*	1.98 (1.5-2.4)
FEV_1% predicted	48**
K_{CO} (mmol(min/kPa/L)*	1.0 (0.8-1.4)
Adjusted PD15 lung density (g/L)	-955.6 (-1971.0 to -931.6)

*All lung function measurements were performed after dual bronchodilation with inhaled nebulised salbutamol (2.5 mg) and ipratropium bromide (250 mg)
** Median % predicted

A strong statistically significant longitudinal correlation between CT lung density decline rate and annual FEV_1 decline was established (Figure 6).

Figure 6. Longitudinal correlation between annual lung density declines and annual FEV_1 declines in A1-PI subjects



A_1-PI = Alpha$_1$-proteinase inhibitor; FEV_1 = Forced expiratory volume in 1 second; HU = Hounsfield unit; N = Number of subjects; Perc (*Study 115 CSR*) = 15th percentile point; r = regression coefficient.
Source: (Parr et al., 2006)

EXACTLE study outcomes

The EXACTLE trial was a placebo-controlled, randomised, 2-2.5 year study evaluating the effects of weekly 60 mg/kg administration of augmentation therapy in 77 patients with A1PI deficiency (1:1) recruited in three investigational sites in the UK, Sweden and Denmark. The primary endpoint was the change in lung density as assessed by CT scans with pulmonary function and Quality of Life captured by SGRQ, as key secondary endpoints (Dirksen et al., 2009). Baseline characteristics are given in Table 10.

Table 10. EXACTLE study, baseline patient characteristics (SD)

Baseline characteristic	Active subjects (n=38)	Placebo subjects (n=39)
Age (years)	54.7 ± 8.4	55.3 ± 9.8
Sex (male/female)	25/13	16/23
α1-AT levels (μM)	4.6 ± 1.6	4.6 ± 1.7
Smoking status (never/ex-smokers)	4/34	4/35
Caucasian (%)	100	100
BMI (kg/m2)	24.3 ± 3.2	24.3 ± 3.5
FEV_1 (L)	1.44 ± 0.60	1.35 ± 0.62
FEV_1% predicted	46.3 ± 19.6	46.6 ± 21.0
DL_{CO} (mmol/min/kPa)	4.73 ± 2.09	4.72 ± 1.70
DL_{CO}% predicted	50.7 ± 19.5	52.2 ± 15.2
K_{CO} (mmol(min/kPa/L)	0.82 ± 0.32	0.86 ± 0.24
K_{CO}% predicted	55.3 ± 21.0	56.5 ± 14.8
SGRQ total score	41.9 ± 17.9	46.1 ± 17.2
Adjusted PD15 lung density (g/L)	54.55 ± 17.37	53.90 ± 15.97

Four methods were used to analyse the lung density loss, i.e., lung volumes were either adjusted with by a statistical methodology or physiologically adjusted (PD15) and the change from baseline as well as a slope analysis was conducted with each adjustment method. All four methodologies reported findings in favour of augmentation therapy over placebo (Dirksen 2009). No favourable findings were reported in the key secondary endpoints.

The sensitivity scores were calculated as the mean changes from baseline reported in the placebo group divided by the standard error for each measurement respectively, as shown in Table 11. This was done to estimate the signal-to-noise ratio for each endpoint and assess the suitability for each endpoint to evaluate the ability of an interventional therapy to slow disease progression given (*Study 115 CSR*) the availability of patients with A1PI deficiency to recruit into clinical trials, and (2) ethical concerns regarding the use of placebo over extended study durations.

Table 11. Sensitivity indices for CT parameters compared with lung function and quality of life endpoints from the EXACTLE study

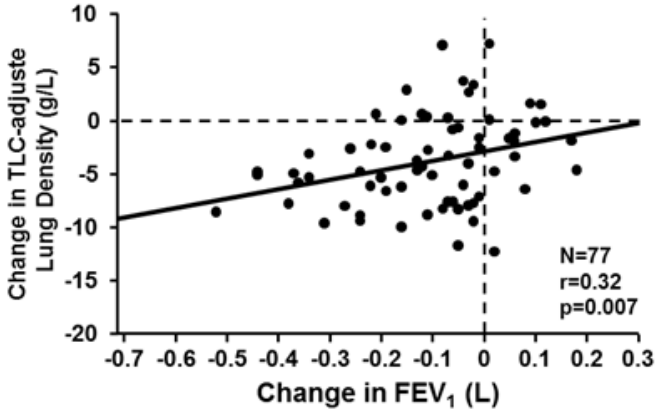
Measure	Mean change ± SE	Sensitivity index a	F-test b p-value
CT parameters			
TLC Adjusted P15 (Method 1), g/L/year	-2.24 ±0.333	6.7	NS
Statistically Adjusted P15 (Method 2), g/L/year	-1.81 ±0.263	6.9	NS
TLC Adjusted P15 (Method 3) c, g/L	-4.80 ±0.671	7.2	NS
Statistically Adjusted P15 (Method 4) c, g/L	-4.12 ±0.539	7.6	–
Lung function tests			
FEV_1, mL/year	-23 ±10.4	2.2	<0.01
DL_{CO}, mmol/min/kPa/year	-0.37 ±0.058	6.4	NS
K_{CO}, mmol/min/kPa/L/year	-0.036 ±0.0075	4.8	<0.05
SGRQ			
Overall, Units/year	0.81 ±0.800	1.0	<0.01
Symptoms domain, Units/year	-0.09 ±1.577	0.06	0.01
Activity domain, Units/year	2.58 ±0.890	2.9	<0.05
Impacts domain, Units/year	-0.15 ±0.776	0.2	<0.01

Adjusted P15 = Lung volume-adjusted 15th percentile of the lung density; CT = Computed tomography; DLCO = Diffusion capacity of the lung for carbon monoxide; FEV1 = Forced expiratory volume in 1 second; KCO = Transfer coefficient for the lung for carbon monoxide; NS = Non significant; SE = Standard error; SGRQ = St. George's Respiratory Questionnaire; TLC = Total lung capacity.
Ratio of mean change divided by SE.
Ratio of outcome measure compared with statistically Adjusted P15 (Method 4) as the most sensitive approach.
Results based on mean change from endpoint analysis from baseline to last available measurement.
Source: (Dirksen et al., 2009)

CT lung density proved to be the most sensitive measurement over the relatively short treatment period studied.

A moderate statistically significant longitudinal correlations was demonstrated between CT lung density decline rates and the annual rate of FEV_1 decline (Figure 7).

Figure 7. Longitudinal correlation between annual lung density declines and annual FEV1 declines in A1-PI subjects in the EXACTLE study



A_1-PI = Alpha$_1$-proteinase inhibitor; FEV_1 = Forced expiratory volume in 1 second; N = Number of subjects; r = regression coefficient; TLC = Total lung capacity.
Source: (Dirksen et al., 2009)

REPAIR trial outcomes

Although the placebo-controlled REPAIR study failed to demonstrate the utility of retinoid treatment in 133 patients with A1PI deficiency, it did assess the sensitivity of various measurements to quantify disease progression and determined that CT lung density was the most sensitive followed by DL_{CO} and FEV_1 (Stolk et al., 2010). The baseline characteristics are given in Table 12.

Table 12. REPAIR study, baseline patient characteristics (SD)

Baseline characteristic	Subjects (n=133)
Age (years)	53.9 ± 8.6
Sex (% male/female)	73/27
Smoking status (%, never/ex-smokers)	11/89
Pack-years	19.0 ± 12.3
Caucasian (%)	100
Body weight (KG)	77.0 ± 13.2
FEV_1 (L)	1.56 ± 0.6
FEV_1% predicted	46.8 ± 16.7
FEV_1/FVC	0.38 ± 0.1
DL_{CO}% predicted	48.2 ± 14.5
K_{CO}% predicted	41.7 ± 10.8
SGRQ total score	44.0 ± 16.1
15th percentile HU	-962.0 ± 14.0
Dyspnea index total score	6.3 ± 2.3
ISWT (m)	412.2 ± 206.7
Exacerbation in previous year	1.0 ± 1.1

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; SGRQ, St George's Hospital Respiratory Questionnaire; HU, Hounsfield units; ISWT, incremental shuttle walk test.

Similar to previous investigations, the cross-sectional correlations between CT lung density measurements and pulmonary function assessments, i.e., FEV_1 and DL_{CO} and K_{CO}, were moderate and statistically significant (Table 13).

Table 13. REPAIR study, cross-sectional correlations at baseline

	FEV_1 (L) n=133	**DL_{CO} (mmol/min/KPa) n=132**	**K_{CO} (mmol/min/KPa/L)* n=132**
Adjusted PD15 lung density (g/L)	0.4218 p<0.0001	0.3770 p<0.0001	0.3029 p<0.0001

*$K_{CO} = DL_{CO}/V_A$

CT lung density proved to be the most sensitive outcome with a signal-to-noise ratio of 4.9 compared to 4.6 for DL_{CO} and 3.5 for FEV_1. These findings intuitively match to the known pathophysiology of the disease; imperceptible losses of parenchymal lung tissue accumulate over time before distinct functional losses in DL_{CO} accumulate and well before structural changes measured by FEV_1 are reported.

Given the findings above, i.e., sensitivity of CT lung density>DL_{CO}>>FEV_1, the REPAIR investigators explored the long-term correlations between initial lung density losses detected in the first year with the annual loss of pulmonary function as measured by post-bronchodilation FEV_1 or K_{CO} over the following 8-years. The study population was limited to patients with A1PI deficiency (n=46) recruited in Sweden, the Netherlands and the UK with lung density measurements at Baseline, Month 6 and Month 12 (Stolk et al., 2015). Baseline characteristics for this sub-population are given in Table 14.

Table 14. REPAIR sub-study, baseline patient characteristics (SD)

Baseline characteristic	Subjects (n=46)
Age, year	53.9 ± 6.3
Sex M/F, %	27/73
Subjects who stopped smoking more than 1 year, %	85
Pack-years	19.0 ± 12.3
SGRQ total score	44 ± 16
FEV_1% predicted*	46.8 ± 16.7
K_{CO}% predicted	± 10.8

* post bronchodilator values (400 µg salbutamol)

The average annual FEV_1 decline rate was -66 ± 60.9 mL with an annual K_{CO} decline of -27.5 ± 25.9 mmol/kPA/L/min. The annual decline in lung density was 2.15 ± 3.27 g/L and correlated with the annual FEV_1 decline rate (r = 0.41, p=0.003), however the magnitude of the correlation was greatly reduced with the annual K_{CO} decline rate (r=0.18, p=0.185) (see Figure 8). Somewhat counterintuitively, the annual decline rates in FEV_1 and K_{CO} also did not correlate (r=0.21, p=0.165).

Figure 8. Longitudinal correlations between (A) annual lung density decline and annual FEV_1 declines, and (B) annual FEV_1 declines and annual K_{CO} declines in A1-PI subjects in the REPAIR study

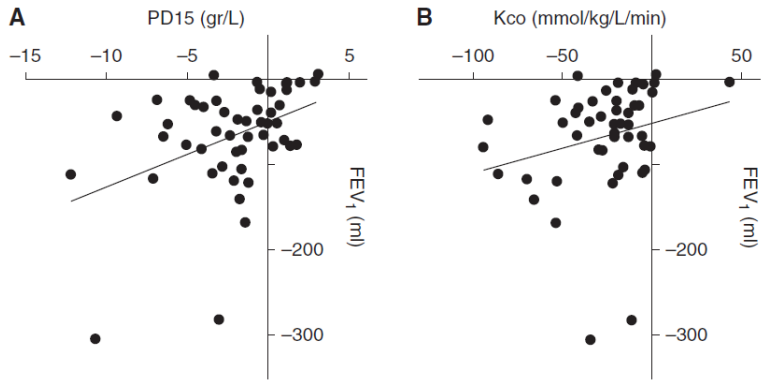


Figure 1. (*A*) Relation between change in lung density (PD15) in grams per liter in 1 year and annual change in FEV_1 in milliliters during a mean period of 8 years. The Pearson correlation is 0.41 (P = 0.003). (*B*) Relation between annual change in FEV_1 in milliliters during a mean period of 8 years and annual change in gas transfer Kco (mmol/kPa/L/min) over the same period of time. The Pearson correlation is 0.21 (P = 0.165).

RAPID program findings

The RAPID trial was a randomised, double-blind, placebo-controlled, multinational, multicentre study that investigated the clinical efficacy of CE1226 in terms of slowing the progression of emphysema in patients with A1PI deficiency. Primary efficacy was assessed by the decline in volume-adjusted lung density, as measured by CT scans. Secondary endpoints included change in exercise capacity, subject-reported respiratory symptoms score, PFTs, and rate of pulmonary exacerbations. A total of 180 subjects were randomised 1:1 to receive weekly 60 mg/kg of either CE1226 or placebo for a period of 24 months. Baseline characteristics are given in Table 10 beneath.

Table 15. RAPID study, baseline patient characteristics (SD)

Baseline characteristic	**Active subjects (n=93)**	**Placebo subjects (n=87)**
Age (years)	53.8 (6.9)	52.4 (7.8)
Sex (% male/female)	52/48	57/43
α1-AT levels (μM)	6.38 (4.62)	5.94 (2.42)
Caucasian (%)	100	100
BMI (kg/m2)	25.5 (4.79)	26.6 (4.07)
FEV_1% predicted	47.4 (12.1)	47.2 (11.1)
CT lung density at TLC (g/L)	45.5 (15.8)	48.9 (15.5)

A significant reduction in annual lung density decline rates in favour of augmentation therapy (0.74 g/L/y, p=0.017 one sided test) was established. No significant changes were noted in the annual FEV1 or FEV1% decline rates over the 2-year treatment period, neither within a group nor between the treatment groups.

Further statistically significant modest-to-moderate cross-sectional correlations between CT lung density declines and declines in DL_{CO}, FEV_1 % predicted, the Incremental Shuttle Walking Test (ISWT), and the St. George's Respiratory Questionnaire (SGRQ) activity score were also established (Table 16). Taken together these results suggest that reduced CT lung density measurements are reflective of the disease state as assessed by more standard measurements, e.g., DL_{CO}, FEV_1 %, ISWT, SGRQ activity scores.

Table 16. Cross-sectional correlations between lung density (Adjusted P15) at the TLC state and clinical parameters in the RAPID study (per-protocol population)

	Pearson correlation coefficient	
Clinical parameter	**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)

Adjusted P15 = Lung volume-adjusted 15th percentile of the lung density; DL_{CO} = Diffusion capacity of the lung for carbon monoxide; FEV_1 = Forced expiratory volume in 1 second; ISWT = Incremental shuttle walk test; N = Number of subjects (this is the maximum number of subjects assessed; for some correlations the numbers of subjects assessed may be less); SGRQ = St. George's Respiratory Questionnaire; TLC = Total lung capacity.
Based on per-protocol population and subjects who had both measurements at given time points. The computed tomography density is based on the TLC state.
Values highlighted in bold indicate correlation coefficients that are statistically significant at $p \leq 0.05$.
Source: derived from section 5.3.5.1.1, CE1226_4001 CSR, Table 14.4-2 and a post-hoc analysis of Study Data Tabulation Model dataset "qs"

As demonstrated in all previous studies CT lung density proved to be most sensitive measurement. It was four times more sensitive than FEV_1 and four to nine times more sensitive than SGRQ outcomes as shown in Table 17.

Table 17. Sensitivity Analysis from the RAPID study

Measure	Sensitivity Index
Inspiratory CT lung density (TLC)	7.6
FEV_1, mL/year	1.9
Total score St George's Respiratory Questionnaire	1.5
Activity domain	1.9
Symptoms domain	0.8

CT = Computed tomography; FEV1 = Forced expiratory volume in 1 second; TLC = Total lung capacity.
Ratio of mean change divided by SE.
Source: section 5.3.5.1.1, CE1226_4001 CSR

The RAPID OLE was an open-label, uncontrolled, multicentre, multinational extension of the RAPID study with the primary objective of investigating the long-term effect of a disease-modifying benefit of CE1226 on the progression of emphysema. A total of 140 subjects, outside of the US, were enrolled in the RAPID OLE directly after completing the last study visit in the RAPID trial. Baseline characteristics are given in Table 18.

Table 18. RAPID OLE study, baseline patient characteristics at Month 24 (SD)

Baseline characteristic	Early Start subjects (n=76)	Delayed Start subjects (n=64)
Age (years)	56.4 (6.9)	53.3 (7.8)
Sex (% male/female)	54/46	59/41
α1-AT levels (μM)	15.9 (3.7)	5.9 (2.5)
Caucasian (%)	100	100
BMI (kg/m2)	25.2 (4.11)	25.94 (3.62)
FEV_1 (L)	1.49 (0.48)	1.59 (0.48)
FEV_1% predicted	45.01 (12.6)	46.34 (12.0)
CT lung density at TLC (g/L)	42.24 (15.2)	43.12 (14.02)

The initial findings to preserve lung tissue established in the RAPID trial were confirmed in the smaller RAPID OLE population (n=140): 0.75 g/L/y, p=0.021, one-sided test. Furthermore a statistically significant reduction in lung density decline rates was established within the Delayed Start group temporal to the switch from placebo to active treatment: 0.52 g/L/y, p=0.001. No significant changes were noted in the annual FEV_1 or FEV_1% decline rates over the 4-year treatment period, neither within a group nor between the treatment groups

Four-year data from the RAPID and RAPID OLE studies demonstrated statistically significant, modest-to-moderate longitudinal correlations between CT lung density decline and pulmonary function as shown in Table 19.

Table 19. Correlation between changes from baseline to Month 48 in Adjusted P15 at TLC and changes in spirometry variables (ITT/Completer population)

	Pearson correlation (p-value)		
Analysis	Early Start N=63	Delayed Start N=58	Overall N=121
FEV_1, L	(N=62)	(N=56)	(N=118)
	0.308 (0.015)	0.263 (0.050)	0.286 (0.002)
FEV_1 % predicted, %	(N=62)	(N=56)	(N=118)
	0.346 (0.006)	0.339 (0.011)	0.338 (<0.001)
FVC, L	(N=62)	(N=55)	(N=117)
	0.302 (0.017)	0.313 (0.020)	0.296 (0.001)

A_1-PI = $Alpha_1$-proteinase inhibitor; FEV_1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; ITT = Intention-to-treat; N = Number of subjects; P15 = 15th percentile of the lung density; TLC = Total lung capacity.
Source: Section 5.3.5.1.2, CE1226_3001 CSR, Table 25

Conclusions on CT lung density decline and other clinical measurements of emphysema

Overall, CT lung density has been shown to be the most sensitive measurement for use in clinical trials assessing disease progression in emphysema due to antitrypsin deficiency.

Two independent meta-analyses have confirmed significant reductions in the annual lung density decline rates with augmentation therapy in comparison to untreated patients. The Dutch-Danish (n=56) and EXACTLE (n=77) studies both posted trends towards preserving lung tissue, 1.07 g/L/y (p=0.07) and 0.86 g/L/y (p=0.068) respectively (Dirksen et al., 1999,

Dirksen et al., 2009). When analysed together, a statistically significant preservation of 1.01 g/L/y in lung density was recorded (Stockley 2010). The second meta-analysis combined the results of all three placebo-controlled trials, including the larger RAPID trial (n=180) where a statistically significant reduction in annual lung density rates was established independently (0.74 g/L/y p=0.017 one sided test), and posted a 0.79 g/L/y treatment difference in favour of augmentation therapy (p=0.002) (Chapman et al., 2015, Edgar et al., 2017).

These trials were necessarily underpowered to demonstrate efficacy signals using more traditional tools, e.g., FEV_1, FEV_1%, DL_{CO}, exercise capacity, Quality of Life instruments, due to the slow rate of disease progression, limited pool of eligible patients, and ethical concerns regarding extended exposure to placebo.

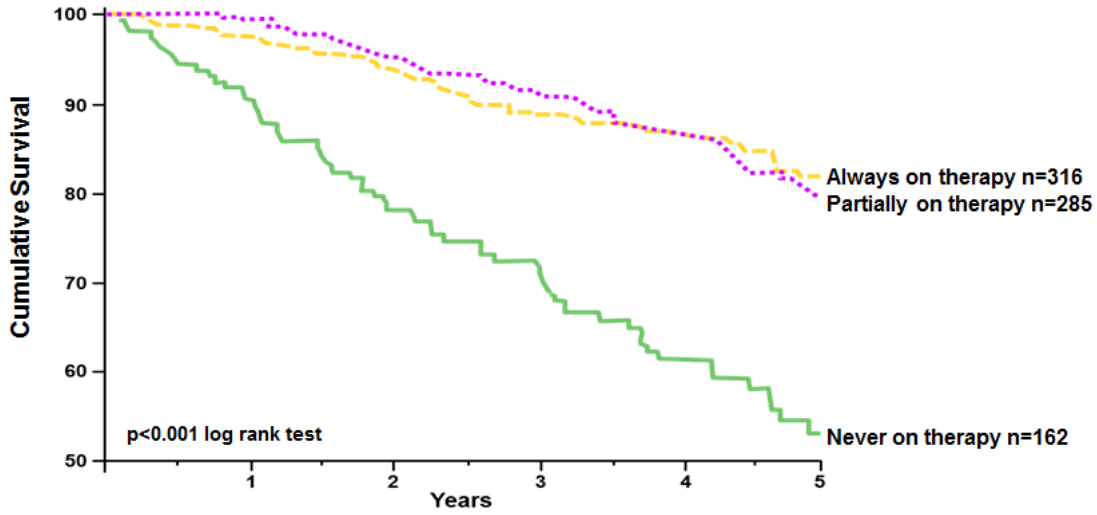
Lung density as measured by CT correlates cross-sectionally with baseline pulmonary function tests, exercise capacity and Quality of Life measurements, demonstrating its utility to evaluate disease severity and progression.

Longitudinal correlations have been established between lung density declines and declines in FEV1, FEV1%, FVC, and SGRQ outcomes, suggesting that lung tissue loss detectible on CT scans manifests in the loss of lung function and eventual reductions in the Quality of Life on time scales outside of feasible treatment periods in clinical trials.

Mortality in A1-PI deficient subjects

The National Heart, Lung, and Blood Institute of the US National Institutes of Health (NHLBI) registry was established as a post marketing commitment following the approval of Prolastin®, a similar A1PI augmentation therapy, in the United States (US). Comprising data from 1,129 treated and untreated A1PI deficient subjects for a period of 8 years, it is the largest and longest study in the field and demonstrates a mortality benefit for the subjects who received A1PI augmentation therapy. A1PI deficient subjects with an FEV_1%< 50% at baseline and not treated with A1PI augmentation therapy were approaching median survival at the end of 5 years, whereas subjects who did receive A1PI augmentation therapy maintained a distinct benefit, as shown in Figure 9.

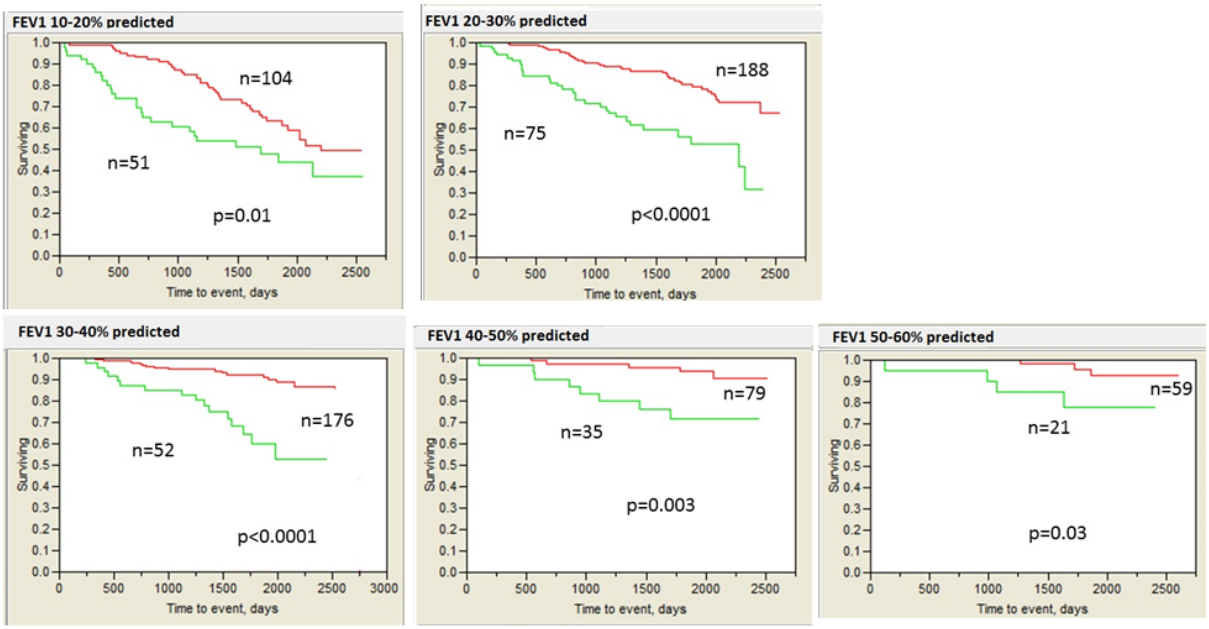
Figure 9. NHLBI registry Kaplan-Meier plot of survival time of enrolment using data from all subjects (FEV_1 <50% of predicted)



FEV_1 = Forced expiratory volume in 1 second; n = number of subjects; NHLBI = National Heart, Lung, and Blood Institute.
Source: (The Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998)

Furthermore, augmentation therapy was associated with significantly longer survival than non-augmentation in all baseline FEV_1 strata 10% to 60% predicted as shown in Figure 10 (Rahaghi et al., 2014).

Figure 10. Effect of A1-PI augmentation therapy on survival by baseline FEV_1 strata



Red lines = Augmentation therapy; Green lines = Non-augmentation therapy.
Source: (Rahaghi et al., 2014)

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Highly Specialised Technologies Evaluation

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

Dear Christian,

The Evidence Review Group, BMJ Group, and the technical team at NICE have looked at the submission received on 21 February 2019 by CSL Behring. The ERG and the NICE technical team would like further clarification relating to some of the data: please see the questions listed below.

Please provide a written response to these questions by **5pm** on **Friday 8 March**.

Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed. Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Lorna Dunning, Technical Lead lorna.dunning@nice.org.uk . Any procedural questions should be addressed to Jo Ekeledo, Project Manager joanne.ekeledo@nice.org.uk

Yours sincerely

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
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Encl. checklist for in confidence information

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1. Please provide more detailed description of the methods implemented to carry out the matched analysis. Has the analysis been carried out in line with a DSU document? Or other standard methods? Have additional characteristics been matched other than those reported in the new submission?

2. For the Cox regression of the full cohort, the analyses exclude those with the SZ genetic variant: please clarify the clinical rationale for excluding these people. Also, the submission comments that the control group includes people without symptoms of emphysema or COPD. Please provide the number of people in the analysis of the ADAPT cohort without a diagnosis of emphysema or COPD.

3. Please provide the Kaplan–Meier data associated with the figure below (in Excel, with respective numbers at risk and numbers of events)?

4. The submission states that the majority of patients in RAPID had FEV1% <65% at baseline. Please clarify how many patients were in the 50% to 65% FEV1% at baseline and provide the respective data?

5. Please clarify if PSA was run for the updated analysis and provide the tabulated results for the latter?

6. The ICERs reported in the submission of additional evidence do not match those in the excel model. Please can you clarify which are the correct results?

7. The company's updated model uses a different number of specialist consultations (tab "Costs" in the model, cells B30:B32) compared to the company's original model. This change has not been reported in the company's report of additional evidence. Please justify the change in the number of specialist consultations.

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8. Please clarify if any other model inputs were changed in the economic model, which has not been reported in the company's written submission of additional evidence.

9. Please clarify where in the updated model are the additional annual CT scan costs, which the company reports were added to the economic model.

Highly Specialised Technologies Evaluation

Human alpha1-proteinase inhibitor for treating emphysema [ID856]

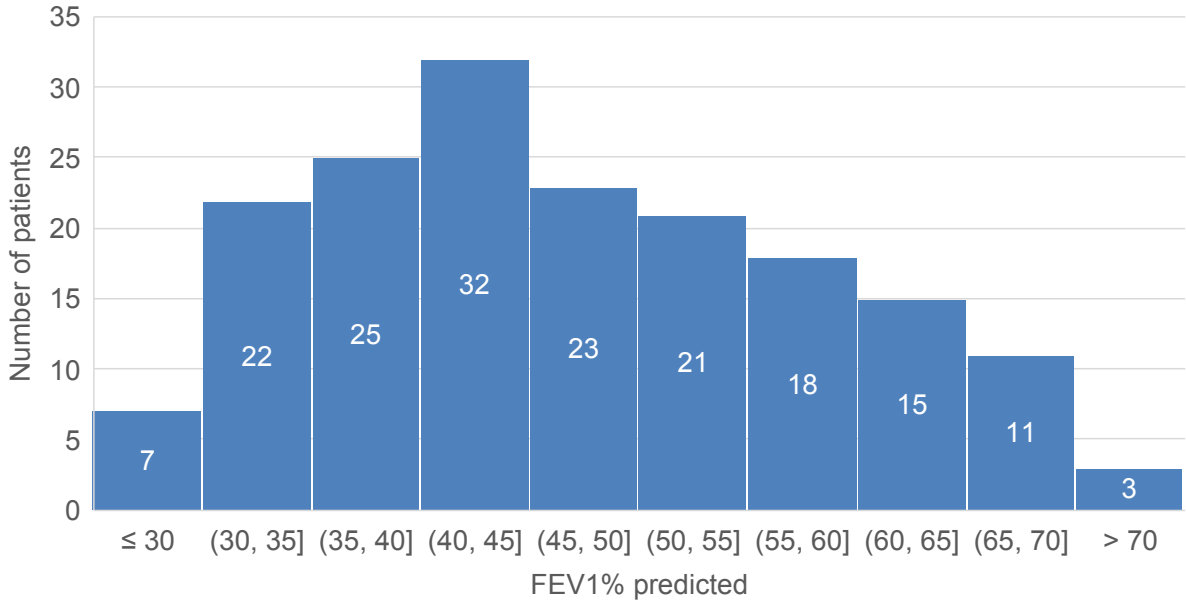
Company Response to Clarification Questions Received on the 1st and 4th March 2019

The first three questions received relate to the survival analysis that was conducted by clinical experts rather than the manufacturer. Dr Alice Turner has provided a response to these three questions. This response document is therefore for questions 4-6 received on the 1st March and questions 7-9 received on the 4th March.

4. The submission states that the majority of patients in RAPID had FEV1% <65% at baseline. Please clarify how many patients were in the 50% to 65% FEV1% at baseline and provide the respective data?

The number of patients from RAPID stratified by known FEV_1 groups is illustrated in Figure 1. This is based on 85 patients that received placebo and 92 patients that received Respreeza. In the 68 patients with an FEV1% >50%, 54 (79%) had an FEV1% <65%.

Figure 1. Number of patients in RAPID grouped by baseline FEV_1



5. Please clarify if PSA was run for the updated analysis and provide the tabulated results for the latter?

PSA results were not presented in the prior evidence submission and so these are presented below with the 1.5% discount rate. In the revised model, the hazard ratio has been incorporated into the probabilistic parameters using a normal distribution. For completeness, the hazard ratio is also included in the DSA using the 95% confidence interval around the hazard ratio.

The base case of the probabilistic sensitivity analysis is presented in Table 1. The probabilistic analysis of Respreeza compared to BSC alone gave an expected ICER of £191,202 per QALY.

Table 1. Summary of probabilistic results (discounted)

	BSC	Respreeza
Total Costs	£30,995	£398,820
Total QALYs	3.713	5.637
Total life years	5.756	8.898
Incremental costs	-	£367,826
Incremental QALYs	-	1.924
Incremental life years	-	3.142
Cost per QALY	-	£191,202

Probabilistic results are also summarised in Figure 2 and a cost effectiveness acceptability curve is presented in Figure 3.

Figure 2. Cost-effectiveness plane showing probabilistic results for Respreeza compared with BSC alone

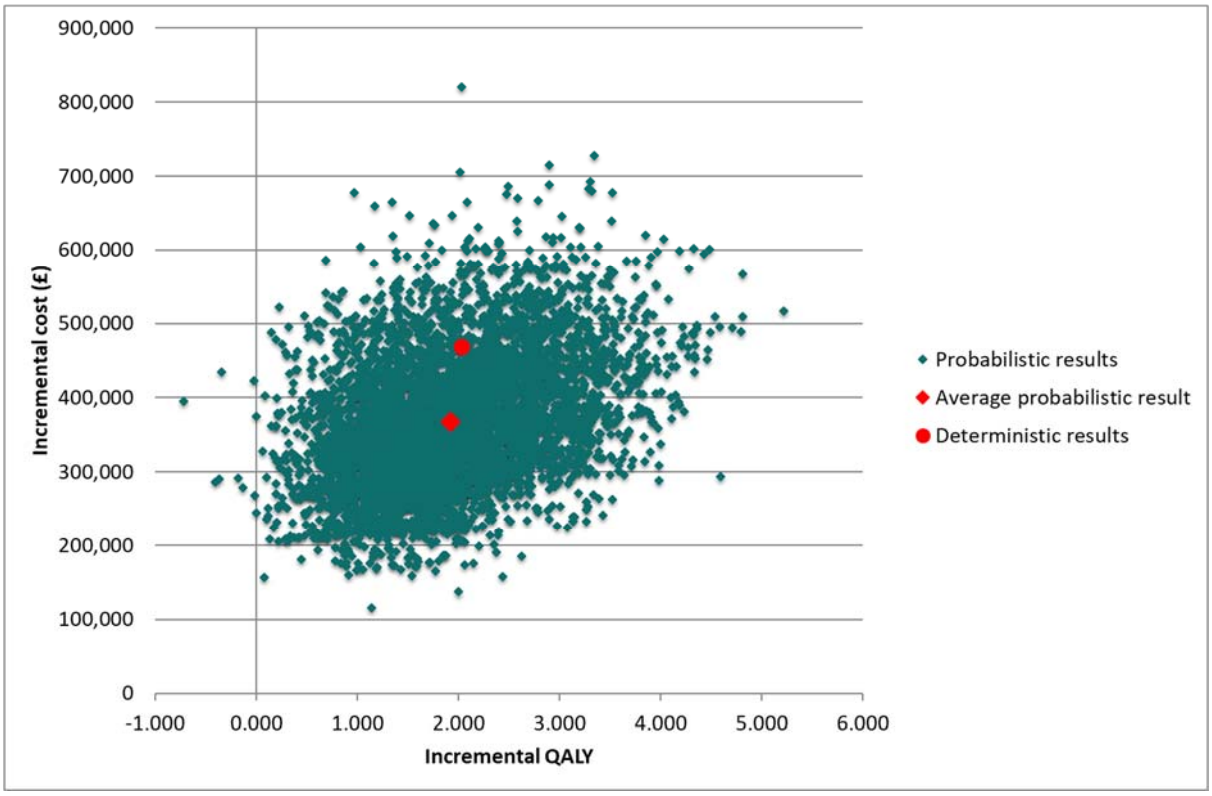
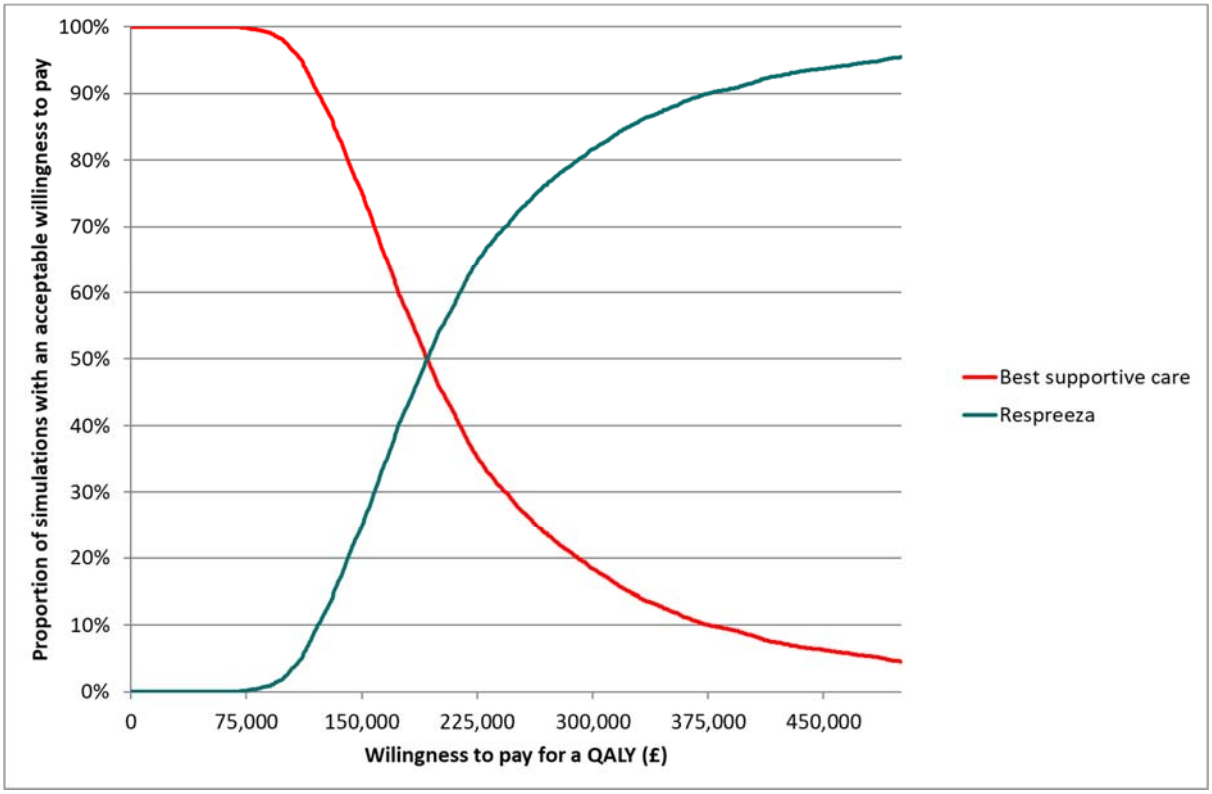


Figure 3. Cost-effectiveness acceptability plane



6. The ICERs reported in the submission of additional evidence do not match those in the excel model. Please can you clarify which are the correct results?

The ICERs reported in the submission of additional evidence are the correct result. The model sent to NICE reflected the scenario incorporating the statutory scheme rebate payment of 9.9% for 2019, 14.7% for 2020 and 20.5% for 2021 for Respreeza. This has now been removed from the model.

7. The company's updated model uses a different number of specialist consultations (tab "Costs" in the model, cells B30:B32) compared to the company's original model. This change has not been reported in the company's report of additional evidence. Please justify the change in the number of specialist consultations.

In the report of additional evidence, we had stated that we had included the cost of additional annual CT scan costs, but actually this should have stated that we included the cost of specialist consultations, at a cost of £149 per patient per year. The cost of a CT scan is less than this so using the cost of a consultation is more conservative than including the cost of a CT scan. Apologies for this confusion.

8. **Please clarify if any other model inputs were changed in the economic model, which has not been reported in the company's written submission of additional evidence.**

We believe that all model input changes have been reported in the evidence submission.

9. **Please clarify where in the updated model are the additional annual CT scan costs, which the company reports were added to the economic model.**

Please see the response to question 1 above.

Human alpha 1-proteinase inhibitor for treating emphysema

ERG critique of the company's response to the Evaluation Consultation Document

This report was commissioned by the NIHR HTA Programme as project number 15/121/01

BMJ Technology Assessment Group

1 SUMMARY

This document provides a critique of the company's response to the Evaluation Consultation Document (ECD) regarding the clinical and cost-effectiveness of Respreeza for adults with severe alpha-1 proteinase inhibitor (A1PI) deficiency who have progressive lung disease. The subsections below list the ERG's key original concerns with the company's analysis, along with the ECD conclusions after the first Evaluation Committee Meeting (ECM). The ERG also provides a critique of the company's new analysis, encompassing whether and to what extent the additional data mitigate the committee's and the ERG's original concerns.

1.1 Impact of augmentation therapy on FEV1%

1.1.1 ERG's critique of the meta-analysis and conclusions from the ECD

In their response to the ECD, the company outlined that they disagree with the approach taken by the ERG when modelling the effects of treatment on FEV1 (forced expiratory volume in 1 second). The ERG's exploratory analysis suggested that people receiving Respreeza have the same probability as those not receiving augmentation in transitioning from FEV1 ≥50% predicted to ≥30% FEV1 <50% predicted. To reflect the patient population enrolled in RAPID, the company proposes that the transition from FEV1 ≥50% predicted should be based on the treatment effects in the FEV1 30–65% predicted category as most people enrolled in RAPID had an FEV1% predicted of >35% and <65% at baseline.

As noted in the ERG's original report, results are available from three systematic literature reviews evaluating the effect of A1PI augmentation on rate of decline in lung function in those with A1PI deficiency are available.[1-3] In their original submission, the company utilised results in their economic evaluation from a meta-analysis from 2009 by Chapman and colleagues[1] that synthesised results from one RCT and four observational studies and presented results by baseline FEV1% predicted. As part of the clarification process, the ERG requested that the company update the analysis to include studies published subsequent to the search date of the review and identified by the company's literature review. Based on results from two more recent systematic reviews,[2, 3] the ERG was aware of two RCTs that were of potential relevance.[4, 5] The ERG notes that the company did not include the Dirksen 2009 study in their updated analysis (Forest plot from company's updated analysis presented in Appendix 1).

The marketing authorisation for Respreeza does not specify an upper or lower limit of FEV1% predicted for eligibility for treatment, only that people have progressive lung disease. However, the ERG considers it appropriate to analyse the impact on decline in FEV1 in a population that matches those enrolled in RAPID, that is, people with a baseline FEV1% predicted of between 35% and 70%. To maximise the homogeneity of the studies analysed in terms of comparability with RAPID,[4] the ERG

independently critiqued the RCTs and observational studies identified by the three literature reviews, focusing on:

- Baseline range of FEV1% predicted;
- Diagnosis of emphysema secondary to A1PI deficiency;
- Ex-smokers (not smoked tobacco in 6 months prior to enrolment).

Two reviewers independently assessed the studies for appropriateness of synthesis of data via pairwise meta-analysis. Despite the ERG's best efforts to analyse a comparable set of studies, the ERG's preferred analysis was a random effects model due to the likely differences in patient populations, study design, and methods of assessment.

Overall, the ERG synthesised data from three RCTs and two observational studies for the outcome of annual change in FEV1 (millilitres per year; ml/y). In the RCTs, treatment with A1PI was given for two years in two studies,[4, 5] and for at least 3 years in the third study.[6] By contrast, maximum duration of follow-up in the two observational studies was considerably longer at 7 years.[7, 8]

The ERG's analysis indicated that augmentation is associated with a decrease in the rate of decline in FEV1, but the difference does not reach statistical significance (mean difference in FEV1 of 2.62 ml/y; 95% CI: –11.41ml/y to 16.65 ml/y; p=0.71; Figure 1). The ERG notes the presence of significant statistical heterogeneity in the analysis (I^2=70%; p=0.009) and the marked difference in the direction and magnitude of effect in subgroups of study type (RCT versus observational data).

The ERG's clinical experts suggested that several factors could be contributing to the disparity between study types in estimate of effect of augmentation on FEV1:

- People with deterioration in lung density detected by computed tomography (CT) may not a corresponding decline in lung function that is detectable by assessment of FEV1;
- Variation in duration of follow-up, with follow up being shorter in RCTs, and potentially insufficient to assess decline in FEV1;
- Disparity across centres and studies in measuring FEV1;
    - Consistent recordings of FEV1 are difficult to achieve from a technical perspective, and there a margin of error for readings should be considered;
    - Observational studies are more likely to be carried out at a single centre, capture multiple values and have longer follow up, all of which maximises consistency of

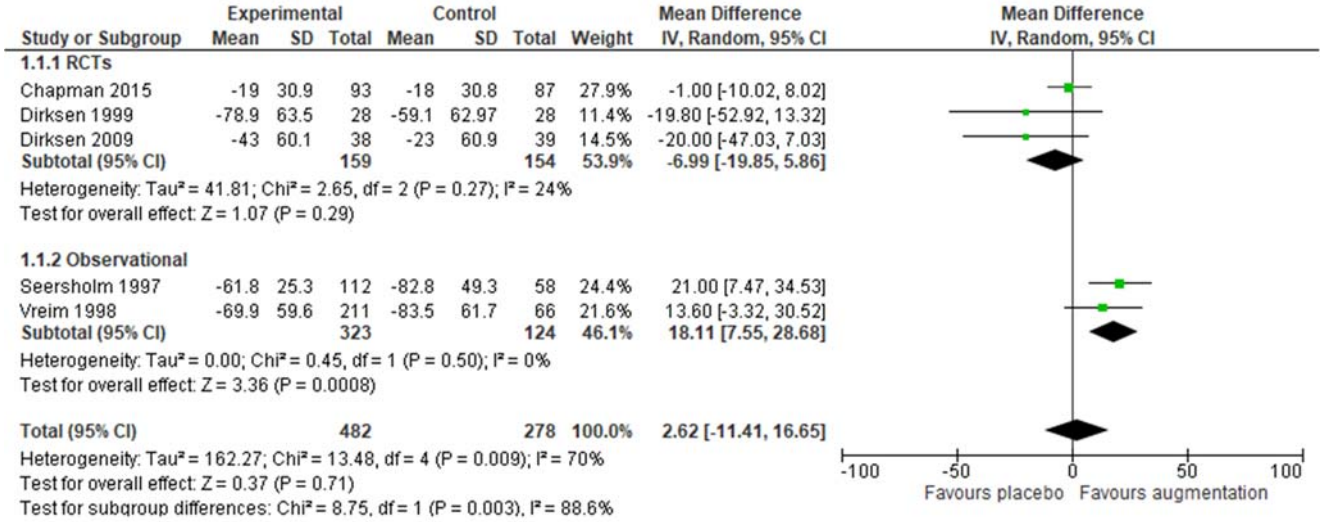
assessment of FEV1, and, potentially, a more accurate assessment of impact of augmentation on decline in FEV1 than provided by RCTs.

- People enrolling in multicentre RCTs are likely to have had to commit to travelling to a specialist centre every week for 2 years to receive their infusion. Individuals who are able to adhere to the treatment schedule are more likely to be of a stable condition. Although baseline disease status would not affect the relative treatment effect as, due to randomisation, treatment and control groups should have similar baseline disease characteristics, the potentially higher stability of disease could lead to minimal deterioration in lung function, which would impact the potential to detect differences between groups in decline in FEV1.

Considering the evidence base as whole, the ERG notes the variation in treatment effect with study design, and that the observational studies suggest a shift in effect of augmentation on decline in FEV1, with a statistically significant beneficial effect on reducing decline in FEV1 seeming to appear in the longer term (p=0.0008). However, the ERG also considers RCTs to be the most methodologically robust study design and suggests that an appropriately designed RCT is required to determine the long-term effect of augmentation with A1PI on FEV1 in those with emphysema secondary to A1PI deficiency.

A more detailed description of the rationale and critique of the studies by subgroup included in the meta-analysis is presented below.

Figure 1. Forest plot of ERG's meta-analysis of RCTs and observational studies



1.1.1.1 RCTs

A description of the RCTs identified by the reviews is available in Table 69 of the ERG's original report (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.[2] In brief, the inclusion criteria for the two RCTs additional to RAPID – Dirksen 1999[6] and Dirksen 2009[5] – 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[5]). The ERG considers the baseline characteristics of the populations of the three studies to be comparable. Key differences across studies that should be borne in mind when interpreting results were:

- Prolastin® was the A1PI assessed in Dirksen 1999[6] and Dirksen 2009[5], rather than Respreeza. Data from a biochemical comparison of four A1PIs given intravenously suggest that A1PIs can be considered equivalent to each other;[9]

- Whereas the Dirksen 2009[5] and RAPID[4] RCTs implemented a standard dose of A1PI of 60 mg/kg infused weekly, dose of A1PI in the Dirksen 1999[6] 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;

- FEV1 was measured post-bronchodilator at baseline and follow-up assessments in both Dirksen 1999[6] and Dirksen 2009[5], but not in RAPID,[4] in which use of bronchodilator was optional, and was required if optimal therapy for the person's emphysema was interrupted for any reason.

As noted in the ERG's original report, the meta-analyses by Edgar and Gotzsche found no statistically significant difference between augmentation and no augmentation in change in FEV1, with the direction of effect favouring placebo:

- Edgar 2017: mean difference in FEV1 per cent predicted –0.56% (95% CI –1.41% to 0.29%; p=0.20);[2]

- Gotzsche 2016: standardised mean difference –0.19 (95% CI –0.42 to 0.05; p=0.012).[3]

Using the change in FEV1 in millilitres per year reported by the company in their updated analysis, synthesis of data from three RCTs aligns with the results from two other systematic reviews in that, for those with emphysema secondary to A1PI deficiency, augmentation is associated with a greater rate of decline in FEV1 (ml/y) compared with placebo (i.e., results favour placebo), but the difference does not reach statistical significance (mean difference of –3.96 ml/y; 95% CI: –12.24 ml/y to 4.32 ml/y; p = 0.35; **Error! Reference source not found.Error! Reference source not found.**).

1.1.1.2 Observational studies

Of the six observational studies included by the company in their meta-analysis,[7, 8, 10-13] the ERG excluded four of the studies,[10-13] two of which were included in the Chapman 2009 meta-analysis.[12, 13] One of the references was available as only a conference abstract, which the ERG was unable to locate.[13] Additionally, as a result of the progressive nature of emphysema secondary to A1PI deficiency, the ERG considered it inappropriate to include studies of a design in which a person acted as their own control (i.e., retrospective pre- and post-studies), which led to the exclusion of two studies.[10, 12] Finally, the ERG excluded the data reported by Tonelli and co-authors[11] that indicated association of augmentation with an increase in FEV1 ml/y from baseline because this result is likely not clinically plausible.

The prospective study reported by Seersholm evaluated ex-smokers in a multicentre drug surveillance study (Germany) who had PiZZ genotype and a serum level of A1PI <35% of normal, together with FEV1 <65% of predicted or >120 mL annual FEV1 decline.[8] Untreated index cases forming the control group were derived from a Danish registry and were those with PiZZ phenotype or serum level of A1PI of <12 μM. Those receiving augmentation were given 60 mg/kg of A1PI, and spirometry was assessed post-bronchodilator at 1 week, 3 and 6 months and every 6 months thereafter. By contrast, in the control group, spirometry was carried out by the referring physician or at a chest clinic. Mean follow up was 3.2 years in those receiving augmentation compared with 5.8 years in the control group.

The second study was carried out by the Alpha-1-Antitrypsin Deficiency Registry Study Group in the USA.[7] People with serum A1PI levels <11 μM or a PiZZ genotype were followed for 3.5 to 7 years with spirometry measurements every 6 to 12 months. People were classified as always, partly, or never receiving augmentation therapy with A1PI. A1PI dosage was determined by the managing physician. The "always receiving" therapy group encompassed those on therapy continuously, beginning at or within 3 months of enrolment. The "partly" on therapy group included those who began therapy 3 months after enrolment or who discontinued therapy for 1 month after enrolment. The authors evaluated 1,129 eligible people from the registry enrolled from 37 centres. Assessment of effect of augmentation on FEV1 is based on 927 people with two or more FEV1 measurements separated by more than one year. The authors present results based on baseline FEV1% predicted based on various categories, including 35–79%, which the ERG incorporated into the meta-analysis.

Based on the ERG's meta-analysis, augmentation was associated with a statistically significant decrease in rate of decline of FEV1 (ml/y) compared with placebo (mean difference of 18.11 ml/y; 95% CI 7.55 ml/y to 28.68 ml/y; p <0.001; **Error! Reference source not found.Error! Reference source not found.**).

1.2 Impact of augmentation therapy on survival

1.2.1 ERG's initial critique and conclusions from the ECD

The company used RAPID and RAPID-OLE data to model mortality for four years in the Respreeza arm of the model and for two years in the BSC arm. Thereafter, the company used the analysis by Green *et al.*[14] to extrapolate mortality in the long-term economic analysis. Green *et al.*[14] analysed UK registry (ADAPT) data for patients with A1PI deficiency, and categorised lung function decline using the same thresholds as the company's model.[14, 15] Mortality data in the study were analysed in a multivariate Cox regression by lung function decline (no decline [ND], slow decline [SD] and rapid decline [RD]) and FEV1 categories (>50%, ≥30% to ≤50% and <30%).

The ERG had several concerns with the company's original approach. Firstly, the ERG disagreed 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 was further compromised by the baseline imbalances in the trial and placebo patients crossing over to the Respreeza arm of RAPID-OLE after 2 years, without any data adjustments (for more details please refer to the ERG's original report).

Secondly, the company's approach to "transitioning" from the trial survival to the registry survival curve led to an overestimation of the survival benefit associated with Respreeza (more details on this issue can be found in the ERG's original report).

Thirdly, the company's approach assumed that survival in the RAPID, and in the ADAPT registry populations was the same, as patients simply joined from the RAPID survival curves into registry survival curves from ADAPT, without any data adjustments. However, 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% predicted category. Therefore, the ERG concluded that survival data were not comparable in these sources, and thus could not be used interchangeably, possibly because survival estimates from RAPID were unreliable, given the extremely small number of events.

The ERG was also concerned with the use of the Green *et al*. data to estimate CT lung density – related mortality (stratified by FEV1% status) in the long-term model. The ERG highlighted that the survival outcomes in the study were not statistically significantly associated with lung density decline as the authors of the analysis concluded that in the [redacted]. The ERG concluded that even though the use of Green *et al*. data to model survival might have reflected the best available survival data, caution was needed when interpreting the survival outcomes in the economic analysis.

Furthermore, the company used the FEV1 30–50% survival data from Green *et al*. to model survival for ≥30% FEV1%<50% and FEV<30% states in the model. The ERG disagreed with this simplification and considered that the company should have used the appropriate survival data to model each FEV1 category in the analysis given that the population survival groups analysed in Green *et al*. are an exact match to the company's modelled FEV1 groups.

The committee considered whether there was any survival benefit associated with human A1PI. It understood that, because of the size and duration of the RAPID studies, it was not possible to draw conclusions about survival from these data. The committee considered USA survival data from the Alpha-1-Antitrypsin Deficiency Registry Study Group (1998).[16] It noted that people who were taking, or who had previously had, human A1PI had a higher probability of survival than those who had not. The committee recognised the limitations of this observational evidence but concluded that this suggested that human A1PI may improve survival.

The committee acknowledged that there were methodological issues with the company's approach to modelling survival and agreed that the benefits of human A1PI were already captured by it slowing transition to states of poor lung function. Therefore, it considered that the ERG's approach to modelling survival was methodologically more appropriate. The committee considered the plausibility of the estimates of overall survival gain with human A1PI produced by the company (3 years) and ERG (7 months). It recalled real-world survival data from the USA registry and accepted that it was plausible that human A1PI could substantially increase survival. The committee recognised that a 7-month survival gain might be conservative but was unable to establish whether a 3-year gain would be plausible. It considered that the USA registry data could be used to inform the survival modelling, or, at a minimum, validate the modelled survival outcomes. The committee concluded that given the evidence presented, the ERG's approach was more appropriate to use in its decision-making but agreed that mortality remains a critical uncertainty in the model.

1.2.2 Company's updated analysis

To generate an estimate of effect of augmentation with A1PI on mortality in those with A1PI deficiency, the company reported an analysis of data [redacted]. The company reports that, "[redacted]. Results are presented from a [redacted].

One of the experts involved in the analysis of data clarified that the analysis was [redacted]. People were matched based on:

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

Consensus of factors on which to match led the researchers carrying out the analysis to choose characteristics that are thought to, "[redacted].

The company applied the whole cohort matched analysis HR (0.76) to the original Green *et al.* data to estimate long-term survival (after 4 years in the Respreeza arm and 2 years in the BSC arm) in the updated model. The company pointed to the risk of double counting the survival benefit in the model as the impact of Respreeza on mortality was already captured through the impact of the drug on slowing lung density decline, and the latter is connected to mortality through the Green *et al.* data. Nonetheless, the company concluded that using the HR in the analysis led to a survival benefit of [redacted] years in the analysis, which was deemed reflective of the UK-AlphaNet analysis.

The company also considered a scenario analysis removing the RAPID and RAPID-OLE data from the model but concluded that the survival gain generated in such analysis ([redacted]) was not reflective of the UK-AlphaNet analysis' conclusions.

1.2.3 ERG's critique of company's updated analysis

In their response to the ECD, the company presents an estimate for impact of augmentation on mortality, compared with no augmentation, based on [redacted]. The ERG considers the [redacted]).

Limited discussion is available in the response to ECD on the methods [redacted]. The company reports that, "[redacted]

[redacted]. Dr Alice Turner helpfully clarified that the assessment [redacted].

Within the response, the company outlines points that should be considered when interpreting the results of the analysis, of which the ERG considers the most important to be that [redacted]. During the ERG's consideration of the company's response to ECD, Dr Alice Turner helpfully [redacted]. Limiting the analysis to people [redacted] generated a cohort of [redacted], with [redacted] and [redacted] people forming the augmentation and control groups, respectively. Dr Turner reported that people who had received A1PI augmentation had a mean time to death of [redacted] compared with a mean time to death of [redacted] for those in the control group (HR [redacted]; 95% CI: [redacted]; p<[redacted]; Figure 2). The ERG notes that the analysis includes people enrolled in the databases before 2007, and for whom full matching on [redacted] for reasons outlined in the ECD response: [redacted]

Figure 2. Kaplan–Meier plot of survival in matched cohort as supplied by Dr Alice Turner

[redacted]

In terms of the [redacted], the ERG notes that the analysis is based on data from cohorts derived [redacted].

Although utilising data from [redacted] is a limitation of the analysis, the ERG highlights that, because no A1PI therapy has been approved for use in the UK, [redacted].

[redacted].

In terms of the modelling of survival data, the ERG's concerns regarding the use of RAPID and RAPID-OLE data to model survival remain and have not been mitigated to any extent by the company's updated analysis. Therefore, the ERG's opinion remains that these data should not be used in the economic analysis.

The ERG's concerns regarding the use of the Green *et al*. data to model survival also remain. The survival outcomes in the analysis are not statistically significantly related to lung density decline and thus, using these data in the model is a source of considerable uncertainty.

The ERG is concerned with the company's use of the HR derived from the Cox model using the AlphaNet-ADAPT analysis. Firstly, the company used the HR derived from the matched analysis which includes patients without lung disease in the ADAPT dataset. The ERG considers that the most robust analysis is the one provided to the ERG by Dr Alice Turner, which uses lung disease as a matching criterion (therefore, only including patients with lung disease from both datasets). Secondly, applying the Cox model's HRs to the Green *et al.* data is not a robust approach from a methodological point of view, given the differences in the underlying data and groups of patients across the two analyses. Furthermore, the use of the HR in the company's updated base case analysis introduces a third, disconnected source of evidence for the estimation of the survival benefit of Respreeza, to an already uncertain chain of evidence compounding the existing methodological issues.

Given all the available options to estimate mortality in the economic analysis, and in light of the new evidence presented by the company and by Dr Alice Turner, the ERG considers that the most robust method to try to quantify the survival benefit of augmentation therapy is to conduct survival analysis using the AlphaNet-ADAPT observational data, restricted to patients with lung disease in both cohorts, and estimating survival independently by treatment arm in the model (i.e. to estimate survival in the Respreeza and in the BSC arms of the model separately). This approach overcomes the problems inherent due to the immaturity of the survival data in RAPID and the lack of statistical significance between lung density decline and survival outcomes found in the Green *et al.* analysis.

Therefore, the ERG carried a survival analysis using the AlphaNet-ADAPT dataset for patients with lung disease. Using this approach means that survival in the economic model is no longer directly related to lung density decline or FEV1% status, but instead to patients' allocation to treatment group. Given the lack of robust evidence to connect lung density decline or FEV1% status with survival (and amongst themselves), the ERG considers this to be a more robust analysis, with fewer challenging assumptions and thus less uncertainty regarding survival outcomes. The main methodological issue with this approach is the use of observational data from two different populations for each treatment arm.

Moreover, using the new survival data in the economic model is incompatible with the implementation of lung transplant-related mortality in the analysis. Given that the AlphaNet-ADAPT survival data does not relate to FEV1% status in the model, when the ERG used these survival data in the model, patients having early lung transplants were experiencing a higher probability of death in the years following lung transplant than in the FEV1<30% state, therefore, implying that lung transplant would not have been a preferable clinical outcome for these patients. Even though the ERG heard from clinical experts that lung transplant has a poor survival prognosis, it seems illogical to assume that the transplant yields a worse outcome than offering no alternatives to a patient in need of transplant. The company's base case model also has the same issue, however to a smaller extent, given that in the company's analysis this inconsistency only happens for the first 6 to 10 years of the analysis, while in the ERG's updated model this was the case for the first 30 years of the model. This reflects the ERG's original concern that measures of clinical effectiveness in the model were not taken from a coherent clinical source. This issue, allied with the uncertainty surrounding lung transplant outcomes in the model (discussed in the next section), gives the ERG confidence that using the AlphaNet-ADAPT survival data and removing lung transplants from the model provides a more robust analysis of cost-effectiveness for Respreeza, with fewer methodological issues and so less uncertainty in the analysis.

To note is that in order to incorporate lung transplants in the model, the latter would likely need to be restructured to be based on a partitioned survival analysis, where patients moving to the lung transplant state could have survival curves estimating their probability of death per cycle in the economic model. Alternatively, the AlphaNet-ADAPT survival data could be used to estimate overall survival (including post-lung transplant survival) in the company's original model structure. This would require re-analysing the AlphaNet-ADAPT survival KM data without censoring lung transplant events (as is done in the current analysis) so that the data could reflect the impact of lung transplants on survival. This modelling approach would also require an assessment of the comparability of lung transplant management and outcomes in the AlphaNet dataset (i.e. in the USA) and in UK clinical practice.

The ERG digitised the survival curves reported in Dr Alice Turner's manuscript (shown above in Figure 2) using the Guyot *et al*.[17] method. This approach simulates the pseudo-individual patient-level data, using the algorithm in the *survHE R* package, which allowed the ERG to reproduce the KM curves in the manuscript (reproduced curves shown in Figure 3). The ERG then proceeded to fit survival functions to these data and extrapolated survival into the long-term economic analysis (50 years). The ERG fitted a loglogistic, lognormal, exponential, Gompertz, Weibull and gamma models to the KM data, independently, for each treatment arm in the model. Based on the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), the ERG concluded that the gamma and the lognormal models were the best fitting models (Table 1 and

Table 2) for the augmentation arm. The best fitting models for the control arm were also the lognormal and the gamma distributions, with the log-logistic also presenting a good statistical fit. To ensure that the same type of statistical model was fit to each treatment arm (albeit independently), the ERG decided to use the gamma and the lognormal models in the analysis.

Visual inspection of the fitted models (Figure 4 for augmentation group and Figure 5 for control group) revealed that the best fitting curves presented a slight plateau, predicting clinically implausible long-term survival rates. The ERG compared the extrapolated survival curves for A1PI patients with the background general population survival, matched for gender distribution and age in the economic analysis. Figure 4 and Figure 5 show how the general population survival is lower than that of A1PI patients, which is clinically implausible.

This disconnect might result from the immaturity of the AlphaNet-ADAPT data, considering the slow nature of the disease, and a low number of patients at risk at the end of the KM curves. To overcome this issue in the model, the ERG compared the underlying hazard in the best fitting survival curves (gamma and lognormal) for the AlphaNet-ADAPT patients, with the hazard in the general population survival curve, in every cycle of the economic model. When the former exceeded the latter, the ERG used the general population hazard (approximately after 25 and 30 years in the Respreeza, and in the BSC arm of the model, respectively) to estimate the proportion of patients alive in the next cycle of the model. The resulting survival curves used in the analysis are shown in Figure 6. The results of using the ERG's approach to estimating survival in the model are reported in Section 6, using the lognormal model for the base case and the gamma model as a scenario analysis.

Figure 3. Overall survival KM curves derived by the ERG in *R* statistical package

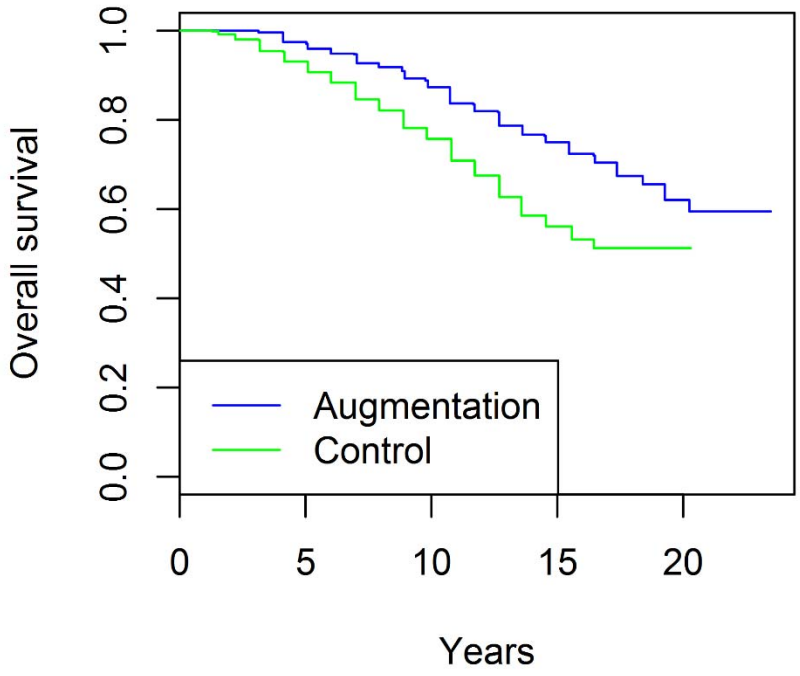


Table 1. Goodness-of-fit statistics for augmentation therapy data

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
AIC	1675.667	1588.462	1578.113	1585.095	1613.685	1578.908
BIC	1680.331	1597.791	1587.442	1594.424	1623.014	1592.901
AIC, Akaike information criterion; BIC, Bayesian information criterion						

Table 2. Goodness-of-fit statistics for control data

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
AIC	1698.204	1634.782	1621.357	1625.851	1665.507	1623.313
BIC	1702.826	1644.025	1630.559	1635.094	1674.750	1637.178
AIC, Akaike information criterion; BIC, Bayesian information criterion						

Figure 4. Extrapolated survival curves for augmentation therapy and general population survival

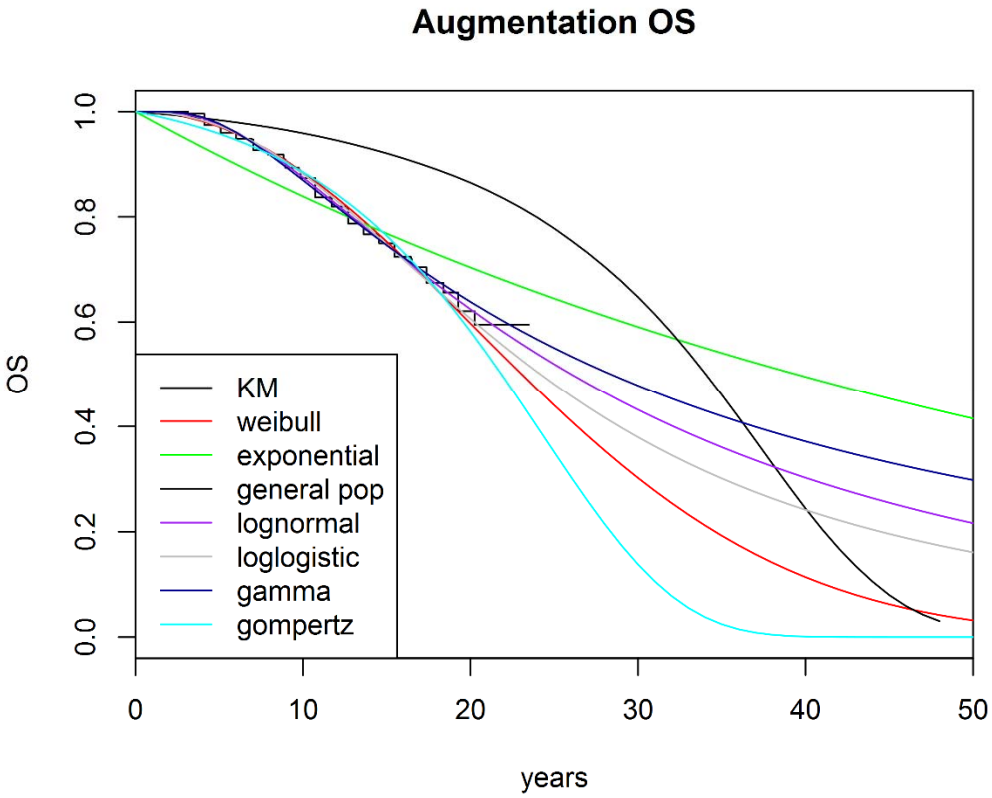


Figure 5. Extrapolated survival curves for control arm and general population survival

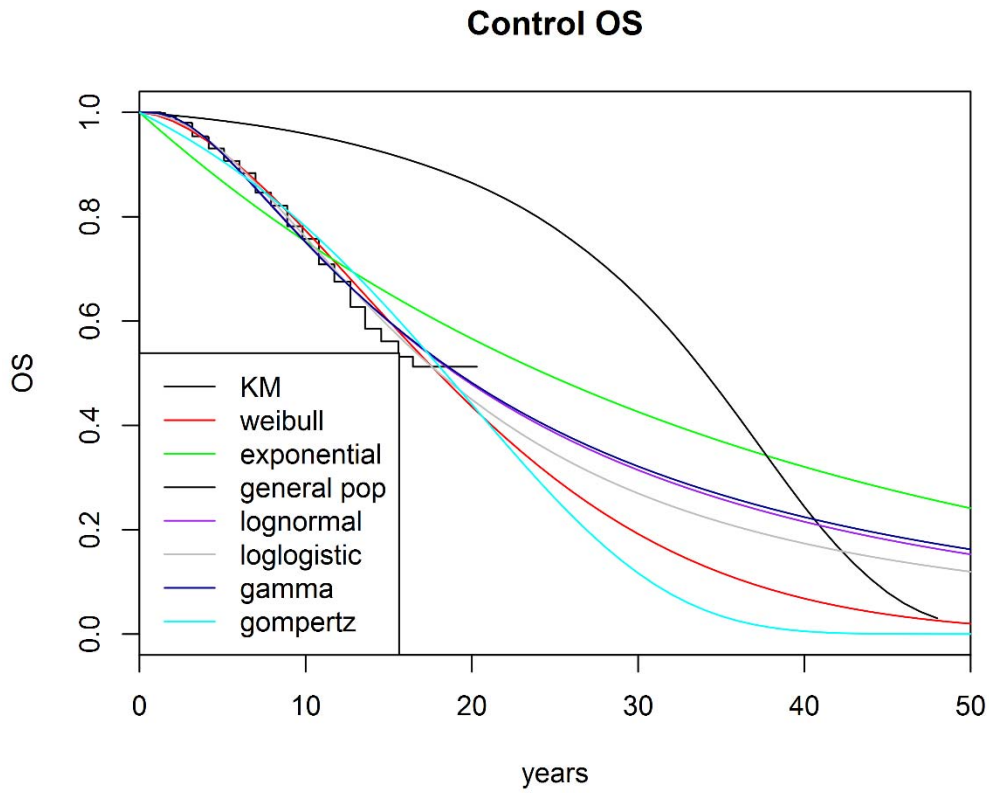
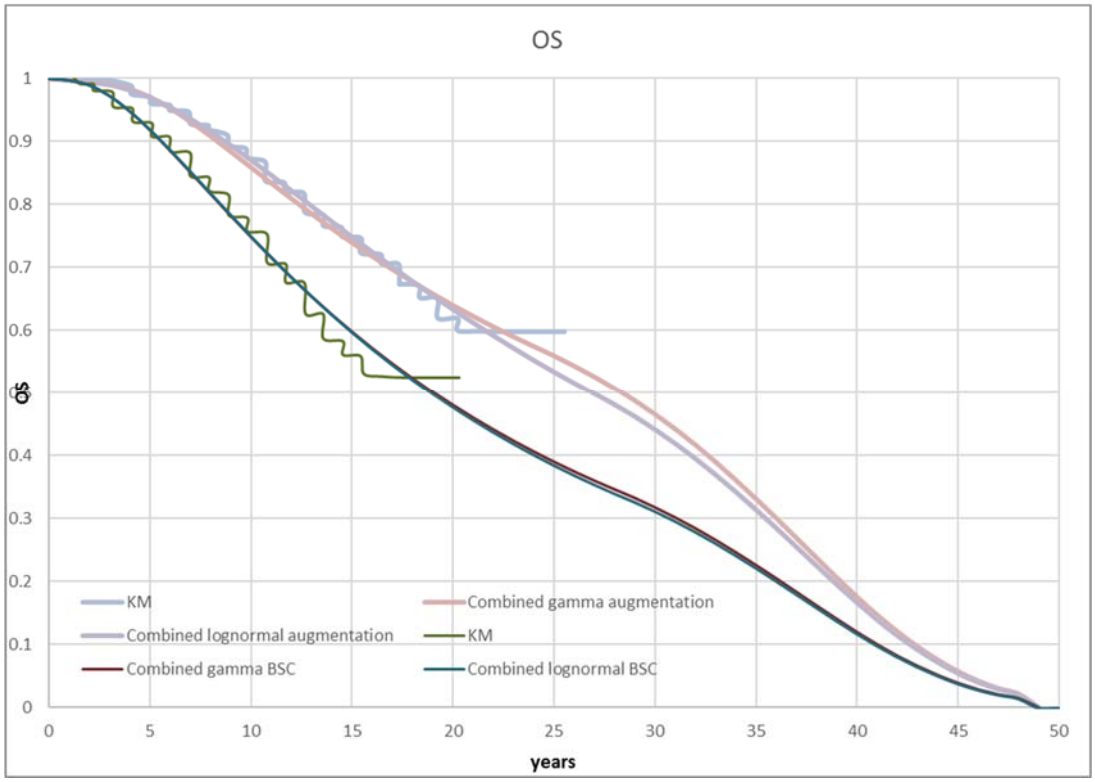


Figure 6. Capped survival surves used in the ERG's analysis



1.3 Lung transplant

1.3.1 ERG's initial critique and conclusions from the ECD

Post-lung transplant survival and quality of life

The ERG noted that the company could have used survival curves to model mortality post-lung transplant, given these were available in the NHS BT report.[18] The company used the survival estimates of 82% and 59%, at year 1 and year 5, respectively. Clinical expert opinion provided to the ERG was consistent in reporting that survival after lung transplant is generally poor, with one clinical expert stating 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.[19]

The committee concluded that modelling survival after transplant using a survival curve may have been preferable. The committee noted that survival after transplant was a key driver of the model and acknowledged that both (the company's and the ERG's) survival estimates were uncertain. The clinical experts explained that the ERG's estimates were reasonable. The committee concluded that survival after transplant is uncertain and agreed that further evidence would be welcome. Overall, the committee agreed that the ERG's figures were acceptable for decision-making.

The committee noted that the company, ERG and clinical experts did not raise concerns about the validity or plausibility of the post-transplant quality of life estimates. The committee took this to mean that any reduction in quality of life due to the complications of transplant were captured in these utility values. However, it considered that the fear expressed by patient experts (which it understood was substantial and caused much anxiety) was not captured. The committee agreed that it would be reasonable to include pre-transplant anxiety in the model, noting that this could be done using utility estimates for people who had been on the transplant waiting list. The committee concluded that the health effects of lung transplant after transplant had been appropriately captured, but the additional health effects before the transplant were not.

1.3.2 Company's updated analysis

The company assumed that 30% of patients in the FEV1<30% category would not be eligible for a transplant and that there is no age cap to receive a transplant in the model.

The company considered that the post-transplant survival estimates used by the company were preferable to those proposed by the ERG (and agreed by the committee). The company reiterated that

its proposed survival estimates after lung transplantation are based on survival data for all UK lung transplants published by the NHS Blood and Transplant Report from 2017 and therefore, are based on the most robust evidence source. The company acknowledged that the NHS BT report does not report survival by indication but mentions a presentation conducted by Dr Andrew Fisher (Professor of Respiratory Transplant Medicine Institute of Transplantation, at the Freeman Hospital in Newcastle), which illustrated survival after lung transplantation using a Kaplan-Meier curve from January 1990 to June 2011 by indication. For patients with A1PI deficiency, 1- and 5-year survival rates were 80% and 58%, further supporting the survival figures in the NHS Blood and Transplant Report for 2017 of 82% and 59% accordingly. The company also mentions a study published in 2015 by Stone *et al.* showing survival rates post-transplantation of UK patients with A1PI at 74.2% after 1 year and 52.9% after 5 years.

The company also included a pre-transplant utility value in their updated analysis to reflect patients' anxiety while waiting for transplantation. The company used the pre-transplant utility value from Anyanwu *et al.* (2002) of 0.31. This was the same study that was used to generate post-transplant utilities in the model. As per the assumption that only 70% of FEV1%<30% patients are eligible for a lung transplant, the company estimated a weighted average utility in the corresponding model health state (FEV1%<30%) of 0.37, based on 70% of patients having a utility of 0.31 and 30% of patients retaining the original utility of 0.51.

Furthermore, the company has provided a scenario in which lung transplantation was excluded from the model. The company reported that with the removal of lung transplantation from the model, the ICER increased by 11% from £278,615 to £310,480 in the company's analysis.

1.3.3 ERG's critique of company's updated analysis

The ERG notes that the company's updated analysis reduces the proportion of patients eligible for lung transplant by 30% in the FEV1%<30% health state, in accordance with the committee's conclusions. Nonetheless, after reading the response documents to the ECD from several clinical experts and other stakeholders, the ERG noticed a common concern around the assumption that all patients in the FEV1%<30% would be eligible for lung transplant, as this was considered an overestimation of the number of transplants in the UK (even when the population was reduced to 30%).

The ERG considers that the two sources reported by the company to substantiate its estimates of post-lung survival do not alleviate the uncertainty around the estimation of the latter. Even though the presentation conducted by Dr Andrew Fisher (for which no reference was provided to the ERG) reported 1- and 5-year survival rates of 80% and 58%, the Stone *et al*. paper (again for which no reference was provided to the ERG) reported survival rates of 74.2% after 1 year and 52.9% after 5 years. While the first source mentioned by the company is closer to the company's original estimates of 82% and 59%

for 1- and 5-year survival, respectively, the second is closer to the ERG's proposed estimates of 70% and 50%, respectively. The ERG concludes that these remain uncertain estimates and that survival analysis should have been carried by the company as a more robust step to explore the uncertainty around survival outcomes after lung transplant.

The ERG original report discussed the issues around the synergies in the model caused by the relationship between mortality; the benefits of lung transplant; and the link between clinical outcomes (FEV1% and CT lung density) and mortality in the model. Furthermore, the ERG pointed to the fact that lung transplant is one of the key drivers of the economic model and that there was an inconsistency in the company's proposed value of Respreeza with regards to lung transplant (i.e. whether the purpose of the drug is to obliviate the need to lung transplant or increase the proportion of patients eligible for the procedure). Given the uncertainty around the benefits of lung transplant and how these compare to the benefits associated with remaining in the ≥30% FEV1%<50% state for the longest time possible in the model; and in light of the new survival data provided to the ERG, the ERG considered that removing lung transplants from the model would be the most robust way to estimate the benefits of Respreeza based on the data available to the ERG.

Once patients reach the lung transplant state in the economic model, patient-related costs and outcomes are the same. Therefore, the impact of lung transplant in the model is determined by the incremental number of patients reaching this state, and when in the model the latter happens. If there is a different number of patients reaching this health state across treatment arms, then the magnitude of the benefits associated with lung transplant (compared to the alternative states in the model) also becomes an important driver of the analysis. For example, Table 3 shows how patients receiving a lung transplant have a much higher quality of life than patients in the FEV1 30–50% state and are not too different from patients in the FEV1 ≥50% category.

Removing lung transplants from the model in this context means that the benefits of Respreeza are still captured through: 1) the survival benefit captured by patients receiving augmentation therapy estimated with the AlphaNet-ADAPT dataset; 2) given that Respreeza patients live for longer and that Respreeza patients have a lower probability of FEV1% decline, they experience higher utility values (compared with BSC patients) for longer.

Table 3. Utility values used in the company's model

Health state	HSUV	Source
FEV1 ≥50% predicted	0.79	Ejiofor and Stockley, 2015[20] and Anyanwu *et al.* 2001[21]
FEV1 30–50% predicted	0.63	
FEV1 ≤30% predicted	0.37	
LT: year 1	0.76	Anyanwu *et al.* 2001[21]
LT: year 2+	0.77	

1.4 Quality of life analysis

1.4.1 ERG's initial critique and conclusions from the ECD

The company reported its concerns that the benefits of Respreeza were underestimated in the original analysis by not capturing the effect of reducing lung density decline on HRQoL, however, it stated that there were no data to allow such analysis. The ERG noted that there were data available in one of the manuscripts used by the company (Green *et al.*) showing [redacted] This is illustrated in Figure 14.[14]

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 in the economic model, the ERG considers that the company could have use this source to model differences in HRQoL, according to baseline lung density and lung density decline in the analysis.[14]

Figure 14. [redacted]

The committee understood that the utility values in the economic model were linked to FEV1% predicted categories, but not to lung density decline. The patient and clinical experts explained that FEV1% predicted can vary substantially, with people not having any noticeable change in their health.

The committee recognised that the link between FEV1% predicted and quality of life was unclear. The committee agreed that, given its concerns about the link between FEV1% predicted and quality of life, it would have liked to consider an analysis in which utility values varied according to lung density.

The committee considered whether there may have been alternative sources of evidence to inform the utility values in the economic model. Alternative sources of data that needed mapping to EQ-5D may have limitations, but it was agreed that these could be considered given the concerns with the modelling of quality of life. The committee concluded that it was not convinced that the approach to modelling quality of life appropriately reflected the course of the disease and agreed it would have liked to consider the effect of lung density decline on utility values. It further concluded that the health benefit of behaviour change had not been captured quantitatively and it would therefore be considered qualitatively.

1.4.2 Company's updated analysis

The company reported that there are not sufficient data available to be able to model the relationship between SGRQ and lung density decline, so instead provided additional scenario analysis to explore this. Different scenarios were included where patients with no decline in lung density have greater utilities than patients with slow lung density decline and patients with a rapid decline in lung density have lower utilities than patients with a slow decline in lung density. The factors considered were 5%, 10%, 15%, 20% and 25%.

1.4.3 ERG's critique of company's updated analysis

The ERG's original concerns remain unchanged. The ERG considers the Green *et al.* data could have been used by the company to attempt modelling the relationship between lung density decline and patients' quality of life to mitigate the concerns around lung density function and its impact on quality of life. The data available categorises lung density decline in the same way as the company's model, and more importantly, shows a statistically significant relationship between lung density decline and changes in SGQR. The company's updated analysis is based on arbitrary thresholds, which are based on weak assumptions rather than the data available in Green *et al.*

Furthermore, upon inspection of the economic model, the ERG noted that the updated base case includes the assumptions originally made by the company in a scenario analysis, adjusting utilities in the model to incorporate the EQ-5D utilities reported by age and sex in the Kind *et al*. 1999 study.[86] The ERG originally disagreed with the methods used by the company in their scenario analysis, and described the issues related with the latter in the ERG's original report. The ERG's original concerns are not mitigated and the ERG disagrees with the use of the adjusted utilities in the base case analysis. However, when the ERG removed the option to adjust utilities in the model, it encountered an implementation error, as

the model engine did not account for the removal of the adjustment scenario in all the relevant QALY estimations. Therefore, the ERG corrected this mistake and reports the respective results in Section 6.

1.5 Lung density decline in the economic analysis

The ERG's concerns around the estimation of Respreeza's effect on lung density decline remain unchanged. The company did not update their analysis on this regard and did not provide any new evidence to be considered. Therefore, the ERG reiterates its original concerns in this section.

During the original 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 respond to the ERG's request. The ERG remains unclear to the methods used to estimate transition probabilities between lung density decline states in the model. 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 flawed.

The ERG remains 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. During the original clarification stage, the ERG requested the company 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 did not provide these data.

The ERG also asked the company to use the requested Respreeza data 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. However, the company ignored the ERG's request to exclude placebo patients from the 4-year data analysis of Respreeza.

The ERG also remains concerned with the fact that the thresholds used by the company to define lung density decline are not based on clinically standardised thresholds, and as such 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 and this would have a direct impact on the final ICER.

As pointed out by the company during the factual accuracy check, a recent a study by Subramanian *et al*. derived a minimal clinically important difference (MCID) of -2.89g/l. The study derived a MCID for annual CT lung density decline in patients with A1PI using the anchor and distribution method and used the Birmingham A1PI cohort to validate the proposed MCID. The ERG considers that if a lung density decline threshold 2.89 g/l/year was to be used in the economic model, the estimated benefit of Respreeza in the economic analysis would decrease (based on the RAPID effectiveness data).

The committee concluded that the definitions used to categorise lung density decline in the model lacked validation and agreed that further validation could reduce some of its concerns about the model structure.

1.6 Costs

1.6.1 ERG's initial critique and conclusions from the ECD

In the original model, the company only costed treatment with Respreeza, and not with BSC, 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 ERG noted that the company underestimated the additional costs associated with Respreeza treatment. Therefore, the ERG searched 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] More details on the costs reported in the study can be found in the ERG's original report. The impact of adding BSC costs to both treatment arms was minimal in the original model, increasing the ICER from £236,409 to £236,535. The ERG was also concerned with the exclusion of routine CT scanning costs from the company's analysis.

The ERG also noted that patients in the Respreeza arm of the model were assumed to have a mean weight of 75.9kg, which translated into 5 required vials per patient, per treatment cycle (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 recommended that the company looked at patients' weight categories in the trial and assessed the proportion of patients requiring a different number of vials in order to estimate a weighted treatment costs given that the cost of treatment with Respreeza is a key driver in the model.

The committee agreed that best supportive care costs would be unlikely to cancel out across treatment groups but recognised that excluding these did not have much effect on the economic results. The

committee recalled expert comments that CT densitometry was a valuable tool for assessing emphysema associated with A1PI deficiency and would increasingly be used in clinical practice. The committee recognised that CT densitometry may be used for assessing A1PI deficiency regardless of the availability of human A1PI but because survival rates would not be equal across treatment groups, the costs of CT densitometry would differ between people having human A1PI and people having BSC. The committee concluded that it had concerns with the modelling of costs and agreed that it would prefer best supportive care and CT densitometry costs to be included.

1.6.2 Company's updated analysis

The company initially reported including the costs of conducting one CT scan per year in the analysis. However, after a clarification request from the ERG, the company explained that instead of including CT scan costs, it included the costs of one specialist consultation (£149) a year per patient, adding that the cost of a consultation is more expensive than the cost of one CT scan, thus making this approach a conservative one. The company decided not to include the costs of BSC in either arm of the economic model.

1.6.3 ERG's critique of company's updated analysis

The impact of adding BSC costs to both treatment arms was minimal in the original model. However, the longer the survival benefit with Respreeza is in the analysis, the bigger the impact of adding BSC costs to both treatment arms is. Therefore, the ERG included BSC costs in both treatment arms and presents the results in Section 3.

The ERG is confused by the company's justification around the costing of CT scans in the analysis. The company's original analysis already included the cost of a consultation with an A1PI deficiency specialist in secondary care (£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. The company's updated analysis assumed the same cost of consultation; however, reduced the number of consultations per year with all patients receiving only one consultation a year. Therefore, the company's updated approach reduced the costs associated with disease management for all patients in the model, instead of adding the costs associated with annual CT scans.

The ERG disagrees with the company's approach, thus corrected the disease management costs to reflect the previously accepted resource use. The impact of this correction on the final ICER is reported in Section 3. The ERG also ran a scenario analysis adding the annual cost of a CT scan (£100 as per the 2017/2018 National Tariff RD22Z) per patient in both treatment arms of the model. Results are reported in Section 3.

The ERG remains concerned that the cost of treatment with Respreeza is being underestimated in the model by not using a weighted cost by weight category from patients in RAPID.

1.7 Discount rate

The ERG did not have any concerns with the company's original approach to discounting in the economic model. However, in their updated analysis, the company included an option in the economic model to use a discount rate of 3.5% for costs and 1.5% for QALYs. The company states that the differential approach aligns with the most recent UK HM Treasury Green Book, which specifies its use for all health outcomes, specifically for QALYs.

The ERG notes that the latest NICE's guide to the methods of technology appraisal specifies that the discount rate that should be used in the reference case is 3.5% for both costs and health effects. The NICE guide also states that a non-reference case rate of 1.5% for costs and health effects may be used when: treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives; if it is highly likely that there will be long-term benefits (normally sustained for at least 30 years); and if the treatment does not commit the NHS to significant irrecoverable costs.

Therefore, neither the reference case nor the non-reference case in the NICE methods support the use of differential rates for costs and health outcomes. Regarding the use of the 1.5% discount rate for both costs and health outcomes, the ERG does not consider that the evidence presented by the company supports that Respreeza returns people to full or near-full health, given that emphysema is a progressive disease and, by nature, deterioration in lung tissue and lung function is irreversible, or that it brings long-term health benefits sustainable for 30 years (the company's base case updated model estimates a survival benefit of [redacted] years with Respreeza). In conclusion, the ERG considers that the reference case discount rate should be used for costs and outcomes in the economic analysis.

1.8 Correlation between FEV1% and lung density decline

The ERG acknowledges that CT lung density and FEV1 are correlated, but maintains that the extent of the relationship is unclear, with weak to modest indicators of correlation between the two outcomes when assessed by linear regression.[4, 6, 22, 23] The ERG suggests that the relationship between decline in CT lung density and in FEV1 might not be linear in nature and is an area requiring substantial further investigation. Although the ERG remains concerned that the company's probabilistic sensitivity analysis (PSA) does not account for the correlation between lung density and lung function, given the uncertainty in the relationship between the measures, the ERG appreciates that it might not be possible to correlate the parameters appropriately based on the available information. However, the ERG cautions that not correlating the parameters in PSA potentially renders the PSA unreliable.

1.9 Statutory scheme rebate payments

The company reported that recent changes to the Statutory Scheme for 2019 mean that the company is now subject to rebate payments for the first time. As a result, the company stated that the sales of Respreeza will now be liable to rebate payments of 9.9% in 2019, rising to 14.9% in 2020 and 20.5% in 2021. As a result, the company decided to model a scenario reducing the total annual cost of treatment with Respreeza by 9.9% in the first year, 14.7% in the second year, and 20.5% in the third year. The company presented an ICER corresponding to this scenario analysis amounting to £264,334 (compared to £278,615 in the company's base case).

The ERG notes that the company did not provide an updated budget impact model in their economic analysis. Therefore, the discount applied by the company does not relate to sales volume or growth.

2 RESULTS

The company's updated ICERs are reported below in Table 4 Table 4(with differential discounting) and in

Table 5 with the reference case discount rate. The ERG ran PSA for the company's base case (using a 3.5% discount rate for costs and outcomes) and presents results in

Table 6.

Table 4. Company's base case results (with 3.5% discount on costs and 1.5% discount on outcomes)

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
Respreeza and BSC	£524,220	12.790	8.320	£468,991	3.247	2.032	£230,810
BSC	£55,230	9.543	6.289	-	-	-	-

Table 5. Company's base case results (with 3.5% discount on costs and outcomes)

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
Respreeza and BSC	£524,220	12.790	7.277	£468,991	3.247	1.683	£278,615
BSC	£55,230	9.543	5.594	-	-	-	-

Table 6. Probablistic sensitivity analysis results (with 3.5% discount on costs and outcomes)

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
Respreeza and BSC	£ 395,691	8.802	5.026	£365,022	3.091	1.645	£221,931
BSC	£ 30,668	5.712	3.381	-	-	-	-

3 ADDITIONAL WORK UNDERTAKEN BY THE ERG

The scenario analyses undertaken by the ERG are explained throughout Section 1 of the report. The analyses consist on the following:

1. The ERG removed the option to adjust utilities in the model and corrected the implementation error related with the latter;

2. The ERG used its updated meta-analysis based on observations studies to estimate the impact of augmentation therapy on FEV1% decline;

3. The ERG included BSC costs in both treatment arms of the model;

4. The ERG changed the disease management costs to reflect the previously accepted resource use based on patients with an FEV1≥50% seeing a specialist twice per year, patients with a ≥30%FEV1<50% seeing a specialist three times per year, and patients with an FEV1<30% seeing a specialist four times per year;

5. The ERG added the annual cost of a CT scan per patient in both treatment arms of the model;

6. The ERG used the AlphaNet-ADAPT survival analysis to estimate mortality and removed lung transplants from the economic model (using the lognormal model);

7. To reflect the committee's preferred post-transplant survival estimates, the ERG ran a scenario analysis using the 1- and 5-years survival rates of 50% and 70% in the company's updated base case model.

Table 7 reports the impact of the ERG's scenarios on the final ICER for Respreeza vs BSC. Consistent with the original ERG's conclusion, the key driver of the economic results is the survival data used in the model. Using the AlphaNet-ADAPT data and removing lung transplants from the model led to an increase in the company's base case ICER from £278,615 to £622,401 per QALY gained. When the ERG uses the AlphaNet-ADAPT data in the model (and removes lung transplants from the model), there is a survival benefit of [redacted] years with Respreeza (higher than the [redacted] years estimated by the company in their base case model). This compares to the [redacted] years predicted in the company's AlphaNet-ADAPT analysis and [redacted] years in Dr Alice Turner's analysis (excluding patients without lung disease).

The ERG's predicted survival benefit corresponds to a total undiscounted life years of 25.8 years for Respreeza and 21.6 for BSC. This compares to the company's base case figures of 12.8 years for Respreeza and 9.5 years for BSC. Even though the survival benefit in the ERG's model is only slightly

longer than in the company's analysis, the absolute life years in both treatment arms is radically different. The ERG's analysis is a close approximation than the company's analysis to the survival shown in the AlphaNet-ADAPT study. Despite the ERG's model predicting higher survival (in absolute and incremental terms), the ERG's ICER increased in scenario 6. Comparing scenario 0 with scenario 6 in Table 7, it can be observed that even though QALYs increased in both treatment arms in the ERG's scenario, the incremental QALY gain is slightly smaller. Respreeza costs increased substantially in scenario 6 compared to scenario 0 as patients live longer in the ERG's model and also don't get lung transplants (and therefore are on treatment until death). Perhaps counterintuitively, BSC costs decreased in scenario 6 compared with scenario 0. This is related to removing lung transplant costs in the model: in the company's base case the main source of costs in the BSC arm are lung transplant costs (£36,270 compared to £18,960 for disease management costs), whereas in the ERG's scenario 6 the only cost associated with BSC are disease management costs, which increased from £18,960 in the company's base case analysis to £49,725 in the ERG's scenario 6.

Table 7. 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 base case (using 3.5% discount rates)**			
	Total costs (£)	£524,220	£55,230	£468,991
	QALYs	7.277	5.594	1.683
	ICER			**£278,615**
1	**Removing the option to adjust utilities in the model and correcting the implementation error related with the latter**			
	Total costs (£)	£524,220	£55,230	£468,991
	QALYs	6.679	5.098	1.581
	ICER			**£296,642**
2	**Using meta-analysis results for observational studies**			
	Total costs (£)	£523,085	£55,230	£467,855
	QALYs	7.284	5.594	1.690
	ICER			**£276,854**
3	**Including BSC costs in both treatment arms of the model**			
	Total costs (£)	£525,508	£56,165	£469,342
	QALYs	7.277	5.594	1.683
	ICER			**£278,824**
4	**Changing the resource use based on patients with an FEV1≥50% seeing a specialist twice per year, patients with a ≥30%FEV1<50% seeing a specialist three times per year, and patients with an FEV1<30% seeing a specialist four times per year**			
	Total costs (£)	£526,319	£56,811	£469,507
	QALYs	7.277	5.594	1.683
	ICER			**£278,922**
5	**Adding the annual cost of a CT scan per patient in both treatment arms of the model**			
	Total costs (£)	£524,991	£55,790	£469,201
	QALYs	7.277	5.594	1.683

Analysis from list	Results per patient	Respreeza (1)	Best supportive care (2)	Incremental value (1-2)
	ICER		**£278,740**	
6	**Using the AlphaNet-ADAPT survival analysis and removing lung transplants**			
	Total costs (£)	£1,021,765	£49,725	£972,040
	QALYs	10.702	9.141	1.562
	ICER		**£622,401**	
7	**Using the committee-accepted survival estimates for post-lung transplant**			
	Total costs (£)	£521,723	£52,741	£468,982
	QALYs	7.033	5.368	1.664
	ICER		**£281,756**	
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.				

Table 8 presents the cumulative ICERs, including the ERG's preferred assumptions in the economic model. The ICER incorporating all the ERG's preferred assumptions amounts to £648,948 per QALY gained if it is assumed that augmentation therapy has an effect on FEV1 decline. If it is assumed that augmentation therapy does not have an impact on FEV1 (as discussed in Section 1.1.1.), the corresponding ICER incorporating all the ERG's preferred assumptions amounts to £846,350 per QALY gained.

When the gamma distribution is used in the survival analysis, and assuming that augmentation therapy has an effect on FEV1 decline, the ICER incorporating all the ERG's preferred assumptions amounts to £625,195 per QALY gained (with a survival benefit of [redacted] years). If it is assumed that augmentation therapy does not have an impact on FEV1, the corresponding ICER amounts to £805,137 per QALY gained.

The ERG advises that the clinical plausibility of the absolute survival estimates predicted in the ERG's preferred scenario are discussed by the committee, together with the underlying assumption that patients could be on Respreeza for approximately 26 years as these are the key drivers in terms of costs and benefits.

The ERG also remains concerned with the estimation of Respreeza's treatment effect on lung density decline, given the use of unadjusted RAPID-OLE data analysis including cross-over patients. The company's decision to not provide the information requested by the ERG related to this issue essentially renders the company's analysis of treatment effectiveness a "black box".

Even though the new survival approach used by the ERG (i.e. using the AlphaNet-ADAPT data) mitigated some concerns around the weak sources of evidence in the economic model, the effect of Respreeza on FEV1 and lung density decline, and the clinical thresholds used to define the latter, are still important drivers of the economic analysis. The ERG remains concerned that the cost of treatment

with Respreeza is likely to be underestimated in the model by not using a weighted cost by weight category from patients in RAPID. The ERG notes that patients' weight is a key driver of costs in the model (given it determines how many vials of Respreeza are needed per patient) and that the impact of weight increases, as time on treatment with Respreeza increases in the model.

Table 8. Cumulative results of ERG's exploratory analysis

	Results per patient	**Respreeza (1)**	**BSC (2)**	**Incremental value (1-2)**
0	**Company's base case**			
	Total costs (£)	£524,220	£55,230	£468,991
	QALYs	7.277	5.594	1.683
	ICER	£278,615		
1	**Removing the option to adjust utilities in the model and correcting the implementation error related with the latter**			
	Total costs (£)	£524,220	£55,230	£468,991
	QALYs	6.679	5.098	1.581
	ICER (compared with base case)	£296,642		
	ICER with all changes incorporated	**£296,642**		
1+2	**Using meta-analysis results for observational studies**			
	Total costs (£)	£523,085	£55,230	£467,855
	QALYs	7.284	5.594	1.690
	ICER (compared with base case)	£276,854		
	ICER with all changes incorporated	**£294,818**		
1+2+3	**Including BSC costs in both treatment arms of the model**			
	Total costs (£)	£525,508	£56,165	£469,342
	QALYs	7.277	5.594	1.683
	ICER (compared with base case)	£278,824		
	ICER with all changes incorporated	**£295,036**		
1+2+3+4	**Changing the resource use based on patients with an FEV1≥50% seeing a specialist twice per year, patients with a ≥30%FEV1<50% seeing a specialist three times per year, and patients with an FEV1<30% seeing a specialist four times per year**			
	Total costs (£)	£526,319	£56,811	£469,507
	QALYs	7.277	5.594	1.683
	ICER (compared with base case)	£278,922		
	ICER with all changes incorporated	**£295,360**		
1+2+3+4+5	**Adding the annual cost of a CT scan per patient in both treatment arms of the model**			
	Total costs (£)	£524,991	£55,790	£469,104
	QALYs	7.277	5.594	1.683
	ICER (compared with base case)	£278,740		
	ICER with all changes incorporated	**£295,491**		
1+2+3+4+5+6	**Using the AlphaNet-ADAPT survival analysis and removing lung transplants (lognormal distribution)**			

	Results per patient	Respreeza (1)	BSC (2)	Incremental value (1-2)
	Total costs (£)	£1,021,765	£49,725	£972,040
	QALYs	10.702	9.141	1.562
	ICER (compared with base case)	£622,401		
	ICER with all changes incorporated	**£648,948**		
1+2+3+4+5+6+ alternative distribution	**Using the AlphaNet-ADAPT survival analysis and removing lung transplants (gamma distribution)**			
	Total costs (£)	£1,033,133	£49,860	£983,273
	QALYs	10.801	9.160	1.641
	ICER (compared with base case)	£599,352		
	ICER with all changes incorporated	**£625,195**		
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.				

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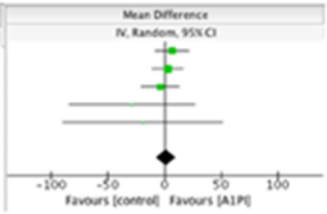
5 APPENDICES

5.1 Forest plot of company's updated meta-analysis (reproduced from response to clarification questions)

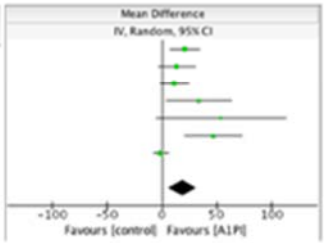
< 30%

Study or Subgroup	A1PI Mean	A1PI SD	A1PI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Seersholm et al., 1997	-24.2	23.4	75	-30.9	36.4	27	33.1%	6.70 [-8.02, 21.42]
AATD Registry Study ...	-43.9	63.5	349	-46.5	61.7	99	37.3%	2.60 [-11.26, 16.46]
Wencker et al., 2001	-19	18	25	-15.3	38.5	25	25.8%	-3.70 [-20.36, 12.96]
Chapman et al., 2005	-57.8	60.6	5	-28.7	45.2	29	2.3%	-29.10 [-84.71, 26.51]
Tonelli et al., 2009	0.86	96.6	30	20.1	53.8	3	1.5%	-19.24 [-89.25, 50.77]
Total (95% CI)			484			183	100.0%	1.28 [-7.19, 9.74]



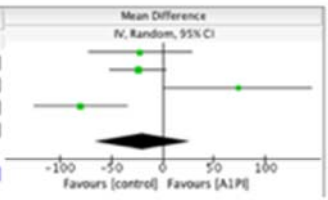
30-65%

Study or Subgroup	A1PI Mean	A1PI SD	A1PI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Seersholm et al., 1997	-61.8	25.4	112	-82.8	49.5	58	18.1%	21.00 [7.42, 34.58]
AATD Registry Study ...	-69.9	59.6	211	-83.5	61.7	66	16.3%	13.60 [-3.32, 30.52]
Wencker et al., 2001	-37.8	24.8	60	-49.3	43.4	60	18.6%	11.50 [-1.15, 24.15]
Chapman et al., 2005	-23.3	51.5	15	-57	66.7	79	10.2%	33.70 [3.77, 63.63]
Tonelli et al., 2009	2.08	213.6	79	-51.92	57.4	10	3.9%	54.00 [-5.03, 113.03]
Barros-Tizón et al., ...	-20	20	36	-67	60	21	11.5%	47.00 [20.52, 73.48]
Chapman et al., 2015	-19	5.6	93	-18	30.8	87	21.4%	-1.00 [-7.57, 5.57]
Total (95% CI)			606			381	100.0%	18.90 [6.06, 31.74]



> 65%

Study or Subgroup	A1PI Mean	A1PI SD	A1PI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Seersholm et al., 1997	-162	28.9	11	-140	83.1	12	24.6%	-22.00 [-72.02, 28.02]
AATD Registry Study ...	-63	58.7	21	-39.2	69	152	30.5%	-23.80 [-51.20, 3.60]
Wencker et al., 2001	-48.9	55.1	11	-122.5	108.5	11	19.0%	73.60 [1.69, 145.51]
Tonelli et al., 2009	-108.77	67	15	-29.24	79.4	27	25.9%	-79.53 [-124.77, -34.29]
Total (95% CI)			58			202	100.0%	-19.30 [-66.44, 27.85]



Total

Study or Subgroup	A1PI Mean	A1PI SD	A1PI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Seersholm et al., 1997	-53	38	198	-74.5	60.1	97	16.3%	21.50 [8.42, 34.58]
AATD Registry Study ...	-51.8	65.1	581	-56	67.7	317	18.3%	4.20 [-4.94, 13.34]
Dirksen et al., 1999	-78.9	63.5	28	-59.1	63	28	7.5%	-19.80 [-52.93, 13.33]
Wencker et al., 2001	-34.3	29.4	96	-49.2	60.7	96	16.0%	14.90 [1.41, 28.39]
Chapman et al., 2005	-26.7	55.4	21	-59	83.7	143	9.4%	32.30 [4.92, 59.68]
Tonelli et al., 2009	10.61	238	124	-36.96	76.8	40	4.4%	47.57 [-0.61, 95.75]
Barros-Tizón et al., ...	-20	20	36	-67	60	21	9.8%	47.00 [20.52, 73.48]
Chapman et al., 2015	-19	30.9	93	-18	30.8	87	18.3%	-1.00 [-10.02, 8.02]
Total (95% CI)			1177			829	100.0%	14.70 [3.33, 26.08]

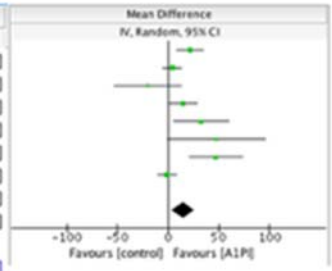


Table 1. Cumulative results of ERG's exploratory analysis

	Results per patient	Respreeza (1)	BSC (2)	Incremental value (1-2)
0	**Company's base case**			
	Total costs (£)	£524,220	£55,230	£468,991
	QALYs	7.277	5.594	1.683
	ICER	£278,615		
1	**Removing the option to adjust utilities in the model and correcting the implementation error related with the latter**			
	Total costs (£)	£524,220	£55,230	£468,991
	QALYs	6.679	5.098	1.581
	ICER with all changes incorporated	**£296,642**		
1+2	**Using meta-analysis results for observational studies**			
	Total costs (£)	£523,085	£55,230	£467,855
	QALYs	6.685	5.098	1.587
	ICER with all changes incorporated	**£294,818**		
1+2+3	**Including BSC costs in both treatment arms of the model**			
	Total costs (£)	£524,367	£56,165	£468,202
	QALYs	6.685	5.098	1.587
	ICER with all changes incorporated	**£295,036**		
1+2+3+4	**Changing the resource use based on patients with an FEV1≥50% seeing a specialist twice per year, patients with a ≥30%FEV1<50% seeing a specialist three times per year, and patients with an FEV1<30% seeing a specialist four times per year**			
	Total costs (£)	£526,463	£57,747	£468,716
	QALYs	6.685	5.098	1.587
	ICER with all changes incorporated	**£295,360**		
1+2+3+4+5	**Adding the annual cost of a CT scan per patient in both treatment arms of the model**			
	Total costs (£)	£527,231	£58,307	£468,924
	QALYs	6.685	5.098	1.587
	ICER with all changes incorporated	**£295,491**		
1+2+3+4+5+6	**Using the AlphaNet-ADAPT survival analysis and removing lung transplants (lognormal distribution)**			
	Total costs (£)	£1,031,724	£58,597	£973,127
	QALYs	9.690	8.190	1.500
	ICER with all changes incorporated	**£648,948**		
1+2+3+4+5+6+ alternative distribution	**Using the AlphaNet-ADAPT survival analysis and removing lung transplants (gamma distribution)**			
	Total costs (£)	£1,043,218	£58,758	£984,460
	QALYs	9.783	8.209	1.575
	ICER with all changes incorporated	**£625,195**		

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 2. Cumulative results of ERG's exploratory analysis with the impact of ERG's survival analysis and lung transplants removal disentangled

	Results per patient	**Respreeza (1)**	**BSC (2)**	**Incremental value (1-2)**
1+2+3+4+5	**All ERG's changes described in the ERG report**			
	Total costs (£)	£527,231	£58,307	£468,924
	QALYs	6.685	5.098	1.587
	ICER with all changes incorporated	**£295,491**		
1+2+3+4+5+removing lung transplant from the model (and use company's survival analysis)				
	Total costs (£)	£572,678	£25,862	£546,816
	QALYs	5.415	3.831	1.584
	ICER with all changes incorporated	**£345,124**		
1+2+3+4+5+using the AlphaNet-ADAPT survival analysis (and include lung transplants in the model)				
	Total costs (£)	£706,157	£104,296	£601,861
	QALYs	9.479	8.205	1.273
	ICER with all changes incorporated	**£472,684**		
1+2+3+4+5+removing lung transplant from the model+using the AlphaNet-ADAPT survival analysis				
	Total costs (£)	£1,031,724	£58,597	£973,127
	QALYs	9.690	8.190	1.500
	ICER with all changes incorporated	**£648,948**		
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.				

Removing lung transplants from the model leads to an increase in the ICER of 17%, while using the AlphaNet-ADAPT survival data leads to an increase of 60% in the ICER (using the £295,491 ICER as reference). Both changes combined lead to an increase of 120% in the ICER. Please note that the impact of combining these two changes does not have a linear impact on the final ICER.

Table 3. Discounted and undiscounted QALY gain

	Discounted	Undiscounted
Company submission	1.683	2.369
ERG exploratory analysis	1.500	2.766