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Supplementary appendix

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Supplement to: Chapman KR, Burdon JGW, Piitulainen E, et al, on behalf of the RAPID Trial Study Group. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015; published online May 28. http://dx.doi.org/10.1016/S0140-6736(15)60860-1.

Supplementary Appendix

Intravenous Augmentation Therapy Preserves Lung Density in Severe Alpha-1 Antitrypsin Deficiency; The Randomized, Placebo-Controlled RAPID Trial

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Variability of CT scan data acquired during the RAPID trial at different levels of inspiration

Previous publications have now consistently shown that CT lung density measured at TLC is less variable than when measured at FRC[1,2]. This was confirmed during the RAPID trial, in which the standard deviations for PD15 values were lowest at TLC (Table S1).

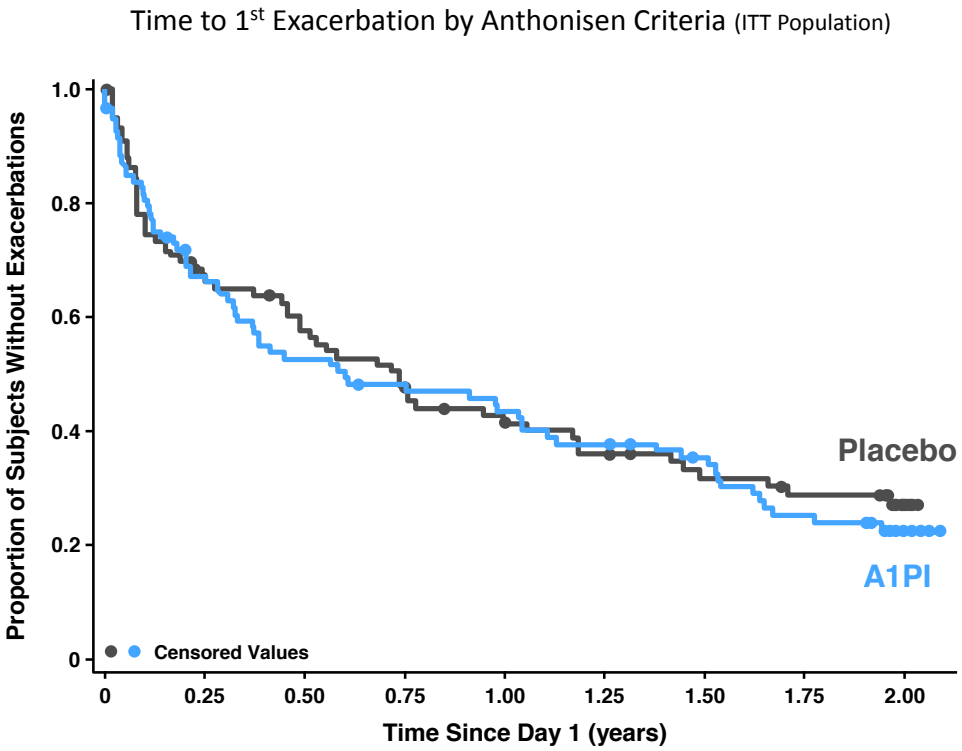
Table S1 Unadjusted PD15 values in g/L at baseline and Month 24 (study end) at the TLC, FRC, and TLC plus FRC combined states in the RAPID study (ITT population)

	Mean (Standard Deviation)	
Lung volume	**Baseline (n = 173)**	**Month 24 (n = 151)**
TLC	41.2 (16.2)	38.1 (14.9)
FRC	55.2 (23.2)	52.0 (22.6)
TLC/FRC	48.2 (19.1)	45.2 (18.5)

FRC = Functional residual capacity; ITT = Intention-to-treat; N = Maximum number of scans; P15 = 15th percentile of the frequency histogram of the lung voxels; TLC = Total lung capacity.

Exacerbations

The time to first exacerbation did not differ between treatment groups. Cox proportional hazards model estimation of the time to first exacerbation (as defined by Anthonisen criteria[3]) in the intention to treat population was not different between the treatment groups [HR 1.2 (0.82 - 1.69) p = 0.371] – see Figure 1(suppl) below:



A_1-PI extends the time to terminal respiratory function compared to placebo

The efficacy of A_1-PI observed in RAPID is clinically meaningful because slowing the loss of lung tissue extends the time to terminal respiratory failure (leading to lung transplantation or death). To illustrate this, we performed a post-hoc analysis using data from a small number (n=5) of RAPID patients who underwent terminal respiratory failure. In this analysis, we estimate that the gain in life-years (extension in time to terminal respiratory failure) in patients receiving A_1-PI may reach approximately 6 years when compared with that on placebo – with placebo the rate of lung density decline is not reduced (Table S2).

Table S2 Extrapolation of A_1-PI effect on the time to reach putative terminal respiratory function (data from the RAPID trial)

	A_1-PI (N=93)	**Placebo (N=87)**
Baseline lung density at TLC state (g/L)	47.1	
Annual change in lung density at TLC state (g/L/year)	-1.5	-2.2
Lung density at terminal respiratory function (g/L)	20	
Change in lung density to terminal respiratory function (g/L)	27.1	
Time to terminal respiratory function (y)	**18.1**	**12.3**

N = Number of subjects; TLC = Total lung capacity
Formula used for calculation of time to terminal respiratory function/death:
Change in lung density to terminal respiratory function / annual change in lung density

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