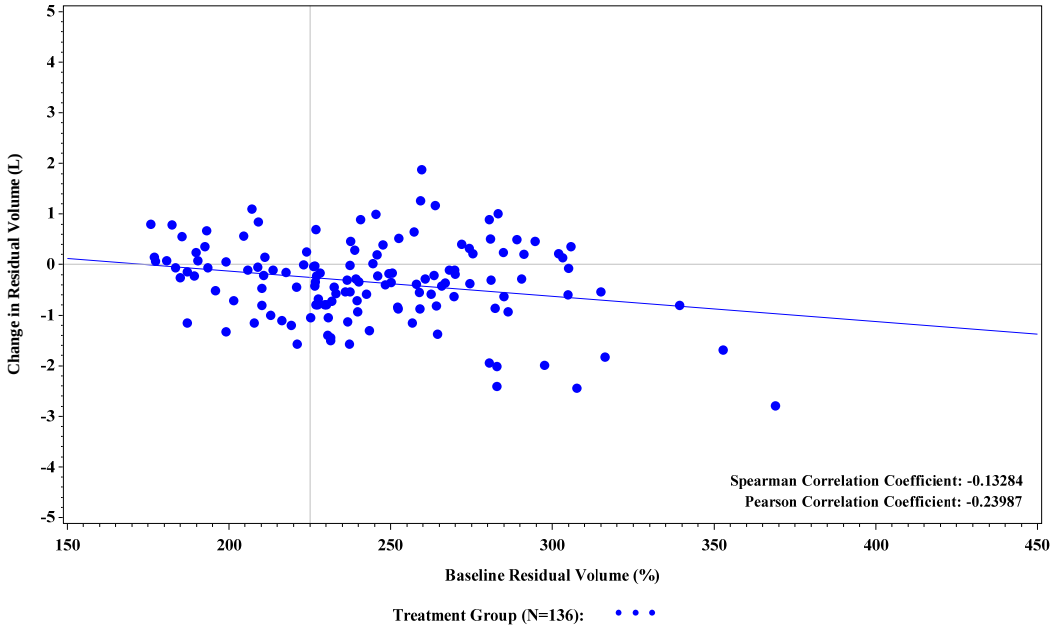
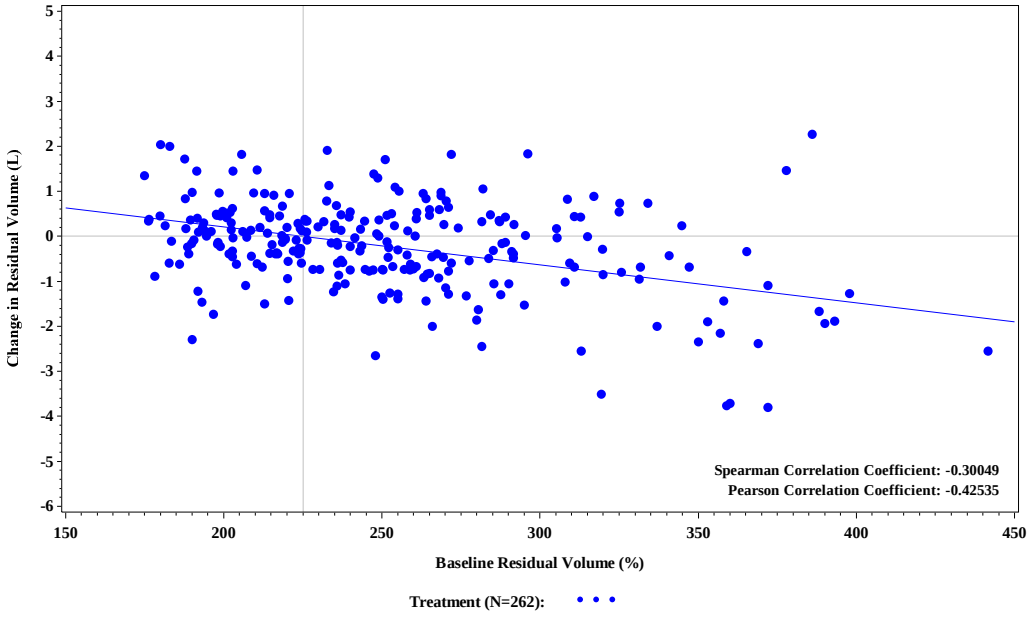
Residual Volume Reduction: Mechanistic Dependence on Baseline RV%pred

RENEW ITT (N=136)

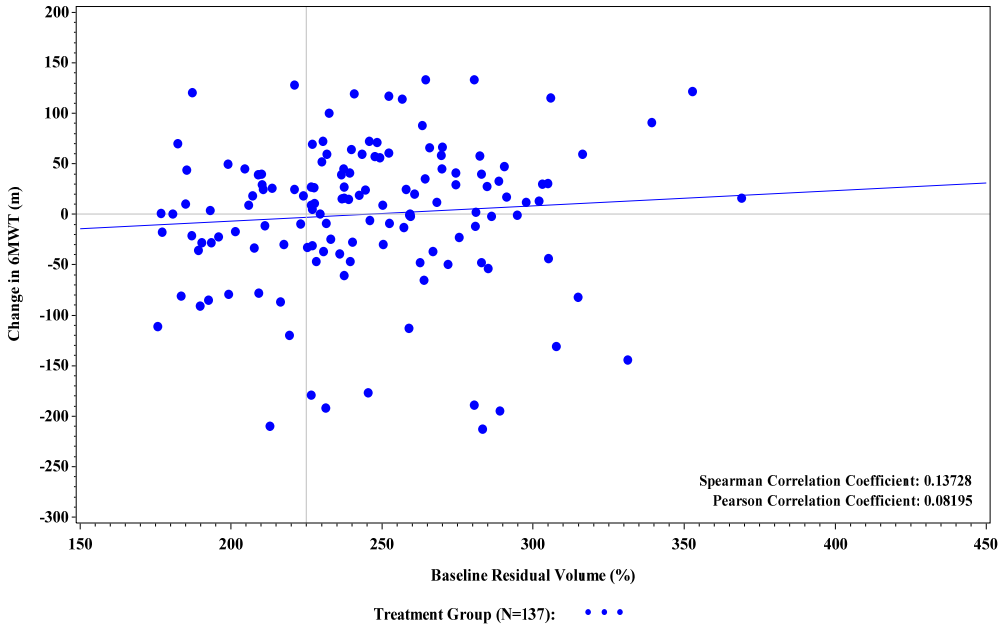


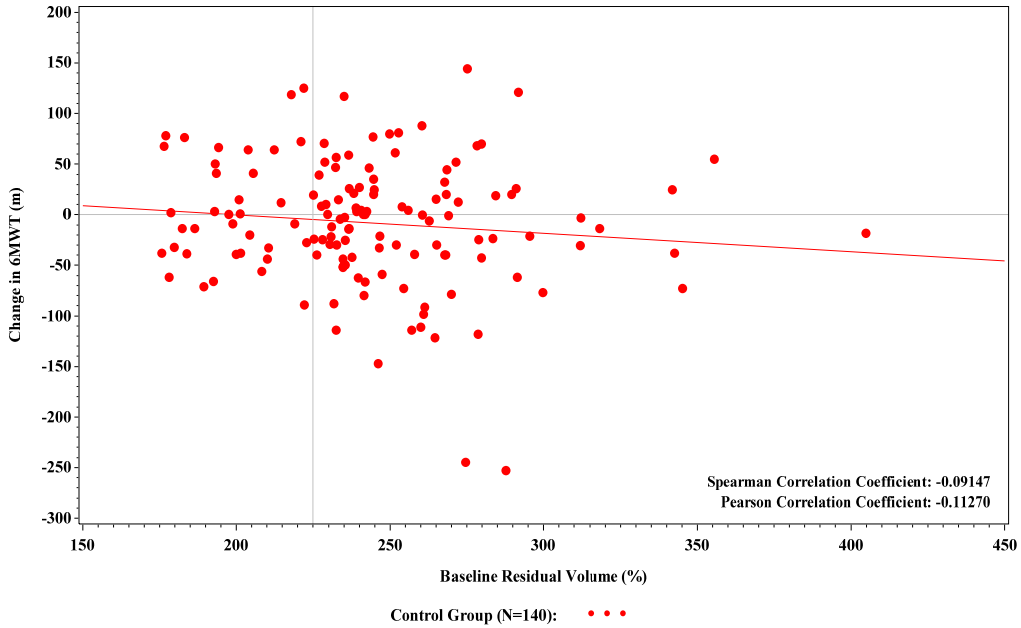
EU Registry (N=262)



Scatterplot of Change in 6MWT at 12 Months by Baseline RV

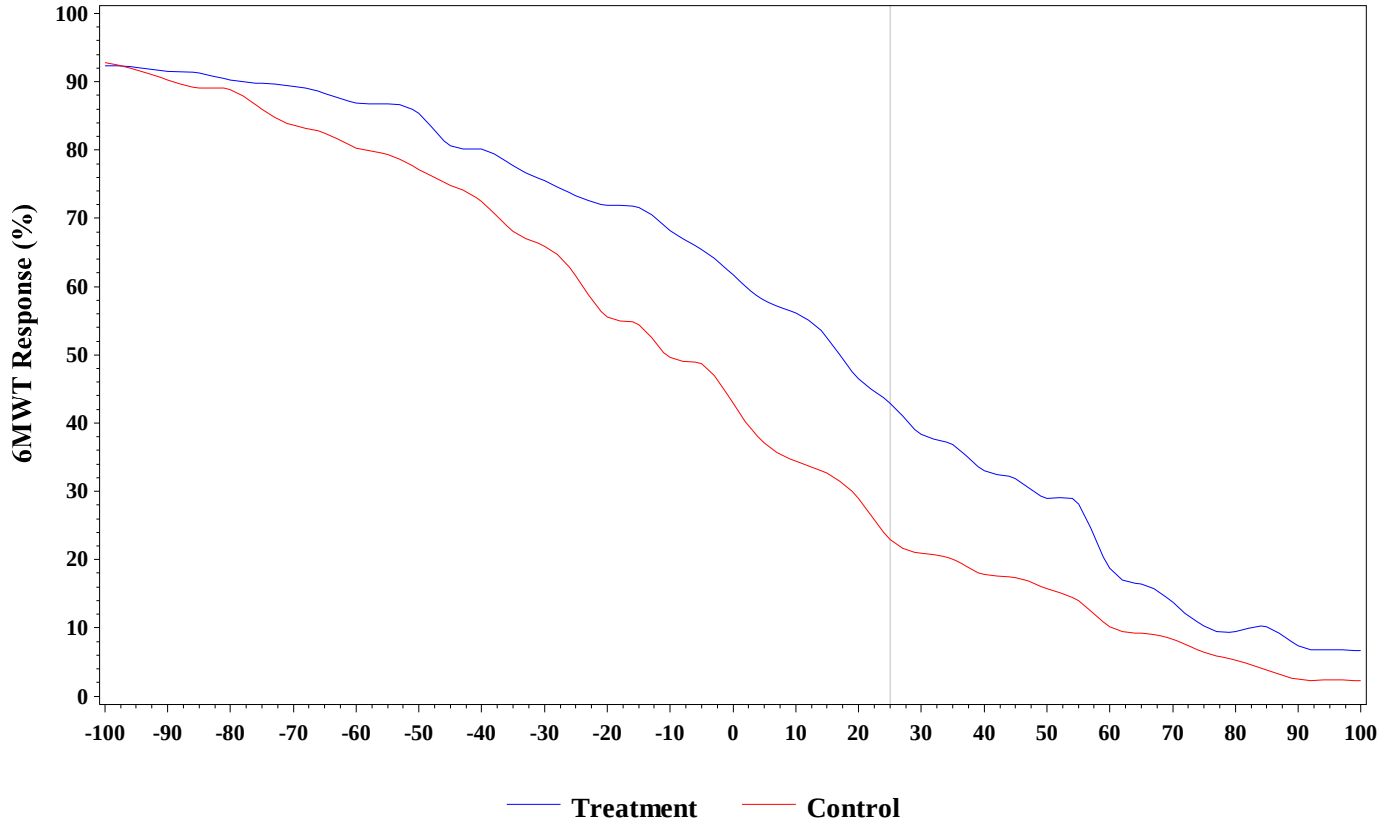
RENEW ITT Population





6MWT Responder by Thresholds

RENEW RV ≥225% (Full Range)



Based on MCMC imputation results of logistic regression with factors of treatment, baseline 6MWT and emphysema heterogeneity as covariates, with a random factor of analysis center.

Change in Effectiveness Endpoints at 12 Months Pneumonia and CAO Events

RENEW Randomized

	Treatment		Control	
	With pneumonia N=52	Without pneumonia N=106	With Pneumonia N=14	Without pneumonia N=143
Primary endpoint				
Median change in 6-minute walk distance (meters)	6.8	10.3	-19.5	-5.6
Secondary endpoints				
6-minute-walk distance responder rate, %	44.6	37.8	6.8	28.6
Median percent change in FEV_1, %	7.8	2.1	-3.0	-2.5
Mean change in SGRQ score	-7.7	-7.9	0.9	0.7

Pneumonia included the following preferred terms: Bronchopulmonary aspergillosis, Lower respiratory tract infection, Lung infection, Lung infection pseudomonal, Pneumonia, Pneumonia staphylococcal, Pseudomonas infection, Respiratory tract infection, Lung consolidation, Lung disorder, Medical device complication, Post procedural complication

All analyses conducted on the full ITT analysis set with multiple imputation. Mean (CI) from ANCOVA adjusted for covariates.
Responder rate (CI) from logistic regression adjusted for covariates.

Healthcare Utilization

RENEW Randomized

	12 Months prior to Baseline Subjects, n (%)		12 Months Subjects, n (%)	
	Treatment (N=155)	Control (N=157)	Treatment (N=155)	Control (N=157)
Hospitalization	49 (31.0)	43 (27.4)	85 (54.8)	50 (31.8)
Physician Office (Unscheduled)	35 (22.6)	27 (17.2)	69 (44.5)	59 (37.6)
Emergency Room	16 (10.3)	14 (8.9)	27 (17.4)	13 (8.3)

Correlation of SGRQ with Objective Measures

RENEW Randomized

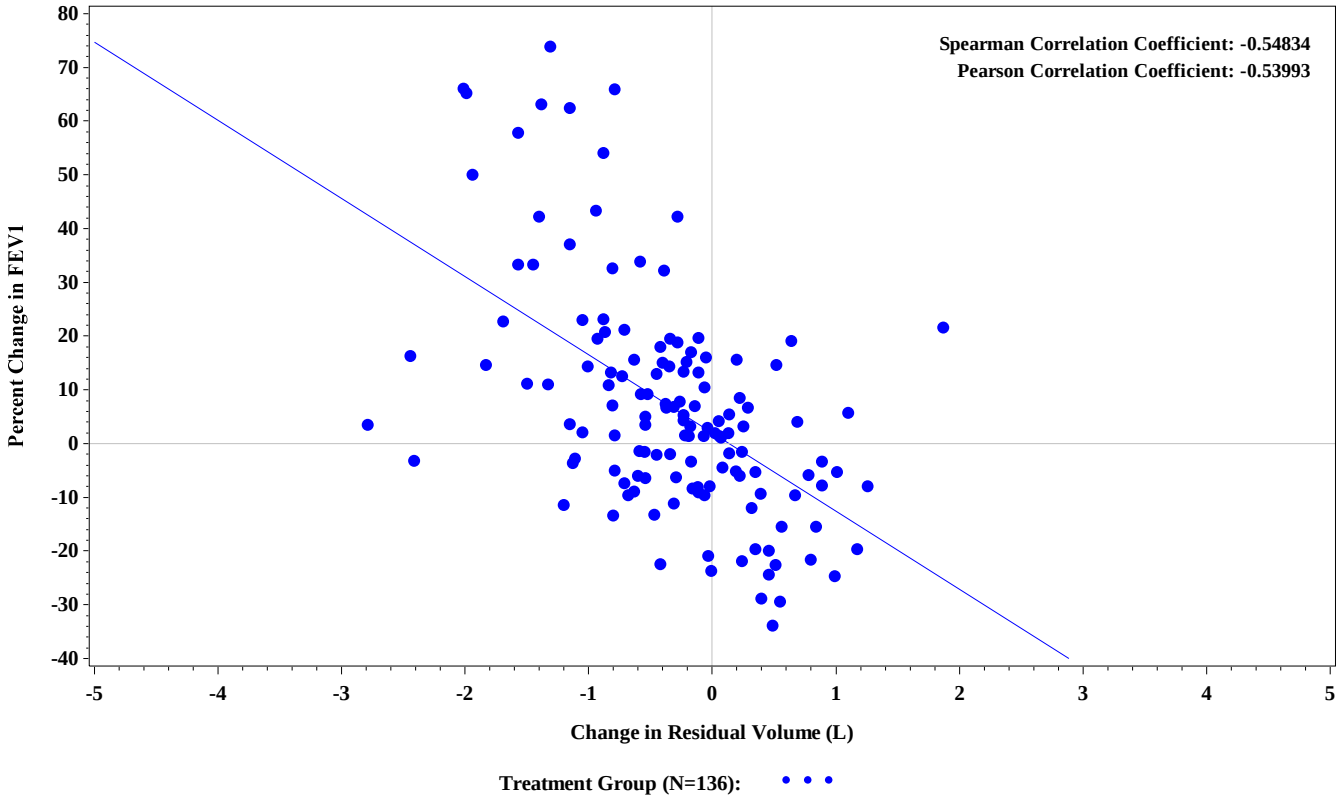
- Correlation of SGRQ with more objective measures assessed (RENEW, 12 months)
- Benefit in SGRQ correlated significantly with lung function and exercise capacity outcomes

		Treatment group (12 months)			
Endpoint	Correlation	6MWT N=137	FEV_1 N=137	RV N=136	RV/TLC N=136
SGRQ	Spearman correlation coefficient, r (n)	-0.393*	-0.249*	0.163	0.224*
	Pearson correlation coefficient, r (n)	-0.361*	-0.284*	0.151	0.274*

Analysis limited to subjects with non-missing values at 12 months (complete cases).
*** Indicates correlation coefficient is statistically significant.**

Scatterplot of Percent Change in FEV_1 at 12 Months by Change in RV

RENEW-ITT Population



Reduce hyperinflation

↓ RV

Improve lung function

↑ FEV_1

Improve patient function

↓ SGRQ

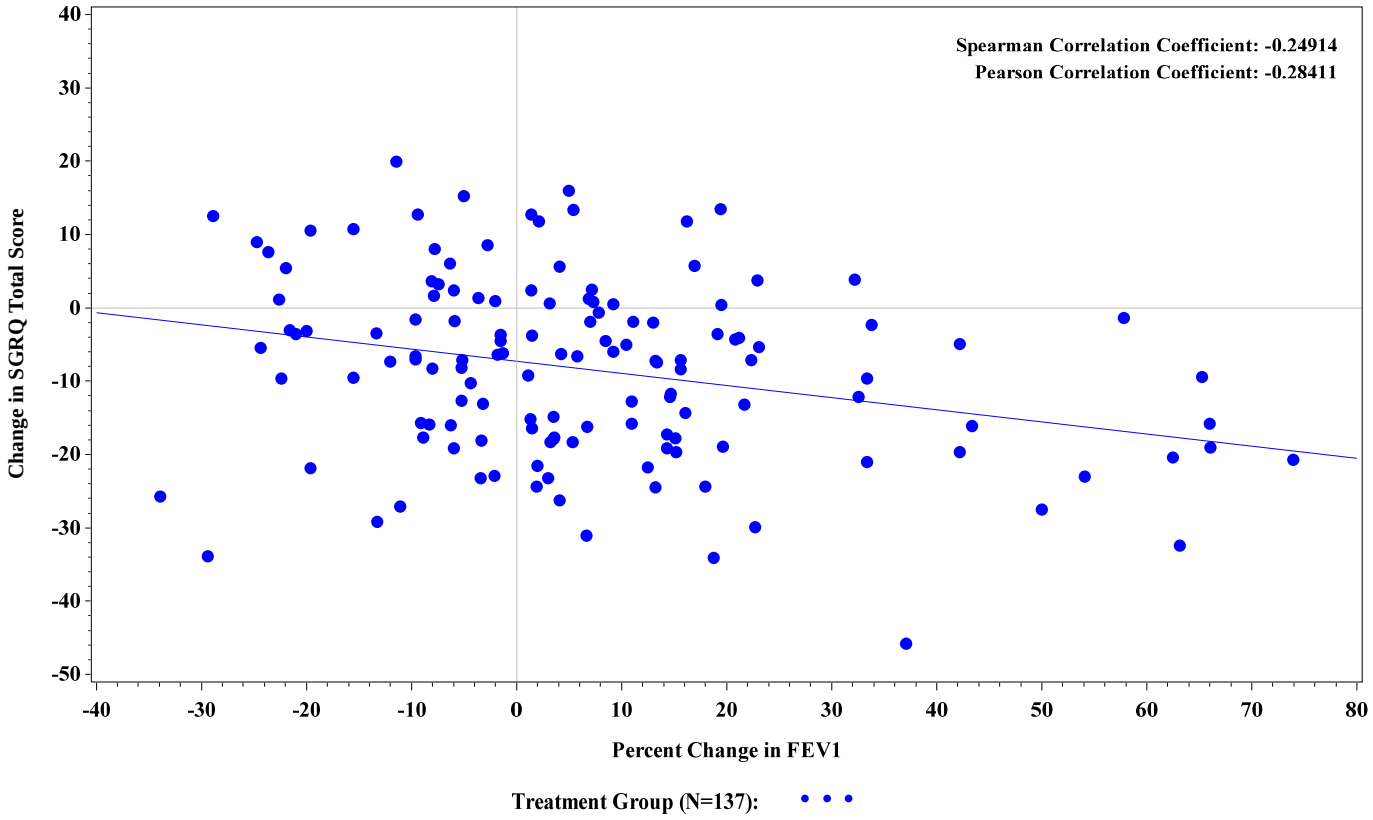
Quality of Life

↑ 6MWT

Exercise capacity

Scatterplot of SGRQ at 12 Months by Change in % Change FEV1

RENEW-ITT Population



Reduce hyperinflation

↓ RV

Improve lung function

↑ FEV_1

Improve patient function

↓ SGRQ

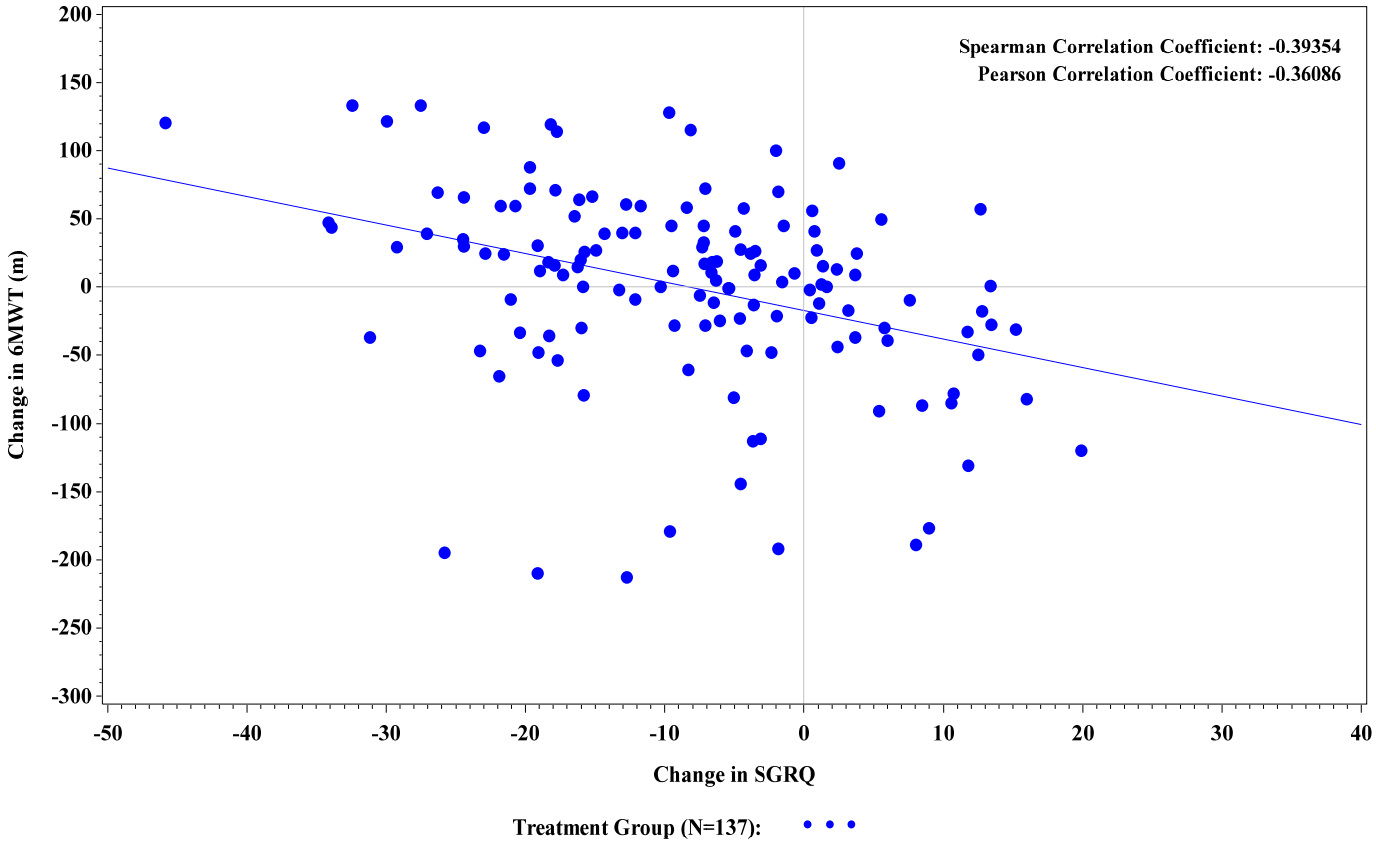
Quality of Life

↑ 6MWT

Exercise capacity

Scatterplot of Change in 6MWT at 12 Months by Change in SGRQ

RENEW-ITT Population



Reduce hyperinflation

↓ RV

Improve lung function

↑ FEV_1

Improve patient function

↓ SGRQ

Quality of Life

↑ 6MWT

Exercise capacity

ΔSGRQ-Δ6MWT Correlations: Comparison between RENEW and NETT

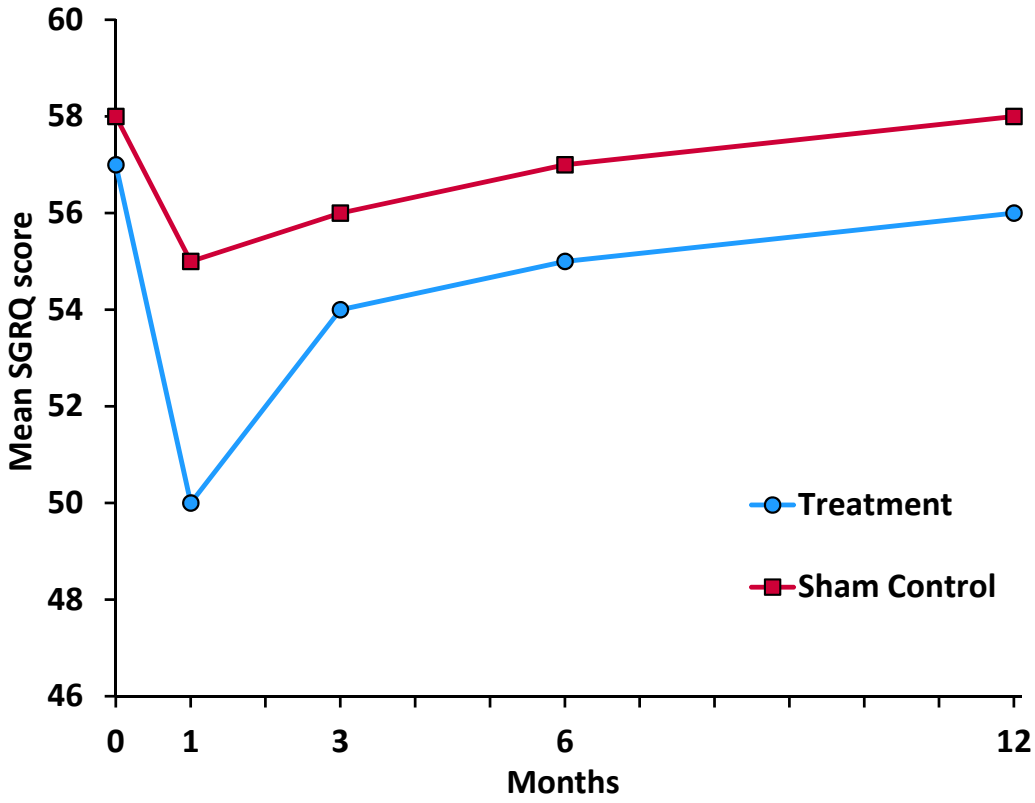
Correlation between Change in SGRQ and Change in 6MWT

	NETT 6-months post-randomization (N=1218)	**RENEW Treated** 12-months post-randomization (N=137)	
		Spearman	Pearson
ΔSGRQ Total	-0.46	-0.39	-0.36
ΔSGRQact	-0.46	-0.41	-0.45
ΔSGRQimp	-0.40	-0.30	-0.21
ΔSGRQsym	-0.18	-0.26	-0.24

*Puhan et al., Eur Respir J 2011; 37: 784–790.

Sham Bronchoscopy in Severe Emphysema Patients: EASE Trial (Exhale Airway Stents for Emphysema)

Demographic[a]	Treatment N=209	Control N=107
Age, yr	64.1 (7.29)	65.2 (7.16)
Men	105 (50%)	56 (52%)
White ethnic origin	208 (100%)	104 (97%)
Smoking history, pack-years	57.65 (28.82)	56.67 (27.11)
BMI, kg/m^2	23.27 (3.97)	23.61 (3.69)
BODE index	5.96 (1.26)	5.93 (1.2)
FEV_1, liters	0.65 (0.19)	0.66 (0.21)
FEV_1, % predicted	23.23 (6.08)	23.55 (7.22)
FVC, liters	2.30 (0.68)	2.22 (0.60)
RV, liters	5.25 (1.16)	5.40 (1.24)
RV, % predicted	244.14 (52.81)	248.46 (51.35)
TLC, liters	7.64 (1.56)	7.70 (1.54)
RV/TLC ratio	0.69 (0.06)	0.70 (0.06)
DL_{CO}, % predicted	30.59 (11.45)	28.39 (10.44)
mMRC, 0-4	2.64 (0.62)	2.65 (0.57)
SGRQ, 0-100	56.6 (12.9)	58.04 (13.25)
Endurance cycle ergometry, sec	320 (235)	318 (220)
6-min walk test, meters	302 (88)	297 (85)



[a] Data are number of patients (%) or mean (SD).

Shah PL, et al. *Lancet*. 2011;378:997-1005.

Deaths in EASE Trial from Sham Bronchoscopy

	Airway bypass (n=208)	Sham control (n=107)
Participants having a composite safety event	30 (14·4%)	12 (11·2%)
Respiratory failure requiring mechanical ventilation for 24 h or longer	4 (1·9%)	0 (0%)
Pneumothorax requiring intercostal tube drainage for more than 7 days	2 (1·0%)	0 (0%)
Major haemoptysis	1 (0·5%)	0 (0%)
COPD or infection needing admission for longer than 7 days	22 (10·6%)	9 (8·4%)
Death at 30 days or earlier and respiratory death after 30 days	4 (1·9%)	4 (3·7%)

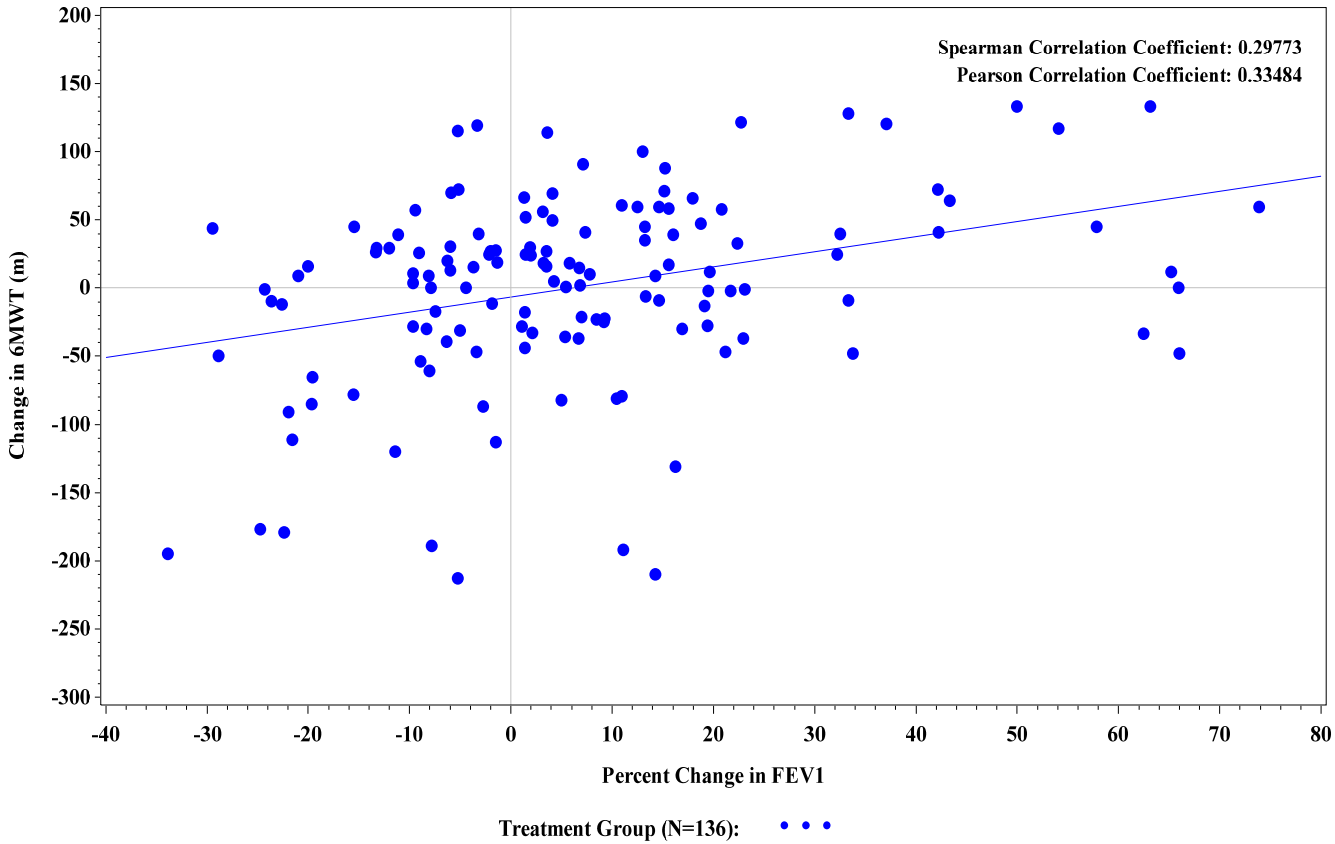
Data are number (%). Three patients assigned airway bypass and one allocated sham had several events. COPD=chronic obstructive pulmonary disease.

Table 4: **Composite primary safety endpoint, 6 months post procedure**

Shah PL, et al. *Lancet*. 2011;378:997-1005.

Scatterplot of Change in 6MWT at 12 Months by Change in % Change FEV1

RENEW-ITT Population



Reduce hyperinflation

↓ RV

Improve lung function

↑ FEV_1

Improve patient function

↓ SGRQ

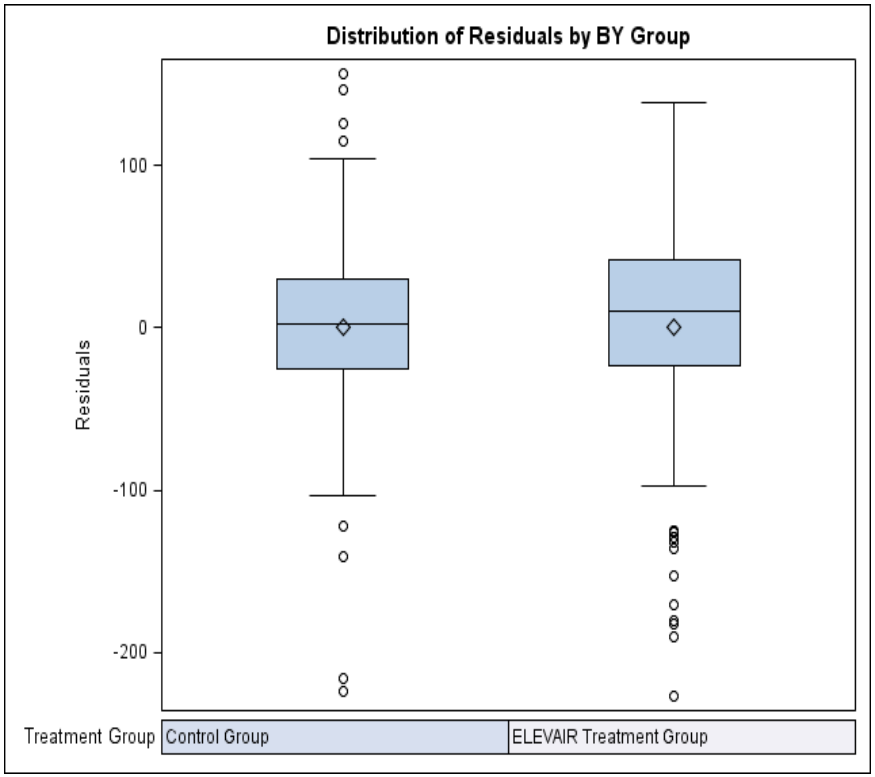
Quality of Life

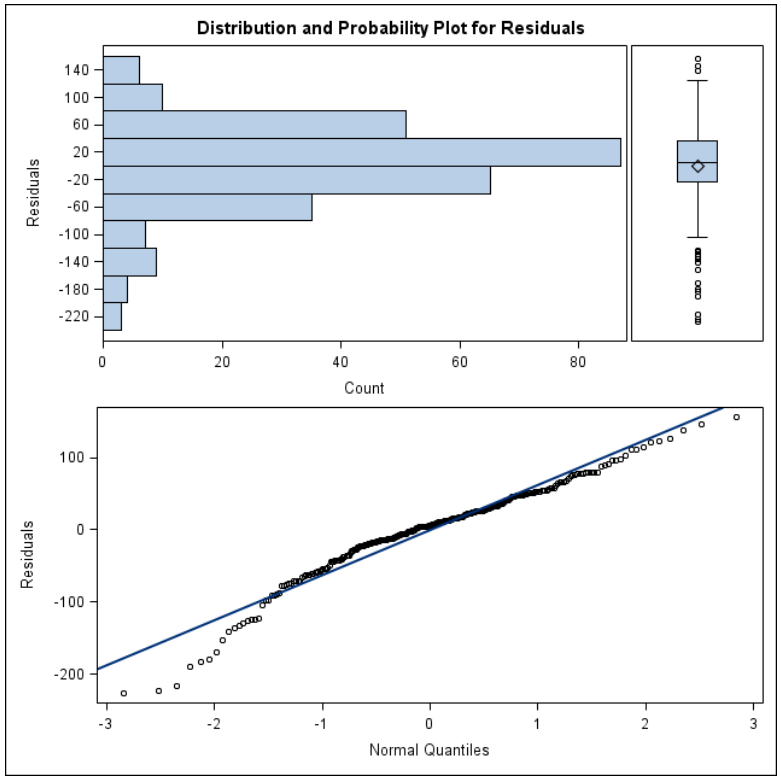
↑ 6MWT

Exercise capacity

Distribution of Change in 6MWT Residuals from ANCOVA

RENEW Randomized-ITT Population





Primary and Secondary Endpoints: Normality Test

RENEW Randomized-ITT Population

Effectiveness endpoints Shapiro-Wilk normality assumptions testing

Endpoint	ITT
Change in 6 MWT	<0.0001
Percent change in FEV_1	<0.0001
Change in SGRQ	0.6302

Includes non-missing (complete) cases only

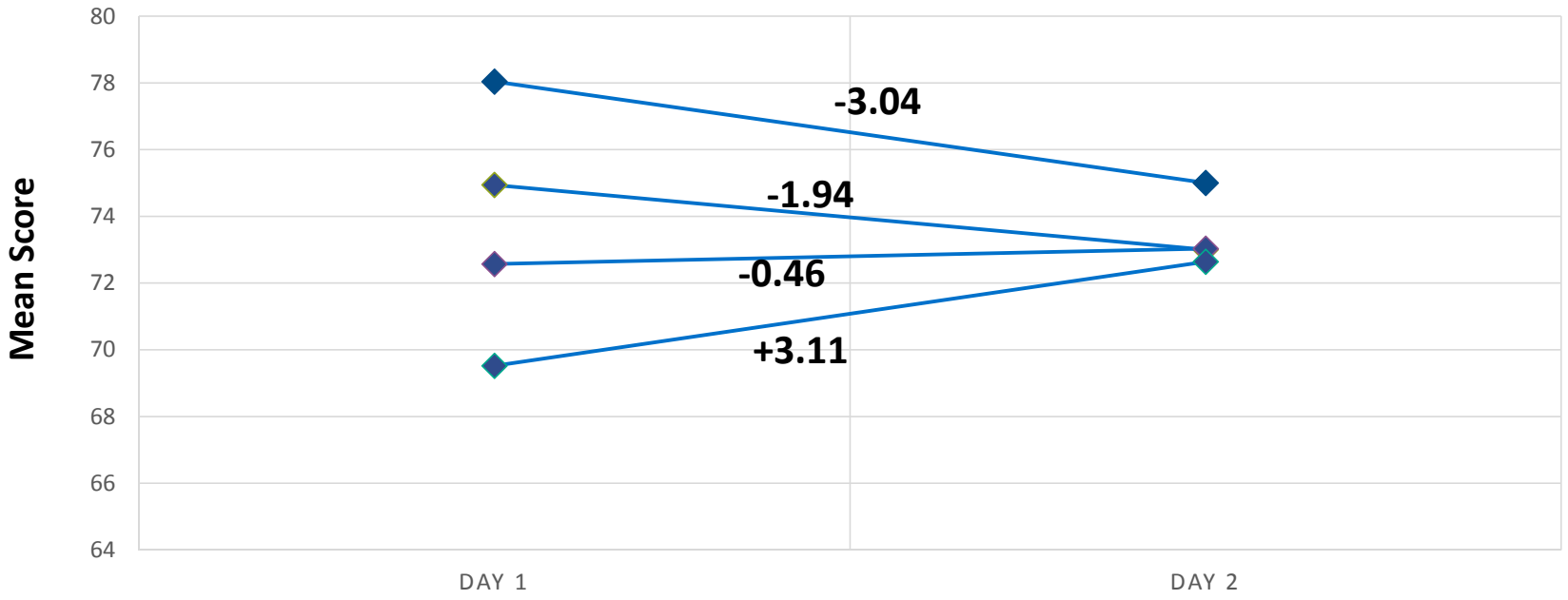
Poolability of RV ≥225% and RV <225% Effectiveness Results

RENEW-ITT population

Endpoint	P-value (Two-sided)
6MWT	0.0550 [a]
Rank-Transformed 6MWT	0.0373 [a]
6MWT Responder [b]	0.0299 [c]
Percent Change in FEV_1	0.0720 [d]
Rank-Transformed Percent Change in FEV_1	0.0467 [d]
SGRQ	0.0146 [e]

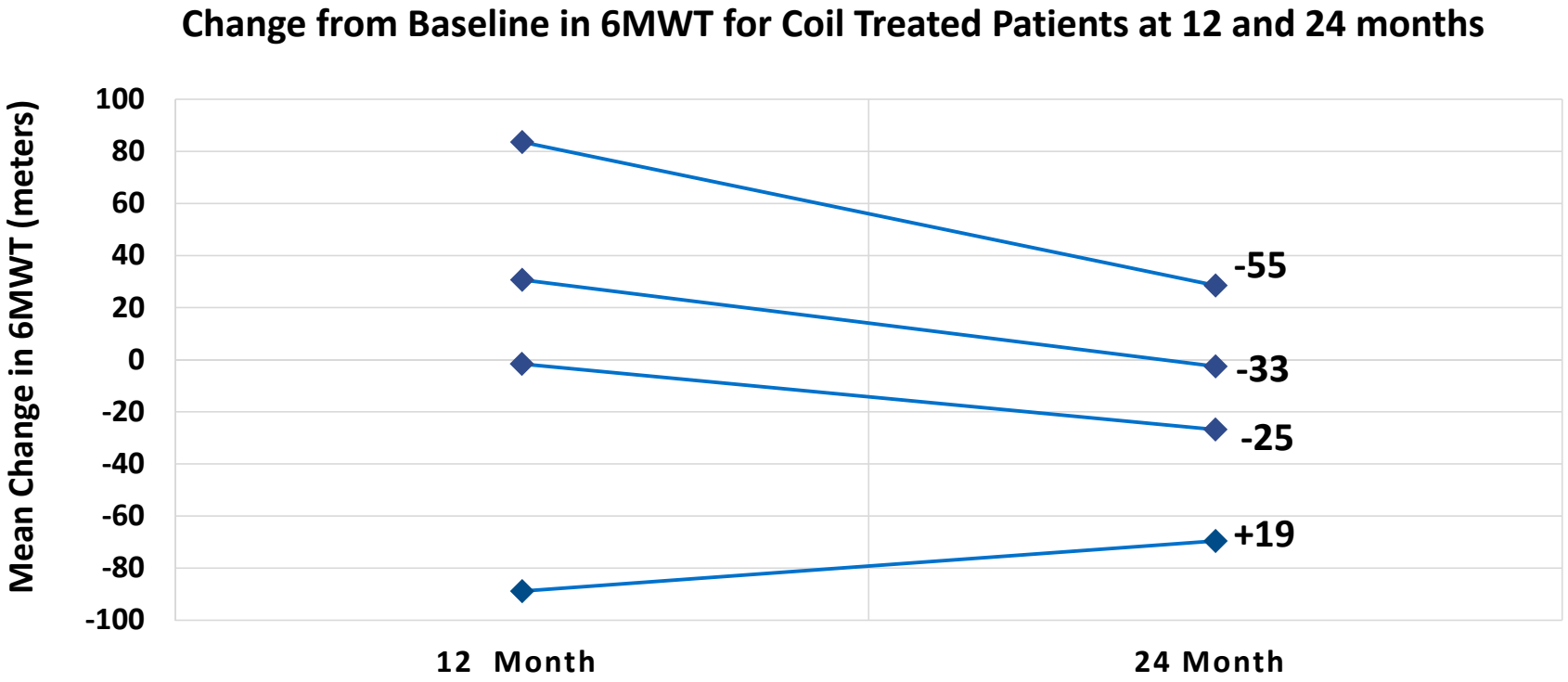
[a] Based on 'complete cases' and ANCOVA model with factors of treatment, RV, and the interaction term of treatment and RV and covariates of baseline 6MWT and emphysema heterogeneity. P-value (for interaction term) is based on two-sided test.
[b] Responder is defined as those with an improvement of greater than or equal to 25 meters in 6-minute walk test (6MWT).
[c] Based on 'complete cases' and logistic regression with factors of treatment, RV, and the interaction term of treatment and RV and covariates of baseline 6MWT and emphysema heterogeneity. P-value (for interaction term) is based on two-sided test.
[d] Based on 'complete cases' and ANCOVA model with factors of treatment, RV, and the interaction term of treatment and RV and covariates of baseline FEV1 and emphysema heterogeneity. P-value (for interaction term) is based on two-sided test.
[e] Based on 'complete cases' and ANCOVA model with factors of treatment, RV, and the interaction term of treatment and RV and covariates of baseline SGRQ and emphysema heterogeneity. P-value (for interaction term) is based on two-sided test.

Regression to the Mean: 2017 US Open



http://www.espn.com/golf/leaderboard?tournamentId=3066

Regression to the Mean: Coil Treated



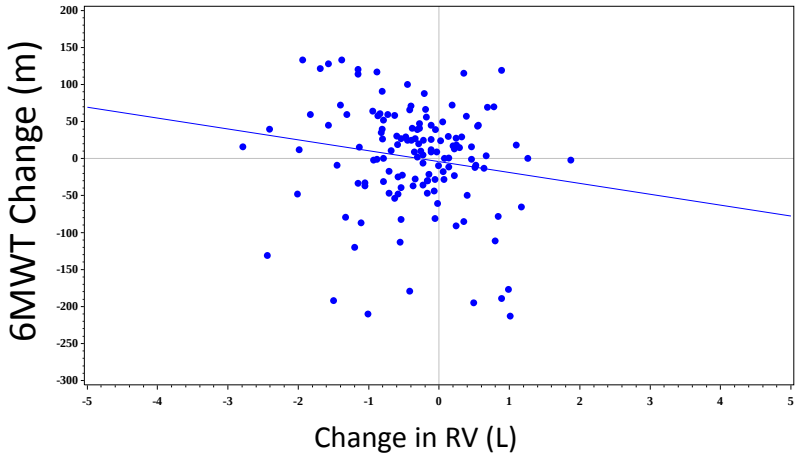
EU Registry Safety Summary - SAEs

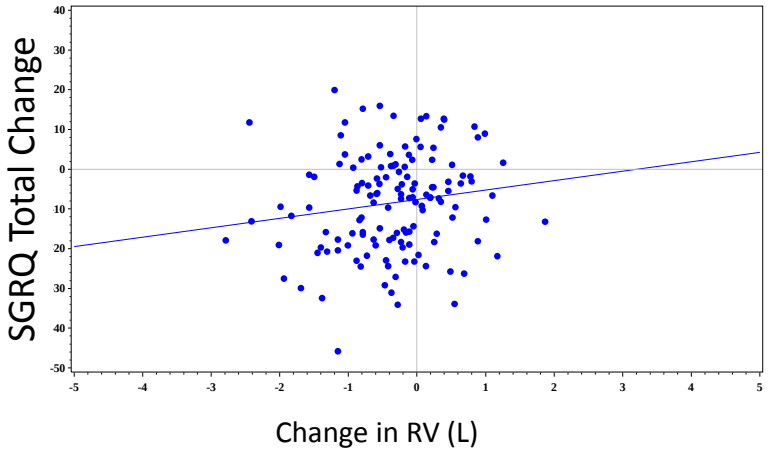
Table 8-117 Serious Adverse Events[1] [CLN0014]

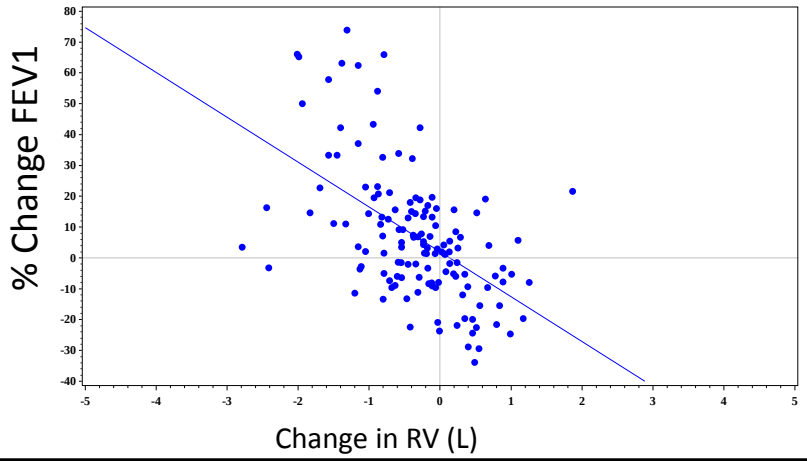
Serious Adverse Events	Treatment Recovery Period[2] (N=831)		Through 6 Months[3] (N=612)		Through 1 Year[4] (N=429)		Through 2 Years[5] (N=163)	
	Subjects n (%)[6]	Events	Subjects n (%)[6]	Events	Subjects n (%)[6]	Events	Subjects n (%)[6]	Events
Chronic Obstructive Pulmonary Disease	68 (7.99%)	71	161 (26.31%)	251	99 (23.08%)	162	52 (31.90%)	96
Pneumonia	25 (3.01%)	25	26 (4.25%)	28	14 (3.26%)	15	10 (6.13%)	10
Hemoptysis	23 (2.77%)	23	14 (2.29%)	16	6 (1.40%)	6	1 (0.61%)	1
Infection	16 (1.88%)	16	12 (1.96%)	15	7 (1.63%)	7	5 (3.07%)	5
Pneumothorax	30 (3.61%)	31	7 (1.14%)	8	2 (0.47%)	2	1 (0.61%)	1
Cardiac Disorder	2 (0.24%)	2	17 (2.78%)	1	8 (1.86%)	8	6 (3.68%)	6

1 SAEs reported by 2.5% or more of subjects in any time window are presented, in order of decreasing total event frequency.
2 Includes all subjects during the treatment recovery period (30 days post either treatment).
3 Includes all subjects with at least one follow-up visit at 6 months or later and all subjects who terminated during the 6-month follow-up window.
4 Includes all subjects with at least one follow-up visit at 1 year or later and all subjects who terminated during the 1-year follow-up window.
5 Includes all subjects with at least one follow-up visit at 2 years or later and all subjects who terminated during the 2-year follow-up window.
6 Subject data represented as n (n/N, in %), where n is the number of subjects with the event and N is the total number of subjects in that particular period. Subjects experiencing one or more AEs per event or category are only counted once per event category.

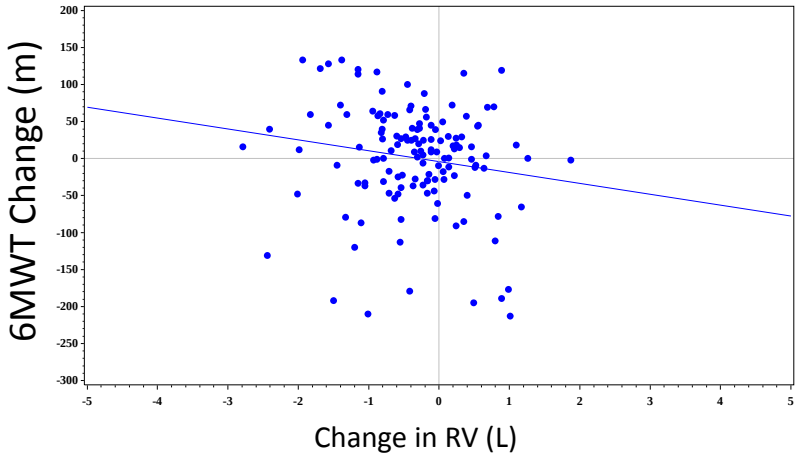
Scatterplot of Endpoints at 12 Months by Change in Residual Volume (L) - ITT Population (RENEW)

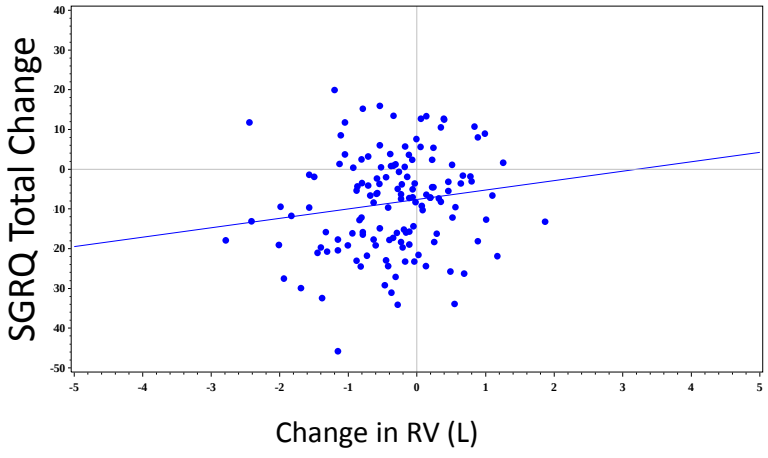


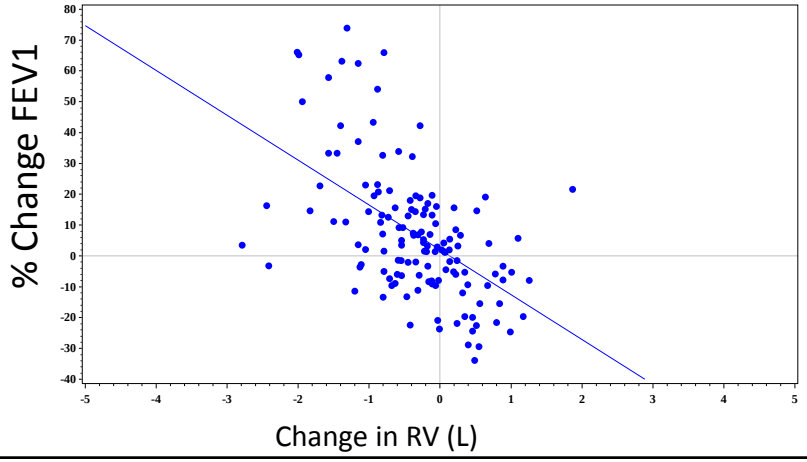




Scatterplot of Endpoints at 12 Months by Change in Residual Volume (L) - ITT Population (RENEW)

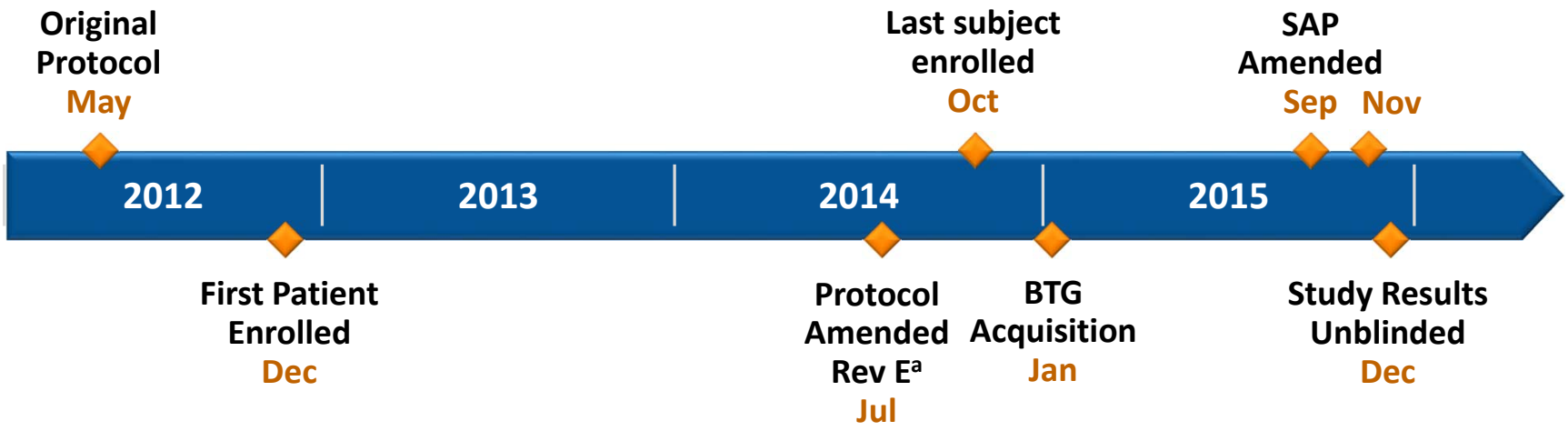






Correlation	Treatment Group (12 Months)		
	Change in 6MWT	Percent Change in FEV1	Change in SGRQ
Spearman correlation coefficient, r (n)	-0.1639	-0.5483	0.1625
Pearson correlation coefficient, r (n)	-0.1649	-0.5399	0.1513

RENEW Study Timeline and SAP Amendment



[a] Changed inclusion criterion for RV from ≥225% to ≥175% predicted.