

ELEVAIR™ Endobronchial Coil System Development and Effectiveness

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Overview of Effectiveness Presentation

- ELEVAIR™ Procedure and CT Lobe Selection
- RENEW Baseline Characteristics and Results
 - ITT
 - RV \geq 225% Predicted
- RENEW Subgroups and Long-Term Follow-Up
 - Region (US, OUS)
 - Disease Distribution (Heterogeneous, Homogeneous)
 - 24-Month Outcomes
- Other Studies and Analyses under the IDE Program
 - Crossover Single-Arm Study
- Summary and Discussion

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Overview of ELEVAIR™ Procedure for Severe Emphysema

- Our objective was to use ELEVAIR to reduce hyperinflation in patients ***with heterogeneous or homogeneous emphysema*** and severe hyperinflation, thereby improving lung function, quality of life, and exercise capacity
- The ELEVAIR Coil System is a minimally invasive, bronchoscopic lung volume reduction procedure
 - General anesthesia or conscious sedation
 - Discharged home next day
- Most damaged lobes are treated, independent of intact fissures
 - 10-14 Coils per lobe
 - Bilateral treatment in two 35- to 45-minute sessions

ELEVAIR™ Lung Volume Reduction Procedure

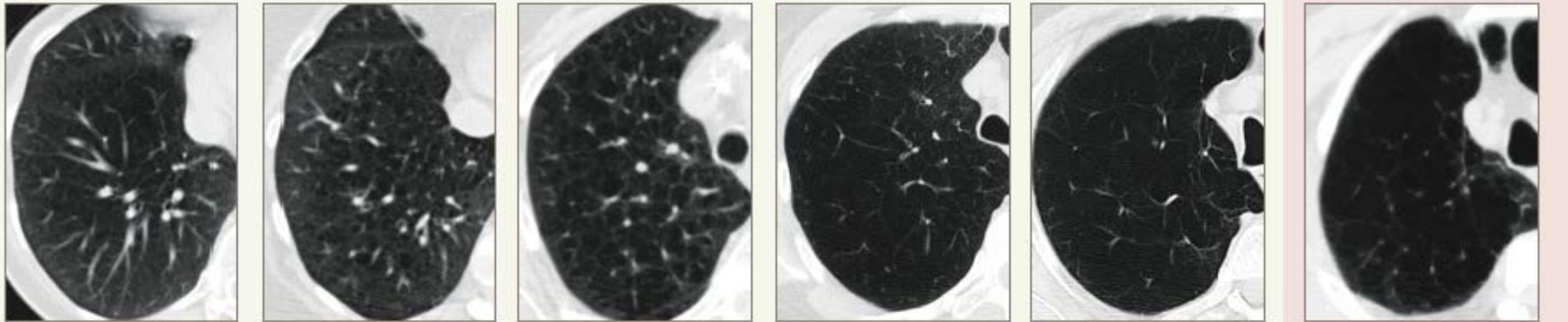


CT Lobe Selection in RENEW

Small
tissue defects



Exceedingly large
tissue defects



0

1

2

3

4

5

- Each lobe was scored by the severity of the emphysema defects on a 6-point scale
- In each lung, the lobe with the highest emphysema score was treated
- Subjects with exceedingly large tissue defects (score of 5) were excluded from treatment

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RENEW ITT Population: Optimal Medical Therapy at Baseline

Medical Therapy	Subjects, n (%)	
	Treatment N=158	Control N=157
Baseline inhaler category		
LABA and/or LAMA + ICS	143 (90.5)	142 (90.4)
LABA and/or LAMA	9 (5.7)	12 (7.6)
SABA and/or SAMA	4 (2.5)	3 (1.9)
None	2 (1.3)	0
Prescribed oxygen	116 (73)	111 (71)
Smoking cessation	158 (100)	157 (100)
Pulmonary rehabilitation	158 (100)	157 (100)

RENEW ITT Baseline Characteristics: Severe and Symptomatic Population

Characteristic ^a	Treatment N=158	Control N=157
Emphysema distribution, n (%)		
Heterogeneous	36 (22.8)	36 (22.9)
Homogeneous	122 (77.2)	121 (77.1)
GOLD status, n (%)		
GOLD 3	38 (24.1)	45 (28.7)
GOLD 4	120 (75.9)	112 (71.3)
FEV ₁ % predicted	25.7 ± 6.3	26.3 ± 6.7
RV % predicted	245.9 ± 39.1	244.5 ± 38.7
6MWT, meters	312.0 ± 79.9	302.7 ± 79.3
mMRC dyspnea scale	2.88 ± 0.74	2.84 ± 0.73
SGRQ, points	60.1 ± 12.8	57.4 ± 14.8
DLCO % predicted	34.1 ± 10.5	34.5 ± 10.7
Number of comorbidities	2.6 ± 2.0	2.3 ± 1.8

^a Mean ± SD, unless otherwise noted.

All Prespecified Effectiveness Endpoints Were Met in RENEW

ITT Population

Endpoint	Between-group difference (95% CI)	P-value	Responder rate treatment vs control	
			(odds ratio)	P-value
6MWT, ^a meters	14.6 (0.4, 28.7)	0.0153	38% vs 26% (2.1)	0.0063
SGRQ, ^b points	-8.9 (-11.6, -6.3)	<0.0001		
FEV ₁ , ^a % change	7.0 (3.4, 10.6)	<0.0001		

^a Median difference; ^b Adjusted mean difference.

Additional Exploratory Effectiveness Endpoints

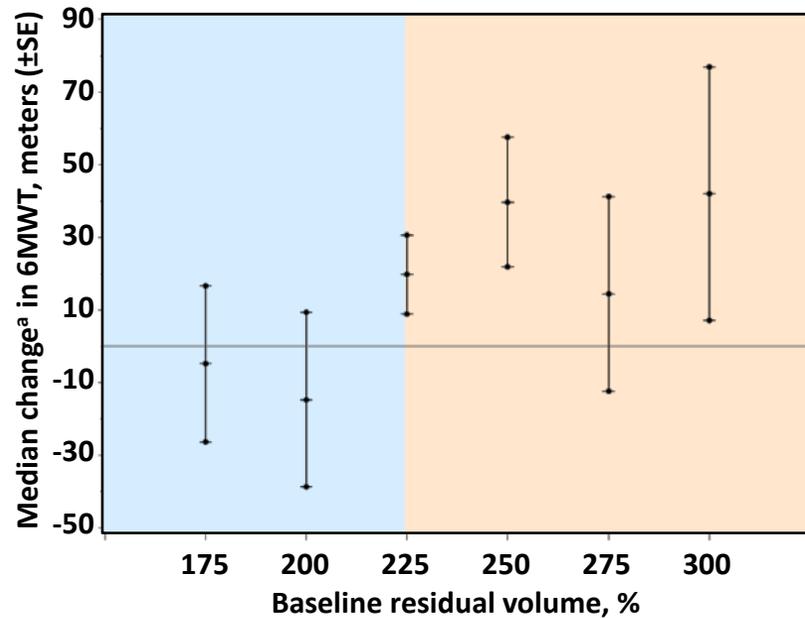
ITT Population

Endpoint	Between-group difference (95% CI)	P-value	Responder rate treatment vs control (odds ratio)	P-value
6MWT, ^a meters	14.6 (0.4, 28.7)	0.0153	38% vs 26% (2.1)	0.0063
SGRQ, ^b points	-8.9 (-11.6, -6.3)	<0.0001	61% vs 28% (4.1)	<0.0001*
FEV ₁ , ^a % change	7.0 (3.4, 10.6)	<0.0001		
RV, liters	-0.31 (-0.50, -0.11)	0.0010*		
RV/TLC, %	-3.5 (-4.9, -2.1)	<0.0001*		

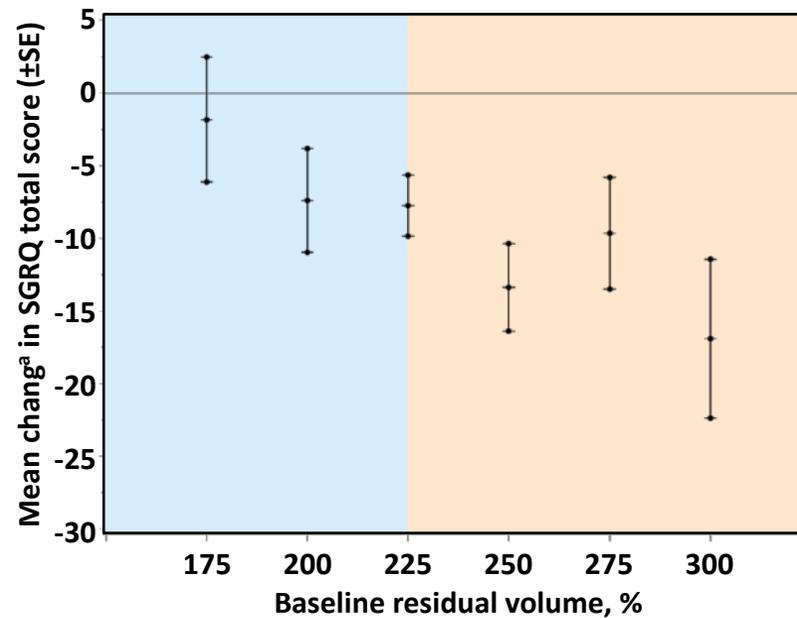
^a Median difference; ^b Adjusted mean difference. *Nominal p-values unadjusted for multiplicity.

Dependence of RENEW Effectiveness Outcomes on Baseline Hyperinflation (RV % Predicted)

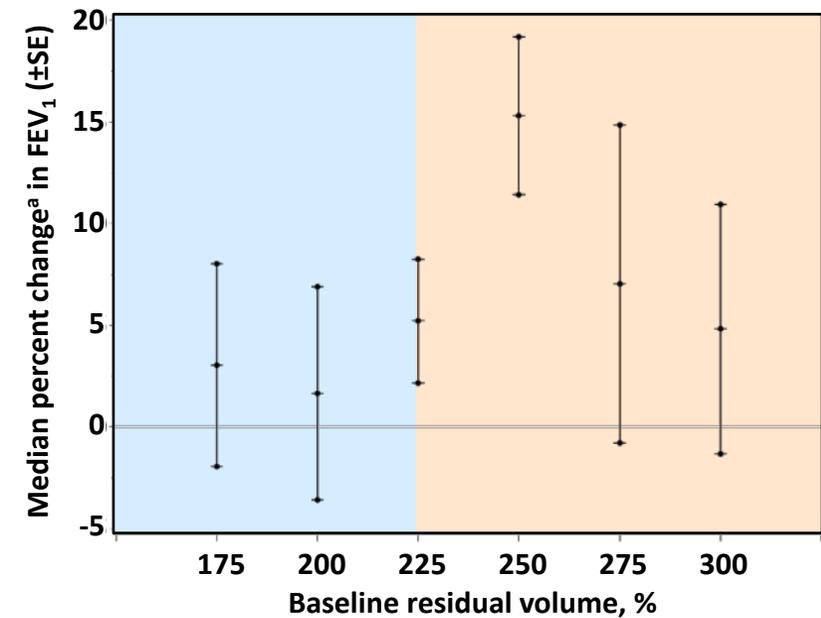
6MWT, meters



SGRQ, total score



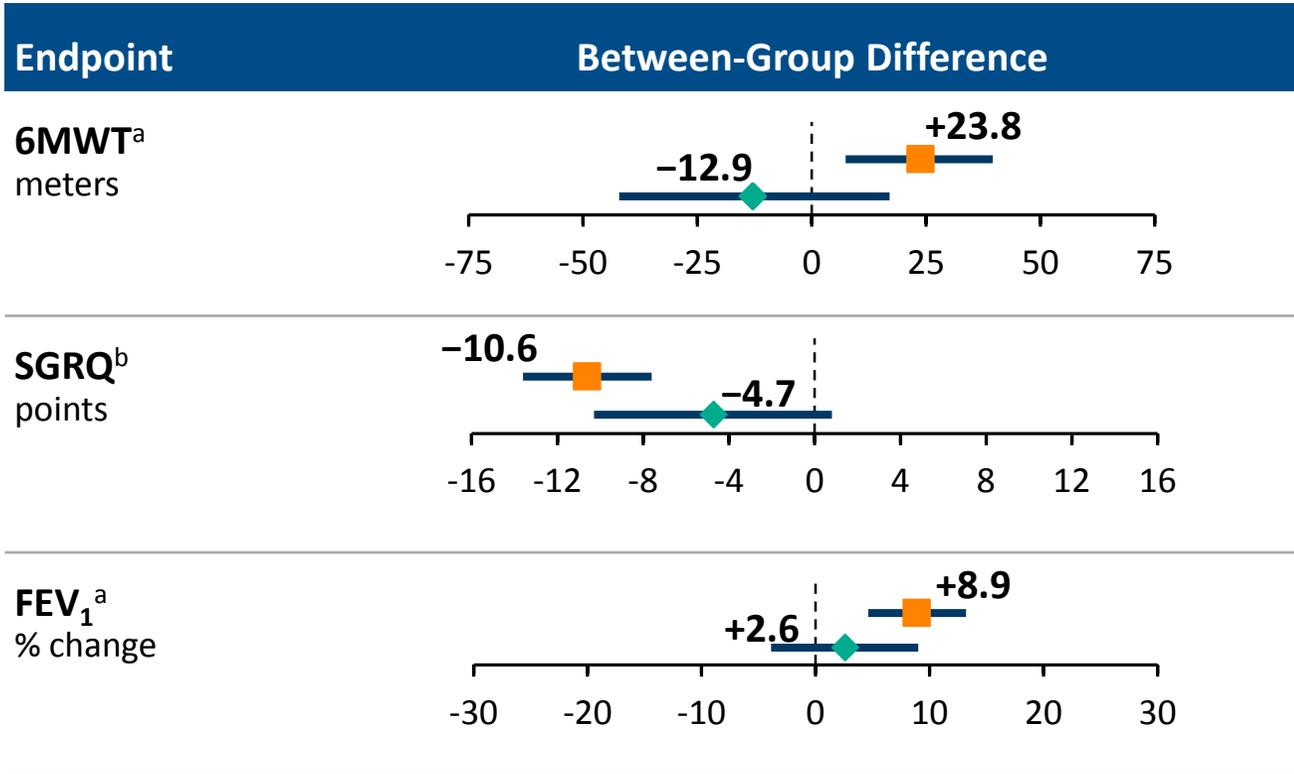
FEV₁, % change



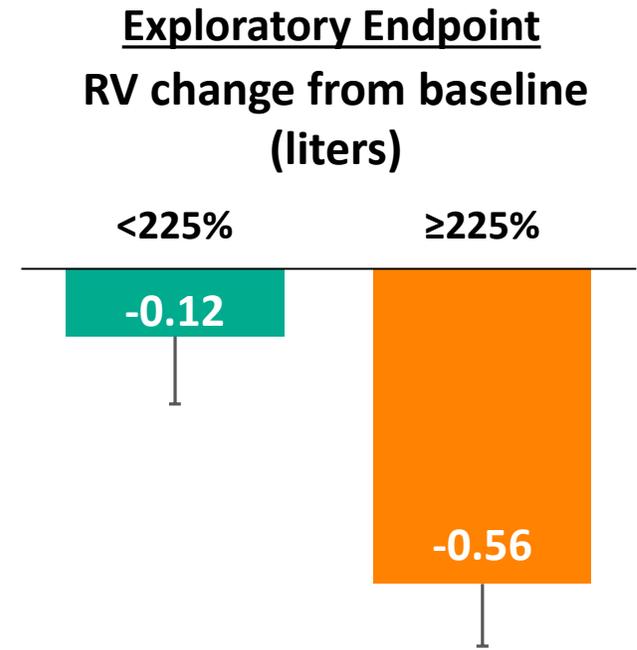
^aMean/Median between-group differences from MCMC multiple imputation.

Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

Effectiveness Outcomes are Consistently Greater in Subjects with RV $\geq 225\%$ Compared to $<225\%$



■ $\geq 225\%$ Pred. N=235
◆ $< 225\%$ Pred. N=80



^a Median difference; ^b Adjusted mean difference.
 All endpoints shown above are prespecified.
 Not shown: 6MWT Responder Rate (secondary endpoint).

Baseline Characteristics in Subjects with RV $\geq 225\%$ are Well-Balanced

Characteristic ^a	Treatment N=115	Control N=120
Emphysema distribution, n (%)		
Heterogeneous	27 (23.5)	31 (25.8)
Homogeneous	88 (76.5)	89 (74.2)
GOLD status, n (%)		
GOLD 3	23 (20.0)	32 (26.7)
GOLD 4	92 (80.0)	88 (73.3)
FEV ₁ % predicted	25.1 ± 6.4	25.4 ± 6.5
RV % predicted	262.9 ± 31.1	258.9 ± 31.9
6MWT, meters	314.6 ± 82.0	308.0 ± 83.6
mMRC dyspnea scale	2.88 ± 0.77	2.87 ± 0.73
SGRQ, points	60.4 ± 13.0	57.7 ± 14.8
DLCO % predicted	34.1 ± 10.7	34.6 ± 10.7
Number of comorbidities	2.3 ± 1.8	2.1 ± 1.7

^a Mean ± SD.

Summary: Proposed Indicated Patient Population

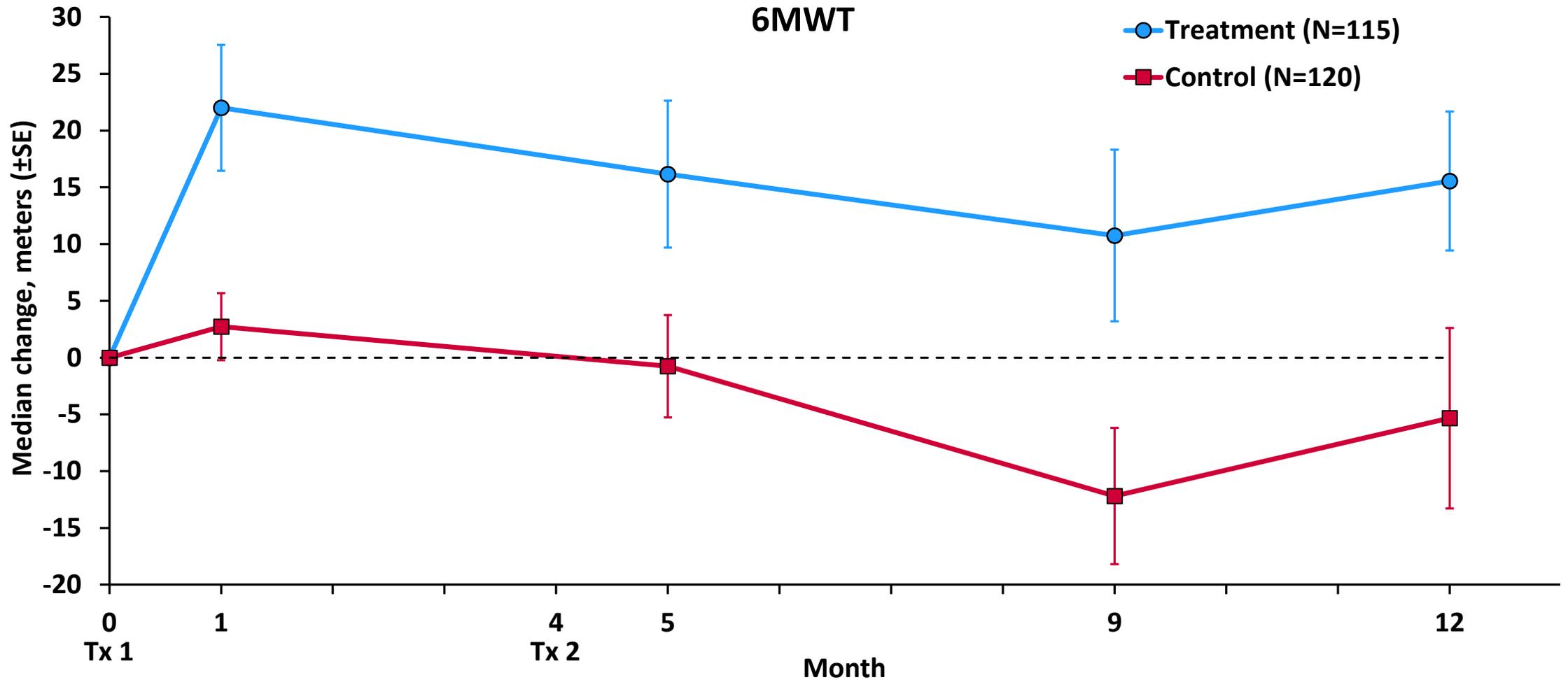
Subjects with $RV \geq 225\%$ show improved outcomes compared to $RV < 225\%$

Baseline demographics were similar between treatment and control in $RV \geq 225\%$

Proposed Indicated Patient Population

$RV \geq 225\%$ predicted

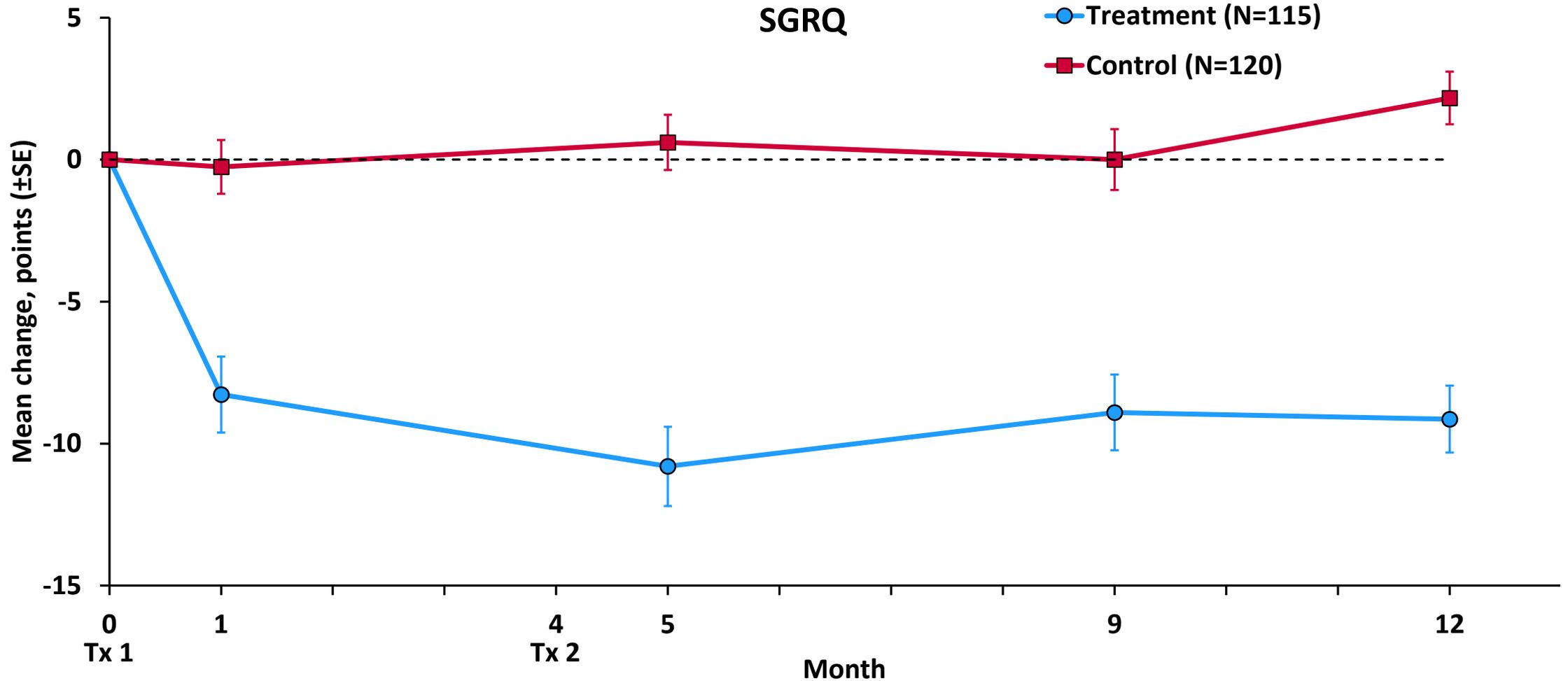
ELEVAIR™ Effectiveness Outcomes are Consistent across Follow-up Visits (RV $\geq 225\%$)



Non-adjusted medians based on available data at each visit.

Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

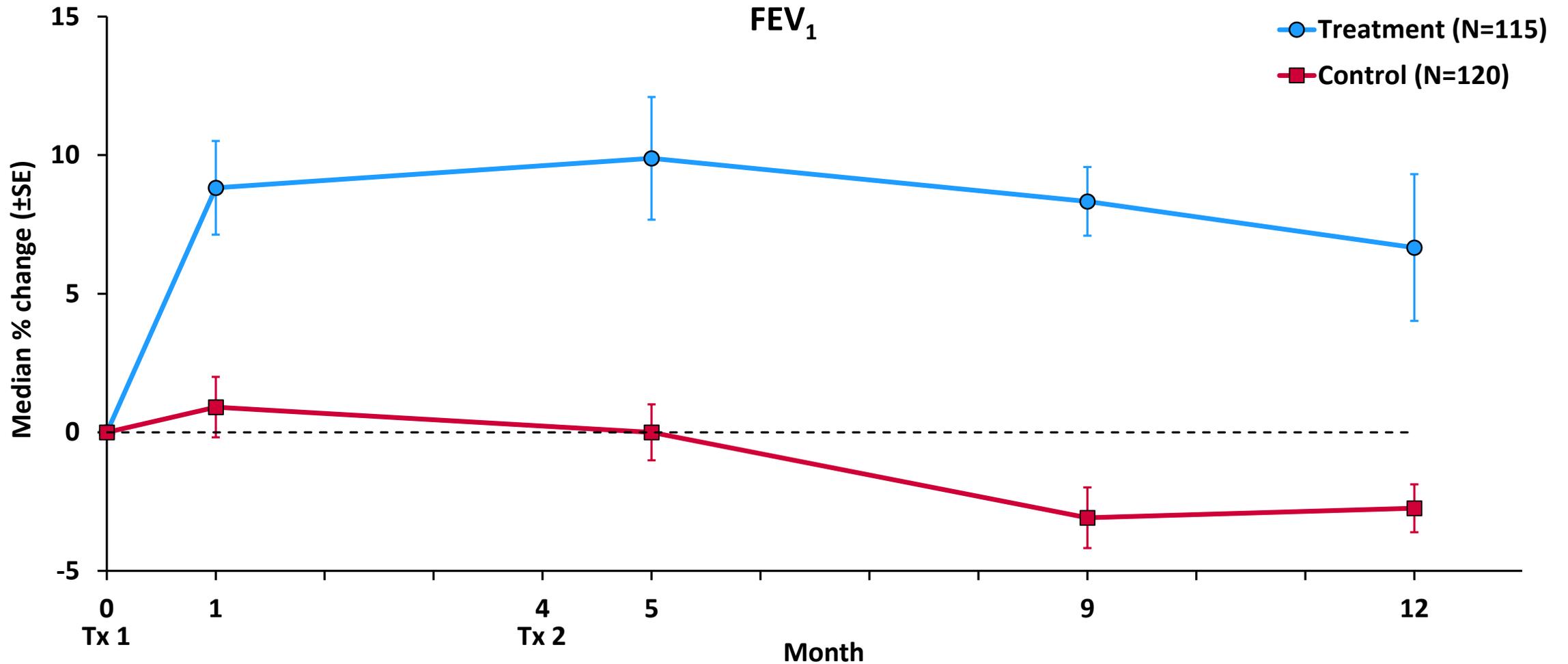
ELEVAIR™ Effectiveness Outcomes are Consistent across Follow-up Visits (RV $\geq 225\%$)



Non-adjusted means based on available data at each visit.

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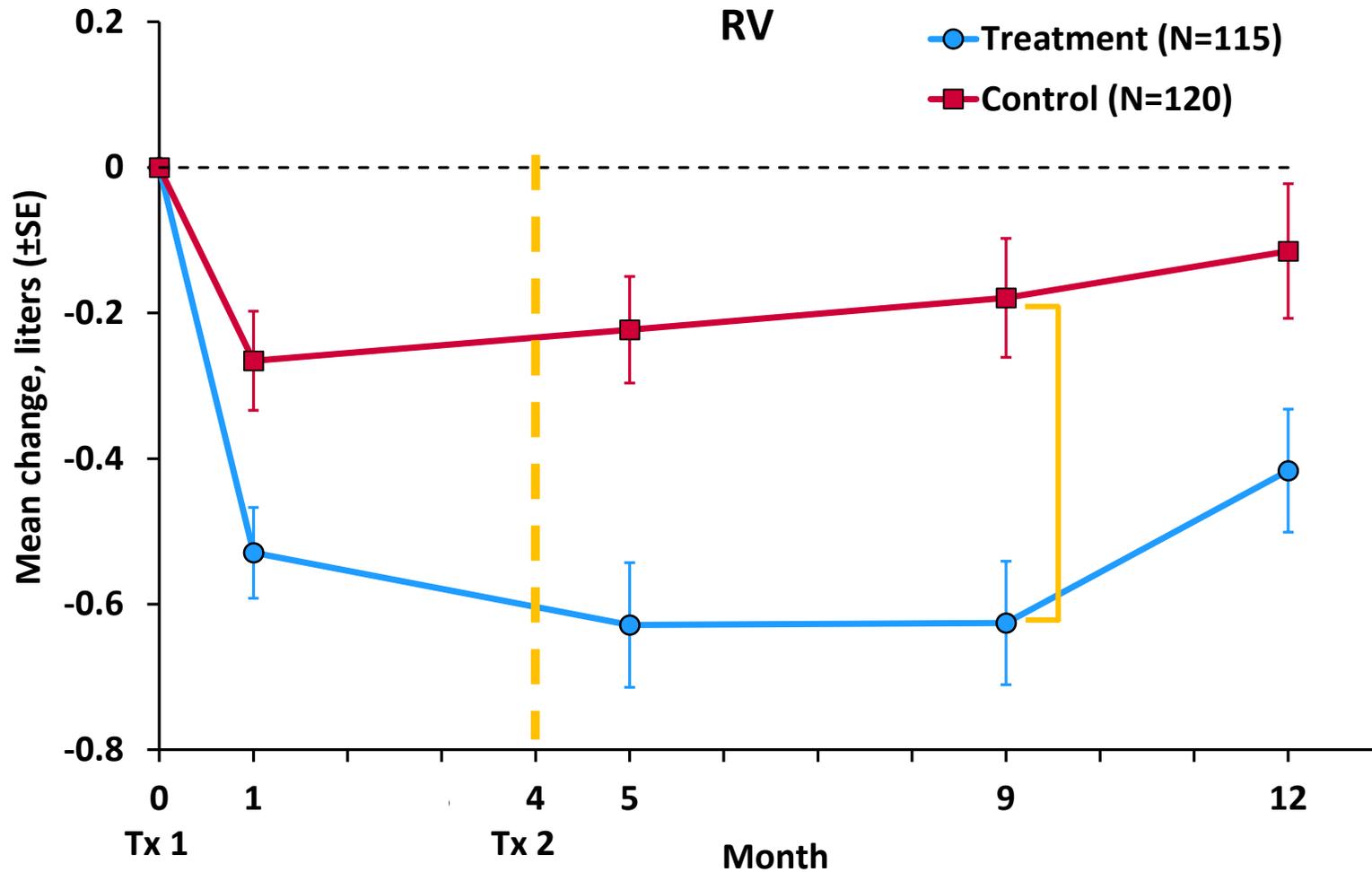
ELEVAIR™ Effectiveness Outcomes are Consistent across Follow-up Visits (RV $\geq 225\%$)



Non-adjusted medians based on available data at each visit.

Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

Reduction of Hyperinflation is Consistent with Intended Treatment Objective in Subjects with $RV \geq 225\%$



Reduce hyperinflation

↓ RV

Improve lung function

↑ FEV₁

Improve patient function

↓ SGRQ

Quality of Life

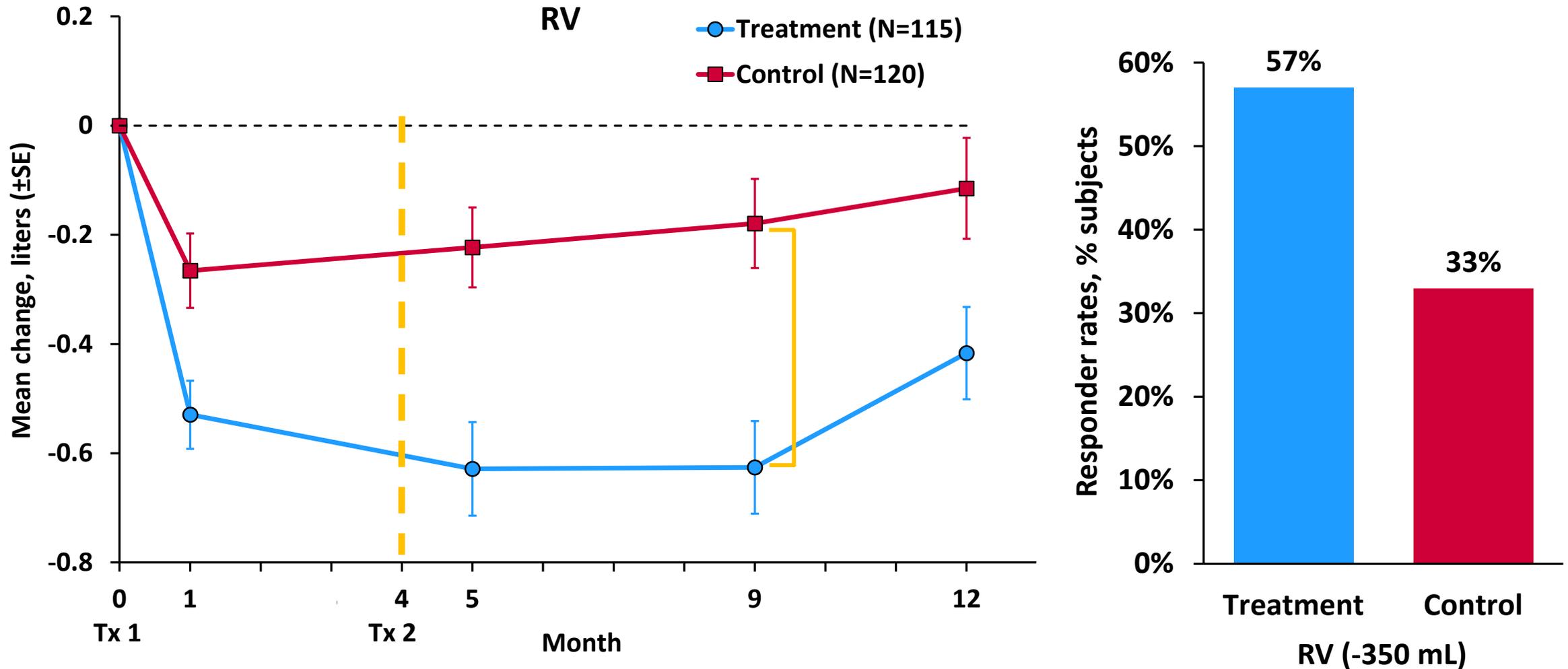
↑ 6MWT

Exercise capacity

Non-adjusted means based on available data at each visit.

Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

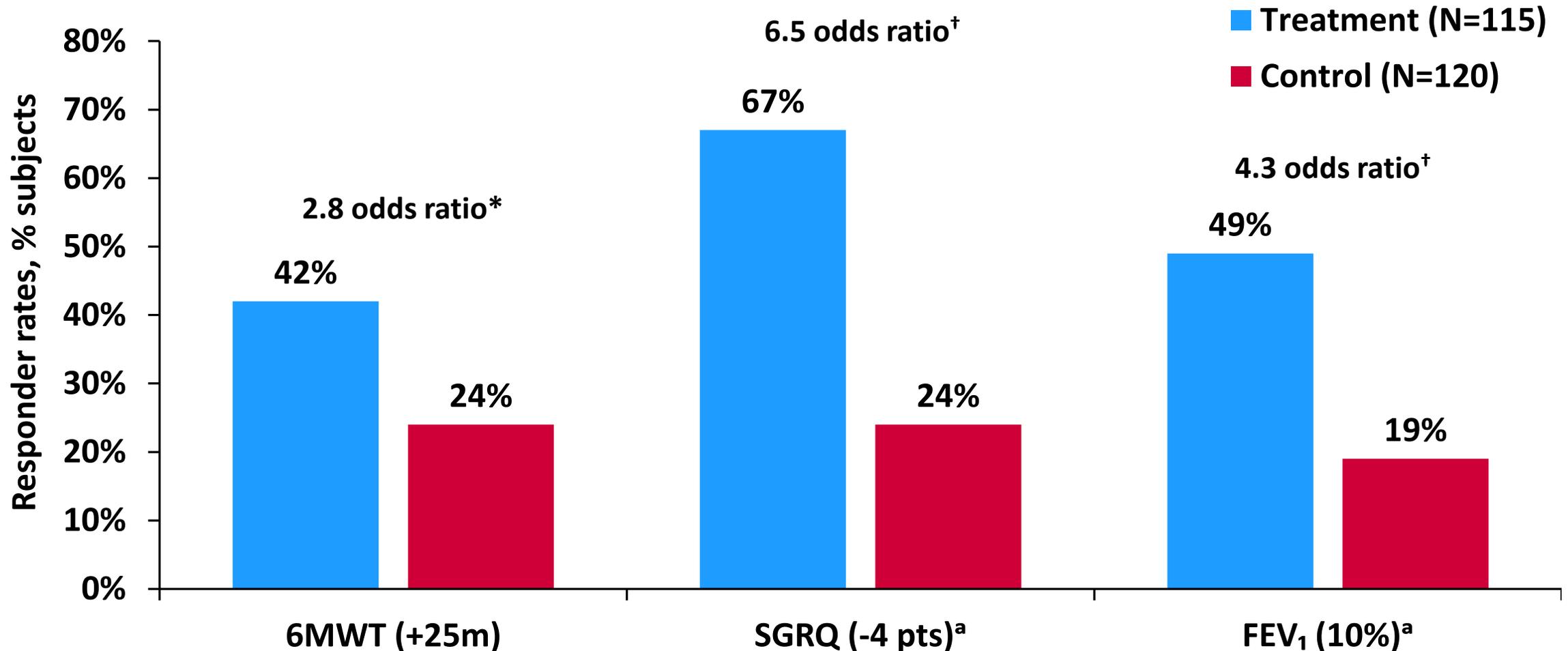
Reduction of Hyperinflation is Consistent with Intended Treatment Objective in Subjects with RV $\geq 225\%$



Non-adjusted means based on available data at each visit.

Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

MCID Responder Analysis Demonstrates Substantial Clinical Benefit in Subjects with RV $\geq 225\%$ Predicted

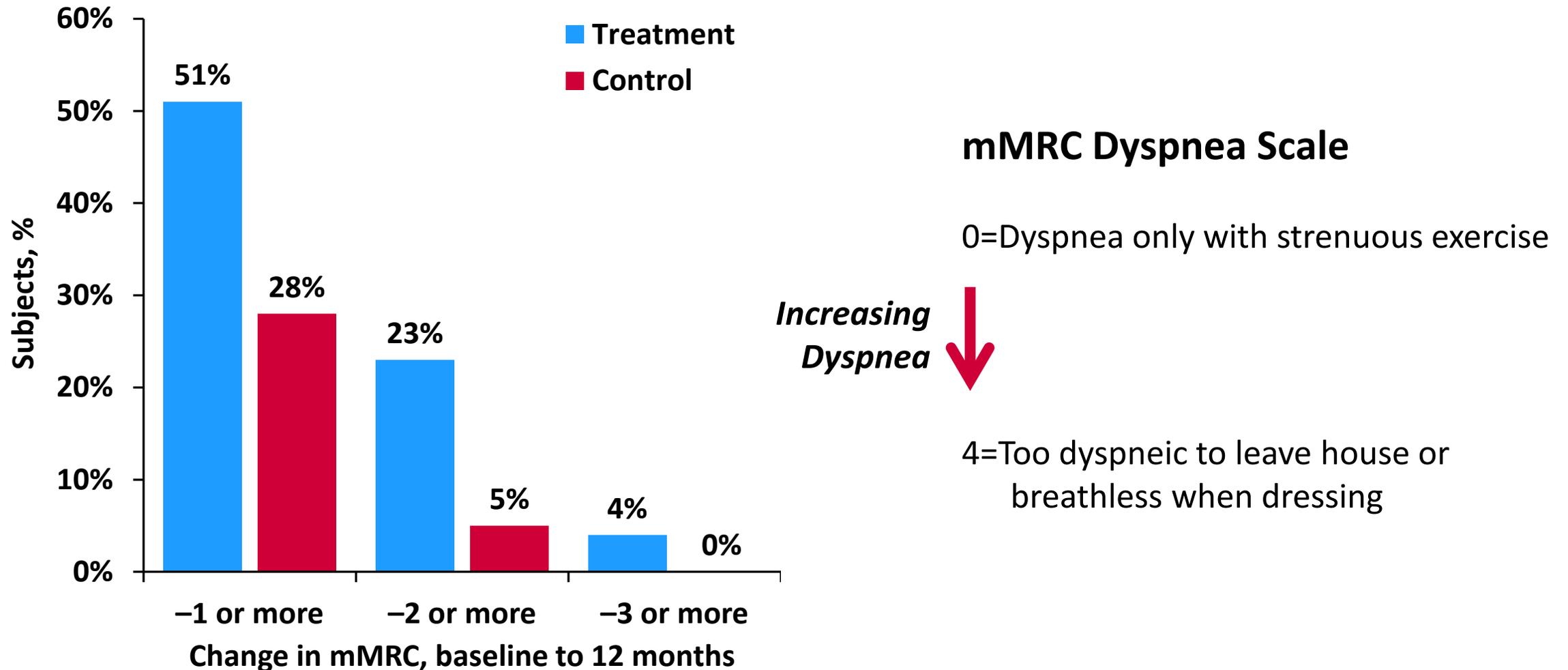


^a Adjusted mean responder rates. *Nominal p-value <0.01 unadjusted for multiplicity. [†]Nominal p-value <0.0001 unadjusted for multiplicity.

Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

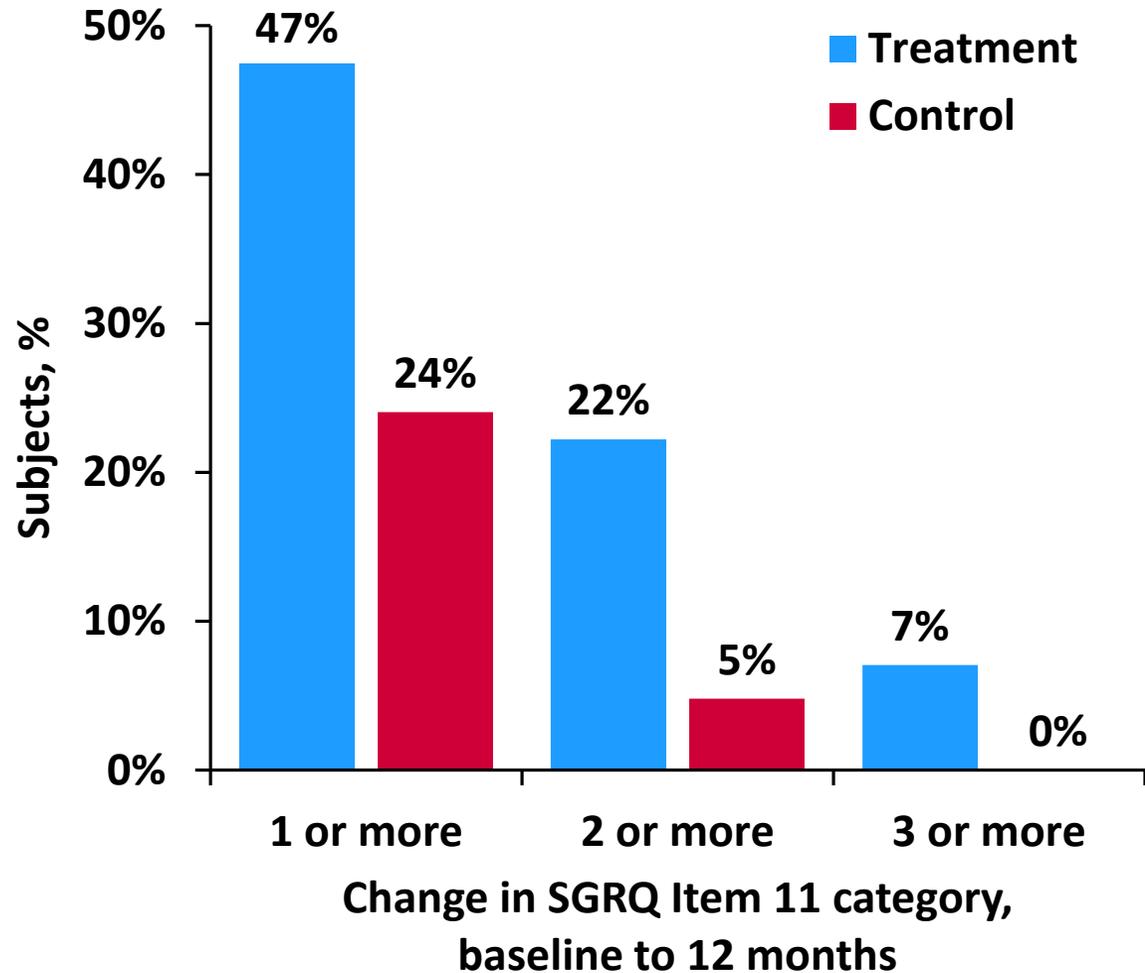
Improvement in Functional Dyspnea Burden in RV $\geq 225\%$

Modified Medical Research Council (mMRC) Dyspnea Scale



Improvement in Functional Dyspnea Burden in RV $\geq 225\%$

SGRQ Question 11



SGRQ Item 11 Categories

Breathless when:

- 0= Sitting or lying still
- 1= Washing or dressing
- 2= Walking around the house
- 3= Walking outside on level ground
- 4= Walking up a flight of stairs
- 5= Walking up hills
- 6= Playing sports

Improvement in Functional Dyspnea Burden

Impact on Activities of Daily Living (SGRQ Question 11)

I don't feel out of breath doing these activities	I do feel out of breath doing these activities					
						
Sitting or lying still	Washing or dressing yourself	Walking around the house	Walking outside on level ground	Walking up a flight of stairs	Walking up hills	Playing sports or other physical activities

Improvement in Functional Dyspnea Burden

Impact on Activities of Daily Living (SGRQ Question 11)

I don't feel out of breath doing these activities			I do feel out of breath doing these activities			
						
Sitting or lying still	Washing or dressing yourself	Walking around the house	Walking outside on level ground	Walking up a flight of stairs	Walking up hills	Playing sports or other physical activities

Improvement in Functional Dyspnea Burden

Impact on Activities of Daily Living (SGRQ Question 11)

I don't feel out of breath doing these activities					I do feel out of breath doing these activities	
						
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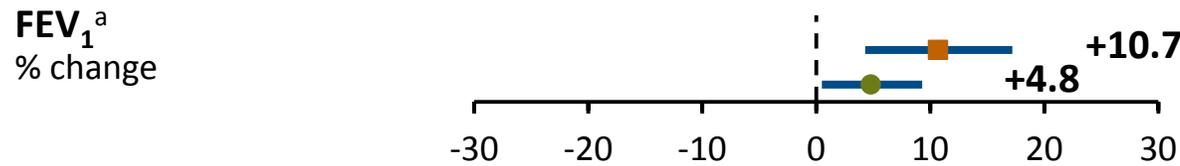
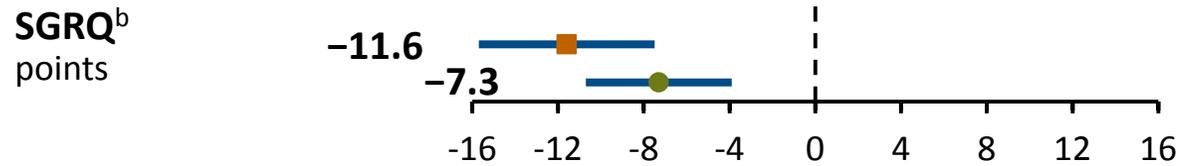
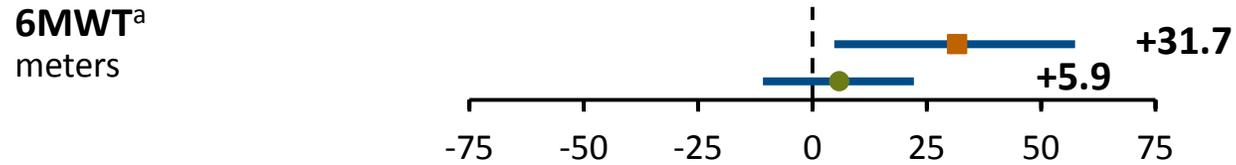
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Differential Effectiveness Outcomes by Region Observed in ITT Population

Endpoint **Between-Group Difference**

■ OUS N=114
● US N=201

Poolability test:
 All p<0.15



	RV	US	OUS
≥225%		128 (64%)	107 (94%)
<225%		73 (36%)	7 (6%)

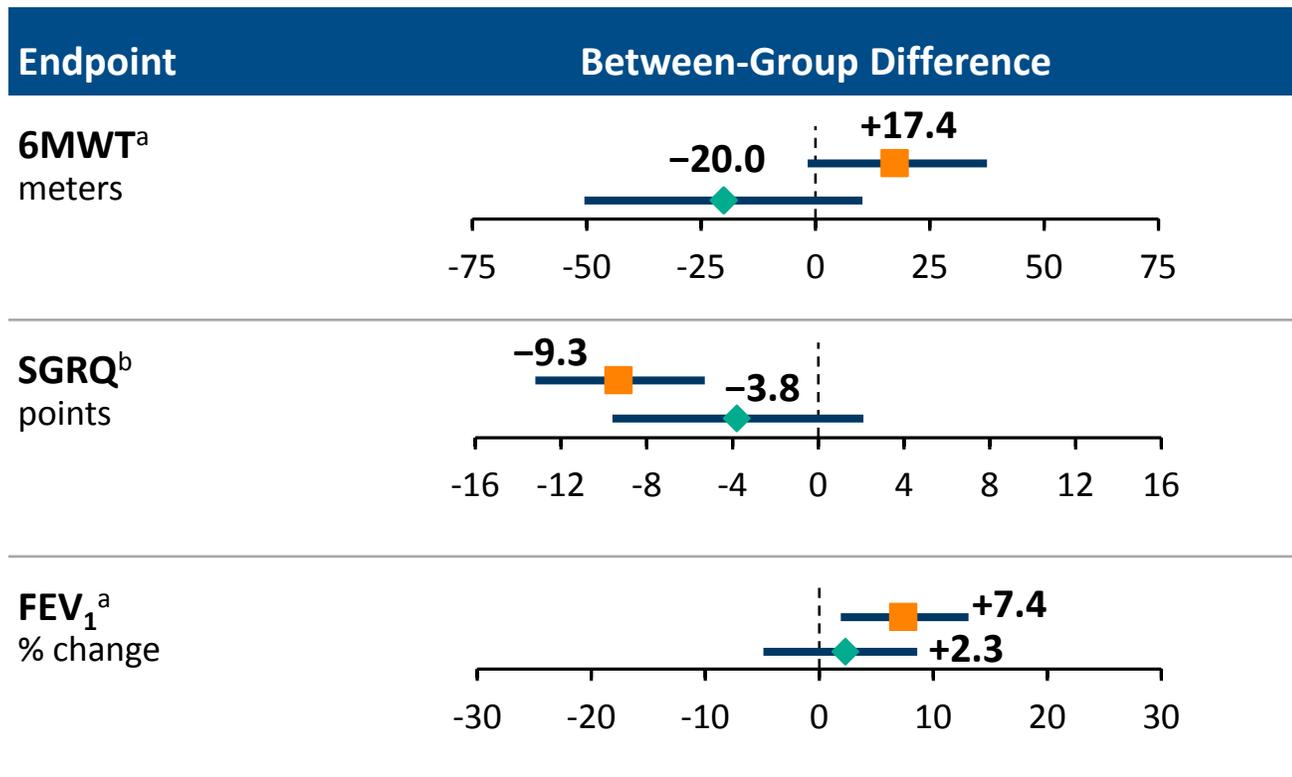
^a Median difference; ^b Adjusted mean difference.

All endpoints shown above are prespecified.

Not shown: 6MWT Responder Rate (secondary endpoint).

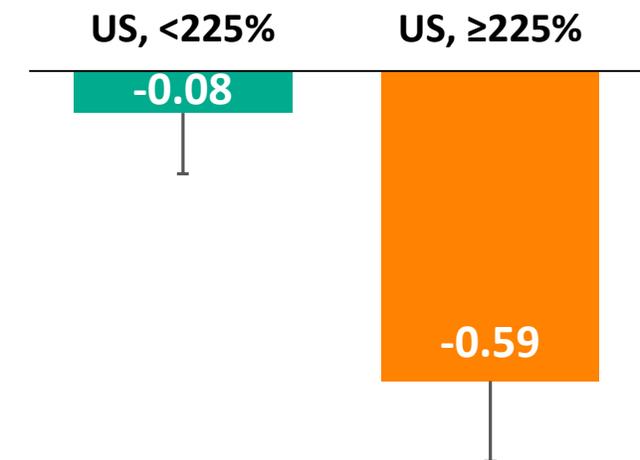
36% of US subjects had RV <225% predicted

US Outcomes are Consistently Greater in Subjects with RV $\geq 225\%$ Compared to $< 225\%$



■ $\geq 225\%$ Pred. N=128
◆ $< 225\%$ Pred. N=73

Exploratory Endpoint RV change from baseline (liters)



^a Median difference; ^b Adjusted mean difference.

All endpoints shown above are prespecified.

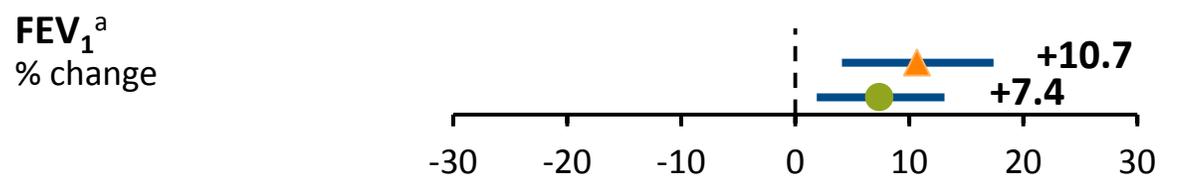
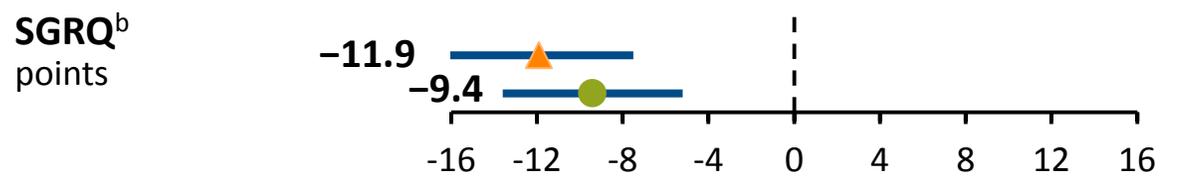
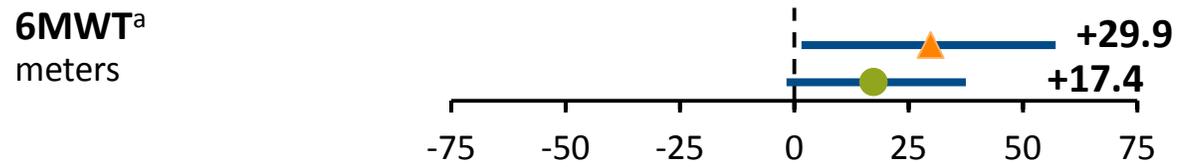
Not shown: 6MWT Responder Rate (secondary endpoint).

Effectiveness in both US and Outside US Subjects with RV ≥225%

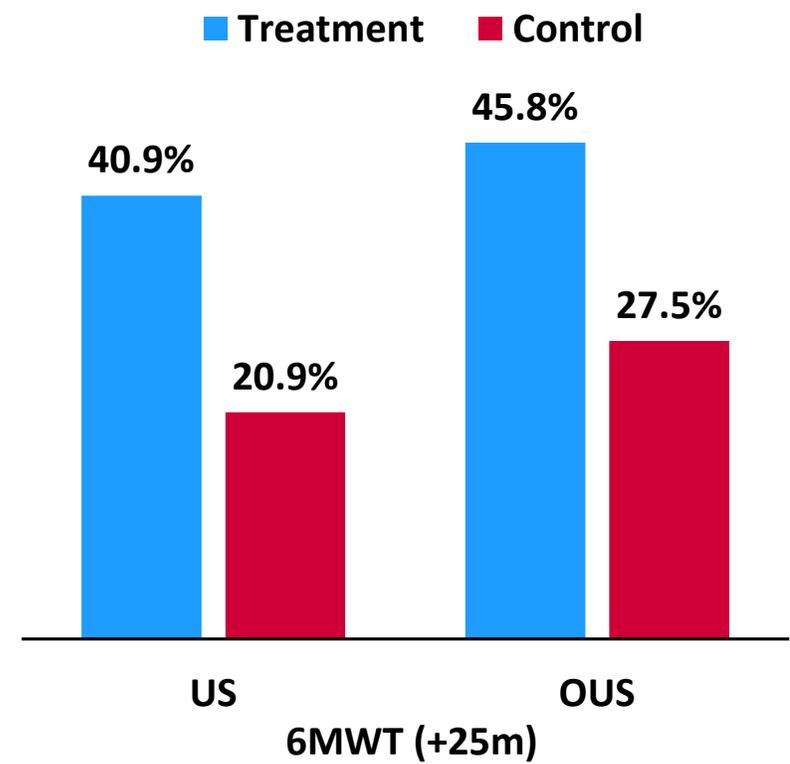
Endpoint **Between-Group Difference**

▲ OUS, RV ≥225% N=107
● US, RV ≥225% N=128

Poolability test:
All p≥0.35



^a Median difference; ^b Adjusted mean difference.
All endpoints shown are prespecified.

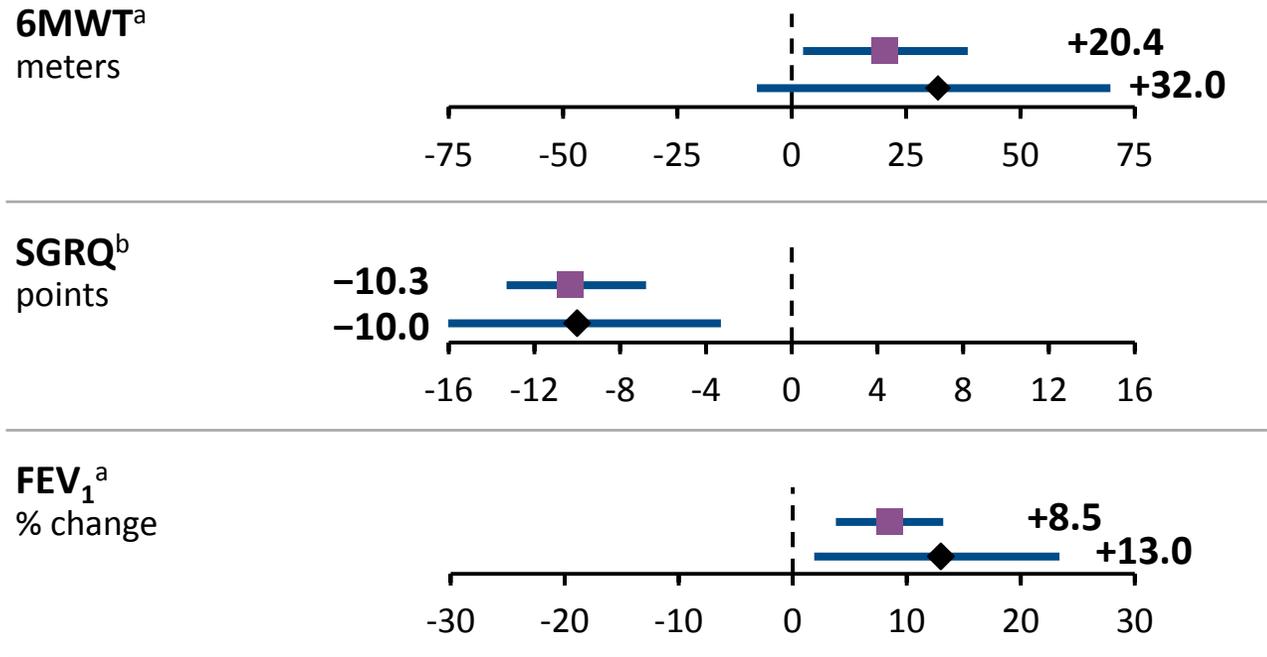


Apparent regional differences in effectiveness were driven by differences in baseline RV by region

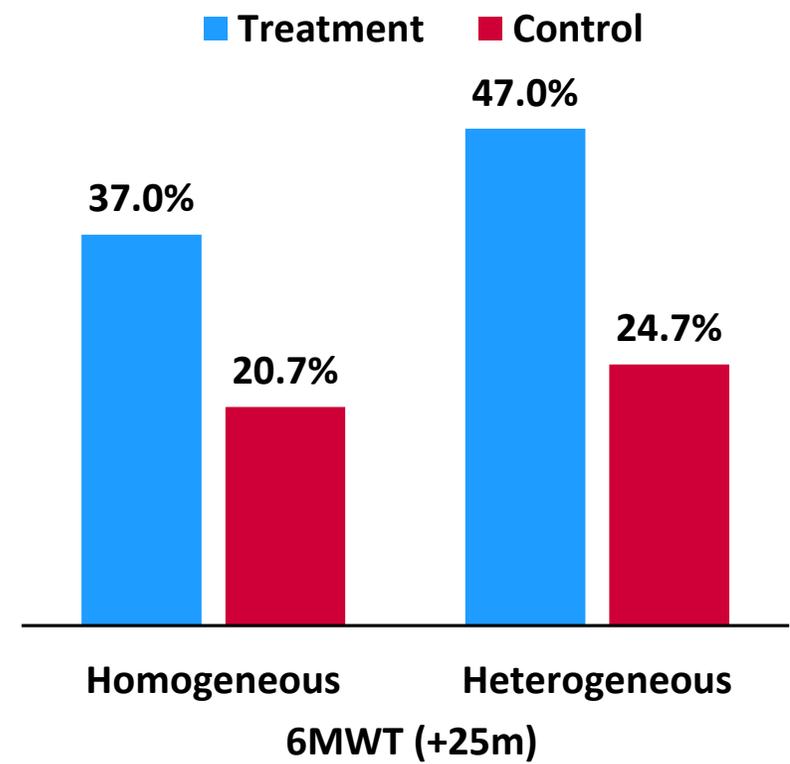
Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

Effectiveness in both Heterogeneous and Homogeneous Emphysema Subjects with RV $\geq 225\%$

Endpoint **Between-Group Difference**



■ Homogeneous, RV $\geq 225\%$ N=177
 ◆ Heterogeneous, RV $\geq 225\%$ N=58

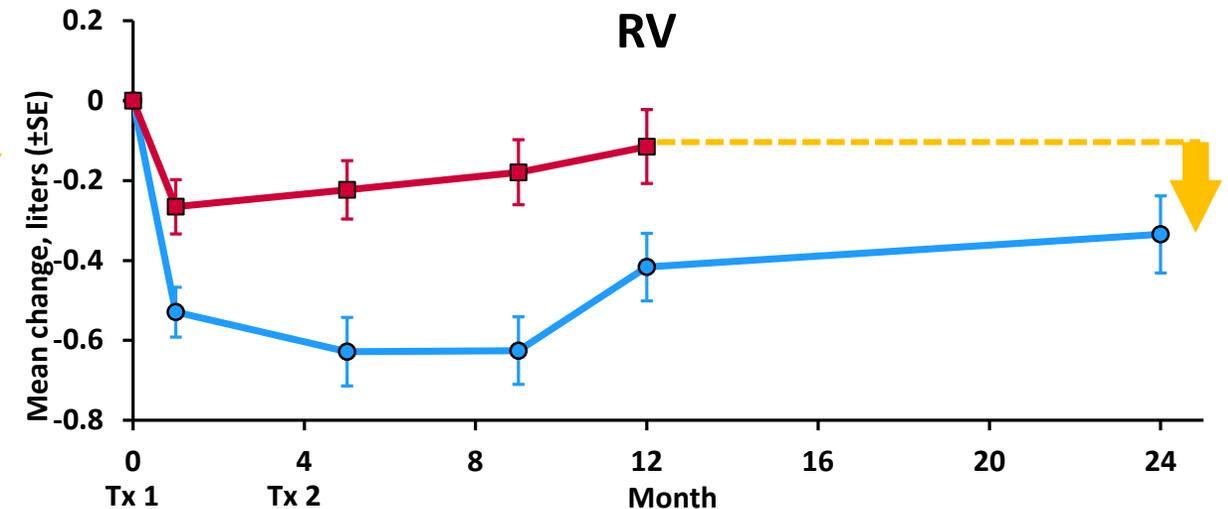
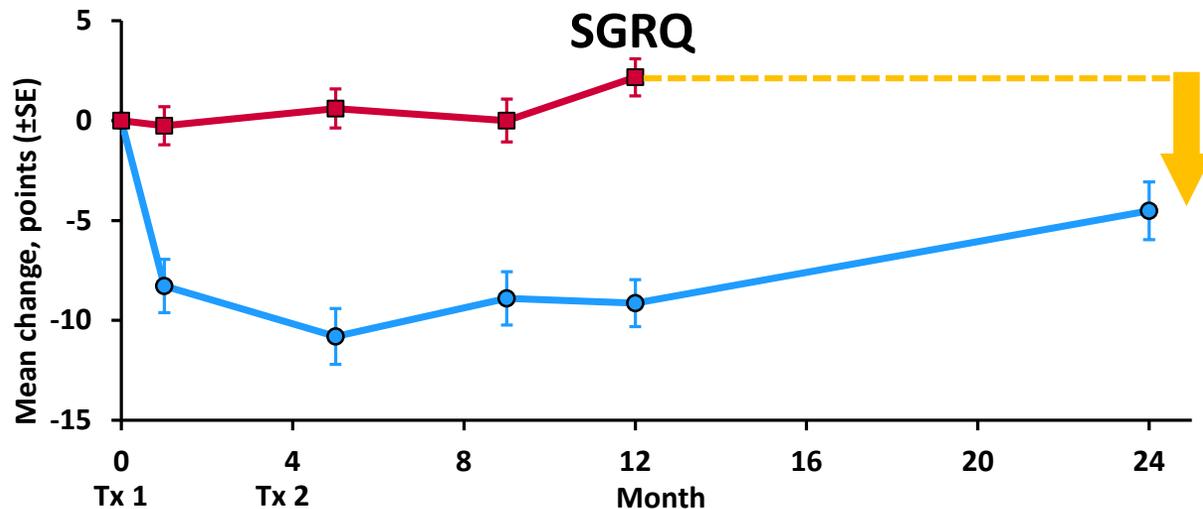
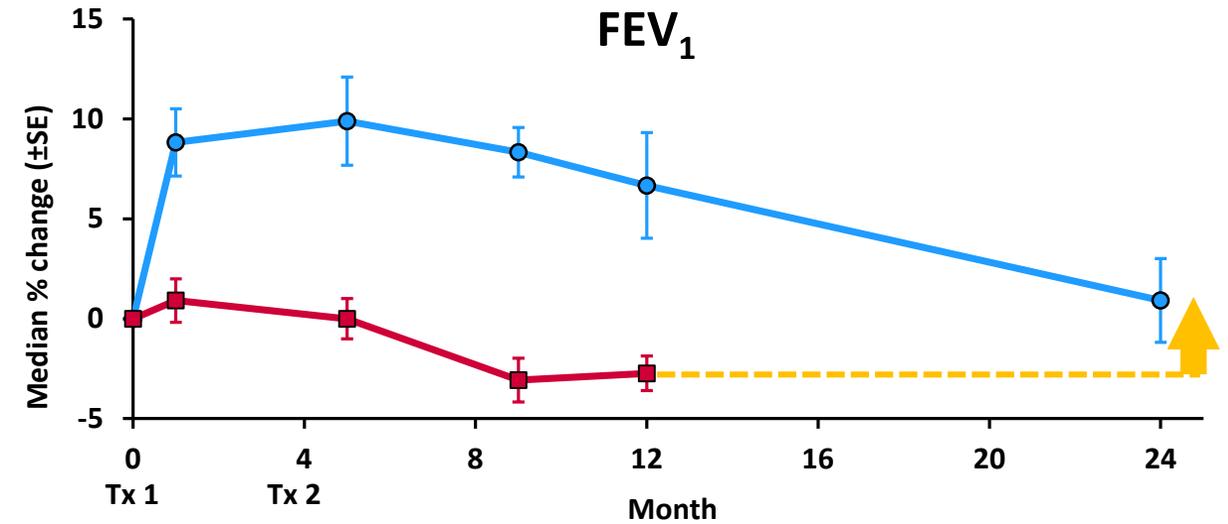
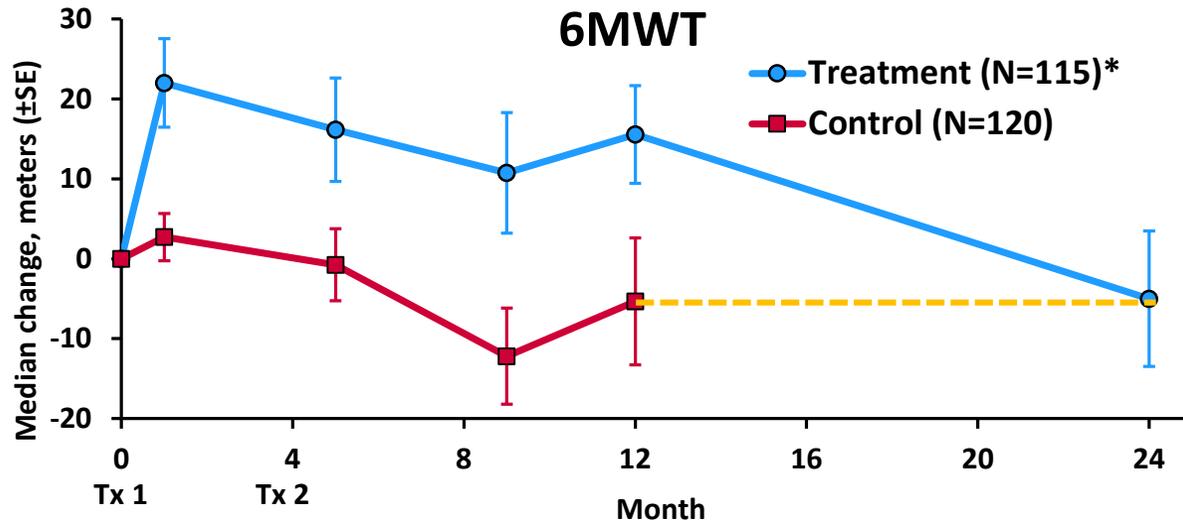


^a Median difference; ^b Adjusted mean difference.
 All endpoints shown are prespecified.

75% of RV $\geq 225\%$ are homogeneous, consistent with the ITT population

Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

Treatment Benefit at 24-Months: Delayed Decline in Clinical Measurements from Emphysema Progression (RV $\geq 225\%$)



Non-adjusted means and medians based on available data at each visit. *N=87 at 24 months

Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

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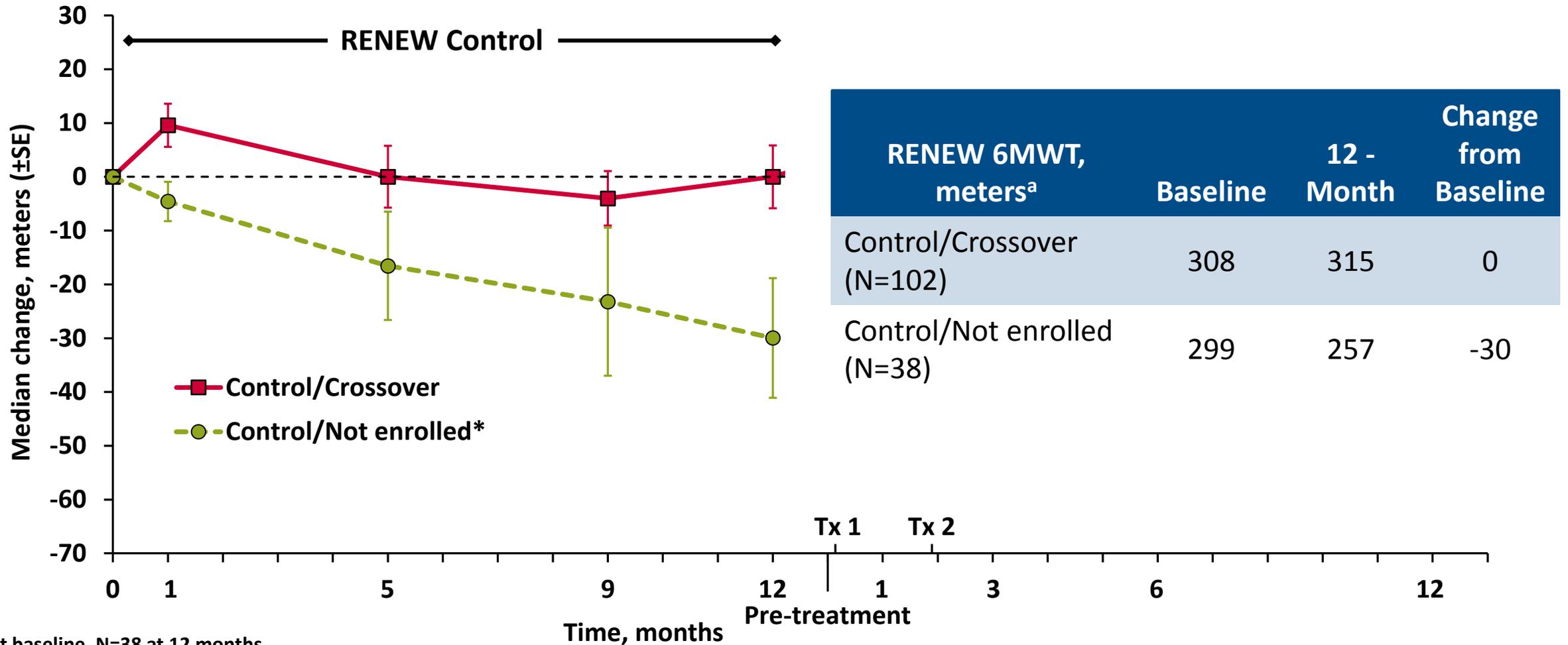
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Crossover Study Results

	Change from Crossover Baseline ^a
6MWT, meters	-22.9 ± 72.6 (80) -14.8
SGRQ, points	-4.8 ± 14.8 (83) -4.7
FEV1, % change	2.2 ± 21.1 (83) -1.3
RV, liters	-0.30 ± 0.70 (81) -0.26

^a Means ± SD (N); Medians. Complete cases.

Crossover Subject Selection



*N=55 at baseline, N=38 at 12 months

^aAll values reported as non-adjusted medians based on available data at each visit.

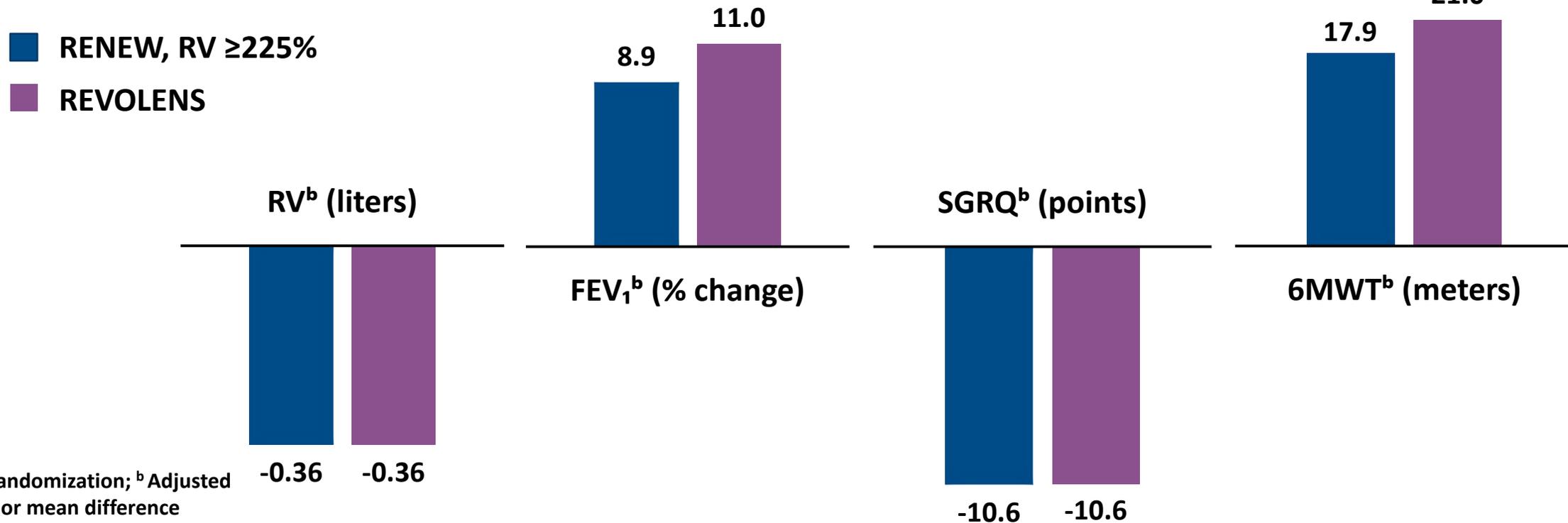
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Summary: RENEW Effectiveness Outcomes are Consistent With Previous ELEVAIR™ RCTs

RCTs		N ^a	RV % Pred	% Homogeneous
RENEW	RV ≥225% Subpopulation	235	225%	75
REVOLENS	Deslée et al, 2016	100	220%	66



^a 1:1 randomization; ^b Adjusted mean or mean difference

RENEW: All endpoints shown are prespecified with the exception of RV (additional endpoint).

REVOLENS: 12-month outcomes are shown. All endpoints shown are exploratory. Not shown: 6MWT Responder (primary endpoint at 6 months).

Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

ELEVAIR™ Effectiveness Conclusions

- All effectiveness endpoints were met in the RENEW RCT
- Treatment with the ELEVAIR system results in substantial clinical benefit to severe emphysema patients with severe hyperinflation compared with optimal medical therapy alone
- The proposed indicated patient population (***RV ≥225%***) is selected using standard pulmonary function testing and lobe selection using CT imaging
- ELEVAIR is an effective minimally invasive bronchoscopic lung volume reduction procedure that improves lung function, quality of life, and exercise tolerance through mechanical reduction of hyperinflation