Elevair™ Endobronchial Coil System
Sponsor Executive Summary
June 14, 2018

Attachment 2: Detailed Summary of Additional Clinical Studies

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1. ADDITIONAL RANDOMIZED CONTROLLED TRIALS OF THE ELEVAIR SYSTEM

1.1. REVOLENS Trial

The REVOLENS Trial was sponsored by Reims University Hospital, France and was primarily financed by the French Ministry of Health under the STIC program.[a] PneumRx has not been responsible for the design or conduct of the study, or for the evaluation of study results. PneumRx did provide training to the study sites on device usage, including support during implantation procedures. In addition, PneumRx provided limited financial support for the conduct of the randomized and long-term follow-up portions of the study, and provided devices at no charge for treatment of crossover subjects only.

PneumRx has no rights to the study data, other than what is presented in the public domain. Outcomes from the 12-month primary follow-up, and from long-term (24-month) follow-up, have been published (Deslée 2016, provided in Attachment 8; Deslée 2017), and a summary of trial outcomes taken directly from these publications is provided herein. Follow-up for up to 5 years is ongoing.

The ClinicalTrials.gov record for this trial is NCT01822795.

1.1.1. Study Design

REVOLENS was a prospective, post-market, multi-center, randomized controlled trial designed to analyze the efficacy, safety, cost, and cost-effectiveness of Coil treatment in patients with severe emphysema.

Subjects were recruited at 10 university hospitals in France and were randomized at a 1:1 ratio (bilateral Coil treatment versus standard of care medical therapy). Bilateral Coil treatments were performed in two separate procedures, separated by 1-3 months, in two contralateral lobes. Computed tomography-based scoring of emphysema heterogeneity and determination of lobes for treatment were determined by each site, without a central radiology assessment or use of any special software scoring system. Patients randomized to the control group could cross over to receive treatment with Coils upon completion of the randomized phase of the study. The randomized phase of the study was 12 months, with long-term follow-up of all treated subjects up to 5 years post randomization. Subjects and Investigators were not blinded to study arm assignment.

[a] The STIC program is sponsored by the French government with the purpose of conducting comparative studies that demonstrate the clinical utility and health economics of innovative diagnostic or therapeutic products whose clinical efficacy has been validated/established (e.g., CE marked medical devices).

The primary effectiveness outcome measure was a comparison between Treatment and Control groups in 6MWT responder rate at 6 months follow-up, using 54 meters as the response threshold. This response threshold was selected based on early literature investigating the minimal important difference in 6MWT (Redelmeier 1997); subsequent studies have demonstrated, however, that an improvement of 25 meters is associated with a meaningful clinical benefit (Holland 2010). Hypothesis testing was a one-sided superiority test at α=0.05 significance level. Secondary endpoints include changes in 6MWT at 6 and 12 months, lung function assessments (FEV_1, FVC, RV, TLC, and RV/TLC), dyspnea, quality of life (SGRQ), morbidity, mortality, and measures of health economics (total cost and cost-effectiveness). Effectiveness endpoints were assessed on the ITT population.

Safety evaluation included assessment of serious and non-serious adverse events, stratified by first 30 days versus post 30 days to 12 months. In addition, two composite safety scores were used. The first included any of the following SAEs occurring within 24 hours after Coil treatment: death, pneumothorax requiring chest tube placement for more than 7 days or surgical treatment, hemoptysis greater than 150 mL, and invasive ventilation for more than 24 hours. The second composite score also included the following SAEs occurring within 12 months in both groups: death, hemoptysis greater than 150 mL, pneumonia requiring hospitalization, pneumothorax requiring chest tube placement for more than 7 days or surgical treatment, invasive ventilation for more than 24 hours, and lung transplantation.

Key inclusion criteria for the REVOLENS trial included:

- Bilateral emphysema on Chest CT Scan
- Post bronchodilator FEV_1 <50% predicted
- Total Lung Capacity >100% predicted
- Residual Volume >220% predicted
- Dyspnea score between 2 and 4 based on the mMRC scale
- Stopped cigarette smoking for more than 8 weeks
- Pulmonary rehabilitation within the previous twelve months

Key exclusion criteria for the REVOLENS trial included:

- Post bronchodilator FEV_1 <15% predicted
- Post-bronchodilator change in FEV_1 >20%
- Severe recurrent respiratory infections requiring more than 2 hospitalization stays within the past twelve months
- COPD exacerbation requiring hospital stay within 3 months
- Pulmonary Hypertension (Pulmonary systolic pressure >50 mmHg on cardiac echo)
- Patient unable to perform a 6MWT in room air (no restriction on distance)
- Giant bulla of more than 1/3 of the lung field on Chest CT
- Strictly homogeneous emphysema on Chest CT (investigator interpreted)
- Clinically significant bronchiectasis
- Past history of lobectomy, lung volume reduction surgery, lung transplantation

- Any extrapulmonary diseases compromising survival or evaluation within the protocol (severe cardiac disease, severe renal insufficiency, cancer)
- Lung carcinoma or pulmonary nodule on CT scan requiring Chest CT scan follow-up
- Contraindication to general anesthesia
- Oral anticoagulant treatment with vitamin K antagonists
- Allergy to nitinol
- Inclusion in another study assessing respiratory treatments

1.1.2. Subject Accountability

Subject disposition for the REVOLENS Trial is summarized in Table 1. Of 100 subjects enrolled between March and October 2013, 96 (96%) were available for primary follow-up analysis at 6 months and 91 (91%) were available follow-up at 12 months.

Table 1. Subject Disposition[1] [REVOLENS]

Subject Status	Treatment Group	Control Group	Total
Subjects enrolled, n	50	50	100
Subjects who completed study to 6 months, % (n)	94% (47)	98% (49)	96% (96)
Subjects who discontinued prior to 6 months, % (n)	6% (3)	2% (1)	4% (4)
Subjects who died, n	3	1	4
Subjects who completed study to 12 months, % (n)	88% (44)	94% (47)	91% (91)
Subjects who died, n	1	2	3
Subjects lost to follow-up, n	2	0	2

1 Data source (Deslée 2016)

1.1.3. Subject Demographics and Baseline Disease Characteristics

No notable differences in subject demographics were reported between Control and Treatment groups.

Selected REVOLENS subject baseline disease characteristics are summarized in Table 2. Similar to the RENEW Trial, REVOLENS enrolled a cohort of subjects with severe emphysema (FEV_1 approximately 26.5% of predicted) and severe hyperinflation (RV approximately 270% of predicted). Both subjects with homogeneous (67%) and heterogeneous (33%) were enrolled, with equal distribution between Treatment and Control groups.

Table 2. Subject Baseline Disease Characteristics[1] [REVOLENS]

Disease Characteristic[2]	Treatment Group (N=50)	Control Group (N=50)
6MWT	300 (112)	326 (121)
Emphysema Distribution, % (n)		
Heterogeneous	34 (17)	32 (16)
Spirometry		
FEV_1 (% Predicted)	25.7 ± 7.5	27.4 ± 6.2
FVC (% Predicted)	67.4 ± 16.5	72 ± 20.1
FEV_1/FVC Ratio	0.31 ± 0.09	0.32 ± 0.08
Lung Volumes		
RV (% Predicted)	271.2 ± 38.1	269.3 ± 44.3
TLC (% Predicted)	141.7 ± 16.6	143.6 ± 18
RV/TLC Ratio	0.70 (0.06)	0.69 ± 0.07
SGRQ Total Score	60.8 ± 12.8	57.1 ± 14.1
Oxygen Therapy, % (n)	64 (32)	58 (29)
mMRC Dyspnea Scale, % (n)		
0	0% (0)	0% (0)
1	0% (0)	2% (1)
2	22% (11)	26% (13)
3	56% (28)	50% (25)
4	22% (11)	22% (11)

1 Data source (Deslée 2016)
2 Mean ± SD unless otherwise indicated.

1.1.4. Procedural Results

Forty-seven (47) of the 50 Treatment group subjects underwent bilateral treatment with Coils, and 3 subjects underwent unilateral treatment (97 procedures in total). Reasons for unilateral treatment included single instances of death prior to second treatment, anaphylactic shock due to penicillin allergy at induction of anesthesia for the second Coil treatment, and pneumonia after the first Coil treatment leading to unwillingness of the patient to undergo a second Coil treatment.

The mean (SD) number of Coils placed per procedure was 9.8 (1.3), with a mean (SD) procedure time of 54 (17) minutes. Approximately 79% of Coils were placed in upper lobes (approximately equal distribution right/left).

1.1.5. Effectiveness Results

Data on 6MWT were obtained at 6 months in 44 Coil-treated subjects and 44 Control subjects. The intention-to-treat analysis, using multiple imputation for missing data, demonstrated that 36% (18/50) of subjects in the Treatment group improved at least 54 meters in 6MWT at 6 months, compared to 18% (9/50) in the Control group (Table 3). Using a multiple imputation analysis for all subjects who didn't perform the 6MWT, the primary endpoint of the study was met (p=0.03).

Selected secondary endpoint outcomes from the REVOLENS trial at 6 and 12 months post treatment are also summarized in Table 3. At both 6 and 12 months, improvements from baseline were seen in the Treatment group compared with the Control group in 6MWT, SGRQ, FEV_1, RV, RV/TLC, and mMRC Dyspnea Scale. Outcomes were comparable in subjects with homogeneous versus heterogeneous emphysema.

Importantly, the 12-month effectiveness outcomes seen in REVOLENS, which enrolled a population of severe emphysema subjects with RV >220% predicted, are consistent with those seen in the RENEW Trial for RV ≥225% subjects.

At 24 months follow-up (n=32), within-treatment group improvements in SGRQ and RV remained substantial (SGRQ: −7.9 ± 14.5 points versus baseline; RV: −0.28 ± 0.69 liters versus baseline), but 6MWT, FEV_1, and mMRC Dyspnea Scale outcomes had returned to baseline or near baseline levels (Deslée 2017, Table 1 therein).

Table 3. Primary and Secondary Effectiveness Endpoints, ITT Population[1] [REVOLENS]

Endpoints	Treatment Group (N=50)	Control Group (N=50)	Difference (One-sided 95% CI)	p-value
Primary Endpoint at 6 Months				
6MWT responder rate (≥54 meters), % (n)	36% (18)	18% (9)	0.18 [0.04, ∞]	0.03
Secondary Endpoints at 6 Months, Mean Change from Baseline [95% CI]				
6MWT, meters	18 [−6, 43]	−3 [−22, 16]	21 [−4, ∞]	0.06
SGRQ, total score	−11.1 [−15.9, −6.2]	2.3 [−1.3, 5.9]	−13.4 [−8, ∞]	<0.001
FEV_1, percent change	9 [4, 14]	−3 [−6, 1]	11 [6, ∞]	0.001
RV, liters	−0.52 [−0.74, −0.31]	−0.15 [−0.41, 0.11]	−0.37 [−0.09, −∞]	0.01
RV/TLC, percent change	−5 [−8, −3]	−1 [−4, 2]	−5.2 [−1.5, −∞]	0.01
mMRC Dyspnea Scale, score	−0.5 [−0.8, −0.2]	−0.1 [−0.3, 0.1]	−0.45 [−0.17, −∞]	0.01
Secondary Endpoints at 12 months, Mean Change from Baseline [95% CI]				
6MWT, meters	−2 [−29, 25]	−23 [−42, −4]	21 [−5, ∞]	0.12
SGRQ, total score	−9.1 [−14.1, −4.2]	1.5 [−1.8, 4.7]	−10.6 [−5.8, −∞]	<0.001
FEV_1, percent change	8 [3, 13]	−3 [−8, 2]	11 [5.2, ∞]	0.002
RV, liters	−0.47 [−0.67, −0.26]	−0.11 [−0.35, 0.12]	−0.36 [−0.10, −∞]	0.004
RV/TLC, percent change	−5 [−7, −2]	0 [−3, 2]	−5 [−1.6, −∞]	0.008
mMRC Dyspnea Scale, score	−0.5 [−0.8, −0.1]	−0.1 [−0.3, −0.1]	−0.4 [−0.05, −∞]	0.02

1 Data source (Deslée 2016)

1.1.6. Safety Results

Safety was evaluated in the REVOLENS trial by assessing SAEs and AEs throughout the study and through a composite safety score (defined in section 1.1.1), assessed at 24 hours and 12 months post treatment.

SAEs were more common in the Treatment group compared to the Control group, with 52% (26 subjects) of Treatment subjects experiencing at least 1 SAE in the 12-month follow-up period compared to 38% (19 subjects) in the Control group (Table 4). The most common SAEs were

COPD exacerbation (26% of Treatment group subjects and 22% of Control group subjects) and pneumonia (18% of Treatment group subjects and 4% of Control group subjects).

The 12-month composite safety score included 17 events in 14 patients (28%) in the Treatment group and 8 events in 6 patients (12%) in the Control group. As seen with the Major Complication outcome from the RENEW Trial (Section 6.6.1 of the Sponsor Executive Summary), the primary driver of the difference in the REVOLENS composite safety score was pneumonia. The incidence of each of the other composite categories was similar between Treatment and Control groups. The mortality rate for both groups was consistent with expectations for the severe emphysema population (11% annually [Fishman 2003]; 15-24% over 3-year period [Jenkins 2009]).

The most frequent non-serious adverse event was mild, self-resolving hemoptysis (<5mL), seen within 30 days of the Coil placement procedure in 48% of Treatment group subjects.

24-month safety follow-up of subjects in the Treatment group was published (Deslée 2017). In the second year after treatment, 2 additional subjects died, and 27 SAEs occurred in 20 subjects (Deslée 2017). Of these, 18 were respiratory events (12 COPD exacerbations, 4 pneumonias, 1 lung transplant, and 1 lung nodule). No pneumothorax, Coil migration, or unexpected SAEs were reported during this period.

Table 4. Summary of Serious Adverse Events through 12 Months[1] [REVOLENS]

Event	Treatment Group			Control Group		Difference, % [95% CI][2]	P-value
	Patients, % (n)	No. of Events		Patients, % (n)	No. of Events at 12 mo		
		≤30 d	>30 d to 12 mo				
COPD exacerbation	26% (13)	4	12	22% (11)	13	4% [−13%, 21%]	0.64
Pneumonia	18% (9)	5	6	4% (2)	2	14% [2%, 26%]	0.03
Pneumothorax	6% (3)	3	1 [3]	2% (1)	1	4% [−4%, 12%]	0.62
Thoracic pain	4% (2)	1	1	4% (2)	2	−2% [−9%, 5%]	0.99
Hemoptysis	2% (1)	1	0	0% (0)	0	2% [−2%, 6%]	0.99
Cardiovascular	2% (1)	1	0	6% (3)	3	−4% [−12%, 4%]	0.62
Other	16% (8)	2	7	12% (6)	7	4% [−10%, 18%]	0.56
Unknown	2% (1)	0	1	0% (0)	0	2% [−2%, 6%]	0.99
Total	52% (26)	17	28	38% (19)	28	14% [−5%, 33%]	0.16

1 Data source (Deslée 2016). Data shown as number of events and number of patients with at least one SAE. Two-sided tests used for safety analyses.
2 Difference between groups in percentage of subjects with events through 12 months.
3 Recurrence of pneumothorax after a first pneumothorax within 1 month after procedure.

Table 5. Composite Safety Score through 12 Months[1] [REVOLENS]

Event	Treatment Group		Control Group		Difference, % [95% CI][2]	P-value
	Patients, % (n)	No. of Events at 12 mo	Patients, % (n)	No. of Events at 12 mo		
Death	8% (4)	4	6% (3)	3	2% [−8%, 12%]	0.99
Pneumothorax	2% (1)	1	0% (0)	0	2% [−2%, 6%]	0.99
Hemoptysis	0% (0)	0	0% (0)	0	n/a	n/a
Invasive ventilation	2% (1)	1	6% (3)	3	−4% [−12%, 4%]	0.62
Pneumonia	18% (9)	11	4% (2)	2	14% [2%, 26%]	0.03
Lung transplantation	0% (0)	0	0% (0)	0	n/a	n/a
Total	28% (14)	17	12% (6)	8	16% [1%, 31%]	0.046

1 Data source (Deslée 2016). Data shown as number of events and number of patients with at least one event. Two-sided tests used for safety analyses.

2 Difference between groups in percentage of subjects with events through 12 months.

1.1.7. Conclusions

The authors of the REVOLENS publication conclude that treatment with the ELEVAIR Coils provides meaningful improvements in exercise capacity, lung function, and quality of life in patients with homogeneous and heterogeneous emphysema. These benefits are sustained for at least 12 months following treatment, with improvement in quality of life (SGRQ) and lung function (RV) continuing through the 24-month follow-up. The types and rates of safety events were similar to expectations from previously published studies of the PneumRx Coils, similar to endobronchial valves, and far less than seen with lung volume reduction surgery. Long-term safety during the second year after treatment was consistent with expectations for the severe emphysema population.

REVOLENS was a randomized clinical trial with a design, duration, patient population, and outcomes assessment that was very similar to that of the RENEW Pivotal Trial. REVOLENS demonstrated comparable safety and effectiveness results to RENEW at both the 12-month primary follow-up and at the 24-month long-term follow-up. The REVOLENS trial population with severe hyperinflation (RV >220%). Thus, REVOLENS supports and confirms the safety and effectiveness of the ELEVAIR System in the treatment of patients with severe emphysema and severe hyperinflation.

1.2. RESET Trial

The summary presented herein focuses primarily on the 3-month randomized phase of the RESET trial (Shah 2013). Outcomes from the crossover portion of the trial, together with follow-up through 12 months have been published (Zoumot 2015).

The ClinicalTrials.gov record for this trial is NCT01334307.

1.2.1. Study Design

RESET was a prospective, multi-center, randomized controlled (standard of care) trial conducted in the United Kingdom to evaluate the safety and effectiveness of the ELEVAIR System in subjects with heterogeneous and homogeneous emphysema.

The study was designed to enroll 45 emphysema subjects, and was powered to test superiority of outcomes in SGRQ total score following treatment with ELEVAIR Coils. Subjects were block randomized to either the Treatment group (ELEVAIR System plus standard of care medical therapy) or the Control group (standard of care medical therapy alone) at a 1:1 ratio. Subjects and Investigators were not blinded to study arm assignment. Subjects randomized to the Treatment group underwent either one or two Coil placement procedures and were followed for 12 months after their final treatment. Following completion of the randomized phase of the study (3 months post-final treatment visit), subjects in the Control group were treated in the "Crossover Phase" with the ELEVAIR System and followed for 12 months following their final Coil treatment, in an identical manner to the subjects randomized to the Treatment group (Zoumot 2015).

Treatment group subjects received either one or two (bilateral) treatments that were separated by approximately 1 month. During individual treatments, Coil placement was restricted to a single lobe in a single lung. Subjects were scheduled for a second treatment if the investigator felt that the subject might benefit from implantation of additional Coils.

The Treatment group underwent the following study procedures and assessments: Pre-Treatment; Treatment #1 followed by 1-week follow-up (phone call only) and 1-month follow-up; Treatment #2 (approximately 1 month after Treatment #1) followed by 1-week follow-up (phone call only) and 1-month and 3-month follow-up visits. The Control group received standard of care medical therapy (without bronchoscopy) and were followed out to 3 months post "treatment" visit.

The safety objective for RESET was to identify the number and type of device and/or procedure-related adverse effects associated with ELEVAIR System therapy. No formal statistical safety hypothesis or prospective success/failure criterion was established. Adverse event information was collected throughout the duration of the study, and the safety analysis consisted of frequency counts and percentage (%) within each adverse event category, as classified using MedDRA terminology. Statistical comparisons between Treatment and Control groups were evaluated with the Fisher's Exact test for AE categories that had an incidence of more than 5% in either study group.

The primary effectiveness endpoint was evaluated at 3 months post-final treatment and assessed the mean absolute change from baseline in SGRQ, comparing Treatment and Control groups. The primary endpoint analysis was based on an analysis of variance (ANOVA) with factors of treatment and investigational site, and study success required that the difference between Treatment and Control groups be statistically significant. Individual subject success criteria (i.e., responder-type analysis) were not prospectively defined.

Secondary effectiveness endpoints were evaluated at both 1 and 3 months post-final treatment and included change from baseline in 6MWT, FEV_1, RV, mMRC Dyspnea Scale, TLC, and supplemental oxygen use, comparing Treatment and Control groups. Secondary effectiveness endpoints were computed following the same methodology specified for the primary endpoint. No prospective success/failure criteria for the secondary effectiveness endpoints were established.

Inclusion criteria for the RESET trial included:

- Patient ≥35 years of age
- High Resolution CT scan indicates unilateral or bilateral emphysema
- High Resolution CT scan indicates homogeneous or heterogeneous emphysema
- Patient has post-bronchodilator FEV_1 ≤45% predicted
- Total Lung Capacity >100%
- Patient has marked dyspnea scoring ≥2 on mMRC scale of 0-4
- Patient has stopped smoking for a minimum of 8 weeks prior to entering the study
- Patient (and legal guardian if applicable) read, understood and signed the Informed Consent form

Exclusion criteria for the RESET trial included:

- Patient has a change in FEV_1 >20% post-bronchodilator.
- Patients DLCO <20% predicted
- Patient has a history of recurrent clinically significant respiratory infection
- Patient has uncontrolled pulmonary hypertension defined by right ventricular pressure >50mmHg and/or evidenced by echocardiogram
- Patient has an inability to walk >140 meters in 6 minutes
- Patient has evidence of other disease that may compromise survival, such as lung cancer, renal failure, etc.
- Patient is pregnant or lactating
- Patient has an inability to tolerate bronchoscopy under heavy sedation or anesthesia
- Patient has clinically significant bronchiectasis
- Patient has giant bullae >1/3 lung volume
- Patient has had previous LVR surgery, lung transplant or lobectomy
- Patient has been involved in other pulmonary drug studies with 30 days prior to the study
- Patient is taking >20mg prednisone (or similar steroid) daily
- Patient is on Plavix or has not been weaned off prior to procedure
- Patient has other disease that would interfere with completion of study, follow up assessments or that would adversely affect outcomes

Subjects in the RESET Trial may or may not have had respiratory rehabilitation therapy prior to their enrollment.

1.2.2. Subject Accountability

Forty-seven (47) subjects were enrolled and randomized at 2 investigational sites in the UK between February 10, 2010 and May 24, 2012. At the primary endpoint analysis (3 months post final Coil treatment), 46 of 47 subjects (97.9%) were available for analysis, with one Control group subject having withdrawn shortly after enrollment.

1.2.3. Subject Demographics and Baseline Disease Characteristics

The Treatment and Control groups were demographically similar, with no notable differences between study arms.

RESET subject baseline disease characteristics are summarized in Table 6. The study arms were imbalanced in emphysema distribution (heterogeneous vs. homogeneous), 6MWT, SGRQ, and mMRC Dyspnea Scale measures. In each case, the Treatment group showed worse baseline values (i.e., more severe disease or greater disability from the disease).

Table 6. Subject Baseline Disease Characteristics [RESET]

Disease Characteristic	Treatment Group (N=23)	Control Group (N=23)	P-value
Emphysema Type, % (n/N)			0.0106
Heterogeneous	52.2% (12/23)	13.0% (3/23)	
Homogeneous	47.8% (11/23)	87.0% (20/23)	
FEV_1 % Predicted, mean ± SD (N)	27.2 ± 8.0 (23)	28.9 ± 6.9 (22)	0.4548
RV % Predicted, mean ± SD (N)	235.8 ± 50.3 (23)	217.6 ± 45.3 (23)	0.2023
RV/TLC Measured (%), mean ± SD (N)	63.7 ± 6.5 (23)	61.6 ± 7.3 (23)	0.3158
6MWT (meters), mean ± SD (N)	293.7 ± 75.5 (23)	346.2 ± 110.9 (23)	0.0673
SGRQ Total Score, mean ± SD (N)	64.3 ± 8.7 (23)	52.5 ± 14.0 (23)	0.0015
Supplemental Oxygen % (n/N)	34.8% (8/23)	21.7% (5/23)	0.5136
mMRC Dyspnea Scale, % (n/N)			0.0472
0	0.0% (0/23)	0.0% (0/23)	
1	0.0% (0/23)	0.0% (0/23)	
2	39.1% (9/23)	73.9% (17/23)	
3	52.2% (12/23)	26.1% (6/23)	
4	8.7% (2/23)	0.0% (0/23)	

1.2.4. Procedural Results

Twenty-one (21) of the 23 subjects (91.3%) randomized to the Treatment group underwent a second (bilateral) treatment, resulting in 44 procedures during the randomized phase of the RESET study. A mean of 9.3 Coils were implanted per procedure, with 78.5% of Coils implanted in the upper lobes (similar distribution left/right). Most procedures were completed in less than 1 hour (mean 44.9 minutes), and 91% of procedures (40/44) resulted in post-procedure hospital stays of 1 day or less.

1.2.5. Effectiveness Results

The primary effectiveness outcome for the RESET Trial was met, with a statistically significant between-group adjusted mean improvement of −10.5 points in SGRQ total score (p=0.004) (Table 7). This improvement is greater than twice the 4-point MCID for SGRQ (Jones 2005, Cazzola 2008, FDA COPD Guidance "Chronic Obstructive Pulmonary Disease: Use of the St. George's Respiratory Questionnaire as a PRO Assessment Tool").

Improvements were also seen in 6MWT, FEV_1, RV, and mMRC Dyspnea Scale in the Treatment group compared to the Control group.

Table 7. Primary and Secondary Effectiveness Endpoints at 3 Months [RESET]

Endpoints[1]	Change vs. Baseline		Difference (Treatment vs. Control)	p-value
	Treatment Group (N=23)	Control Group (N=23)		
Primary Endpoint				
SGRQ (total score)	−9.1 [−14.6, −3.6]	1.4 [−4.1, 6.9]	−10.5 [−17.5, −3.6]	0.004
Secondary Endpoints				
6MWT (meters)	53.0 [29.2, 76.8]	−17.4 [−41.2, 6.4]	70.4 [40.1, 100.7]	<0.001
FEV_1 (percent change)	14.1 [6.7, 21.4]	2.5 [−4.9, 9.9]	11.6 [2.2, 21.0]	0.017
RV (liters)	−0.50 [−0.74, −0.26]	−0.15 [−0.39, 0.08]	−0.35 [−0.65, −0.04]	0.026
mMRC Dyspnea Scale	−0.33 [−0.70, 0.05]	0.15 [−0.22, 0.52]	−0.48 [−0.95, −0.00]	0.049
TLC (liters)	−0.24 [−0.38, −0.09]	−0.13 [−0.28, 0.02]	−0.11 [−0.29, 0.08]	0.264
Supplemental Oxygen (L/min)	−0.04 [−0.25, 0.18]	0.01 [−0.21, 0.22]	0.04 [−0.23, 0.31]	0.750

1 Shown as mean [95% CI]

1.2.6. Safety Results

Safety of the ELEVAIR System was determined through assessment of all reported adverse events. There was no formal statistical safety hypothesis or prospective success/failure criterion.

Deaths: No deaths occurred during the randomized phase of the RESET Trial. During the 12-month follow-up phase of the study, which monitored only Coil-treated subjects from the randomized and crossover phases, 5 deaths occurred, of which none were determined to be device or procedure-related (Zoumot 2015).

Serious Adverse Events: SAEs that were reported during the RESET randomized phase are summarized in Table 8 by incidence and timing relative to the last prior procedure. The most frequent SAEs in the Treatment group were COPD exacerbation (5 events), chest infection (2 events), and pneumothorax (2 events). The most frequent SAEs in the Control group were COPD exacerbation (3 events) and dyspnea (2 events). No meaningful differences were seen between Treatment and Control groups in SAE rates.

Table 8. Serious Adverse Events Reported through 3 Months [RESET]

Serious Adverse Event	Peri-Procedural Period			After Peri-Procedural Period		
	Treatment Group[1] (N=23)	Control Group[1] (N=23)	P-value	Treatment Group[1] (N=23)	Control Group[1] (N=23)	P-value
COPD exacerbation	2 (4.5)	1 (2.4)	>0.9999	3 (6.8)	2 (4.9)	>0.9999
Chest infection	2 (4.5)	0 (0.0)	0.4889	0 (0.0)	0 (0.0)	n/a
Pneumothorax	2 (4.5)	0 (0.0)	0.4889	0 (0.0)	0 (0.0)	n/a
Chest pain	0 (0.0)	0 (0.0)	n/a	1 (2.3)	0 (0.0)	>0.9999
Lower respiratory tract infection	1 (2.3)	0 (0.0)	>0.9999	0 (0.0)	0 (0.0)	n/a
Pneumonia	1 (2.3)	0 (0.0)	>0.9999	0 (0.0)	1 (2.4)	>0.9999
Angina pectoris	1 (2.3)	0 (0.0)	>0.9999	0 (0.0)	0 (0.0)	n/a
Urinary tract infection	0 (0.0)	0 (0.0)	n/a	1 (2.3)	0 (0.0)	>0.9999
Dyspnea	0 (0.0)	0 (0.0)	n/a	0 (0.0)	2 (4.9)	>0.9999

1 Data presented as N events (% procedures).

Adverse Events: AEs that were reported in at least 2.5% of procedures during the RESET Trial, in either the Treatment or Control group, are summarized in Table 9. Of the 94 AEs reported in total, 57 occurred in the Treatment group and 37 occurred in the Control group. Approximately 75% of AEs were respiratory in nature, and 90% were characterized as mild (49.0%) or moderate (41.2%) in severity by the reporting investigator.

The most frequent AEs by procedure were COPD exacerbation, chest infection, and pneumothorax. Similar to the RENEW Trial, the pneumothorax AEs reported during RESET occurred during the peri-procedural period.

No Coil removals or unanticipated adverse device effects (UADEs) occurred during the RESET 3-month follow-up period.

Table 9. Adverse Events Reported through 3 Months[1] [RESET]

Adverse Event	Peri-Procedural Period			After Peri-Procedural Period		
	Treatment Group[2] (N=23)	Control Group[2] (N=23)	P-value	Treatment Group[1] (N=23)	Control Group[1] (N=23)	P-value
COPD exacerbation	10 (22.7)	5 (12.2)	0.3348	8 (18.2)	10 (24.4)	>0.9999
Chest infection	5 (11.4)	1 (2.4)	0.3463	4 (9.1)	2 (4.9)	>0.9999
Chest pain	3 (6.8)	0 (0.0)	0.4889	2 (4.5)	0 (0.0)	0.4889
Pneumothorax	4 (9.1)	0 (0.0)	0.1085	0 (0.0)	0 (0.0)	n/a
Upper respiratory tract infection	3 (6.8)	1 (2.4)	0.6078	0 (0.0)	2 (4.9)	0.4889
Lower respiratory tract infection	1 (2.3)	0 (0.0)	>0.9999	2 (4.5)	1 (2.4)	>0.9999
Productive cough	0 (0.0)	0 (0.0)	n/a	3 (6.8)	0 (0.0)	0.2333
Hemoptysis	1 (2.3)	0 (0.0)	>0.9999	0 (0.0)	0 (0.0)	n/a
Pneumonia	1 (2.3)	0 (0.0)	>0.9999	0 (0.0)	1 (2.4)	>0.9999
Dyspnea	0 (0.0)	0 (0.0)	n/a	1 (2.3)	3 (7.3)	>0.9999
Urinary tract infection	0 (0.0)	0 (0.0)	n/a	1 (2.3)	0 (0.0)	>0.9999

1 Events reported in at least 2.5% of procedures in either study arm are presented.
2 Data presented as N events (% procedures).

Device and/or Procedure-Related Adverse Events: Device and/or procedure-related AEs occurring in the Treatment group during the 3-month follow-up period are summarized in Table 10. The most common related AEs were chest infection (6 events), chest pain (5 events), and pneumothorax (4 events). No subjects withdrew from the study due to an adverse event.

Table 10. Device and/or Procedure-Related Adverse Events Reported through 3 Months [RESET]

Adverse Event	Peri-Procedural Period		After Peri-Procedural Period	
	Events (% Procedures)	Subjects, n (%)	Events (% Procedures)	Subjects, n (%)
Chest infection	4 (9.1)	3 (13.0)	2 (4.5)	2 (8.7)
Chest pain	3 (6.8)	2 (8.7)	2 (4.5)	2 (8.7)
Pneumothorax	4 (9.1)	4 (17.4)	0 (0.0)	0 (0.0)
COPD exacerbation	2 (4.5)	2 (8.7)	1 (2.3)	1 (4.3)
Productive cough	0 (0.0)	0 (0.0)	3 (6.8)	3 (13.0)
Cough	1 (2.3)	1 (4.3)	0 (0.0)	0 (0.0)
Dyspnea	0 (0.0)	0 (0.0)	1 (2.3)	1 (4.3)
Lower respiratory tract infection	1 (2.3)	1 (4.3)	0 (0.0)	0 (0.0)
Pleuritic pain	0 (0.0)	0 (0.0)	1 (2.3)	1 (4.3)
Pneumonia	1 (2.3)	1 (4.3)	0 (0.0)	0 (0.0)
Weight Gain	1 (2.3)	1 (4.3)	0 (0.0)	0 (0.0)

1.2.7. Conclusions

The RESET randomized controlled trial showed that treatment with ELEVAIR Coils can be a safe alternative to standard of care medical therapy, with low SAE rates in a patient population with advanced heterogeneous and homogeneous emphysema. Subjects treated with ELEVAIR Coils showed clinically meaningful benefits over standard of care medical therapy in the trial, with substantial improvements in quality of life (SGRQ, mMRC Dyspnea Scale), lung function (FEV_1, RV), and exercise capacity (6MWT) at 3 months post treatment.

2. OTHER STUDIES AND ANALYSES UNDER THE US IDE PROGRAM

RENEW was a randomized pivotal trial designed to evaluate safety and effectiveness of the ELEVAIR System and to support PMA approval based upon well-defined primary and secondary measures and endpoints. In addition to its randomized phase, RENEW incorporated a Roll-In phase under the same protocol, during which each study site that had not participated in previous clinical trials of the ELEVAIR System (i.e., all North American sites) enrolled up to two subjects who were not part of the randomized study population. These "Roll-In" subjects were intended to provide the investigator and his/her staff with experience in the use of the ELEVAIR System and the treatment procedure prior to initiation of randomization. The Crossover study allows Control subjects who completed the 12-month randomized portion of the RENEW Pivotal Trial and who meet Crossover eligibility criteria to receive treatment with the ELEVAIR System. It was anticipated that the availability of the Crossover study would aid in enrollment into RENEW and would also help to minimize loss-to-follow-up in the RENEW Control group during the control period.

Neither the RENEW Roll-In cohort or Crossover study were designed with the primary goal of demonstrating safety or effectiveness of the ELEVAIR System in the target patient population. These studies were not powered for significance and no success/failure criteria were applied. Subject outcomes at 12 months were compared to baseline values and were analyzed using descriptive statistics.

2.1. RENEW Roll-In Phase

2.1.1. Study Design

The RENEW Roll-In phase enrolled a prospective, multi-center, single arm, assessor-blinded study cohort under the same protocol as the RENEW Randomized Trial. As noted above, the Roll-In phase was intended to ensure that all site investigators and staff participating in the RENEW Trial had experience using the ELEVAIR System prior to initiation of the formal RENEW randomized phase. Data from Roll-In subjects were analyzed separately from that of the RENEW Treatment group.

The first two subjects enrolled during RENEW at each clinical site without prior experience with the device were enrolled as Roll-In subjects. With respect to inclusion and exclusion criteria, treatment and follow-up schedule, and data collection, the Roll-In phase shared the same study design as that of the RENEW Randomized Trial (see Section 6.1 of the Sponsor Executive Summary).

Statistical Methods: The statistical methods pre-specified for analysis of Roll-In data were substantially different from those used for the RENEW Pivotal Trial. Demographics, baseline characteristics, and safety and effectiveness endpoints were summarized using descriptive statistics only. Means, standard deviations and where applicable, medians, minima, and maxima, were reported for continuous endpoints. Categorical variables were reported as percentage, numerator, and denominator. Missing 12-month values for effectiveness endpoints were not imputed.

The proportion of subjects experiencing Major Complications and treatment emergent AEs and SAEs through the 12-month visit were summarized, along with AEs beyond the 12-month visit. MC, SAE, and AE event rates were presented using Poisson regression. AEs were also summarized by time period post-treatment and separately by relatedness to device or procedure.

2.1.2. Subject Accountability

Of 731 subjects screened for the RENEW Trial, 46 were enrolled as Roll-In subjects at 24 North American sites. Forty-one (41) of 46 subjects (89.1%) were available for analysis at the completion of the 12-month follow-up period. Five (5) subjects discontinued prior to the 12-month follow-up; 4 subjects died and 1 subject withdrew consent. 24-month follow-up for the Roll-In cohort is complete, with 32 of 41 (78.0%) eligible subjects completing the study to 24 months.

Table 11. Subject Disposition [Roll-In]

Subject Status	Roll-In
Number of subjects enrolled, n	46
Subjects who completed study to 12 months, %	89.1% (41/46)
Subjects who attended 12-month visit, %	80.4% (37/46)
Subjects who discontinued prior to 12 months, %	10.9% (5/46)
Subjects who died, n	4
Subjects lost to follow-up, n	0
Subjects who withdrew consent, n	1
Subjects withdrawn by investigator, n	0
Subjects who completed study to 24 months, %	78.0% (32/41)
Subjects who attended 24-month visit, %	70.7% (29/41)
Subjects who completed study to 36 months, %	68.8% (22/32) [1]
Subjects who attended 36-month visit, %	56.3% (18/32) [1]

1 36-month follow-up ongoing as of date of data cutoff.

2.1.3. Subject Demographics and Baseline Disease Characteristics

Roll-In subject demographics and baseline characteristics were consistent with those of the RENEW Randomized Pivotal Trial. The Roll-In cohort included subjects with both heterogeneous (34.8%) and homogeneous (65.2%) severe emphysema, characterized by substantial hyperinflation (mean RV of 253% predicted) and flow restriction (mean FEV_1 of 26% predicted) (Table 12).

Table 12. Subject Baseline Disease Characteristics, ITT Population [Roll-In]

Disease Characteristic	Roll-In (N=46)
6MWT (meters), mean ± SD	295.5 ± 90.9
Emphysema Distribution, % (n)	
Heterogeneous	34.8% (16)
Homogeneous	65.2% (30)
Post-bronchodilator Spirometry, mean ± SD	
FVC % Predicted	67.8 ± 17.1
FEV_1 % Predicted	25.5 ± 7.6
FEV_1/FVC (%)	29.3 ± 8.8
Post-bronchodilator Long Volumes, mean ± SD	
RV % Predicted	253.1 ± 43.3
TLC % Predicted	138.7 ± 16.7
RV/TLC Measured (%)	67.9 ± 6.2
Diffusion Capacity (DLCO) % Predicted, mean ± SD	35.5 ± 8.5
Quality of Life	
SGRQ Total Score, mean ± SD	60.9 ± 16.7
mMRC Dyspnea Scale, % (n)	
0	0.0% (0)
1	2.2% (1)
2	37.0% (17)
3	34.8% (16)
4	26.1% (12)
Other Subject Characteristics	
GOLD 4, % (n)	73.9% (34)
BODE Score, mean ± SD	5.9 ± 1.2
Smoking Pack Year History, mean ± SD	53.0 ± 28.3
Number of Comorbidities[1], mean ± SD	2.6 ± 1.7

1 Comorbidities include Arthritis, Cachexia (BMI <18.5 kg/m^2), Cardiac Disease (Angina, Atrial Fibrillation, Congestive Heart Failure, or Coronary Artery Disease), Depression, Diabetes, Edema, GERD, Hyperlipidemia, Hypertension, Obesity (BMI >30 kg/m^2), Osteoporosis, Peripheral Vascular Disease, Renal Dysfunction, Sleep Apnea, and Stroke.

2.1.4. Procedural Results

Apart from procedure time, procedural outcomes for the Roll-In cohort were generally similar to those reported for the RENEW Randomized Trial (see Section 6.4 of the Sponsor Executive Summary). The mean procedure time, defined as the time between bronchoscope insertion and removal, for the Roll-In phase was 58 minutes, compared to 42 minutes for the randomized phase. This finding is likely indicative of the learning curve in a group of investigators who were new to the ELEVAIR System and the placement procedure.

2.1.5. Effectiveness Results

Effectiveness in the Roll-In subjects was evaluated using the same variables (6MWT, FEV_1, and SGRQ) as were used for evaluation of effectiveness for the randomized phase of RENEW. However, the Roll-In phase was not powered for significance and no success/failure criteria were applied.

Descriptive summaries of 12-month effectiveness outcomes versus baseline for the Roll-In subjects are summarized in Table 13 for the ITT and RV ≥225% populations. Roll-In subjects demonstrated improvements in exercise capacity (6MWT), quality of life (SGRQ), and lung function (FEV_1, RV, RV/TLC) compared to baseline that were very similar to those reported for the Treatment group in the randomized phase (see Section 6.5 of the Sponsor Executive Summary). As seen in the RENEW Pivotal Trial, outcomes in the RV ≥225% population were similar to or improved versus those in the ITT population.

Table 13. Effectiveness Outcomes at 12 Months, ITT Population and RV ≥225% Population [Roll-In]

Endpoint	Measure	ITT Population (N=46) [1]	RV ≥225% Population (N=40)[1]
6MWT	Absolute change (meters) Mean ± SD (N) Median Range (min, max)	 6.4 ± 76.0 (36) 8.6 (−174.0, 150.0)	 5.7 ± 74.7 (31) 5.2 (−173.7, 150.0)
	Responder rate, % (n/N)	41.7% (15/36)	38.7% (12/31)
SGRQ	Absolute change (total score) Mean ± SD (N) Median Range (min, max)	 −13.3 ± 18.7 (36) −15.0 (−53.8, 36.5)	 −15.0 ± 18.6 (31) −17.3 (−53.8, 36.5)
	Responder rate, % (n/N)	72.2% (26/36)	77.4% (24/31)
FEV_1	Percent change Mean ± SD (N) Median Range (min, max)	 8.1 ± 30.5 (36) 1.7 (−35.1, 115.9)	 8.7 ± 31.5 (31) 1.7 (−35.1, 115.9)
RV	Absolute change (liters) Mean ± SD (N) Median Range (min, max)	 −0.7 ± 1.0 (35) −0.7 (−3.6, 0.9)	 −0.9 ± 1.0 (30) −0.7 (−3.6, 0.9)
RV/TLC	Absolute change Mean ± SD (N) Median Range (min, max)	 −5.4 ± 8.2 (35) −4.0 (−21.5, 8.0)	 −6.2 ± 7.9 −5.0 (−21.5, 7.0)

1 Missing data were not imputed for the Roll-In cohort.

24-month follow-up for the Roll-In cohort is complete, with follow-up ongoing through 5 years. 6MWT, SGRQ, FEV_1, and RV all continued to show improvement compared to baseline at 24 months in both the ITT and RV ≥225% populations (Table 14).

Table 14. Descriptive Summary of Key Effectiveness Outcomes from Long-term Follow-up, ITT Population [Roll-In]

Outcome	Subjects Who Attended 12 and 24-Month Follow-up Visit			
	ITT Population		RV ≥225% Population	
	Change from Baseline at 12 Months	Change from Baseline at 24 Months	Change from Baseline at 12 Months	Change from Baseline at 24 Months
6MWT (meters)				
Mean ± SD (n)	22.6 ± 68.7 (26)	12.6 ± 78.0 (26)	20.5 ± 71.0 (24)	8.9 ± 80.2 (24)
Median	24.8	16.0	19.7	5.0
Range (min, max)	(−173.7, 150.0)	(−172.2, 161.0)	(−173.7, 150.0)	(−172.2, 161.0)
SGRQ (total score)				
Mean ± SD (n)	−17.0 ± 17.0 (25)	−10.4 ± 18.0 (25)	−18.3 ± 16.2 (23)	−11.0 ± 17.8 (23)
Median	−17.3	−13.0	−17.3	−13.0
Range (min, max)	(−53.8, 19.9)	(−45.4, 17.6)	(−53.8, 19.9)	(−45.4, 17.6)
FEV_1 (percent change)				
Mean ± SD (n)	14.2 ± 32.1 (27)	5.0 ± 37.5 (27)	13.2 ± 32.5 (25)	4.1 ± 38.1 (25)
Median	2.4	−8.0	2.4	−8.0
Range (min, max)	(−27.8, 115.9)	(−35.0, 145.5)	(−27.8, 115.9)	(−35.0, 145.5)
RV (liters)				
Mean ± SD (n)	−1.02 ± 0.95 (25)	−0.69 ± 1.03 (25)	−1.05 ± 0.97 (23)	−0.69 ± 1.07 (23)
Median	−0.73	−0.60	−0.73	−0.60
Range (min, max)	(−3.6, 0.3)	(−3.6, 1.7)	(−3.6, 0.3)	(−3.6, 1.7)

2.1.6. Safety Results

46 subjects were treated with ELEVAIR Coils during the RENEW Roll-In phase. Subjects generally tolerated the procedure well, and in 96% (87/91) of procedures, subjects were discharged from the hospital by the day following the procedure.

Major Complications: 41.3% (19/46) of Roll-In subjects experienced one or more MCs through the 12-month follow-up period (Table 15). As seen in the RENEW Trial, the most common MCs were lower respiratory tract infections (21.7%), including pneumonias, and COPD exacerbations (17.4%). The 12-month mortality rate in the Roll-In cohort was similar to published mortality rates in GOLD 3 and 4 patients (11% annually [Fishman 2003]; 15-24% over 3-year period [Jenkins 2009]). None of the deaths were deemed related to either device or procedure by the reporting investigator.

Table 15. Major Complications through 12 Months, Safety Population [Roll-In]

	Subjects, % (Subject Count) Roll-In (N=46)	Event Rate per Year (Event Count)
Total Major Complication Events [95% CI]	41.3% (19) [27.0%, 56.8%]	0.7241 (34)
Death	8.7% (4)	0.0852 (4)
Pneumothorax	0.0% (0)	0.000 (0)
Hemoptysis	2.2% (1)	0.0213 (1)
COPD Exacerbation	17.4% (8)	0.2981 (14)
Lower Respiratory Infections	21.7% (10)	0.2556 (12)
Respiratory Failure	6.5% (3)	0.0639 (3)
Unanticipated Bronchoscopy	0.0% (0)	0.000 (0)

Serious Adverse Events: SAEs that were reported in at least 2.5% of Roll-In subjects through 12 months are summarized in Table 16. The most common SAEs by subject during the Roll-In phase were COPD exacerbation and pneumonia. The types and incidence of SAEs reported for Roll-In subjects were consistent with safety outcomes for the Treatment group in the RENEW Trial.

Table 16. Most Frequently Reported Serious Adverse Events through 12 Months, Safety Population[1] [Roll-In]

Event (MedDRA)	Subjects, % (Subject Count) Roll-In (N=46)	Event Count
Chronic obstructive pulmonary disease	23.9% (11)	15
Pneumonia[2]	23.9% (11)	16
Pneumothorax	10.9% (5)	5
Respiratory failure	8.7% (4)	4
Pulmonary embolism	6.5% (3)	3
Acute myocardial infarction	4.3% (2)	2
Acute respiratory failure	4.3% (2)	4
Hemoptysis/Hemorrhage[3]	4.3% (2)	2
Myocardial infarction	4.3% (2)	2

1 SAEs reported by 2.5% or more of subjects are presented, in order of decreasing incidence by subject.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.
3 Considered to include any of the following MedDRA preferred terms: Hemoptysis, Post procedural hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Respiratory tract hemorrhage.

Device and/or Procedure-Related Serious Adverse Events: Device and/or procedure-related SAEs that were reported in at least 2.5% of Roll-In subjects through 12 months are summarized in Table 17. The most common device and/or procedure-related SAEs by subject during the Roll-In phase were pneumonia and COPD exacerbation. No notable differences were seen between the device and/or procedure-related SAEs reported for Roll-In subjects and Treatment group subjects enrolled in the RENEW Randomized Trial.

Table 17. Most Frequently Reported Device and/or Procedure-Related Serious Adverse Events through 12 Months, Safety Population[1] [Roll-In]

Event (MedDRA)	Subjects, % (Subject Count) Roll-In (N=46)	Event Count
Pneumonia[2]	21.7% (10)	13
Chronic obstructive pulmonary disease	17.4% (8)	10
Pneumothorax	10.9% (5)	5
Hemoptysis/Hemorrhage[3]	4.3% (2)	2

1 Events that were reported by at least 2.5% of subjects in either study arm are presented, in order of decreasing incidence by subject.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.
3 Considered to include any of the following MedDRA preferred terms: Hemoptysis, Post procedural hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Respiratory tract hemorrhage.

Adverse Events: AEs that were reported in at least 5.0% of Roll-In subjects through 12 months are summarized in Table 18. As seen in the RENEW Trial, the most frequently occurring AEs by subject were COPD exacerbation, hemoptysis, and pneumonia. No Roll-In subjects withdrew from the study during the 12-month follow-up period due to an AE. In general, the types and incidence of AEs experienced in Roll-In subjects are consistent with the adverse event profile seen in Treatment group subjects in the randomized phase of the RENEW Trial.

Table 18. Most Frequently Reported Adverse Events through 12 Months, Safety Population[1] [Roll-In]

Event (MedDRA)	Subjects, % (Subject Count) Roll-In (N=46)	Event Count
Chronic obstructive pulmonary disease	50.0% (23)	38
Hemoptysis	43.5% (20)	32
Pneumonia[2]	26.1% (12)	17
Cough	17.4% (8)	8
Dyspnea	17.4% (8)	9
Non-cardiac chest pain	15.2% (7)	7
Bronchitis	13.0% (6)	10
Edema peripheral	10.9% (5)	5
Nausea	10.9% (5)	6
Pneumothorax	10.9% (5)	6
Upper respiratory tract infection	10.9% (5)	6
Headache	8.7% (4)	6
Medical device complication[3]	8.7% (4)	5
Pleuritic pain	8.7% (4)	4
Productive cough	8.7% (4)	4
Respiratory failure	8.7% (4)	5
Anemia	6.5% (3)	4
Atrial fibrillation	6.5% (3)	3
Cellulitis	6.5% (3)	3
Chest discomfort	6.5% (3)	4
Constipation	6.5% (3)	5
Epistaxis	6.5% (3)	4
Insomnia	6.5% (3)	5
Oropharyngeal pain	6.5% (3)	3
Pulmonary embolism	6.5% (3)	3
Urinary retention	6.5% (3)	3

1 AEs reported by 5.0% or more of subjects are presented, in order of decreasing incidence by subject.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.
3 Adverse events that were recognized as coil-associated opacities (CAOs) at time of diagnosis were categorized under the “Medical device complication” Preferred Term.

Long-Term Safety: 24-month follow-up of Roll-In subjects is complete. Between 12 and 24 months, 32 Roll-In subjects reported 92 AEs, most of which (78.3%, 72/92) were deemed to be unrelated to device or procedure. Five (5) subjects died during this period, and one subject withdrew from the study during this period due to progressive respiratory insufficiency and becoming eligible for lung transplant. The type and frequency of reported AEs is consistent with expectations in a GOLD 3 and GOLD 4 patient population with multiple comorbidities and is consistent with that seen in the Control group of the RENEW randomized study.

Safety in RV ≥225% Population: A post hoc review of safety outcomes was performed for Roll-In subjects with RV ≥225% predicted at baseline, which corresponded to 40 of the 46 total Roll-In subjects in the Safety population. As seen for the RENEW Pivotal Trial, no clinically meaningful differences were seen in the safety profiles between the RV ≥225% subjects and the overall safety population.

2.1.7. Conclusions

The effectiveness and safety outcomes for RENEW Roll-In subjects are consistent with those of the randomized subjects in the RENEW Trial. Improvements in exercise capacity, quality of life, and lung function were seen following Coil treatment and maintained through 24 months. These data support the conclusions from the randomized RENEW Trial that the ELEVAIR System exhibits a positive benefit/risk profile in conjunction with standard-of-care pharmacological treatment in subjects with heterogeneous and homogeneous emphysema.

2.2. Crossover Study

2.2.1. Study Design

The Crossover study was a prospective, multicenter, single-arm study that was established to provide an option for RENEW Control subjects to receive ELEVAIR System therapy upon completion of their 12-month control period, if they continued to meet eligibility requirements.

Subjects enrolled in the Crossover study were screened using similar inclusion and exclusion criteria as the RENEW Randomized Trial population, with the exception that the following non-safety related inclusion criteria were removed: dyspnea score ≥2 on modified Medical Research Council (mMRC) Dyspnea Scale, TLC>100% predicted, and requirement for performing pulmonary rehabilitation. The RV threshold for inclusion into the Crossover study was 175% predicted. Subjects who qualified for study participation based on CT scan findings and the inclusion and exclusion criteria of this study were enrolled for treatment with ELEVAIR Coils.

Pulmonary function tests (excluding spirometry), DLCO, 6MWT, mMRC, and SGRQ data collected for the 12-month visit of the RENEW Trial were reviewed and used as baseline data for the Crossover study, unless the 12-month RENEW data were taken more than 6 weeks prior to a subject's screening for this study. In this case, these tests/questionnaires were repeated. Spirometry was always collected again at Visit 1.

The Crossover subjects followed a similar treatment and follow-up schedule as the RENEW Randomized Trial Treatment group and the Roll-In cohort, except for the timing between Coil placement procedures, which was reduced from 4 months to 2 months based on accumulated safety experience in European studies. Additionally, a more specific recommendation for the initiation of prophylactic corticosteroid treatment was added to the protocol as a result of findings from the RENEW Trial related to CAO. All subjects also received standard-of-care pharmacologic treatment per treating physician determination throughout the study. Following completion of the 12-month visit, subjects will be followed annually for an additional 4 years, for a total of 5 years of follow-up.

Effectiveness in the Crossover subjects was evaluated using the same variables (6MWT, SGRQ, FEV_1, RV) as were used for evaluation of effectiveness for the randomized phase of RENEW. However, the Crossover phase was not powered for significance, no Control group was included for comparison, and no success/failure criteria were applied.

Statistical Methods: The statistical methods for analysis of the single arm Crossover data were substantially different from those used for the RENEW Pivotal Trial. Demographics, baseline characteristics, and safety and effectiveness endpoints were summarized using descriptive statistics only. Means, standard deviations and where applicable, medians, minima, and maxima, were reported for continuous endpoints. Categorical variables were reported as percentage, numerator, and denominator. Missing 12-month values for effectiveness endpoints were not imputed.

The proportion of subjects experiencing Major Complications and treatment emergent AEs and SAEs through the 12-month visit were summarized, along with AEs beyond the 12-month visit. MC, SAE, and AE event rates were presented using Poisson regression. AEs were also summarized by time period post-treatment and separately by relatedness to device or procedure.

2.2.2. Subject Accountability

157 subjects were enrolled in the Control group of the RENEW Trial, and 142 of these subjects completed the RENEW 12-month follow-up period. Of the 124 subjects who completed Crossover study screening, 102 subjects were enrolled into the Crossover study at 23 study sites, and 101 subjects received at least one treatment with ELEVAIR Coils. One additional subject was enrolled, but withdrew consent prior to treatment. The Crossover study began enrollment on December 16, 2013, and subject enrollment was completed on May 25, 2016. 12-month follow-up is complete, with 85% (87/102) of subjects completing the Crossover study through 12 months. 24-month follow-up is ongoing. The disposition of Crossover subjects is summarized in Table 19.

Table 19. Subject Disposition [Crossover]

Subject Status	Crossover (N=102)
Number of subjects, n	
Screened	124
Screen failed	21
Enrolled	102
Enrolled but not treated	1
Subjects who completed study to 12 months, %	85.3% (87/102)
Subjects who attended 12-month visit, %	82.4% (84/102)
Subjects who discontinued prior to 12 months, %	14.7% (15/102)
Subjects who died, n	9
Subjects lost to follow-up, n	0
Subjects who withdrew consent, n	5
Subjects withdrawn by investigator, n	1
Subjects who completed study to 24 months, %	37.9% (33/87) [1]
Subjects who attended 24-month visit, %	29.9% (26/87) [1]

1 24-month follow-up ongoing as of date of data cutoff.

2.2.3. Subject Demographics and Baseline Disease Characteristics

As expected based on study design, subjects enrolled in the Crossover study had demographics and baseline characteristics generally similar to subjects in the RENEW Trial. The study enrolled a group of severe (26.5% GOLD 3 and 73.5% GOLD 4) emphysema patients with substantial hyperinflation (mean RV of 242% predicted), airflow restriction (mean FEV_1 of 26% predicted), and multiple chronic comorbid conditions (Table 20).

Table 20. Subject Baseline Disease Characteristics, ITT Population [Crossover]

Disease Characteristic	Crossover (N=102)
6MWT (meters), mean ± SD	313.6 ± 82.0
Emphysema Distribution, % (n)	
Heterogeneous	19.6% (20)
Homogeneous	80.4% (82)
Post-bronchodilator Spirometry, mean ± SD	
FVC % Predicted	68.6 ± 13.8
FEV_1 % Predicted	26.4 ± 6.2
FEV_1/FVC (%)	29.2 ± 5.9
Post-bronchodilator Long Volumes, mean ± SD	
RV % Predicted	242.1 ± 50.0
TLC % Predicted	140.1 ± 22.4
RV/TLC Measured (%)	67.0 ± 6.4
Diffusion Capacity (DLCO) % Predicted, mean ± SD	34.1 ± 9.9
Quality of Life	
SGRQ Total Score, mean ± SD	57.9 ± 15.6
mMRC Dyspnea Scale, % (n)	
0	0.0% (0)
1	8.8% (9)
2	38.2% (39)
3	33.3% (34)
4	19.6% (20)
Other Subject Characteristics	
GOLD 4, % (n)	73.5% (75)
BODE Score, mean ± SD	5.7 ± 1.4
Smoking Pack Year History, mean ± SD	48.8 ± 21.8
Number of Comorbidities[1], mean ± SD	2.2 ± 1.7

1 Comorbidities include Arthritis, Cachexia (BMI <18.5 kg/m^2), Cardiac Disease (Angina, Atrial Fibrillation, Congestive Heart Failure, or Coronary Artery Disease), Depression, Diabetes, Edema, GERD, Hyperlipidemia, Hypertension, Obesity (BMI >30 kg/m^2), Osteoporosis, Peripheral Vascular Disease, Renal Dysfunction, Sleep Apnea, and Stroke.

2.2.4. Procedural Results

Procedural outcomes for the Crossover study were generally similar to those reported for the RENEW Randomized Trial (see Section 6.4 of the Sponsor Executive Summary). The mean procedure time, defined as the time between bronchoscope insertion and removal, for the Crossover study was 43 minutes, compared to 42 minutes for the randomized phase.

2.2.5. Effectiveness Results

The Crossover study was a single arm study designed to allow Control subjects the opportunity to receive Coil treatment following completion of the RENEW Control period. No power estimates or hypothesis testing were pre-specified in the study protocol. Descriptive summaries of Crossover effectiveness outcomes versus baseline are summarized in Table 21. At 12 months following treatment with the ELEVAIR Coils, improvement was seen in quality of life, and lung function was stable. Exercise capacity, however, declined at 12 months post initial

treatment. Apart from 6MWT, outcomes in the RV ≥225% population were generally similar to or improved versus those in the ITT population.

Table 21. Subject Effectiveness Outcomes at 12 Months, ITT Population and RV ≥225% Population [Crossover]

Endpoint	Measure	ITT Population (N=84)[1]	RV ≥225% Population (N=48)[1]
6MWT	Absolute change (meters) Mean ± SD (N) Median Range (min, max)	 −22.9 ± 72.6 (80) −14.8 (−236.8, 117.4)	 −32.1 ± 79.0 (47) −18.3 (−236.8, 104.0)
	Responder rate, % (n/N)	26.3% (21/80)	25.5% (12/47)
SGRQ	Absolute change (total score) Mean ± SD (N) Median Range (min, max)	 −4.8 ± 14.8 (83) −4.7 (−44.0, 24.5)	 −6.3 ± 13.6 (48) −7.3 (−44.0, 18.6)
	Responder rate, % (n/N)	54.2% (45/83)	60.4% (29/48)
FEV_1	Percent change Mean ± SD (N) Median Range (min, max)	 2.2 ± 21.1 (83) −1.3 (−33.9, 94.4)	 3.0 ± 23.3 (48) −1.9 (−33.9, 94.4)
RV	Absolute change (liters) Mean ± SD (N) Median Range (min, max)	 −0.30 ± 0.70 (81) −0.26 (−2.2, 1.3)	 −0.43 ± 0.74 (47) −0.35 (−2.2, 1.3)
RV/TLC	Absolute change Mean ± SD (N) Median Range (min, max)	 −1.9 ± 6.3 (81) −1.0 (−23.4, 12.5)	 −2.5 ± 6.1 (47) −1.0 (−23.4, 9.0)

1 Missing data in the Crossover study were not imputed.

These 12-month effectiveness outcomes are inconsistent with those seen in the RENEW Randomized Pivotal Trial (see Section 6.5 of the Sponsor Executive Summary), other prior randomized controlled trials of the ELEVAIR System (REVOLENS [Deslée 2016], RESET [Shah 2013]), and a meta-analysis of clinical outcomes across several ELEVAIR System clinical studies (Slebos 2015).

Interpretation of Crossover study outcomes overall is limited due to the absence of randomization, a concurrent Control arm, or pre-specified hypotheses. In addition, several factors may have confounded the Crossover results, including the shorter treatment interval and potential selection bias in those choosing to enroll in Crossover. The non-randomized and uncontrolled nature of the Crossover together with possible confounding factors make the Crossover results uninterpretable.

2.2.6. Safety Results

101 subjects were treated with ELEVAIR Coils during the Crossover study. Subjects generally tolerated the procedure well, and in 96% (188/196) of procedures, subjects were discharged from the hospital within one day of the procedure.

Major Complications: Through the 12-month follow-up, 31.7% (32/101) of the subjects experienced 1 or more MCs (Table 22). The most common major complications by subject were lower respiratory tract infections (16.8%) and COPD exacerbations (9.9%). The proportion of subjects experiencing MCs, as well as the rates of MCs were similar to those reported for the treatment arm of the RENEW Trial. Importantly, the mortality rate in the Crossover study was similar to published mortality rates in GOLD 3 and 4 patients (11% annually [Fishman 2003]; 15-24% over 3-year period [Jenkins 2009]). Six (6) of the 9 deaths were deemed possibly or probably associated with device or procedure.

Table 22. Major Complications through 12 Months, Safety Population [Crossover]

	Subjects, % (Subject Count) Crossover (N=101)	**Event Rate per Year (Event Count)**
Total Major Complication Events [95% CI][2]	31.7% (32) [22.8%, 41.7%]	0.4602 (44)
Death	8.9% (9)	0.0941 (9)
Pneumothorax	0.0% (0)	0.000 (0)
Hemoptysis	4.0% (4)	0.0523 (5)
COPD Exacerbation	9.9% (10)	0.1046 (10)
Lower Respiratory Infections	16.8% (17)	0.1987 (19)
Respiratory Failure	0.0% (0)	0.000 (0)
Unanticipated Bronchoscopy	1.0% (1)	0.0105 (1)

Serious Adverse Events: SAEs that were reported in at least 2.5% of Crossover subjects through 12 months are summarized in Table 23. The most common SAEs by subjects were COPD exacerbation and pneumonia. The types and incidence of SAEs reported during the Crossover study were consistent with safety outcomes for the Treatment group in the RENEW Trial.

Table 23. Most Frequently Reported Serious Adverse Events through 12 Months, Safety Population[1] [Crossover]

Event (MedDRA)	**Subjects, % (Subject Count) Crossover (N=101)**	**Event Count**
Chronic obstructive pulmonary disease	22.8% (23)	29
Pneumonia[2]	17.8% (18)	21
Hemoptysis/Hemorrhage[3]	7.9% (8)	8
Pneumothorax	4.0% (4)	5
Medical device complication[4]	3.0% (3)	3

1 SAEs reported by 2.5% or more of subjects are presented, in order of decreasing incidence by subject.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.
3 Considered to include any of the following MedDRA preferred terms: Hemoptysis, Post procedural hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Respiratory tract hemorrhage.
4 Adverse events that were recognized as coil-associated opacities (CAOs) at time of diagnosis were categorized under the “Medical device complication” Preferred Term.

Device and/or Procedure-Related Serious Adverse Events: Device and/or procedure-related SAEs that were reported in at least 2.5% of Crossover subjects through 12 months are summarized in Table 24. The most common related SAEs by subject were COPD exacerbation and pneumonia. No notable differences were seen between the device and/or procedure-related AEs reported for the Crossover study and the RENEW Trial.

Table 24. Most Frequently Reported Device and/or Procedure-Related Serious Adverse Events through 12 Months, Safety Population[1] [Crossover]

Event (MedDRA)	Subjects, % (Subject Count) Crossover (N=101)	Event Count
Chronic obstructive pulmonary disease	13.9% (14)	18
Pneumonia[2]	12.9% (13)	14
Hemoptysis/Hemorrhage[3]	5.9% (6)	6
Pneumothorax	4.0% (4)	5
Medical device complication[4]	3.0% (3)	3

1 SAEs reported by 2.5% or more of subjects are presented, in order of decreasing incidence by subject.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.
3 Considered to include any of the following MedDRA preferred terms: Hemoptysis, Post procedural hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Respiratory tract hemorrhage.
4 Adverse events that were recognized as coil-associated opacities (CAOs) at time of diagnosis were categorized under the “Medical device complication” Preferred Term.

Adverse Events: AEs that were reported in at least 5.0% of Crossover subjects through 12 months are summarized in Table 25. As seen in the RENEW Trial, the most frequently occurring AEs by subject were COPD exacerbation, hemoptysis, and pneumonia. No Crossover subjects withdrew from the study during the 12-month follow-up period due to an AE. In general, the types of AEs experienced in Crossover subjects are consistent with expectations for this subject group undergoing bronchoscopy (Shah 2011).

Table 25. Most Frequently Reported Adverse Events through 12 Months, Safety Population[1] [Crossover]

Event (MedDRA)	Subjects, % (Subject Count) Crossover (N=101)	Event Count
Chronic obstructive pulmonary disease	61.4% (62)	110
Hemoptysis	57.4% (58)	96
Pneumonia[2]	24.8% (25)	30
Oropharyngeal pain	17.8% (18)	26
Dyspnea	16.8% (17)	21
Cough	15.8% (16)	23
Chest discomfort	14.9% (15)	21
Non-cardiac chest pain	10.9% (11)	14
Bronchitis	8.9% (9)	11
Chest pain	8.9% (9)	9
Headache	8.9% (9)	11
Medical device complication[3]	7.9% (8)	8
Wheezing	6.9% (7)	10
Back pain	5.9% (6)	6
Nasopharyngitis	5.0% (5)	5

1 AEs reported by 5.0% or more of subjects are presented, in order of decreasing incidence by subject.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.
3 Adverse events that were recognized as coil-associated opacities (CAOs) at time of diagnosis were categorized under the “Medical device complication” Preferred Term.

Safety in RV ≥225% Population: A post hoc review of safety outcomes was performed for Crossover subjects with RV ≥225%, which corresponded to 62 of the 101 subjects in the Crossover Safety population overall. As seen for the RENEW Pivotal Trial, no clinically meaningful differences were seen in the safety profiles between the RV ≥225% subjects and the overall safety population.

2.2.7. Conclusions

The safety data collected in the Crossover study to date are consistent with those from the RENEW Trial for use of the ELEVAIR System in conjunction with standard-of-care pharmacological treatment in subjects with bilateral heterogeneous and homogeneous emphysema. Descriptive analyses of 12-month effectiveness results in the Crossover study were inconsistent with those seen in RENEW. Study design factors (non-randomized, lack of concurrent control, change in interval between Coil placement procedures and recommended antibiotic and corticosteroid prophylaxis, potential for selection bias in Crossover enrollment) limit the interpretation and generalizability of these results.

3. OTHER STUDIES CONDUCTED OUTSIDE THE UNITED STATES

In addition to RESET, PneumRx conducted three single-arm clinical studies (CLN0006, CLN0011, and CLN0012) in the EU to support the initial CE mark for the ELEVAIR System[b], as well as to support expansion of the CE mark indications for use. The primary and long-term results of these studies have been published (Herth 2010, Slebos 2012, Deslée 2014, Klooster 2014, Slebos 2015).

These studies incorporated inclusion and exclusion criteria that were similar to the RENEW criteria, and enrolled similar patient populations with severe, bilateral emphysema with substantial flow restriction (mean FEV_1 ≤30% predicted) and hyperinflation (mean RV >240% predicted).

The studies demonstrated consistent and clinically meaningful benefits quality of life (SGRQ), lung function (FEV_1, RV, RV/TLC), and exercise capacity (6MWT) (see Table 26). Adverse events during these studies occurred at rates consistent with expectations for the severe emphysema patient population undergoing multiple bronchoscopy procedures. SAEs reported were generally respiratory in nature (e.g., COPD exacerbation, pneumonia, pneumothorax, hemoptysis, dyspnea, chest pain) and resolved with medical treatment. No deaths occurred during the primary follow-up period in any of the studies.

In addition, PneumRx is conducting a post-market observational Registry in the EU (CLN0014). Enrollment, treatment, and follow-up for the Registry is ongoing. Preliminary outcomes support safety and effectiveness of the ELEVAIR System in the post-market setting (Table 26). Finally, follow-up has recently completed for a small post-market study (n=22) in the EU designed to advance the understanding of the mechanism of action of ELEVAIR Coils (CLN0017 protocol). Analysis of CLN0017 outcomes is ongoing, and results are not available at this time.

[b] At the time these studies were conducted, the ELEVAIR System was branded as the RePneu® (Lung Volume Reduction) Coil System., although the device itself was the same as the current device.

Table 26. Summary of Additional Studies Supporting Use of the ELEVAIR System (Non-IDE)

Clinical Study	Objective	Study Design	Duration of Follow-up	Number of Subjects and Study Sites	Summary of Key Effectiveness Outcomes at Primary Evaluation (Mean Change from Baseline)
CLN0006 (NCT01220908)	Evaluation of safety and performance of the ELEVAIR System in subjects with heterogeneous and homogeneous emphysema	Prospective, multi-center, single-arm, open-label study	3 months post final treatment (extended to 12 months post final treatment at a subset of study sites)	36 subjects, 5 sites	SGRQ: −10.1 points (primary endpoint) 6MWT: +41.8 meters FEV_1: +7.3% RV: −0.32 liters RV/TLC: −2.6%
CLN0011 (NCT01328899)	Evaluation of safety and performance of the ELEVAIR System in subjects with bilateral emphysema	Prospective, multi-center, single-arm, open-label study	6 months post final treatment (extended to 12 months post final treatment at a subset of study sites)	60 subjects, 11 sites	SGRQ: −9.9 points (primary endpoint) FEV_1: +13.0% 6MWT: 33.8 meters RV: −0.58 liters RV/TLC: −4.7%
CLN0012 (NCT01421082)	Evaluation of changes in physiological lung parameters potentially related to ELEVAIR Coil mechanism of action	Prospective, single-center, single-arm open-label study	6 months post initial treatment	10 subjects, 1 site	6MWT: +52.9 meters (primary endpoint) SGRQ: −11.5 FEV_1: +11% RV: −0.66 liters RV/TLC: −7.3%
CLN0014 (NCT01806636)	Post-market registry evaluating patient-reported relief of symptoms following treatment with the ELEVAIR System; advance understanding of patient characteristics that lead to the best outcomes	Post-market, observational, prospective, multi-center registry	3 years post initial treatment	851 subjects, 54 sites	12 months: SGRQ: −5.5 points (primary endpoint) 6MWT: +5.2 meters FEV_1: +1.8% RV: −0.23 liters RV/TLC: −1.6%

4. BIBLIOGRAPHY

For cited references, see the comprehensive bibliography provided with the Sponsor Executive Summary.