ELEVAIR™ Endobronchial Coil System
RENEW Trial Design

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Overview of Trial Design Presentation

- RENEW Trial Design
  - Entry Criteria
  - Effectiveness Endpoints
  - Statistical Methods
  - Pre-specified Subpopulations
- Crossover Study Design
RENEW Pivotal Randomized Trial Design

- **Treatment**:
  - Baseline Visit
  - Randomization (1:1)
  - Treatment 1
  - Treatment 2 (4 months after treatment 1)
  - 12-mo follow-up

- **Control**:
  - Optimal Medical Therapy
  - Bilateral treatment
  - Primary endpoint
  - 12-mo follow-up
  - Long-term follow-up through 5 years
  - Crossover screening

Follow-Up Visits:
- 1-month post-Tx1
- 5-months post-Tx1
- 9-months post-Tx1
RENEW Original Key Trial Entry Criteria

Entry criteria

- CT scan indicated bilateral emphysema, as determined by the Core Radiology Lab using the criteria presented in the "CT Scoring Plan for Core Radiology Lab"
- $\text{FEV}_1 \leq 45\%$ predicted
- Dyspnea scoring $\geq 2$, mMRC scale 0-4
- Smoking cessation $\geq 8$ weeks prior
- Pulmonary or maintenance respiratory rehabilitation
- Ability to walk $>140$ meters (150 yards) in 6 minutes
- RV $\geq 225\%$ predicted
RENEW Amended Key Trial Entry Criteria

Entry criteria

- CT scan indicated bilateral emphysema, as determined by the Core Radiology Lab using the criteria presented in the "CT Scoring Plan for Core Radiology Lab"
- FEV$_1$ \leq 45% predicted
- Dyspnea scoring $\geq$ 2, mMRC scale 0-4
- Smoking cessation $\geq$ 8 weeks prior
- Pulmonary or maintenance respiratory rehabilitation
- Ability to walk $>$ 140 meters (150 yards) in 6 minutes
- RV $\geq 225\%$ predicted, RV $\geq 175\%$ predicted
Subjects assessed for eligibility
N=731

Roll-in N=46

Randomized
N=315

Not enrolled N=370

Treatment
N=158

Completed Month 12
N=138

87% completed

Control
N=157

Completed Month 12
N=140

89% completed

Re-screening

Crossover
N=102
RENEW Effectiveness Endpoints

Primary Endpoint
\( \Delta 6\text{MWT} \) at 12 months

Secondary Endpoints
\%\( \Delta \text{FEV}_1 \)
\( \Delta \text{SGRQ} \)
% 6MWT responders (≥25 m)

Additional Exploratory Effectiveness Endpoints
\( \Delta \text{RV} \)
\( \Delta \text{RV/TLC} \)
% SGRQ responders (≤ -4 points)
RENEW Effectiveness Endpoints
Family-wise Type 1 Error Control

Primary Endpoint
Δ6MWT at 12 months

If significant at α=0.025 1-sided

Secondary Endpoints
%ΔFEV₁
ΔSGRQ
% 6MWT responders (≥25 m)

Hochberg step-up procedure
at α=0.025 1-sided

Additional Exploratory Effectiveness Endpoints
ΔRV
ΔRV/TLC
% SGRQ responders (≤–4 points)

No alpha-control
RENEW Effectiveness Analysis Methods

Non-parametric Rank ANCOVA
\[ \Delta 6\text{MWT} \]
\[ \% \Delta \text{FEV}_1 \]

Parametric ANCOVA
\[ \Delta SGRQ \]

Logistic Regression
\[ \% 6\text{MWT} \text{ responders} \]

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

Primary Endpoint
Δ6MWT at 12 months

Secondary Endpoints
%ΔFEV\textsubscript{1}
ΔSGRQ
% 6MWT responders (≥25 m)

Additional Exploratory Effectiveness Endpoints
ΔRV
ΔRV/TLC
% SGRQ responders (≤ -4 points)

Responder rate analysis
• Clinically meaningful benefit to the subject
• Direct measure of clinical significance
Pre-specified Subpopulations
Not Alpha-Controlled

- Baseline RV status: RV ≥225% vs RV <225%
- Region: US vs OUS
- Disease status: homogeneous vs heterogeneous
- Gender: male vs female
Enrollment in RENEW by Region (OUS vs US) and RV (<225% or ≥225%)

- **US <225%**
- **US ≥225%**
- **OUS <225%**
- **OUS ≥225%**

Subjects enrolled, n

- **US: RV <225%**
- **OUS: RV <225%**
Imbalance of RV (<225% or ≥225%) by Region (OUS vs US)

- Regions were highly imbalanced by baseline RV status
- US enrolled substantially more subjects with RV <225%
- This imbalance drives regional differences in effectiveness

See slides CD-28 through CD-30.
Note: Figure was not provided within the PMA; however, underlying information / analysis was included.
Scientific Credibility of the RV ≥225% Subpopulation

- The trial met the primary analysis for the entire ITT population
- Reduction in RV is the mechanism of action of the coils
- RV ≥225% was the original population and 75% of total enrollment
- Empirical evidence supports the increasing differential benefit for the coils for RV
Crossover Study

- RENEW control group that met similar entry criteria
- Single-armed, observational cohort, with no concurrent control
  - Scientific limitations compared to randomized controlled trials
- Of the 157 controls, 102 subjects crossed over
  - Self-selected, positive performers
  - Potential mathematical regression-to-the-mean
  - Disease progression over time

Subjects elected Crossover screening n=124
Subjects did not elect Crossover screening n=16
Enrolled in Crossover n=102
Completed Crossover 12-month Visit n=84

*1 subject passed screening, but was not enrolled due to physician decision.