Clinical Protocol

Protocol Title:	Study of the **A**eriSeal® **S**ystem for Hy**P**er**I**nflation **R**eduction in **E**mphysema (**ASPIRE**)
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1.0 SYNOPSIS

Title of Study:
Study of the AeriSeal® System for Hyperinflation Reduction in Emphysema (ASPIRE) Trial.

Objective:
Demonstrate the safety and efficacy of AeriSeal System treatment plus optimal medical therapy compared to optimal medical therapy alone in patients with advanced upper lobe predominant (ULP) heterogeneous emphysema.

Phase of Development:
Post-Market in the European Union (EU) and Israel; investigational in the United States (US).

Product Classification:
Class III (US); Class IIb (EU).

Study Design:
Open-label, prospective, randomized, parallel arm, controlled, multi-center through 1 year post treatment with uncontrolled long-term follow-up through 5 years post treatment.

Number of Study Centers Planned:
Approximately 50 international centers.

Number of Patients Planned:
Approximately 300 patients randomized 3:2 treatment:control (180 treatment:120 control)

Randomization Method:
Block randomization per site to ensure an approximately 3:2 distribution of treatment:control patients at each site.

Target Population:
Patients with ULP heterogeneous emphysema as defined in the inclusion/exclusion criteria.

Duration of Study Participation:
Approximately 15 months for screening, pulmonary rehabilitation, baseline, treatment(s) and follow-up to 1 year, and an additional 48 months of long term follow-up for all patients that receive AeriSeal System treatment.

Study Endpoints:
Primary Efficacy Endpoint:
The primary efficacy endpoint is the mean change from baseline in post-bronchodilator Forced Expiratory Volume in 1 Second (FEV_1) at 12 months post treatment.

Secondary Efficacy Endpoints:

1. FEV_1: The proportion of patients achieving at least a 12% and 100 mL increase in post-bronchodilator FEV_1 at 12 months post treatment
2. Upper Lobe Volume by CT Scan: The mean change from baseline in upper lobe volume measured by quantitative CT scan at 12 months post treatment
3. St. George's Respiratory Questionnaire (SGRQ): The proportion of patients achieving at least a 4U decrease in SGRQ total domain score at 12 months post treatment
4. Medical Research Council Dyspnea (MRCD): The proportion of patients achieving at least a 1U decrease in MRCD score at 12 months post treatment
5. Six Minute Walk Test (6MWT): The mean change from baseline in 6MWT at 12 months post treatment

Safety:
AeriSeal System treatment safety will be assessed by monitoring the incidence of Adverse Events (AEs), Serious Adverse Events (SAEs) and Unexpected Adverse Device Effects (UADEs) through the 1st year post treatment. Treatment safety will be assessed during long-term follow-up by monitoring the incidence of a prospectively specified subset of important respiratory related SAEs (pneumothorax, significant hemoptysis, lung cancer, respiratory failure requiring mechanical ventilation > 24 hours, COPD exacerbation, and pneumonia), deaths and UADEs out to 5 years post treatment. Eligible control group patients treated with the AeriSeal System after the first year of follow-up will be included in the assessment of safety during long-term follow-up.

Statistical Analysis:
The primary endpoint will be analyzed by comparing the mean between the two study groups using analysis of covariance adjusting for baseline FEV_1. Study success will be defined as showing a statistically significantly larger mean increase from baseline in the AeriSeal treatment group compared to the control group at 1 year follow-up. For the secondary endpoints, Upper Lobe Volume by CT scan and 6MWT will be analyzed in a manner similar as for the primary endpoint. FEV_1, SGRQ and MRCD will be analyzed by responder analysis. For FEV_1, a positive response will be defined as a $\geq$12% and $\geq$100 mL increase from baseline. For SGRQ, a positive response will be defined as a $\geq$ 4U reduction from baseline. For MRCD, a positive response will be defined as a $\geq$ 1U reduction from baseline.

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3.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADE	Adverse Device Effect
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
aPVA	Aminated Polyvinyl Alcohol
AST	Aspartate Aminotransferase
AT	As Treated
ATS	American Thoracic Society
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CAT	COPD Assessment Test
CO	Carbon Monoxide
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
DL_{CO}	Diffusing Capacity of Carbon Monoxide
DMC	Data Management Committee
ECSC	European Coal and Steel Community
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GA	Glutaraldehyde
GCP	Good Clinical Practices
HbCO	Carboxyhemoglobin
HCG/ β-HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
IC	Inspiratory Capacity
ICF	Informed Consent Form
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to Treat
IV	Intravenous
LVRS	Lung Volume Reduction Surgery
MAC	Medical Assessment Committee
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
MOH	Ministry of Health
MRCD	Medical Research Council Dyspnea
NETT	National Emphysema Treatment Trial
NHLBI	National Heart, Lung and Blood Institute

O_2	Oxygen
PAIR	Post-Treatment Acute Inflammatory Response
PE	Physical Examination
PFT	Pulmonary Function Test
PP	Per Protocol
PT	Prothrombin Time
QOL	Quality of Life
RV	Residual Volume
SAE	Serious Adverse Event
SGRQ	St. George's Respiratory Questionnaire
6MWT	Six-Minute Walk Test
SpO_2	Oxygen Saturation by Pulse Oximeter
TGV	Thoracic Gas Volume
TLC	Total Lung Capacity
TX	Treatment
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
US	United States
VC	Vital Capacity
WHO	World Health Organization

4.0 BACKGROUND

4.1 Emphysema: Current Treatment and Limitations

Emphysema is a progressive, debilitating disease characterized by destruction of lung tissue as a result of inflammation caused by exposure to noxious inhaled agents for extended periods. The most common cause of this condition is cigarette smoking, although genetic, occupational, and environmental causes account for up to 10% of cases.[1] Emphysema is unique among the different forms of chronic obstructive pulmonary disease (COPD) in that it involves irreversible destruction of alveolar tissue of the lung.[2]

The most commonly prescribed therapies for emphysema are bronchodilator and anti-inflammatory drugs, agents that help relieve obstruction to airflow. These agents are beneficial in patients with airway diseases such as asthma and chronic bronchitis, but are less beneficial in emphysema where the primary abnormality is destruction of alveoli, loss of elastic recoil and hyperinflation of the lung. Surgical treatment for emphysema, in the form of lung volume reduction surgery (LVRS), has proven beneficial for selected patients, since it directly addresses the problem of lung hyperinflation through resection of the most damaged tissue. Unfortunately, LVRS involves major thoracic surgery in a high-risk patient population and is associated with substantial morbidity and mortality as well as economic cost.

The AeriSeal System has been shown in prior open-label investigational studies to reduce lung volume, improve lung function, and improve quality of life in patients with advanced emphysema with a favorable risk:benefit profile. Thus the product has been granted CE Mark approval in the European Union (EU) and Ministry of Health (MOH) approval in Israel. The product is Investigational in the US.

4.2 Description of the AeriSeal System

A single subsegmental AeriSeal System treatment consists of 20 mL of Foam Sealant (4.6 mL of Solution A containing 2.1% (w/v) aminated polyvinyl alcohol [aPVA] and 0.5 mL of Solution B containing 1.25% (w/v) of glutaraldehyde [GA]) mixed with 15 mL of air) delivered via a single lumen Catheter.

The procedure for administering the AeriSeal System can be readily taught to pulmonologists skilled in the general technique of bronchoscopy. A training program consisting of didactic and hands-on teaching, case proctoring, and multimedia training materials has been developed for training device users. A similar approach is planned for the post market setting.

Refer to the current AeriSeal System Instructions for Use (IFU) for a description of the product's preparation and administration procedures.

The AeriSeal System is a Class III medical device in the US and a Class IIb medical device in the EU.

4.3 Mechanism of Action

The AeriSeal System functions as a tissue sealant, physically occluding both small airways and collateral air channels, causing the treated areas to collapse via absorption atelectasis. The

resulting reduction in gas trapping and lung hyperinflation restores a more normal physiological relationship between lung and chest wall.

4.4 Nonclinical Information

AeriSeal System treatment has been investigated extensively in large animal models to characterize the acute, subacute, subchronic and chronic effects of treatment exposure as well as in the full array of relevant biocompatibility tests in accordance with ISO 10993. A complete summary of preclinical information regarding the AeriSeal System is available in the Investigator's Brochure.

4.5 Clinical Information

Three open-label, single-arm, multi-center trials of the AeriSeal System have been conducted in Europe and Israel. The first study included 25 patients with upper lobe predominant emphysema who were divided into 3 groups and treated at 2, 3, or 4 unilateral subsegments in a single lobe in a single treatment session. Improvements in spirometry, gas trapping, exercise capacity, symptoms, and health related quality of life were observed at 6 months following AeriSeal System treatment. [3] Short term side effects were more frequent among patients who (i) were treated at 4 subsegments, or (ii) received treatment at adjacent subsegments.

The second study included 56 patients with upper lobe predominant, lower lobe predominant, or homogeneous emphysema. To reduce side effects all patients received peri-procedural steroids and antibiotic prophylaxis and Foam Sealant distribution was limited to non-adjacent subsegments. Patients received initial treatment at 2 subsegments in 1 lobe, and were eligible for repeat treatment after 12 weeks at 2 or 3 additional subsegments in the contralateral lung. Results from this study are summarized in a recent publication and showed that the modified treatment regimen resulted in a substantial improvement in the acute and subacute side effect profile.[4] Patients with upper lobe predominant emphysema and patients with homogeneous emphysema who had reduced perfusion in the upper lobes and were treated in the upper lobes had evidence of improved lung function, gas trapping, and respiratory related quality of life, while results were more variable in patients with lower lobe predominant emphysema and patients with homogeneous emphysema who were treated in the middle and/or lower lobes. Patients with baseline diffusing capacity for carbon monoxide (DLco) values between 20% and 60% responded better to treatment than those outside this range, and patients treated in both lungs (over 2 treatment sessions) had more benefit than those treated in a single lung.

Based upon these results, a third investigational study was undertaken to prospectively confirm that selecting patients with a baseline DLco between 20% and 60% predicted and upper lobe predominant disease or homogeneous disease with decreased upper lobe perfusion, and performing treatment bilaterally in a single treatment session, are associated with improved responses to AeriSeal System treatment. In this study, all patients received treatment bilaterally at 2 non-adjacent subsegments in each upper lobe.

This study was conducted at 2 clinical centers in Israel and enrolled 10 patients with homogeneous emphysema and 10 patients with upper lobe predominant emphysema. All patients received prophylactic antibiotics and steroids. Results from this study show that bilateral upper lobe treatment in patients with advanced upper lobe predominant and

homogeneous emphysema can be performed safely, and is associated with efficacy responses that approximate those reported with surgical lung volume reduction. The treatment algorithm in this study was identical to the treatment algorithm that will be utilized in the present study.[5]

A complete summary of clinical safety and efficacy results from the clinical trials is available in the Investigator's Brochure.

4.6 Risks and Benefits

In prior clinical studies, treatment with the AeriSeal System was shown to reduce lung volume and improve lung function and quality of life in advanced emphysema patients with acceptable risk. Acute side effects following treatment have included transient dyspnea (60%), chest pain/discomfort (50%), fever (20%), leukocytosis, (15%) and pulmonary infiltrates (15%). These are self limited or resolve with supportive care. Side effects that have required hospitalization within the first 90 days include COPD exacerbations (5-10%), pneumonia (1-5%), and bronchitis (2-5%). There has been one treatment-related death associated with AeriSeal System treatment related to an acute pneumothorax (1%) that was attributed to either barotrauma or catheter trauma that developed in the setting of vigorous coughing. This patient died from complications following initial stabilization. Long-term (>12 months) follow-up has shown no significant late treatment-related complications or emergent safety issues.

5.0 STUDY OBJECTIVES AND PURPOSE

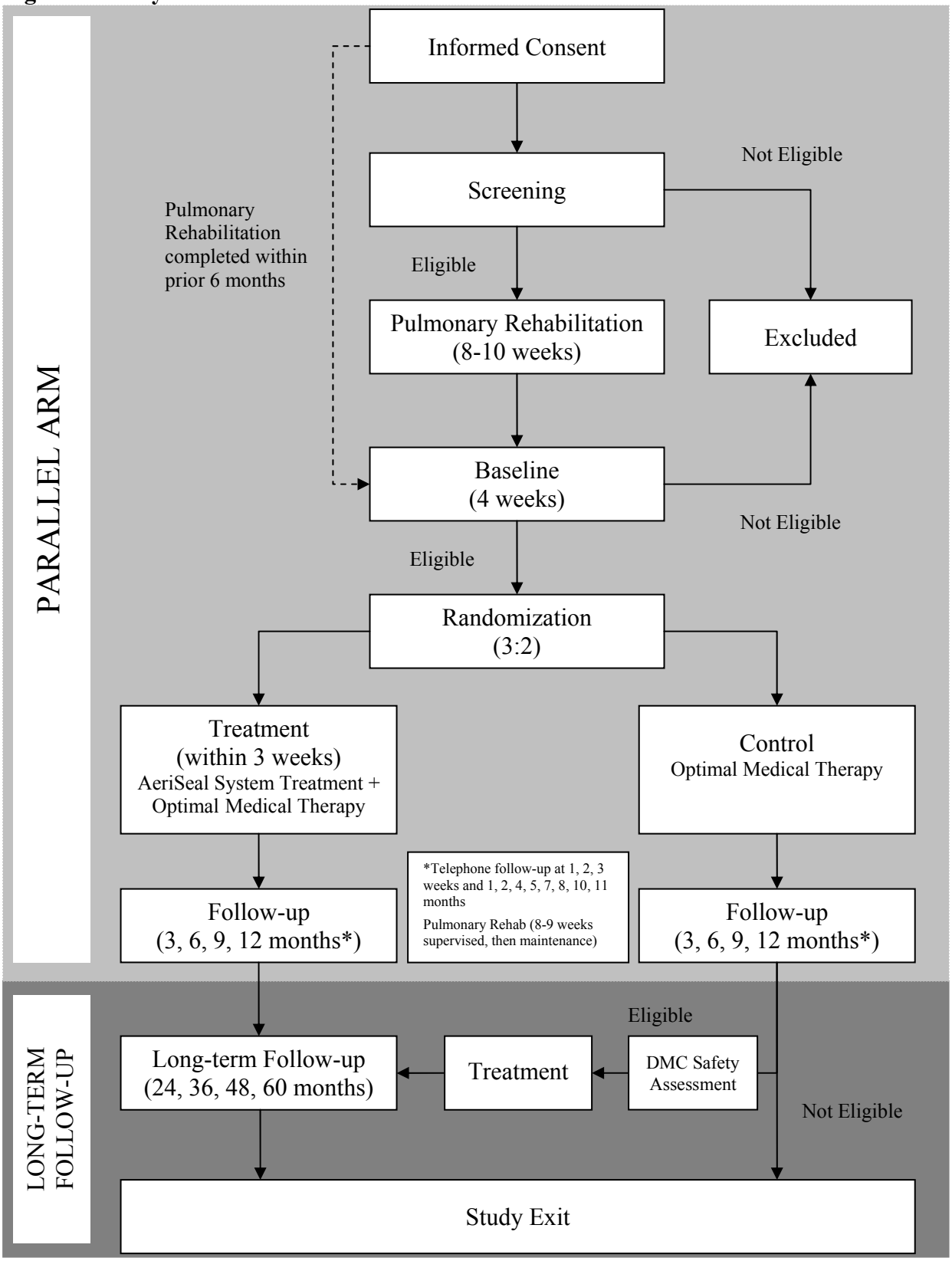
Demonstrate the safety and efficacy of AeriSeal System treatment plus optimal medical therapy compared to optimal medical therapy alone in patients with advanced upper lobe predominant (ULP) heterogeneous emphysema.

6.0 STUDY DESIGN

This is an open-label, prospective, randomized, controlled, parallel group, multicenter clinical trial in which 300 study subjects will be enrolled, treated with either AeriSeal System treatment plus optimal medical therapy or optimal medical therapy alone (3:2 ratio), and followed for 12 months. Control patients will be offered treatment with the AeriSeal System after they have completed their 12 month follow-up if they continue to meet inclusion/exclusion criteria and if treatment of control patients is approved by the DMC and applicable regulatory authorities. All patients treated with the AeriSeal System will be followed for an additional 4 years. The study schema is shown in Figure 1 below.

Only patients with advanced symptomatic emphysema, as defined by study inclusion/exclusion criteria, will be considered candidates for the study. All patients are required to complete a course of pulmonary rehabilitation prior to randomization to ensure that differences in rehabilitation status do not impact patient reported outcomes and to continue pulmonary rehabilitation following randomization. Patients will be assigned to treatment and control groups using a random selection scheme with stratification by site. For patients randomized to the control group, the day of the Randomization visit will be considered the day of treatment.

Figure 1 Study Schema



6.1 Study Endpoints

6.1.1 Primary Endpoint

The primary efficacy endpoint is the mean change from baseline in post-bronchodilator Forced Expiratory Volume in 1 Second (FEV_1) at 12 months post treatment.

Justification of primary endpoint: The primary endpoint will provide an assessment of the effects of treatment on lung function. FEV_1 was selected because:

- FEV_1 is a well-established endpoint that corresponds with disease severity in obstructive lung disease and serves as the basis for the current classification of disease severity;[6]
- In this patient population, FEV_1 is effort independent (as virtually all patients are flow limited) and thus less subject to placebo effects;
- There are well established standards for appropriate measurement and interpretation of FEV_1 and for assuring the quality of the measurements;
- Virtually all patients are familiar with the test and know how to perform it correctly, eliminating potential bias resulting from learning effects.

In summary, FEV_1 is a simple, reproducible, widely-used and relatively unbiased method for objectively assessing response to treatment.

6.1.2 Secondary Endpoints

1. FEV_1: The proportion of patients achieving at least a 12% and 100 mL increase in post-bronchodilator FEV_1 at 12 months post treatment
2. Upper Lobe Volume by CT Scan: The mean change from baseline in upper lobe volume measured by quantitative CT scan at 12 months post treatment
3. St. George's Respiratory Questionnaire (SGRQ): The proportion of patients achieving at least a 4U decrease in SGRQ total domain score at 12 months post treatment
4. Medical Research Council Dyspnea (MRCD): The proportion of patients achieving at least a 1U decrease in MRCD score at 12 months post treatment
5. Six Minute Walk Test (6MWT): The mean change from baseline in 6MWT at 12 months post treatment

6.1.3 Other Outcomes

1. FEV_1: proportion of responders at 3, 6, 9, 24, 36, 48 and 60 months post treatment, mean change from baseline at 3, 6, 9, 24, 36, 48, and 60 months post treatment
2. SGRQ total domain score: proportion of responders at 3, 6 and 9 months post treatment, mean change from baseline at 3, 6, 9 and 12 months post treatment
3. MRCD Score: proportion of responders at 3, 6 and 9 months post treatment, mean change from baseline at 3, 6, 9, and 12 months post treatment
4. Forced Vital Capacity (FVC): proportion of responders and mean change from baseline at 3, 6, 9, 12, 24, 36, 48 and 60 months post treatment
5. Six Minute Walk Test (6MWT) distance: mean change from baseline at 6 months post treatment
6. Residual Volume (RV): mean change from baseline at 12 months post treatment

7. Residual Volume/Total Lung Capacity (RV/TLC): mean change from baseline at 12 months post treatment
8. DL_{CO}: mean change from baseline at 12 months post treatment
9. Oxygen utilization: mean use and proportion of responders at 3, 6, 9 and 12 months post treatment
10. COPD exacerbation rate from 6 to 12 months post treatment
11. BODE index: mean change from baseline at 12 months post treatment
12. COPD Assessment Test (CAT): proportion of responders and mean change from baseline at 12 months post treatment
13. Days alive outside of the hospital from treatment through 7 days (Acute Post-treatment), 8 through 90 days (Early Post-treatment), 91 through 180 days (Intermediate Post-treatment), and 181 days through 1 year (Late Post-treatment)

6.1.4 Safety Assessment

Treatment safety will be assessed by monitoring the incidence of all AEs, SAEs and all UADEs through 1 year post treatment. The incidence of AEs during the first 7 days post treatment (Acute Post-treatment), from 8 to 90 days (Early Post-treatment), from 91 to 180 days (Intermediate Post-treatment), and from 181 days through 1 year (Late Post-treatment) will be tabulated separately. A pre-specified subset of medically significant respiratory events (pleural effusion requiring chest tube drainage, pneumothorax requiring chest tube drainage for > 7 days, massive hemoptysis, lung cancer, respiratory failure requiring mechanical ventilation continuously for > 24 hours, COPD exacerbation requiring hospitalization, and pneumonia requiring hospitalization) will be also be tabulated separately. COPD exacerbations will be further subdivided and analyzed based upon severity.

Safety will be assessed during long-term follow-up by monitoring the incidence of a prospectively defined subset of important respiratory related SAEs (pneumothorax, significant hemoptysis, lung cancer, and respiratory failure requiring mechanical ventilation continuously for > 24 hours), and all COPD exacerbations, pneumonias, deaths and UADEs out to 5 years post randomization. Control group patients treated after the first year of follow-up will be included in the assessment of safety during long-term follow-up. AEs reported in the first year following AeriSeal System treatment of control group patients will be tabulated using the same Acute, Early, Intermediate, and Late Post-treatment windows described above.

7.0 STUDY PARTICIPATION AND TRIAL PERIODS

7.1 Study Duration

Approximately 15 months for screening, pulmonary rehabilitation, baseline, treatment(s) and follow-up to 1 year, and an additional 48 months of long-term follow-up for all patients that receive AeriSeal System treatment. Control group patients enrolled early in the study may need to wait up to several months for treatment after the completion of their 1 year follow-up until the DMC conducts its safety assessment.

8.0 STUDY POPULATION

8.1 Patient Inclusion/Exclusion Criteria (Screening and Baseline)

Inclusion Criteria:

1. Willing and able to provide informed consent and to participate in the study
2. Age ≥ 40 years at the time of the Screening visit
3. On optimal medical therapy (as defined in Section 10.8.1 of the protocol) for more than 1 month prior to Baseline
4. Advanced upper lobe predominant emphysema confirmed by CT scan
5. Two (2) subsegments appropriate for treatment in 2 different upper lobe segments in each lung based upon CT scan (total 4 available subsegments)
6. MRCD score of ≥ 2 post pulmonary rehab (using modified MRCD scale of 0-4)
7. 6MWT distance ≥ 150 m post pulmonary rehab[7]
8. Spirometry 15 minutes after administration of a bronchodilator showing BOTH:
    a. FEV_1 < 50% predicted using the ATS recommended (See NHANES, Hankinson et al. *Am J Respir Crit Care Med.* 1999; 159: 179-187.) calculation for expected value as follows:
        i. Men:
        absolute $FEV_1 = 0.5536 – [0.01303*Age(years)] – [0.000172*Age(years)^2] + [0.00014098*Height(cm)^2]$
        ii. Women:
        absolute $FEV_1 = 0.4333 – [0.00361*Age(years)] – [0.000194*Age(years)^2] + [0.00011496*Height(cm)^2]$
    b. FEV_1/FVC ratio < 70%
9. Plethysomographic lung volumes showing BOTH:
    a. TLC > 100% predicted using the ATS recommended (See ECSC, Stocks and Quanjer. *Eur Respir J.* 1995; 8: 492-506.) calculation for expected value as follows:
        i. Men:
        absolute TLC = [7.99*Height(m)] – 7.08
        ii. Women:
        absolute TLC = [6.6 *Height(m)] – 5.79
    b. RV > 150% predicted using the ATS recommended (See ECSC, Stocks and Quanjer. *Eur Respir J.* 1995; 8: 492-506.) calculation for expected value as follows:
        i. Men:
        absolute RV = [1.31*Height(m)] + [0.022*Age(years)] – 1.23
        ii. Women:
        absolute RV = [1.81*Height(m)] + [0.016*Age(years)] – 2
10. DLco ≥ 20% and ≤ 60% predicted
11. Blood gases and oxygen saturation showing BOTH:
    a. SpO_2 ≥ 90% on ≤ 4 L/min supplemental O_2, at rest
    b. $PaCO_2$ < 65 torr
12. Smoking history of ≥ 20 pack-years with abstinence from 16 weeks prior to the initial Screening visit, confirmed by HbCO, CO, or cotinine

Exclusion Criteria:

1. Prior lung volume reduction surgery, prior lobectomy or pneumonectomy, prior lung transplantation, prior airway stent placement, or prior endobronchial lung volume reduction therapy of any type (unless the stent or device has been removed at least 90 days prior to Baseline and it has been documented that there are no clinical, radiographic or bronchoscopic sequelae). Patients treated with endobronchial fenestrations (Exhale airway stents) are excluded from study participation.
2. Requirement for ventilator support (invasive or non-invasive). Patients on CPAP or BPAP for documented sleep apnea are not excluded from study participation.
3. Three (3) or more COPD exacerbations requiring hospitalization within 1 year of Screening visit or a COPD exacerbation requiring hospitalization within 8 weeks of Screening visit
4. Use of systemic steroids > 20 mg/day or equivalent immunosuppressive agents, heparins, oral anticoagulants (e.g., warfarin, dicumarol; note: antiplatelet drugs including aspirin and clopidogrel are permitted) or investigational medications within 4 weeks of Baseline visit
5. α-1 antitrypsin serum level of <80 mg/dl (immunodiffusion) or < 11 µmol/L (nephelometry) at Screening visit in the absence of enzyme replacement therapy. Patients with documented α-1 antitrypsin deficiency requiring replacement therapy are excluded from study participation.
6. CT scan: ***Presence*** of any of the following radiologic abnormalities:
    a. Pulmonary nodule on CT scan greater than 1.0 cm in diameter (Does not apply if present for 2 years or more without increase in size or if proven benign by biopsy/PET)
    b. Radiologic picture consistent with active pulmonary infection, e.g., unexplained parenchymal infiltrate
    c. Significant interstitial lung disease
    d. Significant pleural disease
    e. Giant bullous disease (a predominant bulla > 10 cm in all dimensions or occupying > approximately 1/3 of the hemithorax)
7. Clinically significant asthma
8. Clinically significant bronchiectasis
9. Pulmonary hypertension, defined as:
    a. Echocardiogram with estimated peak systolic pressure > 45 mm Hg in the presence of tricuspid valve regurgitation stated in the echocardiogram report
    b. If the echocardiogram shows peak systolic pressure > 45 mmHg, right heart catheterization is required to rule out pulmonary hypertension, defined as peak systolic pressure > 45 mmHg or mean pressure > 35 mmHg
10. Allergy or sensitivity to medications required to safely perform AeriSeal System treatment under general anesthesia or conscious (moderate procedural) sedation
11. Participation in an investigational study of a drug, biologic, or device not currently approved for marketing within 30 days prior to the Screening visit
12. Body mass index < 15 kg/m^2 or > 35 kg/m^2
13. Female patient pregnant or breast-feeding or planning to be pregnant in the next year
14. Any abnormal screening laboratory test result as follows:

a. Blood urea nitrogen > 1.5 x upper limit of normal
b. Creatinine > 1.5 x upper limit of normal
c. Aspartate aminotransferase > 1.5 x upper limit of normal
d. Alanine aminotransferase > 1.5 x upper limit of normal
e. Alkaline phosphatase > 1.5 x upper limit of normal
f. White blood cells (total) absolute < 3 x 10^9/L or > 1.25 x upper limit of normal
g. Hematocrit < 34 or > 1.25 x upper limit of normal
h. Platelets < 100 or > 450 K/μL
i. Prothrombin time or INR > 1.5 x upper limit of normal
j. Partial thromboplastin time > 1.5x upper limit of normal
k. Positive β-HCG Pregnancy test (if female)

15. Significant comorbidity that carries prohibitive risks or is associated with less than 2-year expected survival including any of the following:
    a. HIV/AIDs
    b. Active malignancy
    c. Stroke or TIA within 12 months of Screening visit
    d. Myocardial infarction within 12 months of Screening visit
    e. Congestive heart failure within 12 months of Screening visit defined as clinical evidence of right or left heart failure or left ventricular ejection fraction < 45% on echocardiogram
16. Any condition that an Investigator believes would interfere with the intent of the study or would make participation not in the best interest of the patient such as alcoholism, high risk for drug abuse or noncompliance in returning for follow-up visits

9.0 STUDY PROCEDURES

9.1 Informed Consent

Each patient must sign and date a study-specific ICF prior to performing any study-related procedures. This consent form will comply with all applicable regulations governing the protection of human patients.

The Investigator will obtain IRB/IEC written approval of the ICF to be provided to the patients, including IRB/IEC approval of all ICF revisions. Prior to entering the study, the Investigator or an authorized staff member will inform patients about the nature of the study. Patients will have the opportunity to inquire about details of the study and to decide whether to participate. Patients will be instructed that they are free to withdraw their participation in the study at any time without penalty or loss of benefits to which they are otherwise entitled. During the study, the Investigator will inform patients of new information that may be relevant to the patient's willingness to continue participation in the study.

The Investigator will provide each patient with a copy of the signed and dated ICF and will document in the patient's source notes that informed consent was given.

9.2 Medical History

A complete medical history will be elicited for each patient. The medical history will assess the patient for any disqualifying medical conditions as specified in the exclusion criteria.

9.3 Physical Exam

A comprehensive physical exam will be performed at Screening. A directed physical exam (cardiovascular and respiratory systems only) will be performed throughout the rest of the study.

9.4 Vital Signs, Height, Weight and Oxygen Use

Vital signs will include temperature, pulse, blood pressure, SpO_2, height and weight. Oxygen use will be recorded at rest, with activity and during sleep.

9.5 Spirometry

Spirometry will be performed pre and post-bronchodilator administration. Post-bronchodilator measurements should be performed 15-60 minutes following administration of a short-acting beta-agonist bronchodilator (e.g., albuterol 100 μg X 4 puffs) or 30-60 minutes following administration of a short-acting anticholinergic bronchodilator (e.g. ipratropium 40 μg X 4 puffs). Actual values will be reported for the FEV_1 and FVC.

9.6 Plethysmography

Measurement of thoracic gas volume (TGV) and vital capacity (VC) should be performed as linked maneuvers whenever possible to reduce test variability. Performance of the test as an unlinked maneuver should be noted on the Pulmonary Function Test (PFT) form. Plethysmography will be performed only post-bronchodilator administration. Actual values will be reported for total lung capacity (TLC) and VC.

9.7 Diffusing Capacity

Testing will be performed only post-bronchodilator administration. Actual values will be reported for DL_{CO}.

9.8 Six-Minute Walk Test

Whenever possible, patients should complete all 6MWTs using the same amount of supplemental oxygen throughout study participation. For example, if 4 L/min of oxygen is used at Baseline, subsequent 6MWTs should be done on 4 L/min unless this poses a risk to the patient.

9.9 Radiology

The following radiographic tests will be conducted:

1. Chest CT without contrast at full lung inflation
2. Quantitative Perfusion Scan

Investigators will receive detailed training on the evaluation of CT scans for determination of patient eligibility and target site selection. Trained Investigators will perform a visual assessment to determine upper lobe predominance using volumetric CT images obtained at full lung inflation generated according to a uniform, pre-specified acquisition and reconstruction

algorithm which has been validated in Aeris' pilot studies. Investigators will select target sites for treatment by visually identifying the most diseased segments of the upper lobes using the same CT images.

To further ensure consistency in patient and treatment site selection across study sites, CT images will then be forwarded to Aeris where a second visual assessment of disease distribution and appropriate target sites will be performed by a qualified Sponsor representative. In cases of disagreement between the Investigators' and Aeris' evaluations, a third visual assessment will be performed by a different qualified Sponsor representative. If the second Sponsor representative also disagrees with the Investigator's assessment, the patient will be excluded from the study or the Investigator will choose new target sites as appropriate.

A radiology core laboratory will perform quantitative volumetric and densitometry analysis including measurement of Upper Lobe Volumes by CT scan (secondary efficacy endpoint). Core lab assessments will not be used prospectively to assess patient eligibility or select treatment sites.

Quantitative scintigraphy perfusion scanning will be performed at baseline and will be used as an investigational tool to assess whether perfusion scanning can supplement CT imaging.

9.10 Medical Research Council Dyspnea Questionnaire

Dyspnea assessments will be recorded using the modified Medical Research Council Dyspnea (MRCD) questionnaire (0-4 scale). Responses will be recorded directly on the questionnaire by the patient which will be considered a source document. Study personnel will review each questionnaire for completeness.

9.11 St. George's Respiratory Questionnaire

Respiratory-specific health-related quality of life will be assessed using the St. George's Respiratory Questionnaire (SGRQ). Responses will be recorded by the patient directly on the questionnaire which will be considered a source document. Study personnel will review each questionnaire for completeness.

9.12 COPD Assessment Test Questionnaire

COPD specific health-related quality of life will be assessed using the COPD Assessment Test (CAT). Responses will be recorded by the patient directly on the questionnaire which will be considered a source document. Study personnel will review each questionnaire for completeness.

9.13 Cardiology

The following cardiology tests will be conducted:

1. Echocardiogram (ECHO)
2. Electrocardiogram (ECG)

Pulmonary artery pressure and ventricular function should be evaluated as part of the echocardiogram evaluation. If estimated pulmonary artery systolic pressure is assessed by

echocardiography to be > 45 mmHg, but the patient's clinical status is not indicative of clinically significant pulmonary hypertension, a right heart catheterization may be performed to further assess eligibility. Patients in whom pulmonary artery pressure cannot be assessed by echocardiography may be enrolled if right ventricular function is normal and clinical status is not indicative of clinically significant pulmonary hypertension.

9.14 Arterial or Capillary Blood Gases

Blood gas evaluation on **room air** will be utilized to evaluate the patient's gas exchange during the study. Blood gas measurements should be performed after the patient has been seated for 10 minutes breathing room air without supplemental oxygen if the patient can tolerate this.

If a patient is unable to tolerate breathing room air without supplemental oxygen, blood gases may be evaluated on supplemental oxygen. The patient should receive supplemental oxygen at a stable dose for a minimum duration of 10 minutes prior to obtaining the blood gas sample. If the patient is tested on oxygen at Screening, the 12 month blood gas evaluation should be performed on the same amount/method of supplemental oxygen.

9.15 Clinical Laboratory Tests

The clinical laboratory tests to be performed are listed in Table 1. All blood samples for clinical laboratory assays will be collected via venipuncture. Patients should be in a seated or supine position during collection. The clinical laboratory tests will be performed by the local laboratory. The local laboratory will provide detailed instructions on collection, labels, and test requisition forms.

Table 1 Clinical Laboratory Tests

Serum Chemistry	Hematology	Coagulation
Creatinine	White blood cell count	PT or INR
Glucose	Hematocrit	aPTT
Lactate Dehydrogenase	Hemoglobin	
Alkaline Phosphatase	Platelet count	**Other Labs**
Total Bilirubin	Differential (percentage)	β-HCG (serum or urine)
ALT	Neutrophils	HbCO, CO or Cotinine
AST	Lymphocytes	α-1 antitrypsin level
Sodium	Monocytes	
Potassium	Eosinophils	
Total Protein	Basophils	
BUN		
Chloride		
Bicarbonate		

9.16 Telephone Follow-Up

A member of the Investigator's study team will contact the patient by telephone. The patient will be asked about his general well being, AEs, SAEs, changes to medications and participation in maintenance rehabilitation.

10.0 STUDY ACTIVITIES

The Schedule of Events is presented in Table 2.

10.1 Screening

Informed consent must be obtained prior to performing any study-related procedures. After the Informed Consent Form (ICF) has been signed, each patient will be assigned a unique 6-digit patient identification number which includes the 3-digit site number plus a sequential 3-digit patient number starting at 001 (e.g., 801-001) will be assigned. No two patients will have the same six digit patient identification number. This patient identification number will identify the patient throughout the study and will be used for all source documents and CRFs.

Patients will have a Screening visit to assess initial eligibility for inclusion in the trial and pulmonary rehabilitation. Existing imaging and physiology data should be reviewed to determine if the patient is an appropriate study candidate. If the patient is likely eligible, screening PFTs and a chest CT without contrast will be performed to further assess the patient's potential eligibility (the CT will be forwarded to the Sponsor for confirmation of eligibility as described in section 9.9). Conformity with optimal medical therapy as defined in section 10.8.1 will be assessed and changes will be instituted as appropriate. Additional Screening assessments should then be conducted according to the schedule of events in Table 2.

Prior PFTs (spirometry, lung volumes and diffusing capacity), blood gases, CBC, chemistries and echocardiogram may be used for Screening if performed within 6 months of the initial Screening visit and in accordance with the requirements of the protocol. A prior chest CT scan may be used for Screening if performed within 6 months of the initial Screening visit and in accordance with required acquisition and reconstruction algorithms of the study. A prior α-1 antitrypsin test may be used for Screening if adequately documented (date, result, and method of testing). A prior smoking test (HBCO/CO/cotinine) may be used for Screening if performed within 4 weeks of the initial Screening visit.

Patients who fail to meet applicable inclusion/exclusion criteria based upon the results of Screening will be excluded from further study participation.

10.2 Pulmonary Rehabilitation

Pulmonary rehabilitation will include a pre-randomization program, a post-randomization program, and a long-term maintenance program. Pre- and post-randomization pulmonary rehabilitation must be supervised by a physical therapist or respiratory therapist. Long-term maintenance therapy may be completed either as part of a formal supervised program or a home-based program.

Pre-randomization pulmonary rehabilitation will include a minimum of 12 sessions to be completed over 8 - 10 weeks. Programs must include cardiopulmonary exercise, strength training, and disease education components. Every session should include at least 30 minutes of cardiopulmonary exercise consisting of walking or stationary cycling. The educational component should include information about appropriate medication and metered dose inhaler (MDI) spacer usage, smoking cessation, recognition of signs and symptoms of an exacerbation, and nutritional issues related to COPD. Investigators will verify that each patient is enrolled in a program that meets these requirements.

Patients who have completed supervised pulmonary rehabilitation which meets the requirements above within the past 6 months and have continued in either supervised or home-based maintenance will be considered as having completed pre-randomization pulmonary rehabilitation, and will proceed directly to their Baseline visit.

Post-randomization pulmonary rehabilitation will consist of at least 10 sessions over 8-9 weeks. Sessions will meet the same requirements as pre-randomization sessions. For patients in the AeriSeal System treatment group, sessions should begin as soon as possible after the patient has recovered from the procedure. All sessions of post-randomization pulmonary rehabilitation should be completed by the 6 month follow-up visit.

Long-term maintenance rehabilitation will consist of cardiopulmonary exercise twice weekly. Exercise can be performed as part of a home-based walking or cycling program, or a supervised program.

10.3 Baseline

Following completion of pre-randomization pulmonary rehabilitation, patients will complete a Baseline visit. Patients who fail to meet inclusion/exclusion criteria based upon the results of Baseline assessments will be excluded from further study participation and will not undergo additional testing. For those patients who previously completed a satisfactory pulmonary rehabilitation program, test results from the Screening visit will serve as their Baseline (i.e. no replication of procedures). However, in all cases, the tests used to satisfy Baseline requirements must be completed within 4 weeks prior to Randomization. A prior perfusion scan may be used for Baseline if performed within 1 year of the initial Screening visit.

After Baseline testing is complete, the Investigator must review the inclusion and exclusion criteria carefully and determine if the patient meets all eligibility requirements.

In the event of an intervening COPD exacerbation during or after the Baseline testing period, the following assessments must be repeated 2 weeks post resolution of the exacerbation to be eligible for enrollment: physical exam, vital signs, SpO_2, MRCD score, 6MWT, spirometry, plethysmography, DL_{CO}, CAT, and SGRQ.

10.4 Randomization

When Baseline testing is complete, eligible patients will be randomly assigned to the treatment or control group. Whenever possible, patients should be notified of their group assignment in person at the study site. Patients assigned to the control group will be reminded that their continued participation is essential to the conduct of the study and that they will be offered

treatment, if eligible and if treatment of control patients is approved by the DMC and applicable regulatory authorities, after 1 year. They will then immediately enter the follow-up phase of the study. The day of the Randomization visit will be considered the day of treatment for patients in the control group. Patients assigned to the treatment group will be scheduled for treatment and given pre-procedure instructions. AeriSeal System treatment should occur within 3 weeks of randomization.

Randomization will be stratified by study center and will be conducted using a centralized independent randomization system once patient eligibility has been confirmed. Patients will be randomized 3:2 (Treatment:Control). Assignments will be performed using a block randomization scheme to ensure nearly balanced assignments (in accordance with the 3:2 scheme) to treatment and control groups at each study site.

10.5 Treatment

AeriSeal System treatment should occur within 3 weeks of randomization. If a patient has not been treated within 3 weeks of randomization, any Baseline tests conducted more than 7 weeks prior to the planned treatment date must be repeated (quantitative perfusion scan excepted). All patients must be treated within 3 months of randomization.

Two (2) upper lobe subsegments in each lung (4 subsegments total) and 1 potential back-up site on each side will be identified for treatment based upon review of the patient's CT scan as per section 9.9. If during the procedure, the Investigator finds that he/she is unable to access a primary target site because of the airway anatomy, he/she may change one or more target sites to a backup site.

Treatments will be performed in a bronchoscopy suite or operating room under conscious sedation or general anesthesia in accordance with the AeriSeal System IFU. The Sponsor will conduct on-site training during the first treatment(s) at each site. Additional on-site training will be provided as necessary.

Prior to AeriSeal System treatment, patients will be assessed to determine if they are clinically stable to tolerate bronchoscopy and sedation or anesthesia. Patients who are not clinically stable will not be treated. For patients who are clinically stable, cardiac monitoring and continuous pulse oximetry will be initiated. The first dose of a 7-day prophylactic course of systemic antibiotics (e.g. ampicillin/sulbactam or ciprofloxacin) and the first dose of a 7-day steroid taper (prednisolone 100 mg x 1, 75 mg x 2, 50 mg x 2, and 25 mg x 2 or equivalent doses of other corticosteroid) should be initiated 0-2 hours prior to treatment. An inhaled bronchodilator should also be given 15 to 20 minutes prior to treatment. The patient should be adequately sedated or anesthetized including appropriate application of topical anesthesia. If, in the assessment of the Investigator, the patient is not satisfactorily tolerating treatment, the procedure should be terminated.

Once the patient is stabilized, a flexible bronchoscope with an outside diameter of 4.5 to 5.4 mm and a working channel of at least 2mm will be inserted into the airways. A brief survey of the central airways will be conducted. Secretions should be sampled and sent for culture. If any of the following findings are present on endoscopy, the patient should not be treated:

1. Previously unrecognized pharyngeal or laryngeal mass lesion
2. Excessive or purulent secretions suggestive of active infection

3. Significant bleeding
4. Previously unrecognized airway foreign body
5. Previously unrecognized endobronchial mass lesion
6. Airway stenosis, granulation tissue or other abnormality associated with prior airway device placement

Patients with these findings should not be treated until it can be documented that the finding has resolved or would have no effect on study participation.

The orifice of the airway leading to the first target pulmonary subsegment will be identified and inspected. AeriSeal System treatment will be performed in accordance with the AeriSeal System IFU. Treatment sites will be recorded. After treatment of all subsegments is complete, a visual assessment of the airways will be made to verify there are no significant abnormalities before removing the bronchoscope.

The type of bronchoscopy equipment used during the treatment should be documented. Bronchoscope insertion time and removal time will also be documented. Anesthesia medication and oxygen administered will be recorded. AEs and medications given will be documented. A directed physical exam (cardiovascular and respiratory systems only) will be performed upon patient recovery. Patients must be monitored in the bronchoscopy suite or operating room until fully awake before transfer for admission. Patients will be admitted to the hospital for at least overnight observation and discharged when medically stable thereafter.

Patients who are not able to tolerate treatment or who have bronchoscopic findings that prevent treatment may be rescheduled for treatment within 3 months of randomization if the conditions that led to the interruption of the procedure can be resolved. However, patients who receive AeriSeal System treatment in at least one target site prior to the interruption of the procedure are not eligible for additional AeriSeal System treatment and should enter the follow-up phase of the study.

10.6 Follow-up

All patients will be followed to 12 months post treatment. Follow-up visits will occur at 3, 6, 9 and 12 months with telephone follow-up at weeks 1, 2 and 3, and months 1 2, 4, 5, 7, 8, 10 and 11.

10.7 Long-term Follow-up and Treatment of Control Patients

After patients in the control group complete 12 month follow-up, they may elect to undergo AeriSeal System treatment, if eligible and if treatment of control patients is approved by the DMC and applicable regulatory authorities based upon an interim analysis of 12-month safety data on a minimum of 50% of the patients in the treatment group. Treatment with the AeriSeal System must occur within 3 months of the patient's 12 month visit or the DMC's approval, whichever occurs later. If more than 7 weeks have elapsed since the patient's 12 month follow-up visit, Spirometry, DLco, and 6MWT should be repeated to confirm that the patient is still eligible for treatment. All patients treated with the AeriSeal System will enter long-term follow-up for an additional 4 years from their 12 month visit.

Control patients who elect not to undergo treatment after completing their 12 month follow-up or who do not meet treatment eligibility criteria will exit the study.

10.8 Concomitant Medication/Therapy

Concomitant medication use will be recorded from Screening through month 12. Oxygen use at rest, with activity and during sleep will be collected separately. Patients should not decrease or discontinue their baseline COPD medications during the study unless medically necessary. Supplemental oxygen use may be decreased during the study when medically appropriate.

Table 2 Schedule of Events

Event	Screening	8-10 Wks Pulmonary Rehabilitation (12 Sessions)[4]	Baseline[5]	Randomization (Control Group - Day 0)[6]	Day 0 AeriSeal System Tx[7]	Day 1 to discharge[8]	3 Mo (± 3 wks)	6 Mo (± 6 wks)	9 Mo (± 6 wks)	12 Mo (± 6 wks)	Tx of Control Group	24, 36, 48, 60 Mo (± 8 wks)	*Early Term*
Informed Consent	X												
Medical History	X		X										
Adverse Events/Concomitant Medications[9]	X		X		X	X	X	X	X	X	X	X[5]	X
Complete Physical exam	X												X
Directed Physical exam (resp. and cardiac systems only)			X		X (post TX)	X	X	X	X	X	X (post TX)		
Vital Signs, Weight, SpO_2 Height (screening only)	X		X		X	X	X	X	X	X	X		X
O_2 Use	X		X				X	X	X	X			
Spirometry	X[1]		X				X	X	X	X		X	
Lung volumes (Plethysmography)	X[1]		X							X			
DLco	X[1]		X							X			
6MWT	X		X					X		X			
MRCD	X		X				X	X	X	X			
SGRQ	X		X				X	X	X	X			
CAT			X							X			
Blood Gases	X[1]									X			
β-HCG (WOCBP)			X										
HbCO/CO/Cotinine	X[2]							X		X			X
α-1 Antitrypsin	X[3]												
CBC, Chemistries	X[1]		X				X			X			X
Coagulation Labs			X										
Chest CT scan	X[1]									X			
Quantitative Perfusion Scan			X										
Echocardiogram (ECHO)	X[1]												
Electrocardiogram (ECG)	X					X (day 1)							
AeriSeal System Treatment					X						X		
					8-9 Wks Pulmonary Rehabilitation (10 Sessions)				**Maintenance Rehabilitation**					

1. Prior test results may be used for Screening if performed within 6 months of the initial Screening visit and in accordance with the requirements of the protocol.
2. Prior test result may be used for Screening if performed within 4 weeks of the initial Screening visit.
3. Prior test result may be used for Screening if adequately documented.
4. Patients with documented pulmonary rehab may be exempt.
5. Baseline tests must have been completed within 4 weeks prior to Randomization except for Quantitative Perfusion Scan which must have been completed within 1 year prior to Randomization.
6. Randomization will occur if entry criteria are met at Baseline.
7. Treatment is to occur within 3 weeks of randomization.
8. Patients should be hospitalized at least overnight after the AeriSeal System treatment session and discharged when medically stable. The assessments outlined are to be conducted on days 1 through 3 and the day of discharge unless noted above. If a patient is discharged prior to day 3, no additional peri-procedural assessments are required.
9. Long-term follow-up will track only respiratory-specific SAEs, deaths, and UADEs.

Note: If at any time during the course of the follow up in the study, the patient experiences a COPD exacerbation that coincides with a scheduled follow-up visit, the patient should **NOT** be seen for the regularly scheduled study visit. The visit should be re-scheduled within 2 weeks post exacerbation resolution, unless sufficient time has passed to reach another regularly scheduled visit.

Schedule of Telephone Follow-up for AEs/SAEs, ConMeds, Pulm. Rehab	Week 1	Week 2	Week 3	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
	X	X	X	X	X		X	X		X	X		X	X	

10.8.1 Required Medication/Therapy

The AeriSeal System is intended to work in conjunction with optimal medical therapy in patients with advanced emphysema. Guidelines for prescribing medical treatment for emphysema have been published by the American Thoracic Society (ATS) and the National Heart Lung and Blood Institute/World Health Organization (NHLBI/WHO GOLD workshop summary).[5,8,9,10] In accordance with these guidelines, patients enrolled in the study should receive optimal medical therapy as defined in Table 3

Table 3 Optimal Medical Therapy

OPTIMAL MEDICAL THERAPY FOR ASPIRE	
Pharmacologic therapy	
Long-acting bronchodilators:	All patients **must** be on at least 2 long-acting bronchodilators including a beta-agonist and an anticholinergic. Patients with a documented absolute contraindication or medical failure may be on a single long-acting bronchodilator of either class.
Short-acting bronchodilators:	Patients **may** use short-acting bronchodilators (beta-agonist or anticholinergic) as needed in addition to their long-acting bronchodilator(s).
Methylxanthines (Theophylline):	Patients who cannot tolerate inhaled bronchodilators or do not receive adequate relief **may** be on an oral methylxanthine.
Inhaled corticosteroids:	Patients with a history > 1 acute exacerbation in the past year **must** be on an inhaled corticosteroid (unless documented absolute contraindication or medical failure).
PDE-4 inhibitors (Roflumilast):	Patients with a history of > 1 acute exacerbation in the past year **may** be on an oral PDE-4 inhibitor.
Vaccines:	1. All patients **must** receive pneumococcal polysaccharide vaccine x1 (unless documented absolute contraindication).
	2. All patients **must** receive influenza vaccine annually (unless documented absolute contraindication).
Systemic corticosteroids:	Patients **must not** be on systemic corticosteroids at doses greater than prednisone 20 mg/day (or equivalent) except in the setting of an acute exacerbation (or peri-procedure prophylaxis in the AeriSeal System treatment group).
Antibiotics:	Patients **must not** be on systemic antibiotics except in the setting of an acute exacerbation or other infection (or peri-procedure prophylaxis in the AeriSeal System treatment group), with the exception that patients **may** be on once daily azithromycin or equivalent for the prevention of COPD exacerbations.

Table 3 Optimal Medical Therapy (continued)

Non-pharmacologic therapy	
Smoking cessation:	All patients **must** abstain from smoking.
Pulmonary rehabilitation:	All patients **must** participate in pulmonary rehabilitation.
Supplemental oxygen:	Patients with PaO_2 of ≤ 55 torr or SpO_2 ≤ 88% on room air **must** receive long-term supplemental oxygen.

Required medications are detailed in Table 4.

Table 4 Required Medication/Therapy

Medication	Examples
Long-acting bronchodilator inhalers	
Beta-agonist	Salmeterol, formoterol
Anticholinergic	Tiotropium
Inhaled corticosteroids (if > 1 acute exacerbation in past year)	Fluticasone, budesonide, beclomethasone, triamcinolone
Prophylactic antibiotics and steroids (AeriSeal System treatment group only, prior to treatment and continuing for 7 days)	Prednisolone, prednisone or equivalent; ampicillin/sulbactam or ciprofloxacin
Vaccines	
Influenza	
Pneumococcal	
Supplemental oxygen (if PaO_2 of ≤ 55 torr or SpO_2 ≤ 88%)	Nasal cannula 0.5 to 6 L/min
Birth control (if female with childbearing potential)	Birth control pills, birth control patch condom with spermicide, diaphragm

Smoking cessation and pulmonary rehabilitation are also required as described in sections 8.1 and 10.2.

10.8.2 Permitted Medication

Permitted medication is listed in Table 5. Other treatments, including nutrition support programs, homeopathic drugs or herbal medications are also permitted.

In the event a patient experiences a COPD exacerbation post-procedure, they may receive prednisone >20 mg per day per the Investigator's discretion.

Table 5 Permitted Medication

Medication	Examples
Short-acting bronchodilator inhalers	
Beta-agonist	Albuterol, salbutamol
Anticholinergic	Ipratropium
Methylxanthines	Theophylline, aminophylline
Inhaled corticosteroids (if ≤ 1 exacerbation in past year)	Fluticasone, budesonide, beclomethasone, triamcinolone
PDE-4 inhibitors	Roflumilast
Systemic steroids	Prednisone ≤ 20 mg daily (OR > 20 mg/day in setting of acute exacerbation)
Antibiotics (if acute exacerbation or infection or azithromycin once daily or equivalent for prevention of COPD exacerbations)	All types
Nicotine replacement	Gum, patch, inhaler
Other smoking cessation aids	Varenicline, buproprion, clonidine
Benzodiazepines or anti-anxiety agents	Alprazolam, lorazepam, buspirone
Heparin and heparin equivalents (for post-AeriSeal System procedure deep vein thrombosis prophylaxis only)	Heparin, enoxaparin, dalteparin
Antiplatelet drugs	Aspirin, clopidrogel
Other	Other medications to treat concomitant medical problems that are not explicitly listed in prohibited medications list.

10.8.3 Prohibited Medication

The list of medications provided below in Table 6 may increase the risk associated with the procedure. Therefore, the use of these medications is prohibited during the period of **Screening through 6 weeks post-procedure** unless otherwise medically required and documented in the source documents. Immunosuppressive agents, such as those listed in Table 6, and

investigational treatments are prohibited throughout the study. Use of inhaled tobacco products is prohibited for a 16 week period preceding Screening and through the duration of the study.

Table 6 Prohibited Medication

Medication	Examples
4 weeks prior to Baseline through 6 weeks following procedure:	
Anticoagulants except heparin or heparin equivalents for post-procedure deep vein thrombosis prophylaxis	Warfarin, dicumarol
Throughout the study:	
Immunosuppressive agents	Azathioprine, cyclosporine, tacrolimus, methotrexate
Investigational medication or device	Participation in another clinical trial
Inhaled tobacco products	Cigarettes

10.9 Early Termination

When possible, patients who withdraw from the study will be asked to:

1. Perform early termination assessments within 1 week of discontinuation
2. Provide reason for withdrawal

Patients who are within the window of an upcoming study visit should complete assessments for that visit in addition to the early termination assessments. If the patient withdraws because of a treatment related AE/SAE, the patient will be followed until resolution of the event or stabilization. For patients who are lost to follow-up, at least 3 attempts will be made to determine the reason.

11.0 ASSESSMENT OF SAFETY

All AEs, SAEs and UADEs (AEs and SAEs in the control group) must be documented from treatment through 1 year. Medical assessments performed during each scheduled study visit will serve as the primary basis for identifying AEs, SAEs and UADEs. A prospectively defined subset of important respiratory related SAEs (pneumothorax, significant hemoptysis, lung cancer, respiratory failure requiring mechanical ventilation continuously for > 24 hours, COPD exacerbation, and pneumonia), deaths and UADEs must be documented during long-term follow-up of patients treated with the AeriSeal System through 5 years; this will include control group patients treated with the AeriSeal System after their first year of follow-up.

11.1 Definitions

Adverse Event (AE): an unwanted medical occurrence. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease whether or not it is associated with the use of the Investigational Product.

No causal relationship with the clinical trial product is implied by the use of the term "Adverse Event". Exacerbations of a pre-existing condition/illness that are defined as a "more frequent occurrence" or as "an increase in the severity of the pre-existing conditions" are considered AEs.

Serious Adverse Event (SAE): an adverse event that led to a death or led to a serious deterioration in the health of the subject that resulted in a life-threatening illness or injury, a permanent impairment of a body structure or a body function, an in-patient hospitalization or prolongation of existing hospitalization, a medical or surgical intervention to prevent permanent impairment of body structure or a body function, or led to fetal distress, fetal death or a congenital abnormality or birth defect.

Adverse Device Effect (ADE): any untoward and unintended response to a medical device. All adverse device effects (device related AEs) are further categorized as anticipated or unanticipated by the Sponsor. Anticipated events that occur with unusual frequency are also considered unanticipated.

Unanticipated Adverse Device Effect (UADE): any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Post-Treatment Acute Inflammatory Response (PAIR): an expected response following AeriSeal System treatment characterized by fever, dyspnea, cough, chest pain, and or elevated inflammatory markers. PAIR should be diagnosed in patients who have onset of at least 2 of these signs or symptoms in the first 7 days following treatment.

Prolongation of initial post-treatment hospitalization due to PAIR will not be considered an SAE unless the hospitalization extends beyond 7 days. Readmissions for observation for PAIR within the first 7 days following treatment will also not be considered SAEs.

COPD exacerbation: an acute increase or new onset of more than one of the following:

1. cough
2. sputum amount or purulence
3. dyspnea
4. wheeze

beyond a patient's normal day-to-day variation requiring treatment with antibiotics or systemic corticosteroids (or increased corticosteroid dosage).

Onset of these findings in the first 7 days following AeriSeal System treatment should generally be reported as PAIR. Onset of these findings after 7 days should be reported as COPD exacerbation.

COPD exacerbations will be further classified by severity as follows:

1. Mild: treated as outpatient
2. Moderate: requires hospital admission
3. Severe: results in respiratory failure requiring non-invasive or invasive mechanical ventilation.

Pneumonia: Pneumonia will be diagnosed in AeriSeal System treatment patients beyond 7 days post treatment and in all control patients with:

1. fever (T > 101°F or 38.3°C), cough and purulent sputum AND
2. a new or worsened radiographic infiltrate.

In the first 7 days following AeriSeal System treatment, pneumonia will be diagnosed only in patients with:

1. fever (T > 101°F or 38.3°C), cough and purulent sputum AND
2. radiographic infiltrates outside the treatment areas OR cultures growing a respiratory pathogen.

Pneumonias will be further classified by location as follows:

1. Treatment area: new or worsened infiltrate at a site of AeriSeal System treatment
2. Non-treatment area: new or worsened infiltrate at a non-treated site.

Respiratory Failure: dependency on mechanical ventilation continuously for > 24 hrs.

Massive Hemoptysis: hemoptysis resulting in blood loss > 150 mL in ≤ 24 hrs or respiratory failure.

Significant Hemoptysis: non-massive hemoptysis requiring bronchoscopic inspection or hospitalization for management.

Medically Significant Respiratory Events:

1. Pleural effusion requiring chest tube drainage
2. Pneumothorax requiring chest tube drainage for > 7 days
3. Massive hemoptysis
4. Lung cancer
5. Respiratory failure requiring mechanical ventilation continuously for > 24 hours
6. COPD exacerbation requiring hospitalization
7. Pneumonia requiring hospitalization

11.2 Reporting of Adverse Events

Adverse Events and Serious Adverse Events will be documented from the time of treatment (or assignment as a control patient) through 1 year. A prospectively defined subset of important respiratory related SAEs (pneumothorax, significant hemoptysis, lung cancer, respiratory failure requiring mechanical ventilation continuously for > 24 hours, COPD exacerbation, and pneumonia), deaths and UADEs will be documented through study completion. Any changes in a patient's condition noted prior to the procedure should be adequately assessed and included in the medical history for the subject.

When reporting AEs/SAEs, the Investigator will assess the following:

- Description of event
- Outcomes attributed to event
- Onset of event
- Duration of event
- Relationship to device
- Patient Outcome

All AEs/SAEs that result in a patient's withdrawal from the study including death must be reported by calling the Sponsor Safety Line as soon as possible and always within 3 working days of learning of the event.

All SAEs must be reported via written report that is faxed to the Sponsor as soon as possible and always within 3 working days of the Investigator being notified of the event and should include the Investigator's assessment of the event, action that is required, results of any diagnostic tests that were performed, a description of any treatment implemented, a statement of the subject's current clinical status, and the Investigator's signature and date. Investigators shall comply with all local reporting requirements.

The Sponsor is responsible for relaying adequate information on all UADEs to participating Investigators. Regulatory authorities will be informed of all UADEs by the Sponsor. The Sponsor is also responsible for assessing whether a UADE poses an unreasonable risk to patients if the study is continued.

11.3 Follow-up of Patients after Adverse Events / Serious Adverse Events

All AEs/SAEs must be followed until the event has resolved or until the patient has stabilized and follow-up care has been transferred to the patient's primary care physician.

11.4 Medical Assessment Committee

An independent Medical Assessment Committee (MAC) identified prior to the time the first patient is enrolled will be assigned with adjudicating all deaths, SAEs, medically significant respiratory events (as defined in Section 11.1), COPD exacerbations and pneumonias. Other medical questions may also be referred to the MAC at the Sponsor's initiative.

11.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be appointed prior to the time the first patient is enrolled. The DMC will meet bi-annually, or more frequently at the request of the Medical Assessment Committee if specific safety concerns have arisen during the conduct of the study that require independent administrative review. A charter defining the specific functions/duties of the DMC will be developed by the Sponsor and approved by DMC members prior to study initiation. Tasking will include:

1. Reviewing patient enrollment, accrual, and drop-out rates
2. Augmenting enrollment based upon blinded assessment of the drop out rate in the study
3. Assessing the acceptability of treating control patients with the AeriSeal System upon completion of 12 month follow-up of a minimum of 50% of the patients in the treatment group
4. Performing interim safety assessments
5. Reviewing external safety data that could influence study conduct

All deaths occurring during the study will be reported to the DMC Chair within 3 days of the Sponsor's awareness of the event.

12.0 STATISTICS

12.1 General Considerations

This is an open-label, prospective, randomized, parallel arm, controlled, multi-center study through 1 year with uncontrolled long-term follow-up through 5 years. Unless otherwise specified, all safety data, efficacy data, demographic data and other baseline characteristics will be summarized by study group. Continuous data will be summarized by reporting the number of observations, mean, standard deviation, minimum, median, and maximum values. Categorical data will be described using frequency tables showing the number and percentage of subjects falling within a particular category.

12.2 Patient Analysis Sets

12.2.1 Intention to Treat Analysis Set (ITT)

The ITT population will consist of all patients randomized. All efficacy analyses will be carried out on this analysis set. The ITT population will be considered the primary analysis set for efficacy.

12.2.2 As Treated Analysis Set (AT)

The AT population will consist of all patients randomized to the control group and all patients randomized to the treatment group who are taken to the procedure room and begin conscious sedation or anesthesia.

12.2.3 Per Protocol Analysis Set (PP)

The PP population will consist of patients who actually complete therapy according to their randomization assignment and who attend the follow-up visit within the allowable window. Efficacy analyses will also be carried out on this analysis set.

12.2.4 Safety Analysis Set

The AT population will be the primary safety analysis set through 1 year. All patients who receive at least one AeriSeal System treatment will be included in the Safety Analysis set for long-term follow-up.

12.3 Statistical Methods

A detailed prospective Statistical Analysis Plan has been developed for this study and will be finalized prior to the time the first patient is enrolled. Specific information regarding the planned statistical analysis is presented below.

12.3.1 Sample Size Considerations

The primary endpoint of the study is the change in FEV_1 from baseline to 12 months post treatment. The secondary endpoints are (a) incidence of achieving at least a 12% and 100 mL

increase in post-bronchodilator FEV_1 at 12 months post treatment; (b) Upper Lobe Volume by CT scan: change in volume from baseline to 12 months; (c) SGRQ: incidence of achieving at least a 4U decrease in SGRQ total domain score at 12 months post treatment; (d) MRCD: incidence of patients in each group achieving at least a 1U decrease in MRCD score at 12 months post treatment; and (e) 6MWT: change from baseline to 12 months in distance walked.

Assuming a uniform 20% drop-out rate, 300 patients will be randomized (180 treatment, 120 control; see also adaptive sample size plan below). This design ensures adequate power to identify a statistically significant difference between treatment and control response rates for the primary and secondary endpoints with the exception of 6MWT.

The null and alternative hypotheses to be assessed for the primary endpoint are:

$$H_0: \mu_{O+A} = \mu_O$$

vs.

$$H_1: \mu_{O+A} \neq \mu_O$$

where μ_{O+A} and μ_O are the true mean changes from baseline in post-bronchodilator FEV_1 (ml) for the "AeriSeal System treatment plus optimal medical therapy" and "optimal medical therapy alone" study groups, respectively.

Under the assumptions:

- μ_{O+A} = 124ml (corresponds to a 12% increase from baseline, on average, assuming a baseline mean of 1030 ml)
- μ_O = 0 ml
- Standard deviation of 361 ml in the treatment group (based on the observed results in the AeriSeal Pilot Study) and 103 mL in the control group (based on a comparable control group from the literature)
- Two-sided alpha = 0.05

a total evaluable sample size of 240 (144 in the AeriSeal System treatment plus optimal medical therapy group, 96 in the optimal medical therapy group) yields 98% power to reject the null hypothesis in favor of the alternative.

Secondary endpoints will be tested in a sequential manner, in order of clinical importance. The first secondary endpoint to be tested is incidence of achieving at least a 12% and 100 mL increase in post-bronchodilator FEV1 at 12 months post treatment. This will be compared between groups at a two-sided 0.05 level of significance. If a statistically significant beneficial effect of O+A over O is shown, then testing will proceed to the remaining secondary endpoints as detailed below; otherwise, testing on the secondary endpoints will cease.

The null and alternative hypotheses to be assessed for this first secondary endpoint are:

$$H_0: \pi_{O+A=} \pi_O$$

vs.

$$H_1: \pi_{O+A} \neq \pi_O$$

where π_{O+A} and π_O are the true responder rates for the "AeriSeal System treatment plus optimal medical therapy" and "optimal medical therapy alone" study groups, respectively.

Under the assumptions:

- $\pi_{O+A} = 0.56$
- $\pi_O = 0.18$
- Two-sided alpha = 0.05

then a total sample size of 240 (144 in the AeriSeal System treatment plus optimal medical therapy group, 96 in the optimal medical therapy group) yields greater than 99% power to reject the null hypothesis in favor of the alternative.

Again, if this secondary null hypothesis is rejected in favor of O+A at the two-sided 0.05 level of significance, then statistical testing will proceed to the remaining four secondary endpoints. The next secondary endpoint to be tested is Upper Lobe Volume by CT scan: change in volume from baseline to 12 months.

The null and alternative hypotheses to be assessed for this secondary endpoint are:

$$H_0: \gamma_{O+A=} \gamma_O$$

vs.

$$H_1: \gamma_{O+A} \neq \gamma_O$$

where γ_{O+A} and γ_O are the true mean changes from baseline in Upper Lobe Volume by CT scan for the "AeriSeal System treatment plus optimal medical therapy" and "optimal medical therapy alone" study groups, respectively.

Under the assumptions:

- $\gamma_{O+A} = 920$ ml (based on observed results in the AeriSeal Pilot study)
- $\gamma_O = 0$ ml

- Common standard deviation of 525 ml (based on observed results in the AeriSeal Pilot study)
- Two-sided alpha = 0.05

then a total sample size of 240 (144 in the AeriSeal System treatment plus optimal medical therapy group, 96 in the optimal medical therapy group) yields 99% power to reject the null hypothesis in favor of the alternative.

If the CT volume null hypothesis is rejected at the 0.05 level of significance in the appropriate direction favoring AeriSeal, then simultaneous testing will proceed on the next two secondary endpoints of SGRQ: incidence of achieving at least a 4U decrease in SGRQ total domain score at 12 months post treatment; and MRCD: incidence of achieving at least a 1U decrease in MRCD score at 12 months post treatment. The null and alternative hypotheses to be assessed for these endpoints are:

$H_0: \delta_{O+A} = \delta_O$ vs. $H_1: \delta_{O+A} \neq \delta_O$

$H_0: \tau_{O+A} = \tau_O$ vs. $H_1: \tau_{O+A} \neq \tau_O$

where δ_{O+A} and δ_O are the true SGRQ responder rates for the "AeriSeal System treatment plus optimal medical therapy" and "optimal medical therapy alone" study groups, respectively, and τ_{O+A} and τ_O are the true of MRCD responder rates for the "AeriSeal System treatment plus optimal medical therapy" and "optimal medical therapy alone" study groups, respectively. To control Type I error at an overall two-sided 0.05 significance level across the simultaneous assessment of these two hypotheses, the Benjamini-Hochberg procedure will be used. Specifically, if both above null hypotheses are rejected at the two-sided 0.05 level of significance (and in the appropriate direction favoring AeriSeal System treatment) then AeriSeal System treatment will be considered to perform significantly better than control on both endpoints. Otherwise, if one null hypothesis is rejected at the two-sided 0.025 level of significance, and in the appropriate direction, then the experimental treatment will be considered to perform significantly better than control on the one endpoint corresponding to that hypothesis.

With a total sample size of 240 (144 in the AeriSeal System treatment plus optimal medical therapy group, 96 in the optimal medical therapy group), and under the assumptions:

- $\delta_O = 0.18$
  $\delta_{O+A} = 0.39$

- $\tau_O = 0.30$
  $\tau_{O+A} = 0.56$

then there is over 90% power to (a) reject at least one of the secondary endpoint null hypotheses using a two-sided 0.025 level of significance for each, and (b) reject both secondary endpoint null hypotheses using a two-sided 0.05 level of significance for each.

If the Benjamini-Hochberg approach yields a successful result for at least one of these two secondary endpoints, then testing of study group difference will be carried out on the final secondary endpoint of Six Minute Walk Test (6MWT): The mean change from baseline in 6MWT at 12 months post treatment in each group.

The null and alternative hypotheses to be assessed for this final secondary endpoint are:

$$H_0: \lambda_{O+A} = \lambda_O$$

vs.

$$H_1: \lambda_{O+A} \neq \lambda_O$$

where λ_{O+A} and λ_O are the true mean changes from baseline in 6MWT for the "AeriSeal System treatment plus optimal medical therapy" and "optimal medical therapy alone" study groups, respectively. The null hypothesis will be assessed at a two-sided Type I error rate of 0.05.

From the AeriSeal pilot study, a mean change from baseline for AeriSeal of +18.5 was observed, with a standard deviation of 63. Using these assumptions as the true AeriSeal benefit, even if the mean change for the control group is 0, power is only approximately 55% to reject the above null hypothesis in favor of the alternative. The true average control group change in 6MWT would need to be -6 (a worsening from baseline) in order to have 80% power to detect a significant benefit of O+A over O.

12.3.2 Efficacy Analysis

12.3.2.1 Primary Endpoint

The following analysis will be carried out on the ITT and PP analysis sets. The ITT analysis set is considered the primary efficacy analysis set.

The primary endpoint is the change in post-bronchodilator FEV_1 from baseline to month 12. The mean of the primary endpoint will be compared between the study groups using analysis of covariance adjusting for baseline FEV_1. The test will be performed at an overall two-sided significance level of 0.05. Study success will be defined as showing a statistically significantly greater increase in post-bronchodilator FEV_1 in the AeriSeal System treatment group compared to the control group in the ITT analysis set.

For the ITT analysis set, several methods for imputation of missing primary endpoint data at the 12 month time point will be undertaken, with results descriptively compared across the methods to assess sensitivity of results to missing data (missing data is expected to primarily occur due to premature withdrawal from the study). Multiple imputation will be considered the primary analysis method and will be used in the determination of study success. Further details are provided in the Statistical Analysis Plan.

12.3.2.2 Secondary Endpoints

The following secondary endpoints will be analyzed for the ITT and PP analysis sets:

1. FEV_1: The proportion of patients achieving at least a 12% and 100 mL increase in post-bronchodilator FEV_1 at 12 months post treatment
2. Upper Lobe Volume by CT Scan: The mean change from baseline in upper lobe volume measured by quantitative CT scan at 12 months post treatment
3. St. George's Respiratory Questionnaire (SGRQ): The proportion of patients achieving at least a 4U decrease in SGRQ total domain score at 12 months post treatment
4. Medical Research Council Dyspnea (MRCD): The proportion of patients achieving at least a 1U decrease in MRCD score at 12 months post treatment
5. Six Minute Walk Test (6MWT): The mean change from baseline in 6MWT at 12 months post treatment

The secondary endpoints will be tested in a sequential manner, ordered by clinical importance. The ITT analysis set is considered the primary analysis set. Imputation for missing data will be carried out in a similar manner as for the primary endpoint. Detailed analysis methods are described in the Statistical Analysis Plan.

12.3.2.3 Other Outcomes

Other Outcomes for the study will include the following:

1. FEV_1: proportion of responders at 3, 6, 9, 24, 36, 48 and 60 months post treatment, mean change from baseline at 3, 6, 9, 24, 36, 48, and 60 months post treatment
2. SGRQ total domain score: proportion of responders at 3, 6 and 9 months post treatment, mean change from baseline at 3, 6, 9 and 12 months post treatment
3. MRCD Score: proportion of responders at 3, 6 and 9 months post treatment, mean change from baseline at 3, 6, 9, and 12 months post treatment
4. Forced Vital Capacity (FVC): proportion of responders and mean change from baseline at 3, 6, 9, 12, 24, 36, 48 and 60 months post treatment
5. Six Minute Walk Test (6MWT) distance: mean change from baseline at 6 months post treatment
6. Residual Volume (RV): mean change from baseline to 12 months post treatment
7. Residual Volume/Total Lung Capacity (RV/TLC): mean change from baseline to 12 months post treatment
8. DL_{CO}: mean change from baseline to 12 months post treatment
9. Oxygen utilization: mean use and proportion of responders at 3, 6, 9 and 12 months post treatment
10. COPD exacerbation rate from 6 to 12 months post treatment
11. BODE index: mean change from baseline at 12 months post treatment
12. COPD Assessment Test (CAT): proportion of responders and mean change from baseline at 12 months post treatment

13. Days alive outside of the hospital from treatment through 7 days (Acute Post-treatment), 8 through 90 days (Early Post-treatment), 91 through 180 days (Intermediate Post-treatment), and 181 days through 1 year (Late Post-treatment)

Descriptive statistics will be provided for the Other Outcomes for the ITT and PP populations. No imputation for missing values will be performed.

12.3.2.4 Exploratory Analyses

Core lab quantitative CT assessments will be used to conduct exploratory analyses including:

1. Correlation between baseline heterogeneity index (HI) at -910 HU and efficacy
2. Correlation between baseline heterogeneity index (HI) at -950 HU and efficacy
3. Correlation between % Voxels < -910 HU in lower lobes and efficacy
4. Correlation between % Voxels < -950 HU in lower lobes and efficacy
5. HI at -910 HU cutoff corresponding to qualitative upper lobe predominance determination
6. HI at -950 HU cutoff corresponding to qualitative upper lobe predominance
7. % Voxels < -910 HU in lower lobes cutoff corresponding to qualitative upper lobe predominance determination
8. % Voxels < -910 HU in lower lobes cutoff corresponding to qualitative upper lobe predominance determination
9. % Voxels < -910 HU in target areas compared to non-target areas
10. % Voxels < -950 HU in target areas compared to non-target areas

Quantitative scintigraphy perfusion scanning will be used to conduct exploratory analyses on whether perfusion scanning can supplement CT imaging for patient and target site selection.

12.3.3 Safety Data Analysis

The safety analysis will be carried out on the Safety Analysis Set.

12.3.3.1 Adverse Events

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be coded using the MedDRA dictionary to a preferred term and system organ class. The incidence of AEs will be presented for each study group by preferred term and system organ class; patients experiencing more than one AE within a given preferred term or system organ class will be counted once within the preferred term or system organ class.

Prolongation of initial post-treatment hospitalization due to PAIR will not be considered an SAE unless the hospitalization extends beyond 7 days. Readmissions for observation for PAIR within the first 7 days following treatment will also not be considered SAEs.

Due to the severity of illness in the target population and the nature of the treatment, it is anticipated that there may be an increase in peri-procedural AEs and SAEs in the AeriSeal System treatment group. This increase is expected to be balanced by benefit beyond the peri-procedural period. Therefore, the incidence of treatment emergent AEs and SAEs from treatment

through 7 days (Acute Post-treatment), 8 through 90 days (Early Post-treatment), 91 through 180 days (Intermediate Post-treatment), and 181 days through 1 year (Late Post-treatment) will be compared between study groups separately, by preferred term and system organ class.

A pre-specified subset of medically significant respiratory events (pleural effusion requiring chest tube drainage, pneumothorax requiring chest tube drainage for > 7 days, massive hemoptysis, lung cancer, respiratory failure requiring mechanical ventilation continuously for > 24 hours, COPD exacerbation requiring hospitalization, and pneumonia requiring hospitalization) will be also be tabulated separately.

COPD exacerbations will be further subdivided and analyzed based upon severity.

During long-term follow-up, the incidence of a prospectively defined subset of important respiratory related SAEs (pneumothorax, significant hemoptysis, lung cancer, respiratory failure requiring mechanical ventilation continuously for > 24 hours, COPD exacerbation, and pneumonia), deaths and UADEs out to 5 years post randomization will be tabulated. Events in control group patients treated after the first year of follow-up will be included. Events reported in the first year following AeriSeal System treatment of control group patients will be tabulated using the same Acute, Early, Intermediate, and Late Post-treatment windows described above.

12.3.4 Demographic Data

Demographic data consists of demographic characteristics, medical history, respiratory history, COPD maintenance medication usage, and smoking history. Summaries of demographic data will be based on the ITT and AT populations. Categorical data will be summarized using frequencies and percentages based on non-missing values; continuous data will be summarized using mean, standard deviation, median, minimum, and maximum.

12.3.5 Interim Futility Assessment

When at least 100 patients have 6 month data available, the DMC will perform an unblinded assessment of available FEV_1 data to assess futility. Details of this analysis are included in the Statistical Analysis Plan and the DMC Charter.

12.4 Enrollment and Sample Size

12.4.1 Adaptive Blinded Sample Size Selection

Based upon power calculations targeting the most conservative secondary endpoint, 240 evaluable patients, randomized 3:2 (treatment:control) are needed. Assuming a uniform 20% drop-out rate, this will require 300 enrolled patients (180 treatment, 120 control).

A blinded assessment of enrollment status will be performed by the DMC and presented at open session after enrollment of the 270^{th} patient. If at the time of the assessment, >10% (27) patients have dropped out of the study, Aeris will consider enrolling additional patients into the study according to a pre-specified algorithm designed to target an evaluable population of 240 patients. These additional patients will be randomized 3:2 treatment to control. The determination to enroll additional patients will be made based solely on blinded withdrawal rate data.

13.0 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

The Investigator should ensure that all persons assisting with the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he/she has delegated significant trial-related duties. The Investigator must make every effort to ensure adequate blinding of applicable study staff.

13.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approval

The Investigator will not begin the study until the protocol and ICF have been approved by the IRB/IEC. Where the product is Investigational, national health authority approval is also required. The IRB/IEC will also review and approve all advertisements, if applicable. The IRB/IEC approval will be documented in writing and sent to the Investigator. The Investigator will forward a copy of the IRB/IEC approval document to the Sponsor. Any amendments to the protocol must also be approved in writing by the IRB/IEC, prior to implementation by the Investigator, except where necessary to eliminate an immediate hazard to study participants.

The Investigator will submit a progress report to the IRB/IEC at intervals as established by the IRB/IEC. The Investigator will retain a copy of this report in the Investigator's Trial File.

13.3 Ethical Conduct of the Study

This study will be conducted in accordance with 21 CFR §812 and EN ISO 14155: 2011, applicable local regulations, and the ethical principles that have their origin in the Declaration of Helsinki.

13.4 Adherence to Protocol

By signing the Investigator Signature Page of this protocol the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with the Investigator Agreement and applicable regulatory requirements. By signing, the Investigator commits to insuring that all site personnel involved in the execution of this study will be properly trained to perform their responsibilities prior to their involvement and that all personnel will be properly supervised during the course of this study.

13.5 Patient Confidentiality

Patient names will not be supplied to the Sponsor. Only the patient identification number will be recorded in the CRF, and if the patient name appears on any other document (e.g., pulmonary function reports, or source documents), it must be obliterated on the copy of the document to be supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify information

collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

13.6 Study Monitoring

Monitoring visits will be conducted by representatives of the Sponsor in accordance with 21 CFR §812 and ISO 14155: 2011 and relevant local regulations. The Investigator will permit the Sponsor's representative(s) to make regular study center visits during the study. At each previously arranged visit, the Investigator and staff will be expected to cooperate with the Sponsor's representative(s) for the review and verification of protocol compliance, AE/SAE reporting, CRFs, source documents, clinical supplies and inventory records, and any additional pertinent records. In addition to the monitoring visits, frequent communications (letter, telephone, email and fax) by the Study Monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

13.7 Training

The Sponsor will provide formal site initiation training for the AeriSeal System procedure prior to activating each site. Training will review all critical aspects of study conduct as well as patient selection and eligibility, treatment site selection based on radiographic criteria, procedure methods, expected responses to treatment, and necessary care and follow-up required post treatment. On-site training will also be provided for patient treatments. The first case will be proctored at all sites and additional on-site support will be provided as needed.

13.8 Accountability of the AeriSeal System Components

The Investigator is responsible for maintaining records relating to the receipt, inventory and return/destruction of AeriSeal System components. The Investigator may delegate all or part of these responsibilities to a site pharmacy/pharmacist or other qualified personnel.

13.9 Case Report Forms and Study Records

An electronic data capture system will be used for collection of clinical data required by the protocol. Data will be entered into the electronic case report forms (eCRFs) from source documentation by study site personnel as information becomes available. If edits to entries on source documents are required, the change must be recorded in a manner that does not obscure the original entry and the initials of the person making the change and the date that the change is made must be recorded. Changes to eCRFs will similarly be tracked. Patients are not to be identified by name in the study database or on any study documents to be collected by the Sponsor or designee but must be identified by the unique defined patient identifier. The Investigator is responsible for all information collected on patients enrolled in this study and the Investigator must ensure that the data are reviewed and verified for completeness and accuracy.

Data processing will be conducted in accordance with GCPs, 21 CFR §11, EU GMP Annex 11, and an approved Data Management Plan. Database lock will occur once quality assurance procedures have been completed.

13.10 Protocol Violations/Deviations

The Investigator will not alter this clinical study protocol without obtaining written agreement from the Sponsor. Once the study has started, amendments should be made only in exceptional cases. The change then becomes part of the clinical study protocol.

All protocol deviations that occur during the course of the study will be submitted for review by the DMC for assessment of their effect on the study's integrity.

With the exception of an emergency situation, implementation of any change in the protocol that affects the safety of the patients, the scope of investigation, or the scientific quality of the study will not be permitted until the DMC, the Sponsor, the Investigator, and the IRB/IEC responsible for review and approval of the study have reviewed and approved the amendment.

Implementation of changes that do not affect the safety of the patients, the scope of the investigation, or the scientific quality of the study cannot be made until the changes are reviewed and approved by the DMC, the Sponsor and the Investigator. The IRB/IEC must be notified of these protocol changes.

The Investigator will make every effort not to deviate from the protocol. In the event of an emergency, the Investigator shall implement any medical procedures deemed appropriate. However, all such procedures must have written documentation and be promptly reported to the Sponsor and IRB/IEC.

13.11 Access to Source Documentation

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each patient enrolled in the study. The Investigator will allow the Sponsor's representatives, contract designees, and authorized regulatory authority inspectors to have direct access to all documents pertaining to the study.

The Investigator agrees that the Sponsor and its employees or agents, the IRB/IEC and governmental regulatory agencies have the right, from time to time, both during and after termination of this clinical study, to monitor, audit and review records relating to the clinical study, including patient medical and billing records. The Sponsor may request real time transmittal of some source and billing data during the course of the study. Quality Assurance personnel from the Sponsor or designee may audit the clinical trial site and/or study-related materials at any time during the study.

13.12 Retention of Data

The Investigator will maintain essential documents (protocol and amendments, completed CRFs, as appropriate, signed ICFs, relevant correspondence and all other supporting documentation) in accordance with national guidelines for clinical trials. Patient identification codes (patient names and corresponding study numbers) will be retained for this same time period.

Custody of the records may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notice of transfer must be submitted to the Sponsor and to the site's IRB/IEC. The Investigator must contact the Sponsor prior to disposing of any study records.

14.0 SUPPLEMENTS

14.1 Investigator Signature

Investigator's Signature

Title: Study of the **A**eriSeal® **S**ystem for Hy**P**er**I**nflation **R**eduction in **E**mphysema (**ASPIRE**)

I have read the attached protocol and agree that it contains all the necessary details for performing the study. I will ensure adequate and eligible patients are enrolled into the study.

I will provide copies of the protocol and the clinical information on the product, which was furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the product and the conduct of the study.

I understand that the study will not be started without the prior written approval of a properly constituted IRB/IEC. Where the product is Investigational, national health authority approval is also required. No changes will be made to the study protocol. I will submit any informed consent modifications in writing to Aeris Therapeutics and the IRB/IEC.

Written approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it and according to the principles of Good Clinical Practice, 21 CFR §812 and EN ISO 14155: 2011 and relevant local regulations. Information developed in this clinical study may be disclosed by the Sponsor to other clinical investigators, government health protection agencies, foreign or domestic, as required. Subject confidentiality will be maintained at all times unless disclosure is required by government regulation or applicable law.

Signature of Investigator	Date
Name of Investigator	Title

15.0 LIST OF REVISION CHANGES

15.1 Rev 07

15.1.1 Revision Change

1. Number of study sites increased
2. Updated references
3. Clarified use of existing studies for Screening
4. Clarified definitions for Exclusion Criteria 1, 2 and 6e
5. Clarified requirements for Pulmonary Rehabilitation
6. Clarified window for Baseline testing
7. Clarified process for notifying patients of group assignment at Randomization
8. Clarified criteria for aborting AeriSeal System treatment
9. Modified Optimal Medical Therapy definition to allow use of daily azithromycin for prevention of COPD exacerbations
10. Added window for reporting deaths to DMC

15.1.2 Justification

1. Augment enrollment
2. New reference available since last revision
3. Provide clarity
4. Provide clarity
5. Provide clarity
6. Provide clarity
7. Provide clarity
8. Provide clarity
9. Incorporate evidence-based guideline
10. DMC request

15.2 Rev 06

15.2.1 Revision Change

1. Change primary efficacy analysis set from AT to ITT
2. Administrative changes

15.2.2 Justification

1. Compliance with regulatory guidance
2. Provide clarity

15.3 Rev 05

15.3.1 Revision Change

1. Modify timing of DMC safety assessment prior to treatment of control patients
2. Revise statistical analysis to include "As Treated" as primary analysis set
3. Add days alive outside hospital to Other Outcomes
4. Add ECG post-treatment Day 1
5. Add additional exploratory analysis
6. Administrative changes

15.3.2 Justification

1. Compliance with regulatory guidance
2. Compliance with regulatory guidance
3. Compliance with regulatory guidance
4. Enhance post-treatment safety monitoring
5. Provide details on the use of ct scans
6. Provide clarity

15.4 Rev 04

15.4.1 Revision Change

1. Modify primary and secondary endpoints
2. Revise statistics
3. Add radiology core lab
4. Eliminate BDI/TDI Questionnaire
5. Enhance definitions of respiratory events
6. Administrative Changes

15.4.2 Justification

1. Compliance with regulatory guidance
2. Consistency with revised endpoints
3. Enhance integrity of efficacy assessments
4. Eliminate redundant data collection
5. Compliance with regulatory guidance
6. Provide clarity

15.5 Rev 03

15.5.1 Revision Change

1. Substitute Optimal Medical Therapy for Sham Bronchoscopy
2. Expand study to include domestic (U.S.) trial sites
3. Revise statistics to incorporate latest guidance
4. Increase sample size

5. Modify secondary endpoints
6. Augment pulmonary rehabilitation monitoring
7. Add additional Other Outcomes
8. Change endpoint timing
9. Provide greater specificity to Entry Criteria
10. Collect additional clinical data to document patient entry status and post treatment status including follow-up for long term safety
11. Administrative Changes

15.5.2 Justification

1. Ethical considerations
2. Seek broader regulatory approval
3. Compliance with current guidance
4. Seek broader regulatory approval
5. Seek broader regulatory approval
7. Minimize external influences on results
8. Permit exploratory assessments for designing future studies
9. Compliance with regulatory guidance
10. Enhance Investigator's understanding of eligibility
11. Compliance with regulatory guidance
12. Provide clarity

15.6 Rev 02

15.6.1 Revision Change

1. Increase number of participating sites
2. Add Oxygen saturation criteria to the exclusion criteria
3. Add Blinding Assessment
4. Increase the length of recording Adverse Events
5. Administrative changes

15.6.2 Justification

1. Accelerate enrollment
2. Inadvertently left out of previous revision
3. Assess the adequacy of the blinding
4. Provide a more comprehensive safety assessment
5. Provide clarification

15.7 Rev 01

1. Changes from a European only to International study
2. Administrative changes and clarifications

16.0 REFERENCES

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16.2 Dyspnea Scores

MRC Dyspnea: Mahler DA, Wells CK Evaluation of clinical methods for rating dyspnea. *Chest.* 1988; 93: 580-586.

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[1] Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Resp Crit Care Med*. 1995; 152: S77-S121.

[2] *Handbook of Physiology - The Respiratory System Vol III, Mechanics of Breathing*. American Physiological Society, Chapter 37, 1986, Bethesda, Md, *Lung Mechanics in Disease*. Neil Pride and Peter Macklem, Pg 659-692.

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