Bronchial Thermoplasty System
Catheter Model ATS 2-5

℞ Only:	United States federal law restricts this device to sale by or on the order of a physician.
⚠	The Alair Catheter must be used by a physician who has training and experience in performing bronchoscopic procedures.

These Instructions for Use (IFU) are specific to the Alair® Catheter Model ATS 2-5. Do not attempt to operate the Alair Catheter before thoroughly reading this IFU and the Alair® Radiofrequency Controller Model ATS 200 Operator's Manual.

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INSTRUCTIONS FOR USE

ALAIR BRONCHIAL THERMOPLASTY SYSTEM DESCRIPTION

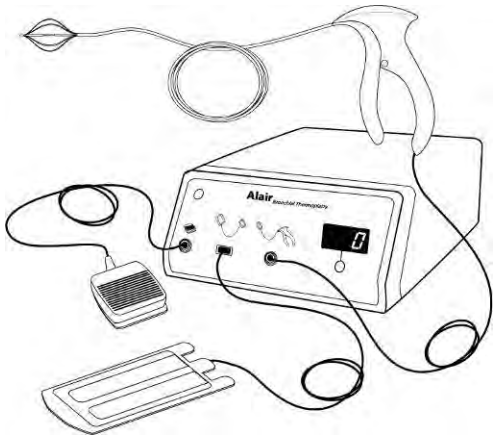

Figure 1: The Alair Bronchial Thermoplasty System

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The Alair Bronchial Thermoplasty System ("Alair System"), manufactured by Asthmatx, Inc. ("Asthmatx"), consists of the Alair Catheter and the Alair Controller System, as described below:

Alair Catheter: The Alair Catheter Model ATS 2-5 ("Catheter") is provided sterile and is a SINGLE-USE ONLY, disposable device. The Catheter delivers energy from the Controller to the desired site in the airway and relays temperature feedback to the Controller. The Alair Catheter Model ATS 2-5 is designed to be used with the Alair RF Controller Model ATS 200.

Alair Controller System

Alair Radiofrequency (RF) Controller: The Alair RF Controller Model ATS 200 ("Controller") is designed to provide controlled delivery of RF energy to the Alair Catheter. Energy from the Controller is delivered to the Catheter through the electrical cable attached to the proximal end of the catheter handle. Actual power delivered is automatically modulated by the Controller based on temperature control algorithms. The Controller delivers low-power, temperature-controlled RF energy to the airway at a predetermined temperature setting for a predetermined time period. The Controller incorporates hardware and software features that limit current, voltage, power, energy, time and temperature during each application of RF energy. The Controller is not intended to come in contact with the patient and therefore is not provided as a sterile device. For information on the installation, use, and other technical specifications, please read the Alair Radiofrequency Controller Operator's Manual that is supplied with Model ATS 200.

Footswitch: The Controller is supplied with a footswitch that allows the operator to start and stop the delivery of RF energy. The Controller is designed to be used with the compatible footswitch provided by Asthmatx. The footswitch is not intended to come into contact with the patient and therefore is not provided as a sterile device.

Patient Return Electrode: The Controller is designed to be used with a gel-type patient return electrode that is compliant with the applicable portions of IEC 60601-2-2:2006 and/or CE marked. The patient return electrode is used to complete the return path for the electrical current. Use only patient return electrodes indicated for use with adults or patients weighing more than 15 kg (33 lbs). Examples of acceptable patient return electrodes include Valleylab E7506 and ConMed 51-7310. Follow the instructions for use (IFU) packaged with the patient return electrode.

INSTRUCTIONS FOR USE

INDICATION FOR USE

The Alair Bronchial Thermoplasty System is indicated for the treatment of severe persistent asthma in patients 18 years and older.

BRONCHOSCOPE REQUIREMENTS

The Catheter is designed to be used with high-frequency compatible flexible bronchoscopes that have a minimum 2.0mm working channel, and maximum 5.0mm outer diameter.

MECHANISM OF ACTION

Airway smooth muscle (ASM) consists of muscle tissue within the airway walls in the lung. Contraction of the ASM is a main cause of airway constriction that leads to difficulty in breathing during asthma attacks. Severe asthma patients also experience an increase in ASM mass. This increase, together with inflammation of the airways, combines to thicken airway walls, which decreases the inside diameter of the airways when the ASM contracts. The resulting decrease in airway diameter causes increased resistance to airflow and further contributes to difficulty in breathing during asthma attacks. **Figure 2** depicts a cross-sectional representation of a normal airway, an asthmatic airway, and an asthmatic airway during an asthma attack.

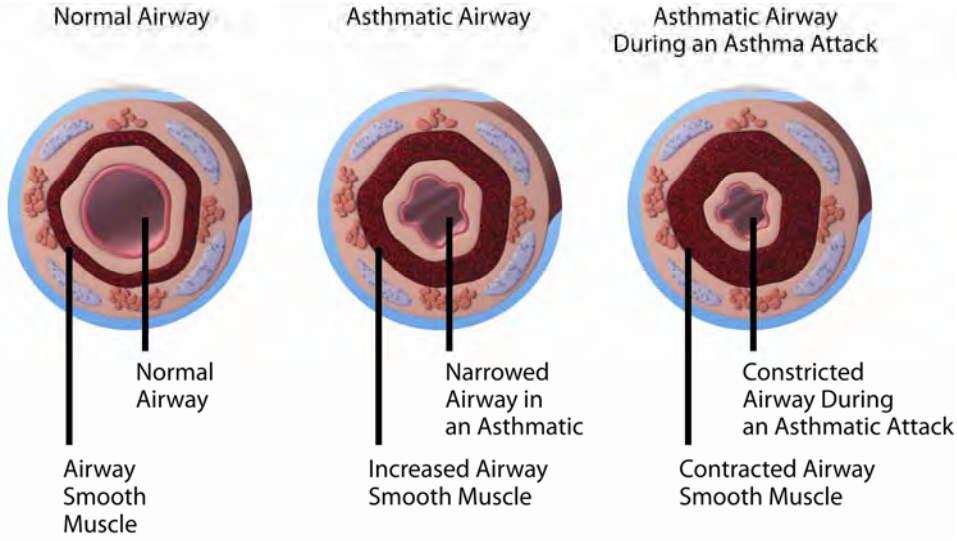


Figure 2: Cross-sectional views of Normal and Asthmatic Airways

The Alair System is used to deliver thermal energy to the airway wall, to heat the tissue in a controlled manner in order to reduce ASM mass. Bronchial thermoplasty is intended to reduce, debulk, or partially eliminate smooth muscle tissue. In preclinical studies (Danek et al. 2004[1], Brown et al. 2005[2]), the reduction of ASM has been shown

[1] Danek CJ, Lombard CM, Dungworth DL, Cox PG, Miller JD, Biggs MJ, Keast TM, Loomas BE, Wizeman WJ, Hogg JC, Leff AR. Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs. J Appl Physiol. 2004, 97(5):1946-53.

[2] Brown RH, Wizeman W, Danek C, Mitzner W. Effect of bronchial thermoplasty on airway distensibility. Eur Respir J. 2005 Aug;26(2):277-82.

to decrease the ability of the airways to constrict/contract, reduce resistance to airflow and responsiveness of the airway, and increase the resting diameter of the airway.

CONTRAINDICATIONS ⚠

Patients with the following conditions should not be treated:

- Presence of a pacemaker, internal defibrillator, or other implantable electronic devices,
- Known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine, and benzodiazepines.

Patients should not be treated while the following conditions are present:

- Active respiratory infection,
- Asthma exacerbation or changing dose of systemic corticosteroids for asthma (up or down) in the past 14 days.

WARNINGS ⚠

READ THIS ALAIR CATHETER MODEL ATS 2-5 IFU IN CONJUCTION WITH THE ALAIR RF CONTROLLER MODEL ATS 200 OPERATOR'S MANUAL BEFORE USING THE ALAIR BRONCHIAL THERMOPLASTY SYSTEM. FAILURE TO FOLLOW ANY INSTRUCTIONS OR FAILURE TO HEED ANY WARNINGS OR PRECAUTIONS MAY RESULT IN HARM OR INJURY TO PATIENT.

This IFU must be followed to ensure safe and proper use of the Alair System.

1. Do not deliver energy if the Catheter's electrode array is in contact with a metal object. This may result in harm or injury to the patient and/or operator.
2. Do not advance the Catheter within the bronchoscope if significant resistance is felt, as this may result in harm or injury to the patient and/or cause damage to the Catheter and/or bronchoscope.
3. Do not advance the Catheter into bronchi in which the Catheter cannot be seen under bronchoscopic vision. Advancing the Catheter beyond this region may cause patient harm or injury such as pneumothorax or pneumomediastinum.
4. Do not reposition the bronchoscope with the Catheter advanced beyond the distal end of the bronchoscope as this may result in patient harm or injury.
5. Use of the Alair Catheter with a Non-Alair Controller may result in harm or injury to the patient and/or operator, or may result in product malfunction.
6. Do not treat the right middle lobe because of the potential susceptibility of the right middle lobe to transient obstruction as a result of inflammation or edema due to certain anatomical characteristics. The narrow diameter of the lobar bronchus and acute take-off angle may create poor conditions of drainage that may cause patient harm or injury such as atelectasis or difficulty in re-inflation (Right Middle Lobe Syndrome).

INSTRUCTIONS FOR USE

PRECAUTIONS ⚠

1. The Alair Catheter is provided sterile and is SINGLE USE ONLY. Do not use the Catheter if the package is opened, torn, or damaged. Use of a Catheter from damaged packaging may result in patient harm or injury. Do not **re-sterilize or reuse** the Catheter, as this may result in patient harm or injury, transmittal of infectious disease or product malfunction.
2. Do not use the Catheter if it comes in contact with a surface that is not aseptic (e.g. floor). This may result in patient infection.
3. Do not use the Catheter if it is damaged or irregular. Use of a damaged or irregular Catheter may result in patient harm or injury.
4. Do not use the Catheter if the marker bands are missing **(See Directions for Use, Figure 11).**
5. Use care when handling the Catheter to avoid kinking the Catheter shaft.
6. Avoid deflecting the bronchoscope while the electrode array is within the bend of the bronchoscope's working channel as this may result in damage to the Catheter and failure of the Catheter to operate properly.
7. Before inserting or removing the Catheter from the bronchoscope, ensure the electrode array is relaxed. Do not use the Catheter if the electrode array does not expand or relax properly **(See Figures 12 and 13)**.
8. Before delivering energy, make certain that all electrodes are in contact with the airway wall.
9. Caution should be taken in patients with the following conditions due to a potential increased risk of adverse events that may be associated with bronchoscopy:
    - Post-bronchodilator $FEV_1 < 65\%$.
    - Other respiratory diseases including emphysema, vocal cord dysfunction, mechanical upper airway obstruction, cystic fibrosis or uncontrolled obstructive sleep apnea.
    - Use of short acting bronchodilator in excess of 12 puffs per day within 48 hours of bronchoscopy (excluding prophylactic use for exercise).
    - Increased risk for adverse events associated with bronchoscopy or anesthesia, such as, pregnancy, insulin dependent diabetes, epilepsy or other significant co-morbidities, such as uncontrolled coronary artery disease, acute or chronic renal failure, and uncontrolled hypertension.
    - Any of the following within the past 12 months:
        i. 4 or more lower respiratory track infections (LRTI)
        ii. 3 or more hospitalizations for respiratory symptoms
        iii. 4 or more OCS pulses for asthma exacerbation
        iv. Intubation or intensive care admission for asthma
10. The Alair System should only be used in a fully equipped bronchoscopy suite by clinicians who are experienced in bronchoscopy and have undergone adequate training with the device. The Alair System should only be used in patients stable enough to undergo bronchoscopy in the judgment of their clinician.
11. Prior to performing the procedure, ensure appropriate training, equipment, medications and staff are in place to handle any potential bronchoscopic, respiratory or anesthesia related emergencies.
12. Follow local governing ordinances and your institution's biohazard procedures regarding disposal of the Alair Catheter and patient return electrode.

ADVERSE EVENTS IN CLINICAL STUDIES

Patient Population

The Alair System was evaluated in a randomized, double-blind, sham controlled, multi-center clinical study. A total of 288 subjects with severe persistent asthma (severe asthma) were randomized -- 190 subjects in the Alair group and 98 subjects in the Sham group. The Sham procedure was identical to the Alair procedure except that no energy was delivered to the Catheter in the sham procedure.

Safety analyses were performed for the Intent-to-Treat (ITT) population that consisted of all randomized subjects who have been administered at least one bronchoscopy.

Observed Adverse Events

The safety of the Alair System was assessed by comparing adverse event profiles of the Alair and Sham group subjects. Adverse event profiles are compared for the Treatment Phase (day of first bronchoscopy procedure to 6 weeks after the last bronchoscopy procedure) and Post-Treatment Phase (6 weeks after the last bronchoscopy to the 12 month follow-up visit).

Adverse events (whether considered procedure-related or not procedure-related by the investigator) occurring with ≥ 3% incidence that were more common in the Alair Group are presented for 288 patients.

Adverse Event	**Alair (N=190) %**	**Sham (N=98) %**	**Alair (N=187) %**	**Sham (N=98) %**
	Treatment[3]		**Post-treatment[4]**	
Average duration of period (days)	84		322	
Ear, Nose, and Throat				
Upper respiratory tract infection	20	11.2*	29.9	25.5
Viral Upper respiratory tract infection	4.2	2.0	5.9	7.1
Nasopharyngitis	4.7	7.1	10.7	5.1*
Sinusitis	3.7	5.1	6.4	7.1
Acute Sinusitis	2.6	2.0	3.7	8.2
Throat irritation	4.7*	12.2	1.1	3.1
Pharyngolaryngeal pain	3.2	5.1	0.5	2.0
Rhinitis	1.6	0.0	4.3	6.1
Rhinitis (allergic)	1.6	3.1	3.7	4.1

[3] Treatment phase represents adverse events reported between the first bronchoscopy and 6-weeks post last bronchoscopy

[4] Post-Treatment phase represents adverse events reported between 6-weeks post last bronchoscopy and the 12 month visit

Adverse Event	Alair (N=190) %	Sham (N=98) %	Alair (N=187) %	Sham (N=98) %
	Treatment[3]		Post-treatment[4]	
Lower Respiratory				
Asthma (Multiple Symptom)	52.1	38.8*	27.3*	42.9
Wheezing	15.3	6.1*	4.3	3.1
Dyspnea	11.1	6.1	2.1	1.0
Cough	12.1	14.3	2.7	5.1
Productive cough	7.4	9.2	2.7	4.1
Bronchitis	3.7	2.0	7.0	5.1
Chest discomfort	8.9	10.2	1.6	1.0
Atelectasis	4.7	0.0*	0.0	0.0
Dyspepsia	3.7	2.0	1.6	4.1
Hemoptysis	3.2	0.0*	0.0	0.0
Lower respiratory tract infection	7.9	2.0*	3.2	6.1
Chest pain	13.7	13.3	2.7	1.0
Neurology				
Anxiety	3.7	0.0*	1.1	2.0
Headaches	14.2	9.2	4.8	3.1
Gastrointestinal				
Nausea	3.2	4.1	1.1	1.0
Non-site specific				
Pyrexia (fever)	4.2	2.0	0.0	1.0
Influenza	4.2	2.0	4.3*	12.2
Musculoskeletal				
Back pain	4.7	6.1	3.2	5.1
Other				
Urinary tract infection	1.1	1.0	3.2	1.0
Hypertension	3.2	2.0	3.2	3.1

Table 1: Adverse Events With ≥ 3% Incidence (% of subjects) that were more common in the Alair Group.

* Posterior Probability greater than 95%

Table 1 includes all adverse events (whether considered procedure-related or not procedure-related by the investigator) occurring with ≥ 3% incidence that were more common in the Alair Group.

Adverse events occurring in both the Treatment Phase and Post-Treatment Phase at a rate of <3% and ≥1% (whether considered procedure-related or not procedure-related by the investigator) that were more frequently reported by the Alair group than the Sham group included pneumonia, operative hemorrhage, abnormal breath sounds, bronchial obstruction, acute bronchitis, bronchospasm, lower respiratory tract infection (viral), pulmonary congestion, discolored sputum (blood-tinged sputum), increased upper airway secretion, and viral pharyngitis.

Potential Risks

There are risks that bronchial thermoplasty may not be effective, may not relieve pre-procedure symptoms, or its benefit may not persist.

Risks with the use of the Alair System include those associated with any bronchoscopy and attendant anesthesia and medications. In addition to the risks described above, potential risks may be associated with:

- Bronchoscopy, including fever, bleeding, laryngospasm, bronchospasm, shortness of breath, excess mucus production, increased airway reactivity, atelectasis, pneumonia and/or infection.
- Conscious sedation/anesthesia including nausea, vomiting, dizziness, drowsiness, shivering, or cardiovascular events.
- Medications required in order to perform bronchoscopy including lidocaine, atropine, or benzodiazepines.

Potential Risks Not Observed in Bronchial Thermoplasty Treated Patients in Clinical Studies

Potential risks not observed in bronchial thermoplasty treated patients in clinical studies include acute respiratory failure, bronchial stenosis, bronchiectasis, pneumothorax, persistent retained secretions and/or the risk of intubation or mechanical ventilation. There may be additional risks that are unknown at this time that may potentially occur as a result of the bronchial thermoplasty treatment of severe asthma patients. There may also be risks associated with the use of radiofrequency energy similar to that used in electrocautery such as thermal damage to adjacent tissues and/or swelling of airways.

During the Treatment Phase, there was a significant transient increase in respiratory adverse events, including asthma (multiple symptoms), upper respiratory tract infection, atelectasis, lower respiratory tract infection, wheezing, and hemoptysis, and anxiety in the Alair group compared to the Sham group. There was a significantly lower incidence of throat irritation in the Alair group compared to the Sham group. There were more unscheduled physician office visits and hospitalizations for respiratory symptoms in the Alair group (0.28/subject and 0.10/subject, respectively) compared to the Sham group (0.18/subject and 0.02/subject, respectively). There was no increase in ER visits for respiratory symptoms in the Alair group (0.07/subject) compared to the Sham group (0.10/subject).

During the Post-Treatment Phase, there was a significantly lower incidence of respiratory symptoms in the Alair group compared to the Sham group, including a 36% reduction in asthma (multiple symptoms) events and proportion of subjects with events (**Figure 3**). There was also a significantly lower incidence of influenza, and a greater incidence of nasopharyngitis, in the Alair Group compared to the Sham group.

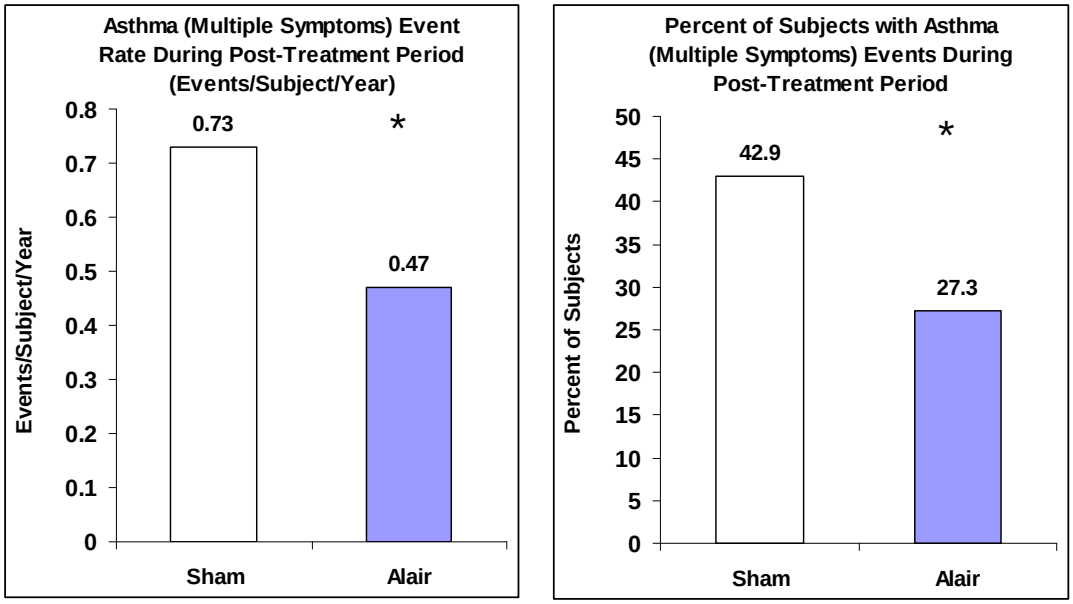


Figure 3: Incidence Rate of Asthma (Multiple Symptoms) Adverse Events
*: Posterior Probability of Superiority: Event Rate = 96.0%; Proportion of Subject = 99.6%

Healthcare Utilization in the Post-Treatment Phase:

A summary of the Healthcare Utilization events that include annualized rates for Unscheduled Physician Office Visits for respiratory symptoms, Emergency Room visits for respiratory symptoms, and Hospitalizations for respiratory symptoms is provided in **Table 2.**

	Post-Treatment Phase		
	Alair (N=190)	Sham (N=98)	95% Credible Interval (CI)
Unscheduled Physician Office Visits (Events/Subject/Year)	0.28	0.36	(-0.108, 0.309)
Emergency Room Visits (Events/Subject/Year)	0.07	0.43	(0.111, 0.832)[a]
Hospitalizations (Events/Subject/Year)	0.04	0.13	[#]
Overall Healthcare Utilization Events (Events/Subject/Year)	0.38	0.90	(0.136, 1.049)[b]

Table 2: Summary of Healthcare Utilization Events

[a]: Posterior Probability of Superiority = 99.9%

[b]: Posterior Probability of Superiority = 99.7%

[#]: One subject in the Sham group had 9 hospitalizations for a single adverse event during the Post-Treatment Phase. This subject may be an outlier making statistical analysis inappropriate.

CLINICAL DATA

Objectives

The pivotal study was a multi-center, randomized, double-blind, sham-controlled study to demonstrate the safety and effectiveness of the Alair System in a population of subjects with severe asthma.

Primary Endpoint

Effectiveness was primarily assessed by comparing the difference between treatment (Alair) and control (Sham) groups in the change in the Asthma Quality of Life Questionnaire (AQLQ) score between baseline and the average of 6-, 9-, and 12- month follow-up visits (integrated AQLQ score).

Methods

This was a multicenter, randomized, double-blind, sham-controlled clinical trial comparing the effects of treatment with the Alair System to a Sham treatment in subjects that were optimized to conventional therapy of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA). All subjects included in the Study were taking ICS (> 1000µg beclomethasone or equivalent per day) and LABA (≥ 100µg Salmeterol or equivalent per day), and were still symptomatic.

Subjects in the Alair and Sham groups were administered the Alair treatment and Sham bronchoscopies, respectively, by an unblinded bronchoscopy team in 3 separate bronchoscopy sessions. Each bronchoscopy session was separated by at least 3 weeks. All bronchoscopy sessions were administered under local anesthesia with conscious sedation. Subjects had follow-up visits with blinded asthma assessment teams at 6-weeks, 12-weeks, 6-months, 9-months, and 12-months after the final bronchoscopy session.

All subjects were prescribed to take 50mg of oral prednisone or prednisolone (or equivalent) each day for 5 days covering the 3 days before the bronchoscopy session, the day of the bronchoscopy session, and the day after the bronchoscopy session (prophylactic indication).

Statistical Plan

Primary and secondary endpoints, as well as adverse events were analyzed using Bayesian statistics. The Posterior Probability of Superiority was calculated for the primary and secondary endpoints, as well as safety outcomes.

Patient Population

Enrollment was limited to patients with severe asthma who were still symptomatic despite being managed on conventional therapy of high dose ICS and LABA. Subjects may have been taking up to 10 milligrams of oral corticosteroids per day. Study subjects were required to meet the following key patient selection criteria:

Study Inclusion Criteria

1. Adult; age 18-65 years.
2. Willingness and ability to give written Informed Consent.
3. Asthma requiring regular maintenance medication that includes inhaled corticosteroids (greater than 1000µg beclomethasone per day or equivalent) and long-acting β_2-agonists (at least 100 µg salmeterol per day or equivalent), with or without other asthma medications. Oral corticosteroids at a dosage of up to, but not greater than 10mg per day, or 20 milligrams every other day are acceptable.
4. Asthma Quality of Life Questionnaire Score during the Baseline Phase of 6.25 or less.
5. Pre-bronchodilator forced expiratory volume in one second ≥60% predicted (after patients stabilized on inhaled corticosteroids and long-acting β_2-agonists during the Baseline Phase).
6. Provocative concentration resulting in a drop of 20% or more from Baseline < 8 milligrams/milliliter per methacholine inhalation test using standardized methods.
7. At least 2 days of asthma symptoms during the 4-weeks of the Baseline Diary Phase.
8. Non-smoker x 1 year or greater (if former smoker, less than 10 pack years total smoking history).
9. Subject must be suitable for bronchoscopy in the opinion of the investigator or per hospital guidelines.
10. Willingness and ability to comply with the Study protocol, including requirements for taking and abstaining from medications.

Study Exclusion Criteria

1. Participation in another clinical trial within 6 weeks of the Baseline Phase involving respiratory intervention that could affect the outcome measures of this Study.
2. Requirement during the Baseline Diary Phase for rescue medication use other than for prophylactic use for exercise exceeds an average of:
   - 8 puffs per day of short-acting bronchodilator
     OR
   - 4 puffs per day of long-acting rescue bronchodilator
     OR
   - 2 nebulizer treatments per day.
3. Post-bronchodilator Forced expiratory volume in one second <65%.
4. Three or more hospitalizations for exacerbations of asthma in the previous year; OR a history of life-threatening asthma, defined by past intubations for asthma, or intensive care unit admission for asthma within the prior 24 months.
5. History of recurrent lower respiratory tract infection requiring antibiotics (more than 3 in the past 12-Months).
6. History of recurrent oral steroid use for asthma (4 or more pulses of oral steroids in the past 12-Months).

7. Known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine, and benzodiazepines.
8. Known systemic hypersensitivity or contraindication to methacholine chloride or other parasympathomimetic agents.
9. Use of immunosuppressant therapy (e.g., methotrexate).
10. Use of systemic β-adrenergic blocking agents.
11. Use of anticoagulants.
12. Insulin-dependent diabetes.
13. Pregnancy, nursing mother, or subject plans to become pregnant within the next year.
14. Presence of other respiratory diseases including emphysema, cystic fibrosis, vocal cord dysfunction, mechanical upper airway obstruction, obstructive sleep apnea, Churg-Strauss syndrome, cardiac dysfunction, allergic bronchopulmonary aspergillosis.
15. Presence of segmental atelectasis, lobar consolidation, significant or unstable pulmonary infiltrate, or pneumothorax, confirmed on x-ray.
16. Interstitial lung disease.
17. Chronic sinus disease as defined by 5 or more episodes of sinusitis in past 12-Months or continuous symptoms of sinus infection (purulent discharge) and significant change in nasal steroid dosage in last 6 weeks.
18. Uncontrolled gastro-esophageal reflux disease as defined by a significant increase in therapy in last 6 weeks.
19. Significant co-morbid illness such as cancer, renal failure, liver disease or cerebral vascular disease.
20. History of epilepsy.
21. Currently has clinically significant cardiovascular disease, including myocardial infarction, angina, cardiac dysrhythmia, conduction defect, cardiomyopathy, or stroke.
22. Bleeding diathesis, platelet dysfunction, thrombocytopenia with platelet count less than 125,000/mm^2 or known coagulopathy (International Normalized Ration > 1.5).
23. Uncontrolled hypertension (>200 mmHg systolic or >100mmHg diastolic pressure).
24. Known aortic aneurysm.
25. Use of implanted electrical stimulation device such as a pacemaker, cardiac defibrillator, or deep nerve or deep brain stimulator.
26. Psychiatric disorder that in the judgment of the Investigator could interfere with provision of informed consent, completion of tests, therapy, or follow-up.
27. Presence of other medical condition that in the judgment of the Investigator would make them inappropriate for Study participation.

Demographics

A total of 288 subjects between the ages of 18 and 65 were randomized 2:1 in this study, 190 to Alair treatment and 98 to Sham control. The Sham procedure was identical to the Alair procedure except that no energy was delivered to the Catheter.

There were no statistical differences in demographic measures between the Alair and Sham groups. Subject demographics are described in **Table 3**.

	Alair (n=190)	**Sham (n=98)**	**p-value**
	(Mean ± SD)		
Age (years)	40.7 ± 11.89	40.6 ± 11.85	0.936 [b]
Gender			
Male	81 (42.6%)	38 (38.8%)	
Female	109 (57.4%)	60 (61.2%)	0.614[a]
Race/Ethnicity			
Caucasian	151 (79.5%)	72 (73.5%)	
African American / Black	19 (10.0%)	15 (15.3%)	
Hispanic	6 (3.2%)	4 (4.1%)	
Asian	4 (2.1%)	1 (1.0%)	
Other	10 (5.3%)	6 (6.1%)	
Height (cm)	166.9 ± 8.88	166.7 ± 10.45	0.881[b]
Weight (kg)	81.7 ± 18.36	82.4 ± 20.07	0.762[b]

Table 3: Subject Demographics (Intent-to-Treat Population)
[a]p-value from a Fisher's exact test
[b]p-value from a t-test

Effectiveness Results

Effectiveness analyses were performed for both the Intent-to-Treat (ITT) population and Per-Protocol (PP) population. The ITT population consisted of all randomized subjects who have been administered at least one bronchoscopy. The PP population excluded all subjects in the ITT population who met any of the following criteria:

- Have taken any interfering concomitant medications.
- Have undergone other interfering treatments.
- Did not attend one of the 6-, 9-, 12-month visits, with the exception of a discontinuation from the Study due to an adverse event related to Study treatment.
- Had missed one or more bronchoscopy procedures.

Primary Efficacy Endpoint

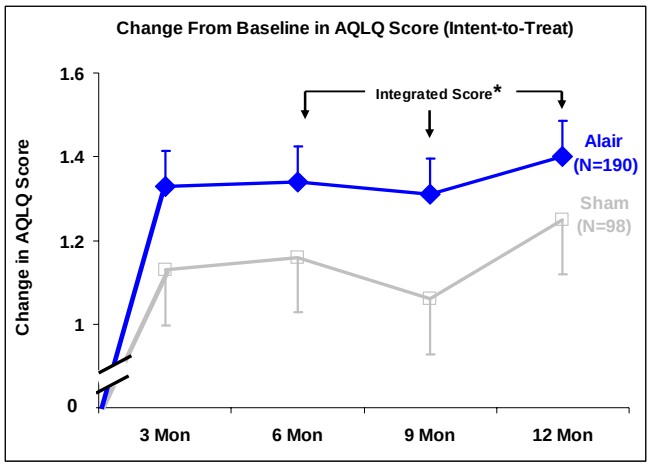
Integrated AQLQ Score

The Alair group was superior to the Sham group as demonstrated by the observed difference between the Alair and Sham groups in the average change in AQLQ score from Baseline at the 6-, 9-, and 12-month follow-up visits. For the ITT population, the difference between the groups had a Posterior Probability of Superiority of 96.0%. For the PP population, the difference between the groups had a Posterior Probability of Superiority of 97.9%.

The results for the change from Baseline of the Integrated AQLQ score for the Intent-to-Treat and Per Protocol populations are summarized in **Table 4** and shown graphically in **Figure 4.**

Population	Difference Between Groups in Integrated AQLQ Score (Posterior Mean ± SD)	Posterior Probability of Superiority (%)
ITT (Intent-to-Treat) (Alair N= 190, Sham N= 98)	0.210 ± 0.120	96.0
PP (Per Protocol) (Alair N= 173, Sham N=95)	0.244 ± 0.120	97.9

Table 4: AIR2 Trial Primary Endpoint: Integrated AQLQ Score



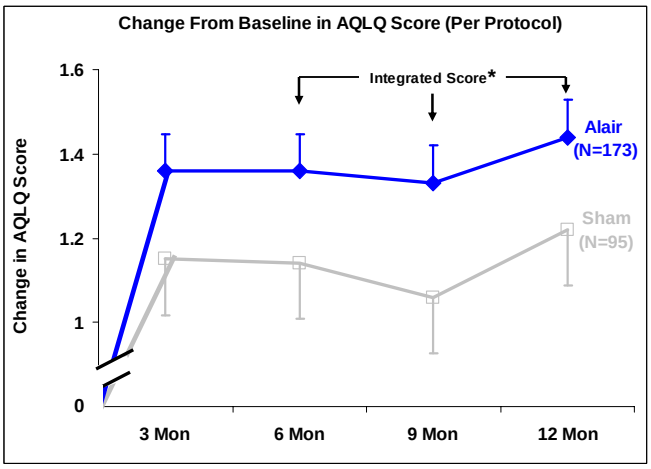


Figure 4: Change from Baseline in AQLQ Integrated Score

* Posterior Probability of Superiority: Intent-to-Treat = 96.0%; Per Protocol = 97.9%

Percent of Subjects with AQLQ score change of ≥ 0.5

The AQLQ data were used to categorize the number of subjects in each group that achieved an improvement in the integrated AQLQ score of ≥ 0.5, or a Minimal Important Difference (MID). The analysis of the within-group changes in AQLQ scores demonstrates superiority of Alair over Sham with regards to the proportion of subjects achieving an improvement in AQLQ score of ≥ 0.5. For both the ITT and PP populations, a greater proportion of subjects in the Alair group compared to the Sham group achieved an improvement in AQLQ score of ≥ 0.5.

The data for the within-group changes in AQLQ for the ITT and PP populations are presented graphically in **Figure 5**.

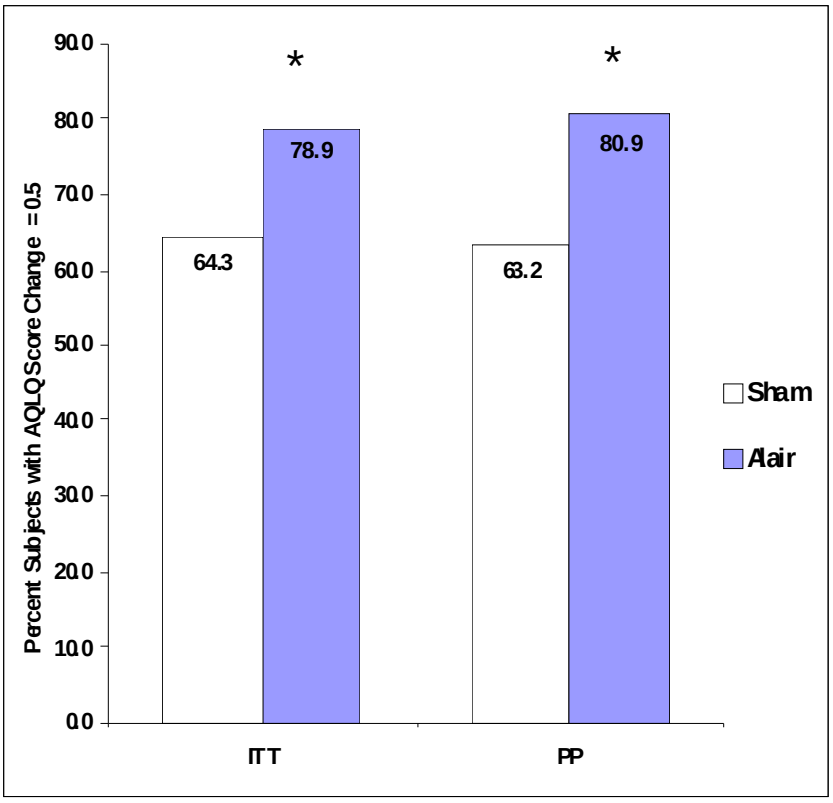


Figure 5: Proportion of Subjects with Integrated AQLQ Change of ≥ 0.5 by Treatment Group

* Posterior Probability of Superiority: Intent-to-Treat = 99.6%; Per Protocol = 99.9%;

.

AQLQ Individual Domain Scores:

The Alair group had a larger change than the Sham group for each of the individual domains at each of the follow-up evaluations at 3-, 6-, 9-, and 12-Months. The change in integrated Domain scores for the ITT and PP populations are shown graphically in **Figure 6**.

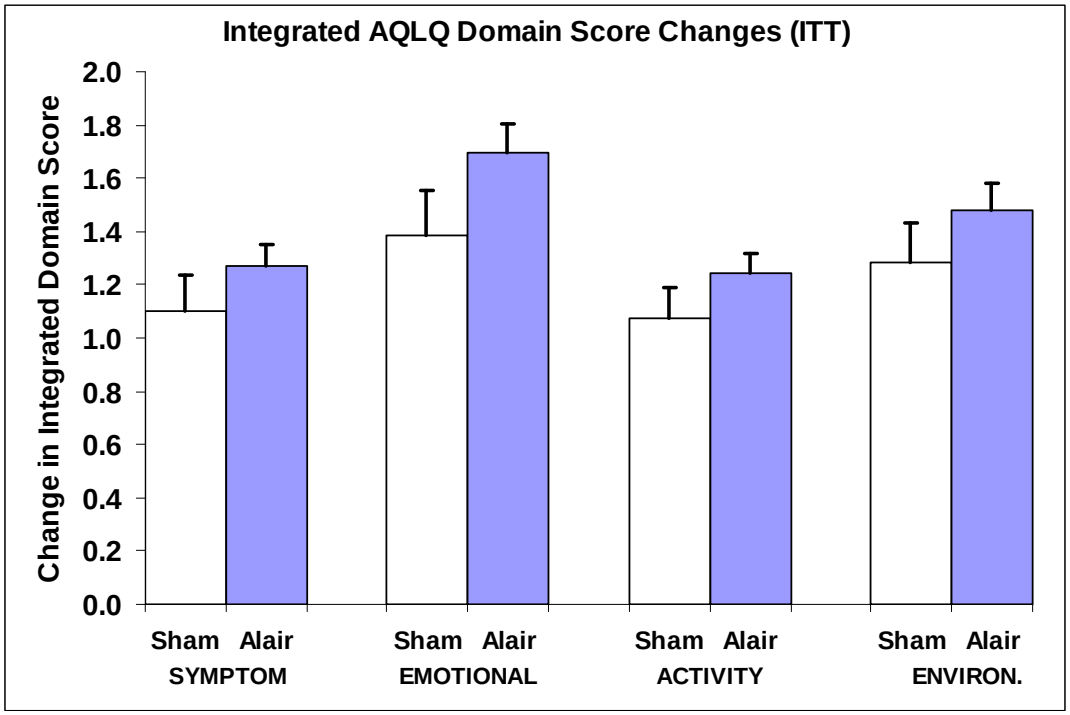


Figure 6: Integrated AQLQ Domain Score Changes (ITT Population)

Secondary Efficacy Endpoints

FEV_1 was tracked as a secondary measure for assessment of safety. No deterioration in FEV_1 was observed in either the Alair or Sham groups throughout the 12 month follow-up. Other secondary endpoints, including %Symptom-Free Days, Total Symptom Score, Rescue Medication Use (puffs per 7 days and % Days Rescue Medication Used), Asthma Control Questionnaire (ACQ) Score, and morning peak expiratory flow (amPEF), were improved in the Alair group compared to Baseline, and generally more improved than the Sham group at each of the 3-, 6-, and 12-Month evaluations. At 12-Months, the Alair group showed more improvement than the Sham group, although the differences between groups were not statistically meaningful. Secondary endpoints for the ITT Population are shown in **Table 5**.

Secondary Endpoints Changes from Baseline at 12 months	**Alair (N=190)**	**Sham (N=98)**	**Trend in Favor of Alair Group**	**Posterior Probability of Superiority (%)**
% Symptom Free Days	24.4	21.0	Yes	77.4
Total Symptom Score	- 1.7	- 1.6	Yes	64.0
Rescue Med Use (Puffs/7days)	- 6.0	- 4.3	Yes	81.4
% Days Rescue Med Used	- 24.0	- 22.0	Yes	67.9
ACQ Score	- 0.82	- 0.77	Yes	64.0
am PEF (L/min)	27.8	22.3	Yes	80.6

Table 5: Secondary Endpoint Outcomes at 12 Month Evaluation (ITT Population)

Other Variables

Severe Exacerbations of Asthma (ITT Population)

Steroid Exacerbations[a]: During the Post-Treatment Phase, the severe exacerbation rate for the Steroid Exacerbations was 0.48 exacerbations/subject/year in the Alair group and 0.70 exacerbations/subject/year in the Sham group, Posterior Probability of Superiority of 95.5% [95% CI (Sham - Alair): -0.031, 0.520]. During the Post-Treatment Phase, the proportion of subjects experiencing Steroid Exacerbations was 26.3% in the Alair group and 39.8% in the Sham group, Posterior Probability of Superiority of 99.0% [95% CI (Sham - Alair): 2.1%, 25.1%].

Steroid Exacerbation rates[a] (annualized rate) and proportion of patients experiencing Severe Exacerbations for the Post-Treatment Phase are presented graphically in **Figure 7**.

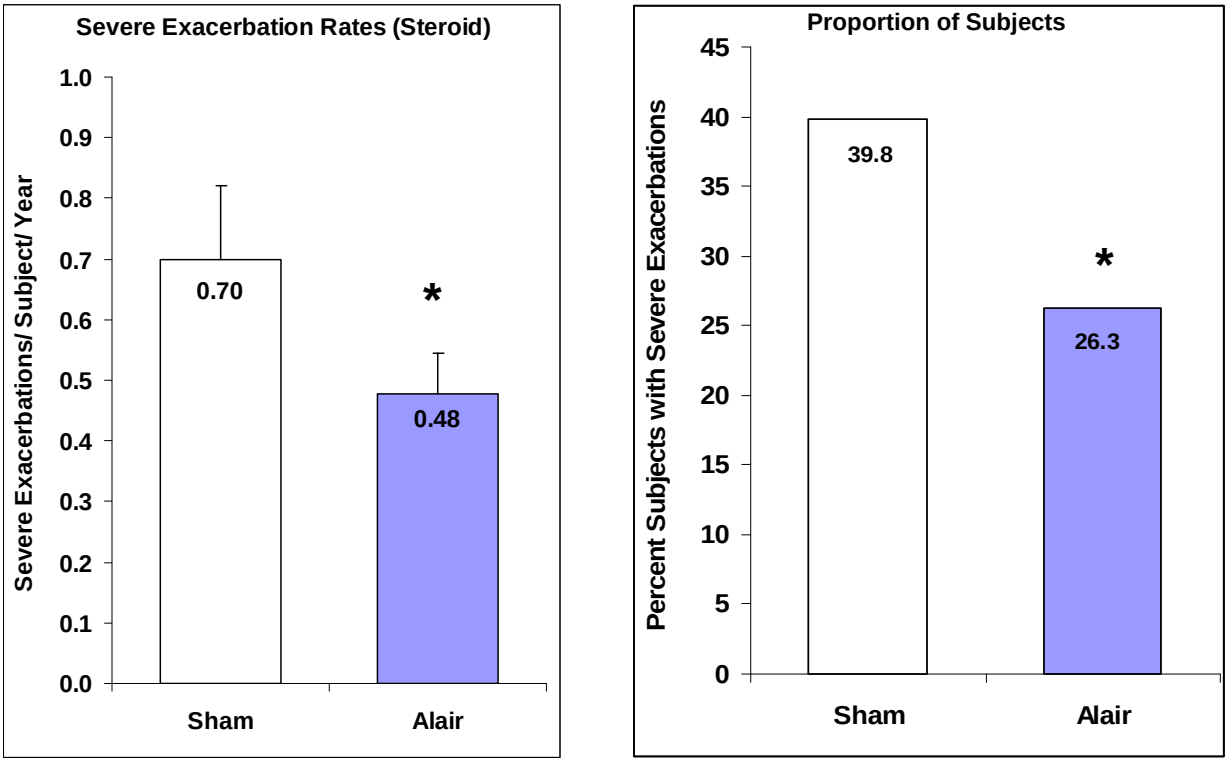


Figure 7: Severe Exacerbations During the Post-Treatment Phase
* Posterior Probability of Superiority > 95%

[a]**Steroid Exacerbations** = Exacerbations treated with oral or intravenous corticosteroids, OR a doubling of the baseline inhaled corticosteroid dose for at least 3 days, OR any temporary increase in the dosage of oral corticosteroids for a subject taking maintenance oral corticosteroids at Study entry. Annualized rates of exacerbations per subject are extrapolated from the 46 week Post-Treatment Phase from 6 weeks after the last bronchoscopy procedure to the 12 month follow-up visit.

Days Lost from Work, School, or Other Daily Activities due to Asthma Symptoms (ITT Population)

During the Post-Treatment Phase, subjects in the Alair group lost an average of 1.3 days/year/subject[a] from work, school, or other activities due to asthma symptoms, compared to the Sham group that lost 3.9 days/year/subject[a], Posterior Probability of Superiority 99.3% [95% CI (Sham - Alair): 0.425, 6.397]. These results are presented graphically in **Figure 8**.

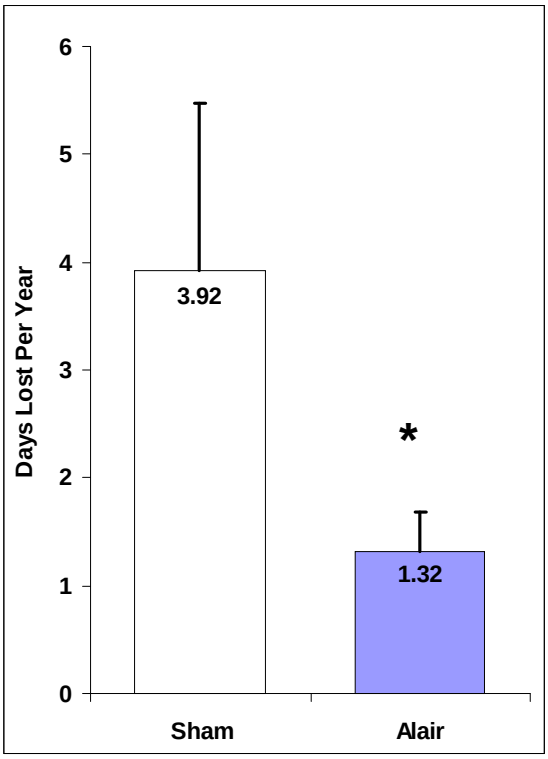


Figure 8: Days Lost from Work, School, or Other Daily Activities due to Asthma Symptoms (ITT Population)
* Posterior Probability of Superiority > 95%

[a]Annualized rates per subject are extrapolated from the 46 week Post-Treatment Phase from 6 weeks after the last bronchoscopy procedure to the 12 month follow-up visit.

Safety Endpoints that Demonstrated Effectiveness

Measures such as Unscheduled Physician Office Visits, Emergency Room Visits, and Hospitalizations for respiratory symptoms are generally considered to be important measures of safety, especially if an intervention results in an increase in the rate of one or more of these events. However, these measures can also be considered important measures of effectiveness if an intervention results in a measurable decrease in the rate of one or more of these events. During longer-term follow-up (> 6 weeks after the last Alair treatment), there was a significant reduction in Emergency Room Visits for respiratory symptoms (Posterior Probability of Superiority of 99.9%), and a reduction in Unscheduled Physician Office Visits and Hospitalizations for respiratory symptoms presented graphically in **Figure 9**. There was a similar reduction in the proportion of subjects having ER visits for respiratory symptoms in the Alair group (3.7% in the Alair group compared to 15.3% in the Sham group. Posterior Probability of Superiority of 99.9% [95% CI (Sham – Alair): 4.6%, 19.7%].

Healthcare Utilization Events Summary:

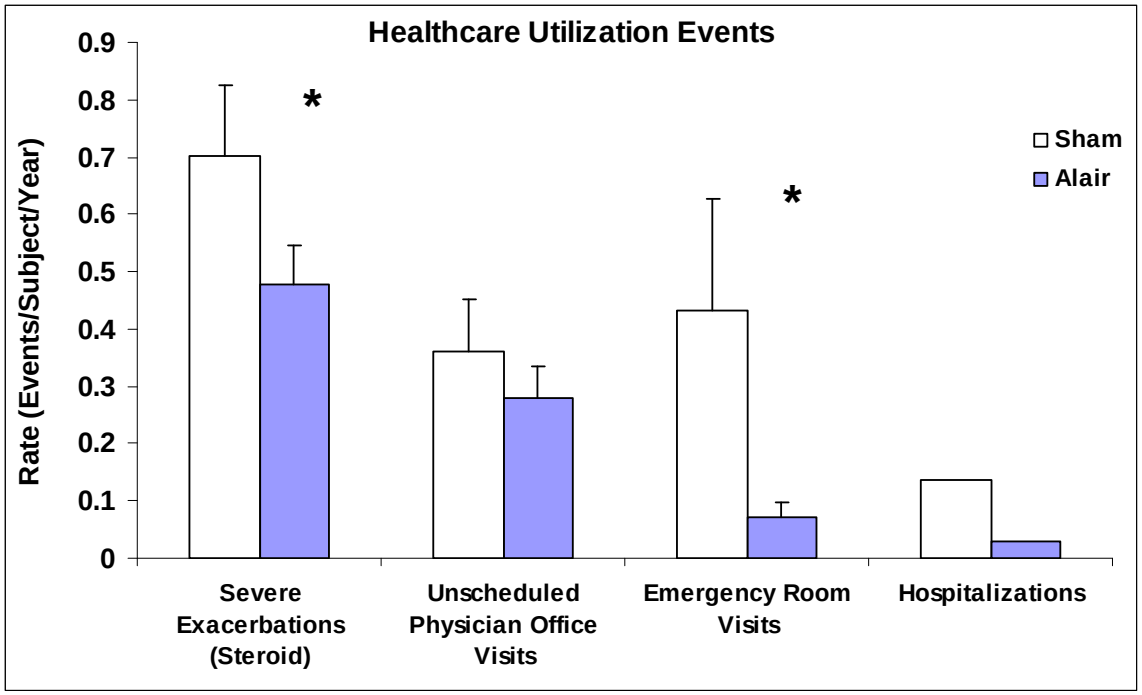


Figure 9: Healthcare Utilization (ITT Population)
* Posterior Probability of Superiority > 95%

Results from the clinical study which evaluated the effectiveness and safety of the Alair System in subjects with severe asthma, demonstrated that Alair treatment results in a statistically meaningful improvement in Asthma Quality of Life, a greater percentage of subjects with clinically meaningful changes in AQLQ, a reduction in severe exacerbations that required systemic steroids, a reduction in the percent of subjects experiencing the severe exacerbations, the number of emergency room visits for respiratory symptoms and days lost from school/work/activities for respiratory symptoms. The Alair group also showed reductions over the Sham group in the number of unscheduled office visits and hospitalizations.

The observed adverse event profile suggests that the procedure is tolerable and safe. In the Post-Treatment Phase, a smaller percentage of patients treated with bronchial thermoplasty experienced respiratory adverse events.

DIRECTIONS FOR USE

Alair Catheter Inspection and Preparation

1. The Alair System should only be used by a physician trained in bronchoscopy. These instructions do not explain bronchoscopic procedures.
2. Please read the Operator's Manual for the Alair RF Controller Model ATS 200 before beginning the procedure.
3. Visually inspect the package for damage before removing the Catheter from the package. Do not use the Catheter if the package is damaged or has been previously opened or torn.
4. Aseptically remove the Catheter from the package tray and inspect for any damage. The Catheter is packaged with the electrode array retracted within the protective, removable orange-colored Catheter tip sheath. Before use, remove the protective orange sheath. Inspect the Catheter for any damage such as broken or crushed areas of the Catheter, sharp or protruding edges at the distal tip, or any excessive bends or kinks in the Catheter shaft. Do not use the Catheter if any damage or irregularity is found. See **Figure 10**.

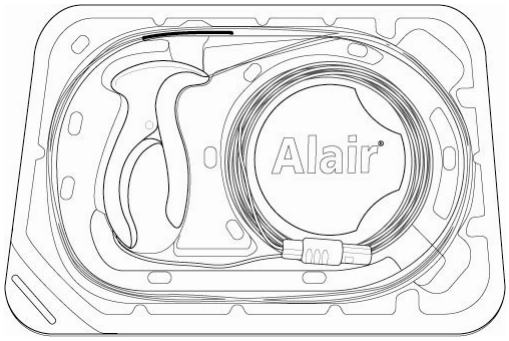


Figure 10: Alair Catheter in Tray

5. The distal portion of the Catheter shaft has marker bands that are spaced 5mm apart to aid in the positioning of the Catheter electrode array. Do not use the Catheter if the marker bands are missing. See **Figure 11.**

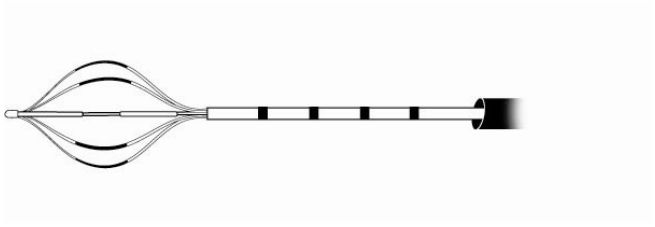


Figure 11: Alair Catheter with its four Marker Bands, spaced 5mm apart

6. Hold the Catheter handle in the palm of your hand, with the thumb and forefinger just below the Alair logo. Then, squeeze the forward handle back towards the back handle, ensuring that the electrode array expands properly. Verify that the electrode array opens fully and evenly. See **Figure 12.**

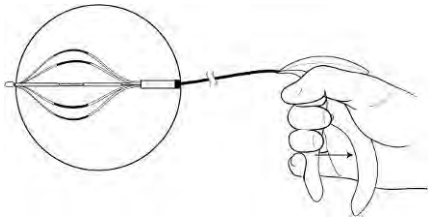


Figure 12: Alair Catheter Electrode Array Expanded

7. Relax the electrode array by releasing the front handle. See **Figure 13.** Do not use the Catheter if the electrode array does not expand or relax properly.

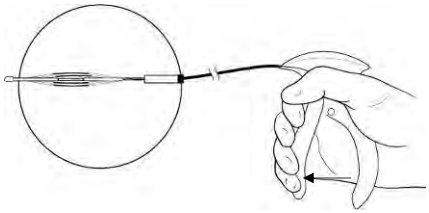


Figure 13: Alair Catheter Electrode Array Relaxed

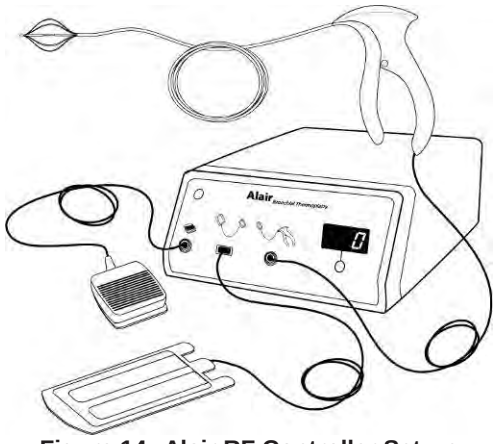


Figure 14: Alair RF Controller Set-up

Alair Bronchial Thermoplasty System Set-up and Operation

The Alair Catheter is intended to be used in conjunction with the Alair Controller. Please read the Alair RF Controller Model ATS 200 Operator's Manual before using the Alair System.

Figure 14 illustrates the Alair RF Controller Model ATS 200 set up.

Consult the Alair RF Controller Model ATS 200 Operator's Manual for specific instructions on:

- Controller Installation;
- Controller Power-Up;
- Connection of Components and Accessories;
- Controller Modes;
- Periodic Maintenance and Repair;
- Troubleshooting; and
- Technical Specifications.

Patient Preparation

1. Administer prophylactic prednisone or equivalent at a dosage of 50 mg/day for the 3 days before the procedure, the day of the procedure and the day after the procedure to minimize post procedure inflammation.
2. Verify the patient remains a good candidate for bronchoscopy under moderate sedation prior to initiation of the procedure (Mayse et al 2007)[5]. Postpone the procedure if any of the following conditions apply:
    - Prescribed prednisone was not taken on the 3 days before bronchoscopy
    - SpO_2 is less than 90% on room air
    - Increase in asthma symptoms in last 48 hours requiring more than 4 puffs/day on average of rescue bronchodilator over pretreatment usage
    - Asthma exacerbation or changing dose of systemic corticosteroids for asthma (up or down) in the past 14 days.
    - Active respiratory infection, active allergic sinusitis, or other clinical instability
    - Physician feels for any reason the procedure should be postponed.
3. Prepare the patient for bronchoscopy. Follow patient management protocols according to staffing, training, and individual institution-specific policies and guidelines for bronchoscopy.
4. Place the patient return electrode securely on the patient in accordance with manufacturer's instructions.
5. Introduce the flexible bronchoscope through the nose or mouth as appropriate. See **Figure 15 below.**

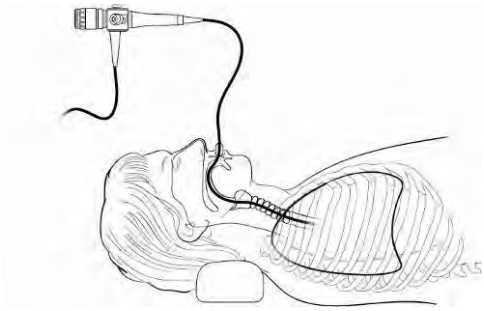


Figure 15: Bronchoscope navigation into patient's airways

6. Navigate the bronchoscope to the targeted site and position the bronchoscope so that the targeted site is in bronchoscopic view.

Alair Catheter Use

1. Before inserting the catheter into the bronchoscope, ensure the electrode array is relaxed. See **PRECAUTIONS.**
2. Avoid deflecting the bronchoscope while the electrode array is within the bend of the bronchoscope's working channel as this could result in damage to the Catheter and failure of the Catheter to operate properly. See **PRECAUTIONS.**
3. Advance the Catheter through the bronchoscope until the distal tip of the Catheter shaft is in bronchoscopic view. If the device encounters significant resistance during insertion, do not force it. In especially tortuous

[5]Mayse ML, Laviolette M, Rubin AS, Lampron N, Simoff M, Duhamel D, Musani, AI, Yung RC, Mehta AC. Clinical Pearls for Bronchial Thermoplasty. J Bronchol. 2007, 14:115-123.

anatomy it may be necessary to relax the bronchoscope's deflection mechanism until the device passes smoothly. See **Figure 16 below.**

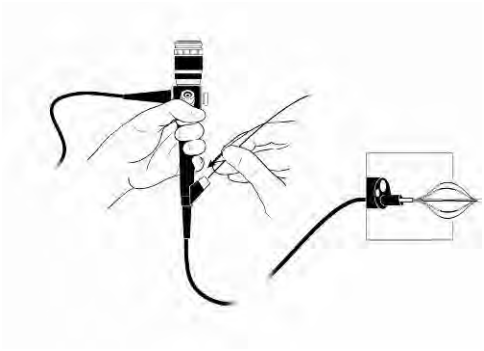


Figure 16: Alair Catheter introduced through working channel of bronchoscope

4. Advance the Catheter to the targeted site under bronchoscopic vision. Do not advance the Catheter into bronchi in which the Catheter cannot be seen under bronchoscopic vision. Advancing the catheter under such conditions may result in pneumothorax, pneumomediastinum or other harm or injury to the patient. See **WARNINGS.**
5. Do not treat the right middle lobe because of the potential susceptibility of the right middle lobe to transient obstruction as a result of inflammation or edema due to certain anatomical characteristics. The narrow diameter of the lobar bronchus and acute take-off angle may create poor conditions of drainage that may cause patient harm or injury such as atelectasis or difficulty in re-inflation (Right Middle Lobe Syndrome). See **WARNINGS.**
6. Do not reposition the bronchoscope with the Catheter advanced beyond the distal end of the bronchoscope as this may result in harm or injury to the patient. See **WARNINGS.**
7. Once at the targeted site, squeeze the handle together to expand the electrode array partially so that the electrodes are close to or just touching the targeted site.
8. With the electrode array partially expanded, adjust the axial position of the electrodes in the airway to position the active electrodes (exposed 5mm center region of the array electrodes) as desired. Expand the array until all four electrodes firmly contact the airway wall. Do not over-expand the electrode array. In many cases, full expansion of the Catheter electrode array will NOT require the catheter handle to be squeezed completely. Proper contact of the electrodes should be confirmed visually. See **Figure 17 below.**

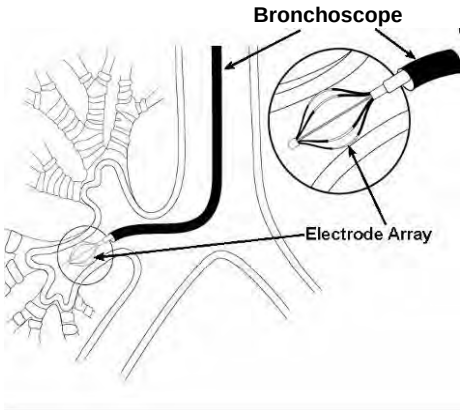


Figure 17: Alair Catheter in the Airway

9. Before delivering RF energy, make certain that all electrodes are in contact with the airway wall. See **PRECAUTIONS.**

10. Deliver RF energy to the targeted region by pressing and releasing the footswitch once. The Controller will deliver energy automatically according to preset parameters for time, energy, power, and temperature.

11. To manually terminate RF energy delivery, if necessary, press and release the footswitch again.

Note: *The Controller will automatically shut off the RF energy if it detects atypical energy delivery or temperature response.*

12. The Controller is programmed to alert the user with both audible and visual cues if re-deployment of the electrode array or replacement of the Catheter is required. Please refer to the Alair RF Controller Model ATS 200 Operator's Manual for more detailed instructions on these audible sounds and light displays.

Note: *If RF energy delivery ends prematurely, it may be necessary to re-deploy the electrode array and begin RF energy delivery again. If the problem persists, replace the Catheter.*

13. Reposition the Catheter and repeat the steps above making 5mm proximally placed contiguous treatments. The catheter's marker bands are spaced 5mm apart to assist with contiguous placement. **See Figure 18.**

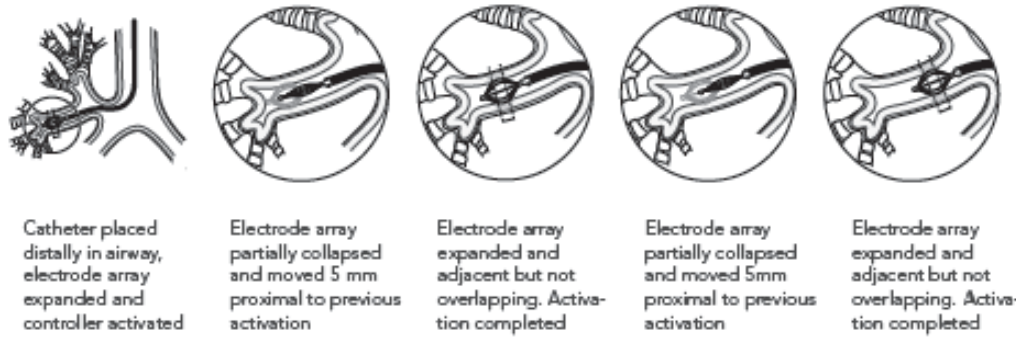


Figure 18: Contiguous Placement and Activation

14. Once the procedure is complete, relax the Catheter handle to relax the electrode array before removing the Catheter from the bronchoscope or before withdrawing the Catheter into the bronchoscope for airway navigation. To manipulate the bronchoscope with the Catheter in the working channel, withdraw the Catheter approximately 10 cm into the bronchoscope so the electrode array is proximal to the bend in the distal tip of the bronchoscope.

15. Once the treatment is complete, remove the Catheter from the bronchoscope. Disconnect the Catheter from the Controller, and dispose of the used Catheter per your institution's biohazard procedures. Remove the return electrode from the patient. Disconnect the patient return electrode from the Controller, and dispose of the patient return electrode per your institution's biohazard procedures.

Post Procedure Care

1. Follow appropriate institutional guidelines for post procedure care. It is recommended that patients should be carefully monitored and discharged only after they are deemed to be stable and have adequate (comparable to pre-procedure) lung function, mental status, and are able to adequately take liquids.
2. Recommended post procedure assessments are based on the criteria that were used in clinical trials of bronchial thermoplasty (Mayse et al 2007) and include:
    - 2 to 4 hour recovery/monitoring period following each procedure
    - Spirometry, breath sounds, and vital signs (heart rate, blood pressure, temperature, respiratory rate, pulse oximetry) before discharge
    - Discharge if post bronchodilator FEV_1 is within 80% of the pre procedure value and patient is feeling well
    - Verify patient has gag reflex and is able to take liquids
    - Verify prophylactic use of prednisone or equivalent the day following bronchoscopy
    - Contact patient via phone calls at 1, 2 and 7 days to assess post procedure status
    - Office visit at 2 to 3 weeks to assess clinical stability and schedule subsequent bronchial thermoplasty procedures as appropriate

HOW SUPPLIED

The Alair Bronchial Thermoplasty System Catheter Model ATS 2-5 is supplied sterile and is for SINGLE USE ONLY. **Do not re-sterilize or reuse** the Catheter, as this may result in patient harm or injury, transmittal of infectious disease, or product malfunction.

MAINTENANCE AND TROUBLESHOOTING

- If mucus builds up in the airways and obscures visualization, remove the catheter from the bronchoscope, provide irrigation with sterile saline, and suction the resulting fluid from the airways.
- If the electrode array does not expand or relax properly, remove the Catheter from the bronchoscope and squeeze and relax the Catheter handle to visually confirm that the electrode array is functioning properly. If it is not functioning properly, replace the Catheter and continue with the bronchial thermoplasty procedure.
- If you are alerted to auditory or visual cues from the Controller, consult the Alair Bronchial Thermoplasty RF Controller Model ATS 200 Operator's Manual for operating and troubleshooting guidelines for the Controller.

PARTS LIST

Part Description	**Part #**
Footswitch	
Power Cord	
Biohazard Kit (for returned product)	

INSTRUCTIONS FOR USE

CUSTOMER SERVICE

All questions or concerns related to the Catheter should be directed to Asthmatx Customer Service or an authorized Asthmatx representative. No product may be returned without prior authorization. Please contact Asthmatx Customer Service or an authorized Asthmatx representative for a Returned Product (RP) number. See **"Contact Us"**.

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SYMBOL LEGEND

	Model Number
	Caution: Consult Accompanying Documents
	Radiation sterilized. Sterility guaranteed if package unopened or undamaged.
	Lot Number
	Manufacturer Name
	Use by
	For SINGLE-USE ONLY.
 Only	For sale or use by or on order of a physician only

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