SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Bronchial Thermoplasty System
Device Trade Name:	Alair® Bronchial Thermoplasty System
Applicant's Name and Address:	Asthmatx, Inc. 888 Ross Drive, Suite 100 Sunnyvale, CA 94089
Date of Panel Recommendation:	October 28, 2009
Premarket Approval Application (PMA) Number:	P080032
Date of FDA Notice of Approval:	April 27, 2010
Expedited:	Granted expedited review status on October 17, 2008 because this device offers a breakthrough technology (technology that has not been approved for this use for any other applicant).

II. INDICATIONS FOR USE

The Alair® Bronchial Thermoplasty System is indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long acting beta agonists.

III. CONTRAINDICATIONS

Patiens 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 previously treated with the Alair System should not be retreated in the same area(s). No clinical data are available studying the safety and/or effectiveness of repeat treatments.

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,
- Known coagulopathy,

- As with other bronchoscopic procedures, patients should stop taking anticoagulants, antiplatelet agents, aspirin and NSAIDS before the procedure with physician guidance.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Alair Bronchial Thermoplasty labeling.

V. DEVICE DESCRIPTION

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

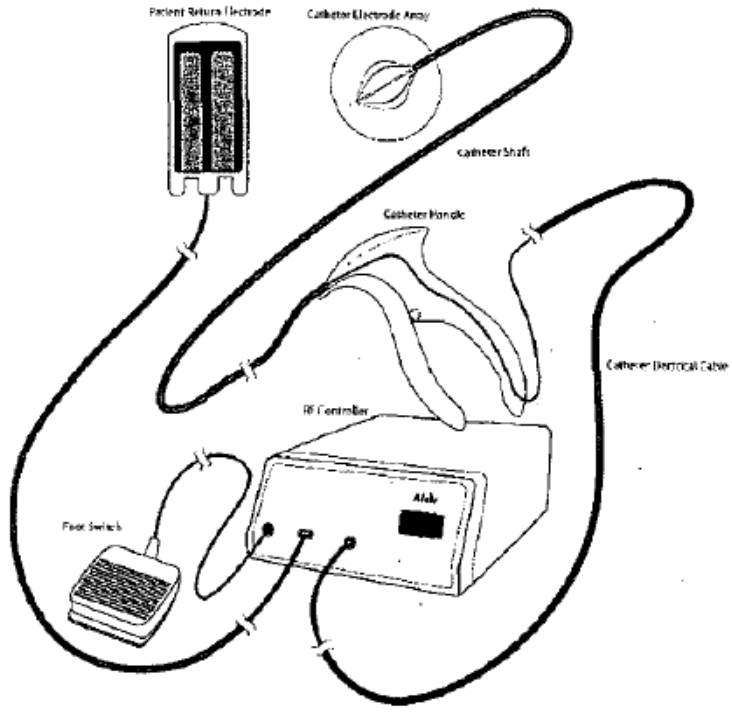
Alair Radiofrequency (RF) Controller: The Alair RF Controller Model ATS 200 ("Controller") is designed to provide controlled delivery of RF energy to the Alair Catheter. Energy from the Controller is delivered to the Catheter through the electrical cable attached to the proximal end of the catheter handle. 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.

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[1] and/or CE marked. The patient return electrode is used to complete the return path for

[1]IEC 60601-2-2:2006: Medical Electrical Equipment – Part 2-2: Particular Requirements for the Safety of High Frequency Surgical Equipment

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.



VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies for the treatment of severe persistent asthma include systemic corticosteroids and Omalizumab. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Alair Bronchial Thermoplasty System has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- Upper respiratory tract infection
- Viral upper respiratory tract infection
- Nasopharyngitis
- Sinusitis
- Acute sinusitis
- Throat irritation
- Pharyngolaryngeal pain
- Rhinitis
- Rhinitis (allergic)
- Asthma (multiple symptoms)
- Wheezing

- Dyspnea
- Cough
- Productive cough
- Bronchitis
- Chest discomfort
- Atelectasis
- Hemoptysis
- Lower respiratory tract infection
- Chest pain
- Anxiety
- Headaches
- Nausea
- Pyrexia (fever)
- Influenza
- Back pain
- Airway bleeding
- Laryngospasm
- Bronchospasm
- Excess mucus production
- Increased airway reactivity
- Pneumonia and/or infection
- Cardiovascular events
- Acute respiratory failure
- Bronchial stenosis
- Bronchiectasis
- Pneumothorax
- Persistent retained secretions and/or the risk of intubation or mechanical ventilation

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Alair Catheter Testing Summary

Alair Catheter Design Verification

Fully functional catheter test samples were manufactured, packaged, and sterilized in accordance with manufacturing instructions and tested for the critical dimensional, mechanical, reliability, and electrical design attributes listed in **Table 1**. The catheter met all of the predetermined acceptance criteria.

Table 1: Alair Catheter Design Verification Results

Category & Design Attribute	Acceptance Criteria	Test Results
Dimensional		
Exposed electrode width	0.0135" ± 0.0014"	Pass
Electrode alignment	90° ± 20°	Pass
Active electrode centration	Center of exposed electrode length within 1.0 mm of apex when electrode array expanded to ≥ 10 mm	Pass
Thermocouple joint: Area overhanging exposed electrode	Combined footprint area of electrode and overhanging thermocouple joint ≤ 0.0032 in^2	Pass

Category & Design Attribute	Acceptance Criteria	Test Results
Reliability		
Deployment and heating cycles without electrode failure or distal or proximal joint failure	Minimum 150 cycles	Pass
Electrical performance		
Dielectric strength for handle	No dielectric breakdown when tested at high frequency at 128 V_{RMS}	Pass
Dielectric strength for catheter shaft and cable	No dielectric breakdown when tested at mains frequency of 3000 V_{RMS} and at high frequency at 128 V_{RMS}	Pass
DC resistance from cable connector to electrodes	30-50 Ω	Pass
Allowable variation in resistance measurement difference between electrodes	5% range maximum	Pass

Alair Catheter Packaging and Transportation Qualification

Environmental conditioning was performed on packages and catheters prior to transit testing to simulate the rigorous set of exposures that may occur during distribution. ASTM D4332-01[2] was used as guidance for the conditioning. ASTM D4169-05[3], distribution cycle 13, assurance level 1 was followed for transit testing. The test results are listed in **Table 2**, below. The catheter and its packaging met the predetermined acceptance criteria.

[2]ASTM D4332-01: Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing

[3]ASTM D4169-05: Standard Practice for Performance Testing of Shipping Containers and Systems

Table 2: Alair Catheter Packaging and Transportation Qualification Results

Category & Design Attribute	Acceptance Criteria	Test Results
Dimensional		
Electrode alignment	90° ± 20°	Pass
Exposed electrode axial length	5.0 ± 0.5 mm	Pass
Active electrode centration	Center of exposed electrode length within 1.0 mm of apex when electrode array expanded to ≥ 10 mm	Pass
Thermocouple joint: Area overhanging exposed electrode	Combined footprint area of electrode and overhanging thermocouple joint ≤ 0.0032 in^2	Pass
Electrode heat shrink insulation integrity	Maximum 0.3 mm^2 break size; Maximum 0.06 mm^2 total break area	Pass
Exposed pull wire insulation integrity between distal and proximal joints	Maximum 0.3 mm^2 break size; Maximum 0.06 mm^2 total break area	Pass
Mechanical Performance		
Distal tip pull-off force	Minimum 2 lbf tensile force	Pass
Electrode pull-off force (distal joint)	Minimum 0.5 lbf tensile force	Pass
Electrode pull-off force (proximal joint)	Minimum 0.5 lbf tensile force	Pass
Label robustness	Label must be legible and withstand exposure to water and/or alcohol	Pass
Reliability		
Deployment and heating cycles without electrode failure or distal or proximal joint failure	Minimum 150 cycles	Pass
Electrical Performance		
DC resistance from cable connector to electrodes	30-50 Ω	Pass
Allowable variation in resistance measurement difference between electrodes	5% range maximum	Pass
Thermocouple accuracy	Measured electrode temperature within ± 3°C of actual temperature over 40°C to 80°C range during RF energy delivery	Pass

Category & Design Attribute	Acceptance Criteria	Test Results
Thermocouple temperature response time	Rate ≥ 60°C/second on a catheter brought from 20°C to 70°C (± 5°C); Maximum rate of change over a 0.2 second period	Pass
Heating at distal tip and proximal joint	Maximum 80°C; Must not exceed average of 55°C over 10 second activation	Pass
Packaging		
Bubble emission	No leak paths	Pass

Alair Catheter Shelf Life

The shelf life evaluation comprised accelerated aging to support a shelf life claim of one (1) year. Accelerated aging was performed according to ASTM F1980[4] and included device functionality and packaging performance testing on sterilized units. The results of this testing are listed in **Table 3**, below. The catheter and its packaging met the predetermined acceptance criteria.

Table 3: Alair Catheter Shelf Life Test Results

Category & Design Attribute	Acceptance Criteria	Test Results
Dimensional		
Electrode alignment	90° ± 20°	Pass
Exposed electrode axial length	5.0 ± 0.5 mm	Pass
Active electrode centration	Center of exposed electrode length within 1.0 mm of apex when electrode array expanded to ≥ 10 mm	Pass
Electrode heat shrink insulation integrity	Maximum 0.3 mm^2 break size; Maximum 0.06 mm^2 total break area	Pass
Exposed pull wire insulation integrity between distal and proximal joints	Maximum 0.3 mm^2 break size; Maximum 0.06 mm^2 total break area	Pass
Mechanical Performance		
Distal tip pull-off force	Minimum 2 lbf tensile force	Pass
Electrode pull-off force (distal joint)	Minimum 0.5 lbf tensile force	Pass

[4]ASTM F1980: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices

Category & Design Attribute	Acceptance Criteria	Test Results
Electrode pull-off force (proximal joint)	Minimum 0.5 lbf tensile force	Pass
Shaft to handle joint tensile strength	Minimum 2.25 lbf tensile force	Pass
Label robustness	Label must be legible and withstand exposure to water and/or alcohol	Pass
Reliability		
Deployment and heating cycles without electrode failure or distal or proximal joint failure	Minimum 150 cycles	Pass
Electrical performance		
Dielectric strength for handle	No dielectric breakdown when tested at high frequency at 128 V_{RMS}	Pass
Dielectric strength for catheter shaft and cable	No dielectric breakdown when tested at mains frequency of 3000 V_{RMS} and at high frequency at 128 V_{RMS}	Pass
Thermocouple accuracy	Measured electrode temperature within ± 3°C of actual temperature over 40°C to 80°C range during RF energy delivery	Pass
Thermocouple temperature response time	Rate ≥ 60°C/second on a catheter brought from 20°C to 70°C (± 5°C); Maximum rate of change over a 0.2 second period	Pass
Heating at distal tip and proximal joint	Maximum 80°C; Must not exceed average of 55°C over 10 second activation	Pass
Packaging		
Bubble emission	No leak paths	Pass
Peel strength	Minimum 0.8 lbf per linear inch of seal	Pass

Alair Catheter Biocompatibility

ISO 10993-1[5] and FDA memorandum G95-1 ("Required Biocompatibility Training and Testing Profiles for Evaluation of Medical Devices") were used as guidance in selecting the appropriate tests for biological evaluation. According to the their classification and

[5]ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process

categorization guidelines, the Alair Catheter is a surface contact device that contacts a mucosal membrane for less than 24 hours, and the biological testing listed below was suggested. Biocompatibility testing of all patient-contacting materials was conducted in accordance with Good Laboratory Practice (21 CFR §58), and the results are summarized in **Table 4**, below. All biocompatibility tests were passed.

Table 4: Alair Catheter Biocompatibility Test Results

Test and Standard	Results
Cytotoxicity Study Using the ISO Elution Method (ISO 10993-5)	Pass
ISO Maximization Sensitization Study – Extract (ISO 10993-10)	Pass
Irritation or Intracutaneous Reactivity (ISO 10993-10)	Pass

Alair Catheter Sterilization Validation

The validation of the sterilization process for the Alair Catheter was performed according to ISO 11737-2:2006[6], and ensured that the process can reproducibly and reliably expose each lot of product to a dose range that will guarantee the required sterility assurance level (SAL) of 10^{-6}. The radiation dose substantiated was 25 kGy.

Alair RF Controller Testing Summary

Alair RF Controller Hardware Testing

Verification testing of the RF Controller hardware consisted of the critical attributes listed in **Table 5**. The RF Controller design met its predetermined acceptance criteria.

Table 5: Alair RF Controller Hardware Verification Test Results

Design Attribute	Acceptance Criteria	Test Results
Power output	Able to deliver 18W	Pass
Protection against short circuits in catheter	Able to withstand any combination of shorts or any number of opens	Pass
Transportation	Fully functional after transportation testing (ASTM D4169-01)	Pass
Electrical safety	Must be able to pass requirements of 60601-1[7], 60601-2-2	Pass

[6]ISO 11737-2:2006: Sterilization of medical devices – Microbiological methods – Part 2: Test of sterility performed in the validation of a sterilization process

[7]IEC 60601-1: Medical Electrical Equipment – Part 1: General Requirements for Safety, 1988; Amendment 1, 1991-11, Amendment 2, 1995

Design Attribute	Acceptance Criteria	Test Results
Electromagnetic compatibility in standby mode	Must be able to pass requirements of 60601-1, 55011[8] class B emission standards	Pass
Time set range	10 seconds default (not adjustable by user)	Pass
Unique audible tone and visual signal present upon fault mode	Feature present	Pass
Unique audible tone and visual signal present when power is being applied	Feature present	Pass
Impedance range monitoring	Impedance must not be outside of a pre-specified range for greater than a pre-specified time (recoverable error and power shutdown when impedance is out of predetermined range)	Pass
Temperature ramp monitoring	The measured temperature must rise by a pre-specified amount after the initialization of RF energy delivery (recoverable error and power shutdown when positive, specific temperature increase is not detected within predetermined time)	Pass
Maximum RF power output	18W (not adjustable by user)	Pass
Temperature set range	65°C (not adjustable by user)	Pass
Maximum RF voltage	85 V_{RMS}	Pass
Maximum RF current output	0-0.90 A_{RMS} + 10%/-0%	Pass
Temperature range monitoring	Temperature must not be lower or higher than pre-specified values	Pass
Temperature drop monitoring	Temperature must not drop by more than a pre-specified value over a pre-specified time (recoverable error and power shutdown when temperature decreases by predetermined amount during treatment)	Pass

Alair RF Controller Software Testing

Software verification was conducted and includes static and dynamic verification on individual modules or groups of modules. Software validation was then conducted on the

[8]EN 55011: Industrial, scientific and medical (ISM) radio-frequency Equipment. Electromagnetic disturbance characteristics. Limits and methods of measurement

complete program assembly to demonstrate that the completed software end product complied with the established software requirements specified in the Software Requirements Specification (SRS). The verification testing is listed in **Table 6** and the validation testing is listed in **Table 7**. All tests were passed.

Table 6: Alair RF Controller Software Verification Test Results

Requirement	Acceptance Criteria	Test Results
CONTROL Subsystem	Verify subsystems that read and control key parameters (voltage, current, power, temperature) perform in both static and dynamic conditions.	Pass
USER Subsystem	Verify subsystem that reads and processes catheter, footswitch, and return electrode conditions switches states appropriately and performs in both static and dynamic conditions. Verify subsystems which increment counters and write data to EPROM perform in both static and dynamic conditions.	Pass
DISPLAY Subsystem	Verify subsystem which manages displays (RF, return electrode, basket, catheter OK, catheter fault, ready, standby and counter LEDs) performs in both static and dynamic conditions.	Pass
SWITCH Subsystem	Verify subsystem that polls switches and updates status performs in both static and dynamic conditions.	Pass
TERMINAL Subsystem	Verify subsystem allows for data collection.	Pass
OTHER Subsystems	Verify subsystems that initialize system, execute self tests, and generate error codes perform in both static and dynamic conditions.	Pass

Table 7: Alair RF Controller Software Validation Test Results

Requirement	Acceptance Criteria	Test Results
POWER ON State	Appropriate displays, non-responses, tones, and fault states are encountered.	Pass
STANDBY State	Appropriate tones, states, non-responses, temperature checks, and displays are encountered.	Pass
READY State	Appropriate states, temperature measurements, and displays are encountered.	Pass
RF ON State	RF energy is delivered and terminated under appropriate temperature, impedance and hardware conditions and appropriate tones and error codes are generated.	Pass
DONE State	Counter is incremented, correct tones and displays are evident, system exhibits proper non-responses and transitions between states.	Pass
ERROR State	Counters are appropriately incremented, correct tones and displays are evident, system exhibits proper non-responses and transitions between states.	Pass
CATHETER FAULT State	Correct tones and displays are evident, system exhibits proper non-responses and transitions between states.	Pass
FAULT State	Correct tones and displays are evident, system exhibits proper non-responses.	Pass
ERROR Codes	Correct recoverable and non-recoverable error codes are generated as a result of errors encountered in hardware self-tests, POST and operating mode.	Pass
Operator Interface	Appropriate displays are generated for all operator interfaces (front panel switch, footswitch, LED's and audible tones).	Pass

Alair RF Controller Safety Testing:

The Alair RF Controller has been evaluated against and found to meet the requirements of the electrical safety standards listed below:

- IEC 60601-1

- IEC 60601-1-2[9]
- IEC 60601-1-4[10]
- IEC 60601-2-2

B. Animal Studies

Four pre-clinical animal studies of this device were performed. All studies were performed in canines. A total of 35 canines have undergone treatment with the Alair System with long-term follow-up out to a maximum of 3 years. These studies were conducted in order demonstrate the feasibility of this treatment from a safety perspective. Please see **Table 8** for brief protocol descriptions; the results and study conclusions are described below.

Table 8: Preclinical Animal Testing

Study	Objective	Description
QT-00334	Evaluate long-term safety of the Alair System at 65°C	N=30 dogs (15 Alair, 15 sham control) Bronchoscopic observations at 6, 12, 18, and 24 months post-treatment. Histology performed at 1 year and 2 years.
QT-00075	Evaluate safety and effectiveness of the Alair System at various treatment temperatures	N=12 dogs Bronchoscopic observations and local methacholine challenge performed at 1, 6, 12, 30, 40, 60, 105, 128 and 157 weeks post-treatment. Histology at 1 week, 6 weeks, 12 weeks, and 157 weeks.
QT-00045	Evaluate safety and effectiveness of the Alair System at various treatment temperatures	N=2 dogs Bronchoscopic observations and local methacholine challenge performed 2, 4, 7, 16, 30, 40, and 53 weeks posttreatment. Histology performed at one year.
QT-00090	Evaluate safety of the Alair System at 65°C	N=6 dogs Bronchoscopic observations and local methacholine challenge performed at 1, 3, 27, 45, 115 and 136 weeks post-treatment. Histology performed at 27 weeks and 136 weeks.

[9] IEC 60601-1-2: Medical Electrical Equipment – Part 1-2: General Requirements for Safety 2. Collateral Standard: Electromagnetic Compatibility – Requirements and Tests

[10] IEC 60601-1-4: Medical Electrical Equipment – Part 1-4: General Requirements for Safety – Collateral Standard: Programmable Electrical Medical Systems, edition 1.1

Study QT-00334

Results: All the dogs tolerated the procedure with minimal respiratory symptoms during the Treatment Phase and maintained good long-term clinical health through 2 years Post-treatment. During the Treatment Phase, there was a transient low level increase in observations of cough, mucus production from cough, and auscultation findings in the Alair group. During the same period there was a similar low level increase in observations of cough in the Sham control dogs. During the Post-treatment period, these observations returned to pre-treatment levels and were comparable between the Alair and Sham control dogs.

The results show that following Alair treatment, there was a reduction in airway smooth muscle. In addition to the reduction in airway smooth muscle, histological examination showed the presence of some necrotic and regenerative cartilage, and mild hypertrophy of mucous glands. Minimal amounts of mucus were observed bronchoscopically in some airway segments. These observed changes are not considered to be clinically significant since all of the Alair treated dogs maintained good clinical health throughout the 2 year study period. There were no clinically significant observations from radiographic review or health examination throughout the 2 year study period.

Conclusion: This study showed that Alair treatment was well tolerated, achieved the desired effect of reducing airway smooth muscle, and that the procedure has an acceptable safety profile.

Study QT-00075

Results: All animals were in good clinical health until sacrifice, with the exception of one dog that was inadvertently treated with more than the desired amount of energy because of an operator error in setting up the RF Controller. (The RF Controller was subsequently modified to limit delivery of energy based on preset parameters. Adjustments by users are not possible.) During the Treatment Phase, transient observations of cough and a slight decrease in arterial blood gas (PaO2) were observed that returned to pre-treatment levels during the Post-Treatment Phase.

Following Alair treatment, resting airway diameter was reduced transiently at 1 week, but returned to baseline levels at the 6-week follow-up and remained stable to 3 years. Clear or white easily suctioned mucus was observed occasionally in both Alair-treated and Control airways. There was a reduction in airway smooth muscle (ASM) in treated airways and a reduction in the ability of airways to narrow in response to methacholine challenge. These reductions were observed for up to 3 years for both the 65°C and 75°C Alair treatment temperatures.

Conclusion: This study showed that the Alair procedure is well tolerated in dogs and effective in reducing airway responsiveness. Histological findings from QT-00075 suggest that a reduction in ASM is the mechanism by which the observed post-treatment reduction in airway responsiveness is achieved.

Study QT-00045

Results: The two animals were in good clinical health until sacrifice at one year. There was no observed trend toward airway narrowing. Moreover, reduction in the ability of airways to narrow in response to methacholine challenge was observed for up to one year for both the 65°C and 75°C Alair treatment temperatures. Histological findings from QT-00045 suggest that a reduction in ASM is the mechanism by which the observed post-treatment reduction in airway responsiveness is achieved.

Conclusion: This study suggested that the Alair procedure is well tolerated in dogs and effective in reducing airway responsiveness.

Study QT-00090

Results: All animals were in good clinical health until sacrifice, with the exception of one dog that developed severe bronchopneumonia more than 2 years after treatment with the Alair System and was euthanized for humane reasons. This bronchopneumonia was from an outbreak of beta-hemolytic streptococcal infection in the animal colony and was determined to be unrelated to the treatment.

During the Treatment Phase, one transient observation of listlessness and transient isolated observations of cough were seen. A slight decrease in PaO2 was seen at one week post-treatment, with recovery to baseline PaO2 at 2 weeks post-treatment.

Resting airway diameter was reduced transiently at 1 week in treated airways, but returned to baseline levels at the 3-week follow-up and remained stable to 136 weeks post-treatment. A reduction in the ability of airways to narrow in response to methacholine challenge was observed to 136 weeks post-treatment.

Conclusion: This study showed that the Alair procedure is well tolerated in dogs and effective in reducing airway responsiveness.

Summary of Preclinical Animal Testing

A total of 35 dogs have undergone treatment with the Alair System, with long-term follow-up out to a maximum of 3 years. Results from these studies demonstrated that the procedure is well tolerated and that tissue effects are stable by 12 weeks post-treatment. The data collected out to 3 years have demonstrated the long-term safety of the treatment, and a persistent reduction in airway smooth muscle.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of bronchial thermoplasty with the Alair Bronchial Thermoplasty System for treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long acting beta agonists in the US, Canada, Europe, and Brazil under IDE # G050082. Data from this clinical study were the

basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The AIR2 (Asthma Intervention Research) pivotal trial study objective was to demonstrate the safety and effectiveness of the *Alair Bronchial Thermoplasty System* in patients with severe asthma who remain symptomatic after conventional high dose inhaled corticosteroids (ICS) and inhaled long-acting β2-agonists (LABA). This study is a multi-center (15 US sites, 15 OUS sites), randomized, double-blinded, sham-controlled pivotal clinical trial. Randomization was 2:1 treatment:sham and stratified by Asthma Quality of Life Questionnaire (AQLQ) score, investigator, and symptom-free days. Patients were enrolled starting in October, 2005. Patients meeting the inclusion/exclusion criteria were randomized at the time of the first procedure to the treatment (Alair) or sham control (Sham) arm of the study. A total of 297 patients were enrolled; 196 patients were randomized to the Alair group, and 101 patients to the Sham group. Two investigative teams were trained at each site, a Treating Team and an Assessment Team. The Treating Team was not blinded to the treatment, but carried out the Sham procedure to mimic the treatment procedure in terms of time, device activation sounds, physician dialogue, etc. Each patient underwent 3 Alair/Sham procedures, separated by 3 weeks each. The right or left lower lobe was targeted in the first session, the opposite lower lobe was targeted in the second session, and the right and left upper lobes in the third session. All patients received prophylactic oral corticosteroids (OCS) (50 mg/day) for 3 days before the procedure, the day of the procedure, and the day after the procedure.

After each Alair/Sham procedure, patients were transferred to a recovery area and the care of the Assessment Team. All Assessment Teams were blinded to the procedure and assumed care of the patients for the remainder of the study. Blinding questionnaires were administered to Assessment Team members and patients after each procedure and at 3, 6, and 12 month visits. Study oversight was provided by an independent Data Safety Monitoring Board.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the AIR2 trial was limited to patients who met the following 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 β2-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 (Pre-BD FEV_1) in one second ≥60% predicted (after patients stabilized on inhaled corticosteroids and long-acting β2-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.

Patients were <u>not</u> permitted to enroll in the AIR2 trial if they met any of the following 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 (Post-BD FEV_1) 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 patient 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/mm2 or known coagulopathy (International Normalized Ratio > 1.5).
23. Uncontrolled hypertension (>200 mmHg systolic or >100 mmHg 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.

2. Follow-up Schedule

After the final treatment session, office visit follow-up occurred at 6 weeks, 3, 6, 9, and 12 months. Evaluations at 3, 6, and 12 months included:

- Pre and post bronchodilator spirometry
- Review of asthma symptoms, exacerbations, adverse events, and Daily Diary
- AQLQ
- ACQ (Asthma Control Questionnaire)
- Methacholine challenge test (Methacholine PC_{20})

Patients who had baseline HRCT studies underwent a follow-up HRCT at 12 months. The 9 month visit did not include spirometry, ACQ, or methacholine challenge testing.

Following completion of the 12 month visit (12 month Part 1), patients were asked to abstain from use of LABA for 2 weeks for final testing, termed 12 month Part 2. At the end of this period, patients underwent repeat assessment including:

- Physical examination
- Review of asthma symptoms, exacerbations, medications, adverse events, and Daily Diary
- Pre and post bronchodilator spirometry
- AQLQ
- ACQ

Following this assessment, patients resumed their normal medications.

3. Clinical Endpoints

Short-Term Safety Endpoints:

Comparison of the adverse event profiles between the treatment and control groups during the Treatment Phase.

Long-Term Safety Endpoints:

Comparison of adverse events profile between the treatment and control groups during the Post-Treatment Phase

Additional Safety Analyses:

Additional variables to be examined:

- FEV_1 differences between baseline and follow-up visits
- Unscheduled physician office visits for respiratory symptoms
- Emergency room visits for respiratory symptoms
- Hospitalizations for respiratory symptoms
- Blinded evaluation of HRCT scans

Primary Effectiveness Endpoint:

The primary effectiveness endpoint was the difference in the AQLQ score between the treatment and sham groups based on the average of the scores from the 6, 9, and 12 month visits (integrated AQLQ score).

Secondary Effectiveness Endpoints:

Secondary endpoints included differences between treatment and control from baseline to 6 and 12 month follow-up visits in the following parameters specified in the original protocol:

- Absolute change from baseline in percent symptom-free days
- Total symptom score
- Morning peak expiratory flow (amPEF)
- Individual Domain scores from the AQLQ
- AQLQ scores at 6, 9, and 12 months (individual, not averaged)
- ACQ
- Number of puffs of rescue medication used

- FEV_1

Other Effectiveness Variables:
"Other" effectiveness measures that Asthmatx tracked included differences between treatment and control from baseline to 6 and 12 month follow-up visits in the following parameters specified in the original protocol:

- Evening PEF (pmPEF)
- Forced Vital Capacity (FVC)
- Methacholine PC_{20}
- Nighttime awakenings for asthma
- Sever asthma exacerbations
- Mild asthma exacerbations
- Change in maintenance asthma medications
- Percent of days lost from work, school, or other daily activities
- Change between key parameters from baseline ON-LABA to 12 Month Part 2 (OFF-LABA)

B. Accountability of PMA Cohort

At the time of database lock, of 297 patients enrolled in the AIR2 trial, 93.6% (278) of the patients are available for analysis at the completion of the study, the one year post-treatment visit. See **Table 9**.

Table 9: AIR2 Patient Disposition

	Alair	Sham
Number of Subjects Randomized	196	101
Number of Subjects Receiving ≥1 bronchoscopy	190	98
Number of Subjects that Completed 12-Month [a] Visit	181	97
Reason for Premature Study Termination [b]		
Subject Voluntary Withdrawal – (Non-Medical)	4	2
Subject Voluntary Withdrawal – (Medical)	2	2
Subject Withdrawn by Investigator	6	0
Lost to Follow Up	6	1
Death	1	0

[a] 12-Month Part 1 visit.
[b] Subjects may have had more than one reason for termination. No subjects were withdrawn due to worsening of asthma.

C. Study Population Demographics and Baseline Parameters

Table 10 shows demographics data for the AIR2 study in the intent-to-treat (ITT) population. Statistical analysis showed no statistically significant differences between the Alair and Sham groups. The AIR2 study population includes multiple US patient populations.

Table 10: Patient Demographics (Intent-to-Treat Population)

	Alair (n=190)	**Sham (n=98)**
Age (years) (Mean ± SD)	41 ± 12	41 ± 12
Gender		
Male	81 (43%)	38 (39%)
Female	109 (57%)	60 (61%)
Race/Ethnicity		
Caucasian	151 (80%)	72 (74%)
African American / Black	19 (10%)	15 (15%)
Hispanic	6 (3%)	4 (4%)
Asian	4 (2%)	1 (1%)
Other	10 (5%)	6 (6%)
Height (cm) (Mean ± SD)	167 ± 9	167 ± 10
Weight (kg) (Mean ± SD)	82 ± 18	82 ± 20

Table 11 shows a comparison of baseline clinical characteristics between study arms (ITT population).

Table 11: Baseline Characteristics

	Alair (n=190)	Sham (n=98)	p-value
ICS Dose (ug/day)			
N	190	98	0.159 [a]
Mean	1960.7	1834.8	
STD	745.19	659.35	
Median	2000.0	2000.0	
LABA Dose (ug/day)			
N	189	97	0.105 [a]
Mean	116.8	110.3	
STD	34.39	26.70	
Median	100.0	100.0	
Number and Percent of Subjects on Other Asthma Maintenance Medications			
OCS	7 (3.7)	1 (1.0)	
Methylxanthines	6 (3.2)	5 (5.1)	
Leukotriene Modifiers	47 (24.7)	18 (18.4)	
Omalizumab	2 (1.1)	3 (3.1)	
Other	15 (7.9)	9 (9.2)	
Any of the Above Maintenance Medications	59 (31.1)	25 (25.5)	0.342 [b]
OCS Dose (mg/day)			
N	7	1	0.522 [a]
Mean	6.4	5.0	
STD	1.97		
Median	5.0	5.0	
AQLQ			
N	190	98	0.908 [a]
Mean	4.30	4.32	
STD	1.17	1.21	
Median	4.34	4.43	
ACQ			
N	190	98	0.729 [a]
Mean	2.1	2.1	
STD	0.87	0.90	
Median	2.0	2.1	

[a] p-value from t-test.
[b] p-value from Fisher's Exact test.

Table 11: Baseline Characteristics (continued)

	Alair (n=190)	Sham (n=98)	p-value
AM Peak Flow (L/min)			
N	190	98	0.849 [d]
Mean	383.8	386.3	
STD	104.32	112.59	
Median	377.7	366.3	
% Symptom Free Days[b]			
N	190	98	0.896 [d]
Mean	16.4	16.8	
STD	24.04	23.10	
Median	3.6	5.7	
Total Symptom Score[c]			
N	190	98	0.841 [d]
Mean	3.8	3.9	
STD	2.34	2.53	
Median	3.4	3.4	
Methacholine PC_{20} (mg/mL)			
N	178	94	0.548 [a]
Geometric Mean	0.27	0.31	
95% CI	(0.22, 0.34)	(0.22, 0.43)	
Pre-BD FEV1 (%pred)			
N	190	98	0.341 [a]
Mean	77.8	79.7	
STD	15.65	15.14	
Median	74.5	78.0	
Post-BD FEV1 (%pred)			
N	190	98	0.459 [a]
Mean	86.1	87.4	
STD	15.76	13.18	
Median	83.5	85.3	

[a, d] p-value from t-test.

[b] % Symptom Free Days is the percent of days in which there were no night awakening and the symptom score of each individual symptom (wheeze during night, cough during night, wheeze during day, cough during day, breathless during day, sputum during day) was 0.

[c] Total symptom score is the sum of individual symptoms collected on daily diary: wheeze during night, cough during night, wheeze during day, cough during day, breathless during day, sputum during day.

Table 11: Baseline Characteristics (continued)

	Alair (n=190)	Sham (n=98)	p-value
Number of Hospitalizations for Asthma in the 12 Months Prior to Study Entry[a]			
0	182 (95.8)	92 (93.9)	0.780 [b]
1	6 (3.2)	6 (6.1)	
2	2 (1.1)	0 (0.0)	
3 +	0 (0.0)	0 (0.0)	
Subjects with Hospitalizations	8	6	
Total Number of Hospitalizations	10	6	
Number of ER Visits for Asthma in the 12 Months Prior to Study Entry[a]			
0	135 (71.1)	67 (68.4)	0.268 [b]
1	25 (13.2)	10 (10.2)	
2	12 (6.3)	8 (8.2)	
3 +	18 (9.5)	13 (13.3)	
Subjects with Emergency Room Visits	55	31	
Total Number of Emergency Room Visits	141	117	
Number of Unscheduled Physician Office Visits for Asthma in the 12 Months Prior to Study Entry[a]			
0	116 (61.1)	62 (63.3)	0.754 [b]
1	29 (15.3)	12 (12.2)	
2	23 (12.1)	15 (15.3)	
3 +	22 (11.6)	9 (9.2)	
Subjects with Unscheduled Physician Office Visits	74	36	
Total Number of Unscheduled Physician Office Visits	162	73	
Number of Pulses of Oral/IV Steroids for Asthma in the 12 Months Prior to Study Entry[a]			
0	92 (48.4)	42 (42.9)	0.245 [b]
1	50 (26.3)	25 (25.5)	
2	27 (14.2)	16 (16.3)	
3 +	21 (11.1)	15 (15.3)	
Subjects with Pulses of Oral/IV Steroids	98	56	
Total Number of Pulses of Oral/IV Steroids	167	102	

[a] Subject reported.
[b] p-value from CMH, stratified by Investigational site.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the intent-to-treat population of 288 patients available for the 12-month post-treatment evaluation. The key safety outcomes for this study are presented below; adverse events are reported in Table 13.

Adverse events that occurred in the PMA clinical study:

Adverse events that occurred in at least 3% of the patients and were more common in the Alair group are reported in **Table 12**.

Table 12: Adverse Events with ≥ 3% Incidence (% of subjects) that were more common in the Alair Group

	Treatment[11]		Post-treatment[12]	
Adverse Event	**Alair (N=190) %**	**Sham (N=98) %**	**Alair (N=187) %**	**Sham (N=98) %**
Average duration of period (days)	84		322	
Ear, Nose, and Throat				
Upper respiratory tract infection	20	11	30	26
Viral Upper respiratory tract infection	4	2	6	7
Nasopharyngitis	5	7	11	5
Acute Sinusitis	3	2	4	8
Rhinitis	2	0	4	6
Lower Respiratory				
Asthma (Multiple Symptoms)	52	39	27	43
Wheezing	15	6	4	3
Dyspnea	11	6	2	1
Bronchitis	4	2	7	5
Chest discomfort	9	10	2	1
Atelectasis	5	0	0	0
Hemoptysis	3	0	0	0
Lower respiratory tract infection	8	2	3	6
Chest pain	14	13	3	1

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

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

Adverse Event	Treatment[11]		Post-treatment[12]	
	Alair (N=190) %	Sham (N=98) %	Alair (N=187) %	Sham (N=98) %
Neurology				
Anxiety	4	0	1	2
Headaches	14	9	5	3
Gastrointestinal				
Dyspepsia	4	2	2	4
Nausea	3	4	1	1
Non-site specific				
Pyrexia (fever)	4	2	0	1
Influenza	4	2	4	12
Other				
Urinary tract infection	1	1	3	1
Hypertension	3	2	3	3

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.

During the Treatment Phase in the AIR2 Trial, there was a transient increase in respiratory adverse events, including asthma (multiple symptoms), upper respiratory tract infection, atelectasis, lower respiratory tract infection, wheezing, hemoptysis, and anxiety in the Alair group compared to the Sham group. There was a lower incidence of throat irritation in the Alair group compared to the Sham group. There were 7 instances of hemoptysis defined as >5.0 mL (1.3% of bronchoscopies) of which 2 occurred on the day of the procedure, 2 occurred within 3 days, 2 occurred at 2 weeks, and one occurred on Day 31 after the procedure. The greatest amount of hemoptysis observed was a cumulative total of 150 mL that occurred over 5 days and was treated with bronchial artery embolization.

During the Treatment Phase (~ 12 weeks period), the rate of Unscheduled Physician Office visits (events / subject / 12 weeks) in the Alair group was 0.230 compared to 0.133 in the Sham group. The rate of hospitalizations for respiratory symptoms (events / subject / 12 weeks) was 0.086 in the

Alair group compared to 0.028 in the Sham group. The rate of Emergency Room visits for respiratory symptoms (events / subject / 12 weeks) was 0.062 in the Alair group compared to 0.075 in the Sham group.

During the Post-Treatment Phase in the AIR2 Trial, there was a 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 asthma (multiple symptoms) events. There was also a lower incidence of influenza, and a greater incidence of nasopharyngitis in the Alair group compared to the Sham group.

2. Effectiveness Results

The analysis of effectiveness was based on the 288 intent-to-treat patients at the 12-month post-treatment evaluation. Key effectiveness outcomes are presented below.

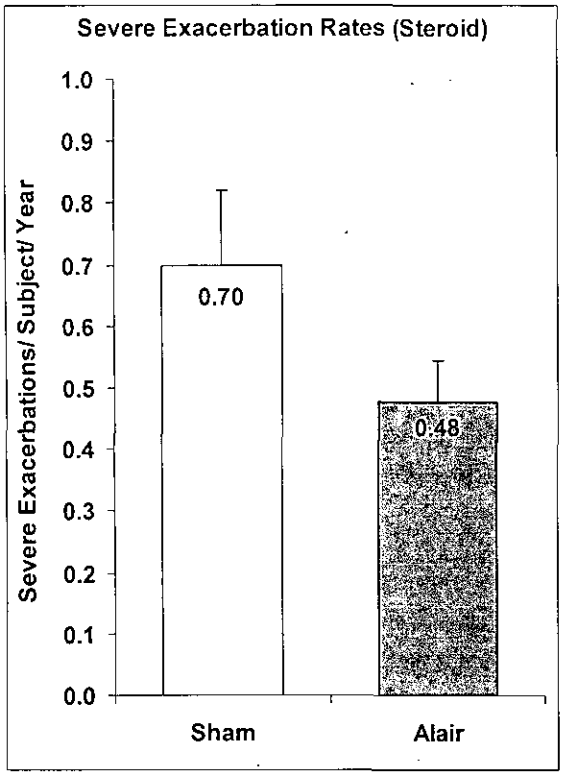
Although the clinical study was powered only for the primary effectiveness endpoint, the analysis of effectiveness was based on several other effectiveness endpoints and safety endpoints that could also be considered effectiveness endpoints. The effectiveness endpoints were rates of severe asthma exacerbations, proportions of patients with severe asthma exacerbations, and days lost from work, school, or other daily activities due to asthma symptoms. The safety endpoints considered for effectiveness were rates of asthma, emergency room visits for respiratory symptoms, and hospitalization rates for respiratory symptoms.

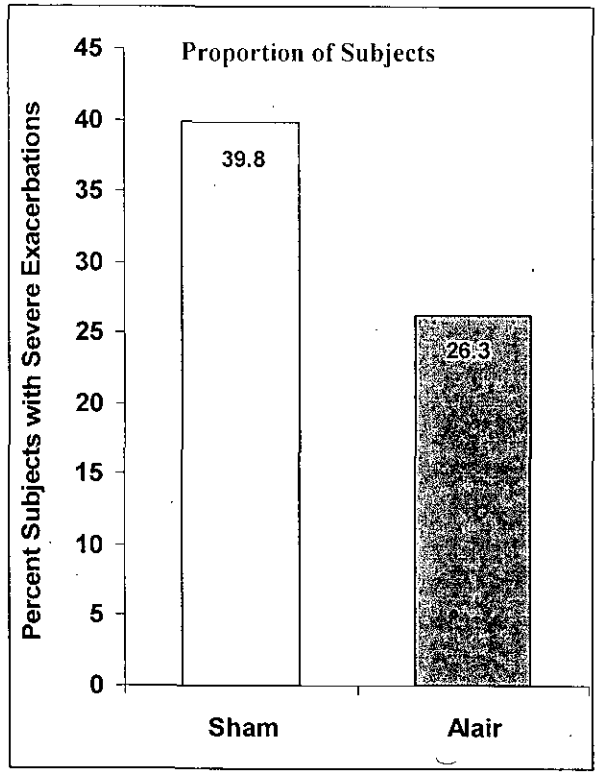
Steroid Exacerbations - Severe Exacerbations Requiring Systemic Corticosteroids (ITT Population):

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 [95% CI (Sham - Alair): -0.031, 0.520]. During the Post-Treatment Phase, the proportion of subjects experiencing Steroid Exacerbations was 26% in the Alair group and 40% in the Sham group [95% CI (Sham - Alair): 2.1%, 25.1%].

Steroid Exacerbation rates (annualized rate) and proportion of patients experiencing Severe Exacerbations for the Post-Treatment Phase are presented graphically in **Figure 1**.

Figure 1: Severe Exacerbations During the Post-Treatment Phase





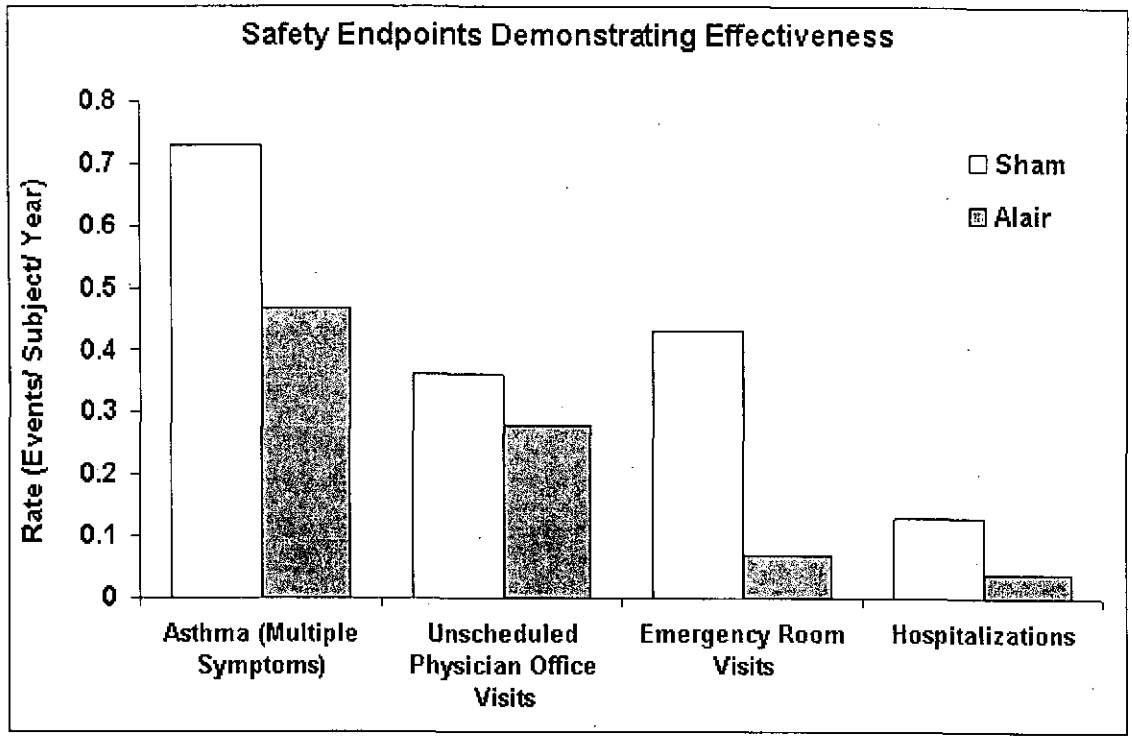
Days Lost from Work, School, or Other Daily Activities due to Asthma Symptoms (ITT Population):
During the Post-Treatment Phase, subjects in the Alair group lost an average of 1.3 days/year/subject from work, school, or other daily activities due to asthma symptoms, compared to the Sham group that lost 3.9 days/year/subject (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) [95% CI (Sham - Alair): 0.425, 6.397].

Safety Endpoints that Demonstrated Effectiveness:
Measures such as 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 reduction in asthma (multiple symptoms) adverse events [95% CI (Sham - Alair): -0.01, 0.001], Emergency Room visits for respiratory symptoms [95% CI (Sham - Alair): 0.11, 0.83], and Hospitalizations for respiratory symptoms (event rate per group) [95% CI (Sham - Alair): 0.025, 0.172], presented graphically in **Figure 2**.

There was a reduction in the proportion of subjects having asthma (multiple symptoms) adverse events ([95% CI (Sham - Alair): 4.0%, 27.3%]), and in the

proportion of subjects having Emergency Room visits for respiratory symptoms in the Alair group (3.7% in the Alair group compared to 15.3% in the Sham group) [95% CI (Sham - Alair): 4.6%, 19.7%].

Figure 2: Safety Endpoints Demonstrating Effectiveness (ITT Population)



Primary Effectiveness Endpoint – Integrated AQLQ Score:

The 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 was 0.210 [95% CI (Alair - Sham): -0.025, 0.445]. The pre-specified Posterior Probability of Superiority for the difference between the groups was 96.4%. For the ITT population, the difference between the groups had a Posterior Probability of Superiority of 96.0%, and for the PP population, the difference between the groups had a Posterior Probability of Superiority of 97.9%, demonstrating an improvement in the Asthma Quality of Life in the Alair group compared to Sham.

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 13**.

Table 13: Primary Effectiveness Endpoint – Integrated AQLQ Score

Population	Difference Between Groups in Integrated AQLQ Score (Posterior Mean, 95% CI)	Posterior Probability of Superiority (%)
ITT (Intent-to-Treat) (Alair N=190, Sham N=98)	0.210 (-0.025, 0.445)	96.0
PP (Per Protocol) (Alair N=173, Sham N=95)	0.244 (0.009, 0.478)	97.9

3. Subgroup Analyses
Differences between investigational sites and regions (US, OUS) were examined. Statistical differences between individual sites and regions were determined to be statistical variations that did not influence the study results.

XI. SUMMARY OF FEASIBILITY CLINICAL STUDIES

Prior to conducting the AIR2 trial, Asthmatx conducted five feasibility clinical studies of the Alair System (see **Table 14**). These studies were submitted to FDA as proof-of-principle and evidence of safety prior to beginning the pivotal AIR2 trial.

Table 14: Alair Feasibility Studies

Title	Date Initiated	Study Description	No. of Sites	No. of Patients	Follow-up Completed
Feasibility Study	November 2000	Safety study in patients with mild-to-severe asthma	2 (OUS)	16	5 years
AIR (Asthma Intervention Research) Trial	November 2002	Randomized, controlled (to standard care) trial to evaluate effectiveness and safety in patients with moderate-to severe asthma	11 (OUS)	55 Alair 54 Control	1 year
AIR Extension Study	March 2005	Long term follow-up of consenting patients who completed the AIR Trial	11 (OUS)	41 Alair 23 Control	4 years for Alair; 3 years for Control
RISA (Research in Severe Asthma) Trial	April 2004	Randomized, controlled (to standard care) trial to evaluate safety and reduction in medications or asthma symptoms in patients with severe, refractory asthma	8 (OUS)	15 Alair 17 Control	1 year

Title	Date Initiated	Study Description	No. of Sites	No. of Patients	Follow-up Completed
RISA Extension Study	January 2007	Long term follow-up of consenting patients who completed the RISA Trial	7 (OUS)	14 Alair	3 years for Alair only

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on October 28, 2009, the Anesthesiology and Respiratory Therapy Devices Panel recommended that the applicant's PMA for the Alair Bronchial Thermoplasty System be conditionally approved with the following conditions:

1. A registry focused on durability of treatment effect and safety in all US patients should be maintained. Patient population parameters such as age and severity of disease should be included in the registry.
2. The Alair System should not be used in patients on anti-coagulative therapy or with impaired coagulation due to risk of hemoptysis.
3. Adequate training of physicians with appropriate medical oversight should be performed before procedures are performed.
4. This procedure should be performed in fully equipped bronchoscopy suites which include full resuscitation equipment to handle hemoptysis, pneumothorax, and other complications.
5. Retreatment with Alair should be contraindicated until data on retreatment is available.
6. Post-approval studies should be performed. Studies details are to be worked out between FDA and Asthmatx Inc.

For more information, please see the complete panel transcript at the 2009 Meeting Materials of the Anesthesiology and Respiratory Therapy Devices Panel webpage.

B. FDA's Post-Panel Action

FDA has fully considered the panel's recommendations and chosen to implement all of them in the following manner: Conditions 1 and 6 were used to create two post-approval study protocols that address durability of treatment effect and long-term safety in US patients. Conditions 2-5 were used to revise the device labeling. The applicant added conditions 2 and 5 as contraindications in their labeling, conditions 3 was used to develop an appropriate treatment precautions, and condition 4 was used to develop an appropriate warning.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in the AIR2 clinical

study conducted to support PMA approval as described above. The safety data from the pivotal trial showed that all adverse events were reversible, and with the exceptions of atelectasis and hemoptysis, which occurred only in the Alair group, all adverse events were common to both the Alair and sham groups. While there were some differences between the study groups in certain adverse events, there were no general trends to indicate a safety risk of the Alair treatment. Serious adverse events during the treatment phase included hemoptysis, respiratory infections, atelectasis, pneumonia, and asthma symptoms. With the exception of hemoptysis and atelectasis, all of these events occurred in both study groups. The Panel stated that these results do not raise serious concerns; they are expected events in the patient population of this study and some may be related to bronchoscopic procedures rather than the Alair treatment. Overall, the safety data demonstrate an acceptable safety profile for the Alair System.

B. Effectiveness Conclusions

The primary effectiveness analysis examined the difference between mean-integrated AQLQ scores between the treatment and sham arms of the pivotal study; this analysis did not meet its prespecified success criterion and is not the basis of approval. Other endpoints, however, provided compelling evidence that the Alair system offers clinical benefits.

According to the Panel, the most important clinical performance measure in the pivotal trial is severe asthma exacerbations; FDA agrees with this statement. The pivotal trial data showed a clinically significant difference in favor of the Alair group for this endpoint. The pivotal trial also measured other endpoints that clinically could be expected to correlate with severe asthma exacerbations. Several of these endpoints – emergency room visits for respiratory symptoms; hospitalizations for respiratory symptoms; rescue medication use; asthma symptoms; days lost from work, school, or other activities; an unscheduled physician office visits for respiratory symptoms – all showed differences in favor of the Alair group. The majority of other secondary and additional endpoints do not reach clinical significance, but almost all slightly favor the Alair group over the sham group. While results that did not exhibit clinical significance cannot be a basis of approval, the fact that these endpoints point in the right direction, and several of the important ones show clinical meaningful differences, adds to the totality of the effectiveness data, a point that was mentioned by the Panel in their deliberations. The results of the pivotal trial demonstrate that this device provides a clinically significant benefit.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The pivotal trial data demonstrates a clinically meaningful benefit for the intended patient population and a reasonable safety profile without evidence of irreversible adverse outcomes.

The Alair System may be approved with the condition that the agreed-upon post-approval studies are satisfactorily conducted. This recommendation is supported by the recommendation of the Anesthesiology and Respiratory Devices Panel.

XIV. CDRH DECISION

CDRH issued an approval order on April 27, 2010. The final conditions of approval cited in the approval order are described below.

In addition to the Annual Report requirements, you have agreed to provide the following data in post-approval study (PAS) reports. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

1. The first post-approval study is to evaluate durability of effectiveness of the Alair System in patients with severe persistent asthma. The study population will consist of Alair-group subjects who are currently in the follow-up phase of the AIR2 Trial (Protocol #04-02).

   The primary endpoint of the PAS is the proportion of subjects experiencing severe exacerbations during the first year after the Alair treatment compared to subsequent 12-month periods out to 5 years. The study hypothesis to be evaluated is that the upper 95% confidence limit of the difference in proportions of subjects experiencing severe exacerbations (i.e., the subsequent 12-month proportion minus the first 12-month proportion) is less than 20%.

   The secondary endpoints will include the following additional safety endpoints for which data are currently being collected in the AIR2 Trial:
   - Severe exacerbation rates (exacerbations / subject / year)
   - Respiratory adverse events (rates of respiratory adverse events, and proportion of subjects with respiratory adverse events)
   - Emergency room visits for respiratory symptoms (rates of emergency room visits, and proportion of subjects with emergency room visits for respiratory symptoms)
   - Hospitalizations for respiratory symptoms (rates of hospitalizations, and proportion of subjects with hospitalizations for respiratory symptoms)
   - Respiratory Serious Adverse Events (detailed narratives will be provided for each event)
   - Forced Expiratory Volume in 1 second (FEV_1)

   For primary effectiveness endpoint, the primary analysis will test the hypothesis whether the upper 95% confidence limit of the difference in proportions of subjects experiencing severe exacerbations (i.e., the subsequent 12-month proportion minus the first 12-month proportion) is less than 20%. The proportions of patients with severe exacerbations at each year will be calculated with the denominator as the number of patients who complete follow-up visits for that particular year. Patients who are lost to follow-up will be excluded from the analysis.

In addition to the primary analyses, a sensitivity analysis will be conducted at 5 years.

Secondary effectiveness endpoints will be evaluated with descriptive statistics with 95% CI. All adverse events (AE) will be summarized by the number of the subjects reporting the adverse events, system organ class, preferred term, severity, relationship to procedure, and the duration of the AEs.

You have also agreed to make every reasonable effort to limit the cumulative loss-to-follow-up to be less than 20% at the 5 year follow-up (with an average yearly loss <5%). Beginning with the subjects entering the study at Year 2, and assuming a 20% dropout, approximately 140 subjects are expected to be evaluable for the 5-year endpoint.

2. The second PAS study will be a prospective, open-label, single arm, multi-center study conducted in the United States. The study objective is to demonstrate durability of treatment effect and to evaluate the short-term and longer-term safety profile of the Alair System in the United States in the intended use population. The sponsor will enroll up to 300 subjects (a minimum of 250 subjects) to achieve 200 evaluable study subjects at the end of 5 years post-treatment; this is based on a 20% lost-to-follow-up over 5 years.

   The primary endpoint will be the proportion of subjects experiencing severe exacerbations during the subsequent 12-month periods (for Years 2, 3, 4, and 5) compared to the first 12-month proportion after the Alair treatment. The study hypothesis is to demonstrate that the proportion of subjects who experience severe exacerbations in the subsequent 12-month follow-up [for Year 2, Year 3, Year 4 and Year 5 (in 12-month periods)] is not statistically worse when compared with the first 12-month proportion, which begins 6-weeks after the last Alair treatment. This objective will be met if the upper 95% confidence limit of the difference in proportions (i.e., the subsequent 12-month proportion minus the first 12-month proportion) is less than 20%.

   The secondary endpoints will include the following additional safety endpoints which will be evaluated annually through Year 5 following treatment with the Alair System:
   - Rates of Severe exacerbations (exacerbations / subject / year)
   - Respiratory adverse events (rates of respiratory adverse events, and proportion of subjects with respiratory adverse events)
   - Emergency room visits for asthma symptoms (rates of emergency room visits and proportion of subjects with emergency room visits for asthma symptoms)
   - Hospitalizations for asthma symptoms (hospitalizations/ subject/ year, and proportion of subjects with hospitalizations for respiratory symptoms)
   - Respiratory Serious Adverse Events (detailed narratives will be provided for each event)
   - Pre- and post-bronchodilator FEV_1

   The analysis plan for the primary and secondary effectiveness endpoints, and the AEs will be the same as described for the first PAS in this order.

You have also agreed to make every reasonable effort to limit the cumulative loss-to-follow-up to less than 20% at the 5 year follow-up (with an average yearly loss <5%). If the follow-up rate is unacceptably low during the 5 year follow-up, FDA will consider other options to limit loss-to-follow-up, including requiring you to recruit more subjects.

You must also update your patient and physician labeling (via PMA supplement) to reflect the results of the post-approval study at 5 years, as soon as these data are available, as well as any other time points deemed necessary by FDA if significant new information from the study becomes available.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study(ies). Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2).

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.