Protocol: Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma

NCT: NCT01350336

Document Date: 26 April 2012

Protocol Title: Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma

Short Title: Bronchial Thermoplasty in Severe Persistent Asthma (PAS2)

Protocol Number: 10-02

Protocol Date: 26 April 2012

Version: 3

Sponsor:

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PROTOCOL CHANGE STATUS

Protocol Version Number	Date
Version 1	25 August 2010
Version 2	02 June 2011
Version 3	26 April 2012

1.0 Study Approval

Asthmatx Protocol No. 10-02

Study Title: Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma

Protocol Date: 26APR2012 (Version 3)

Asthmatx, Inc. has approved this protocol. The following signatures document this approval.

Narinder S. Shargill, PhD. Vice-President, Clinical Affairs	Date
Debera Brown Vice-President, Scientific Affairs	Date

Table of Contents

2.0 List of Abbreviations and Definitions of Terms

AE	Adverse Event
ASM	Airway Smooth Muscle
BD	Bronchodilator
CBC	Complete Blood Count
CRF	Case Report Form
eCRF	Electronic Case Report Form
CXR	Chest X-ray
ECG	Electrocardiogram
FEV_1	Forced Expiratory Volume (in one second)
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
ICS	Inhaled Corticosteroid medication
INR	International Normalized Ratio
IRB	Institutional Review Board
J	Joules
LABA	Long-acting β_2-agonist
PEF	Peak Expiratory Flow
RF	Radiofrequency
SAE	Serious Adverse Event
SpO_2	Oxygen Saturation by Pulse Oximetry
UADE	Unanticipated Adverse Device Effect

3.0 Introduction

3.1 Background

Asthma is a chronic respiratory disease characterized by inflammation of the airways, excess mucus production, and airway hyper-responsiveness, a condition in which airways narrow excessively or too easily in response to a stimulus (*James et al. 1989; Fredberg et al. 1997; Fredberg et al. 1999; Seow et al. 1998; Wiggs et al 1997; King et al. 1998*), and airway remodeling (ref). Chronic asthma is also associated with the presence of excess airway smooth muscle (ASM) (*Bousquet et al. 2000; Cohen et al., 2007; Carroll et al, 1993; Castro et al, 1998*). Although there are many possible triggers, asthma is invariably associated with airways that narrow too easily and/or too much in response to provocative stimuli (*National Institutes of Health Global Initiative for Asthma, GINA 2008 Update*). Thus, regardless of the initial trigger (e.g., allergen, irritant, infection), the cascade ends with ASM contraction with subsequent airway narrowing and airflow obstruction. Asthma has a significant impact on a patient's life, limiting participation in many activities. In severe cases, asthma can be life threatening. Presently, there is no known cure for asthma.

Bronchial thermoplasty delivered by the Alair System is a method of reducing the amount of ASM through delivery of controlled energy to the airway walls. Pre-clinical and clinical studies have demonstrated a reduction of ASM and airway hyper-responsiveness following bronchial thermoplasty with the Alair System (*Danek et al., 2004; Miller at al., 2005*). Clinical studies of bronchial thermoplasty involving patients with differing levels of asthma severity have demonstrated that following bronchial thermoplasty, there is a reduction in asthma symptoms and an improvement in PEF, symptom-free days, and asthma control, resulting in an improvement in asthma quality of life (*Cox et al., 2007; Pavord et al., 2007*).

Results from a recently completed multi-center, randomized, double-blind, sham controlled clinical trial (*Asthma Intervention Research 2 (AIR2) Trial – Asthmatx Protocol #04-02*) conducted under an FDA-approved IDE in patients with severe persistent asthma demonstrated that over the 12-month period following treatment, Alair treated subjects experienced clinically meaningful improvements in a number of outcomes (*Castro et al. 2010*). Although the clinical study was powered only for the primary effectiveness endpoint (Asthma Quality of Life Questionnaire score), several effectiveness endpoints (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) and safety endpoints that could also be considered effectiveness endpoints (rates of asthma, emergency room visits for respiratory symptoms, and hospitalization rates for respiratory symptoms) demonstrated clinically meaningful differences in favor of the Alair group compared to the Sham group. 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.

Additionally, 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%].

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].

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. 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%].

The safety results demonstrated that:

During the Treatment Phase:

- 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.

- 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.

- The respiratory hospitalization rate per bronchoscopy was 3.4% (19/558) in the Alair group compared to a corresponding rate in the Sham group of 0.7% (2/292).

- All adverse events were resolved with standard therapy.

- Median Time to Onset of Respiratory Adverse Events Occurred Within 1 Day of Bronchoscopy: The median time to onset following bronchoscopy for respiratory adverse events was 1.0 day for the Alair group (average within 5.9 days) and 1.0 day for the Sham group (average within 7.2 days). The median time to resolution was 7.0 days in the Alair group and 5.0 days in the Sham group.

- There was no increase in the rate of respiratory adverse events following either the second, or the third Alair treatment bronchoscopy.

During the Post-Treatment Phase:

- 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.

The Investigational Device Exemption (IDE) for the pivotal AIR2 Trial was approved by the U.S. Food and Drug Administration (FDA) on 21July2005. The PMA (PMA 080032) for the Alair Bronchial Thermoplasty System was granted Expedited Review status on 17October2008. The final module for PMA 080032 was received by the FDA on 31December2008. The Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee to the FDA voted 6 to 1 to recommend with conditions the approval of this device for the treatment of severe persistent asthma in patients 18 years and older. The final approval order for the PMA was granted by the FDA on 27April2010.

As Conditions of Approval of the PMA for the Alair System, the FDA requires Asthmatx to generate data to assess the durability of the BT treatment effect as well as safety data in the intended use population in the United States.

Asthmatx is committed to conducting this post-approval study to assess the durability of the treatment effect and short-term and longer-term safety of the Alair System in the United States due to the fact that US population was underrepresented (approximately 30%) in the premarket clinical trial (Protocol 04-02). The study will be conducted at sites in the United States and Canada, limiting the number of subjects enrolled in Canada to no greater than 20%.

Physician-Investigators who wish to participate in this study understand that the study will be conducted under all applicable regulatory requirements. Investigator responsibilities are summarized in Appendix A and Appendix A1. All participating Investigators and Co-Investigators will be asked to sign a Sponsor-generated Investigator's Agreement (Appendix D).

This study is being conducted according to Good Clinical Practices (GCP), in compliance with the principles enunciated in the Declaration of Helsinki (*World Medical Association Declaration of Helsinki, 2008*), applicable local regulations, and Standard Operating Procedures (SOPs) of Asthmatx, Inc.

3.2 Description of the Alair System and Bronchial Thermoplasty

The Alair System (Figure 1) consists of two major components: the Alair Catheter (a basket catheter containing heating and temperature sensing elements), and the Alair Radiofrequency (RF) Controller. A commercially available return electrode is used with the Alair System.

Figure 1: Alair System

The procedure performed with the Alair System is called bronchial thermoplasty. To perform bronchial thermoplasty:

- The catheter is introduced into the lungs through the working channel of a standard flexible bronchoscope.
- The catheter is navigated to the first treatment site. Once the catheter is positioned at the desired location in the airway of the lung, the electrode array is deployed and the RF controller is activated to deliver RF energy to the airway wall.
- Following the completion of an activation the Alair Catheter is repositioned and subsequent activations are performed in a contiguous manner in all accessible airways distal to the main stem bronchi ≥3mm in diameter.
- The deployment of the catheter is from the distal to the proximal end of the airway being treated.
- All visible and accessible airways within the bronchial tree should be treated.

During this study, bronchial thermoplasty will be accomplished during three treatment sessions, each separated by at least 3 weeks. During the first session, the right lower lobe (RLL) of the lung will be treated. The right middle lobe will not be treated. During the second treatment session, the left lower lobe (LLL) of the lung will be treated. During the third

treatment session, both the right upper lobe (RUL) and the left upper lobe (LUL) including the lingula will be treated.

3.3 Report of Prior Investigations

A total of 7 human clinical studies evaluating the Alair System have either been completed or are underway. The studies undertaken to date are:

- **Safety Study in Lobectomy Patients: Protocol No. 1199-04**. Evaluation of Thermal Energy in the Airways. Eight (8) subject open label study (Canada). Initiated in January 2000, and completed in May 2000.

  Published: *Miller JD, G Cox, et al. (2005).* ***A prospective feasibility study of bronchial thermoplasty in the human airway****. Chest 127(6): 1999-2006.*

- **Feasibility Study: Protocol Nos. 0500-05 and 1100-08**. Evaluation of a Novel Therapy for the Treatment of Asthma. Sixteen (16) subject open label study (Canada) involving patients with mild to severe asthma. Initiated in November 2000. Enrollment completed in April 2002. Five (5) year follow-up completed in July 2007.

  Published: *Cox G, JD Miller, et al. (2006).* ***Bronchial thermoplasty for asthma.*** *Am J Respir Crit Care Med. 173(9): 965-969.*

  Wilson SR, G Cox, JD Miller, S Lam (2006). ***Global assessment after bronchial thermoplasty: the patient's perspective.*** *Journal of Outcomes Research 10: 37-46.*

- **AIR Trial (Asthma Intervention Research Trial): Protocol No. 0602-20**. Multicenter randomized controlled clinical trial of the Alair System for the Bronchial Thermoplasty Treatment of Asthma. One hundred and nine (109) subjects with moderate to severe asthma randomized to Alair (55 subjects) or standard of care (54 subjects) (Canada, Denmark, United Kingdom, and Brazil). Initiated in November 2002. Enrollment completed in August 2004. 12-Month follow-up completed in November, 2004.

  Published: *Cox G, NC Thomson, A Sperb-Rubin, R Niven, P Corris, HC Siersted, R Olivenstein, I Pavord, D McCormack, R Chaudhuri, J Miller, M Laviolette, and The AIR Trial Study Group (2007).* ***Asthma control during the year after Bronchial Thermoplasty.*** *N Engl J Med. 356 :1327-1337.*

- **AIR Extension Study: Protocol No. 05-01.** Long-term (five year) follow-up for safety of subjects with moderate to severe asthma who completed the AIR Trial (Study No. 0602-20). (Canada, Denmark, United Kingdom, and Brazil). Initiated in March 2005. Follow-up ongoing.

- **RISA Trial (Research in Severe Asthma Trial): Protocol No. 0903-27**. Multicenter randomized controlled clinical trial of Bronchial Thermoplasty with the Alair System for the Treatment of Severe Asthma. Thirty two (32) subjects with severe refractory asthma randomized to Alair (15 subjects) or standard of care (17 subjects) (Canada, United

Kingdom, and Brazil). Initiated in April 2004. Enrollment completed in December 2004. 12-Month follow-up completed in February, 2005.

Published: *Pavord ID, G Cox, NC Thomson, AS Rubin, PA Corris, RM Niven, KF Chung, M Laviolette, and the RISA Trial Study Group (2007).* ***Safety and Efficacy of Bronchial Thermoplasty in Symptomatic, Severe Asthma****. Am J Respir Crit Care Med 176 : 1185–1191.*

- **RISA Extension Study: Protocol No. 06-01.** Long-term (five year) follow-up for safety of subjects with severe persistent asthma who completed the RISA Trial (Study No. 0903-27). (Canada, United Kingdom, and Brazil). Initiated in January 2007. Follow-up ongoing.

- **AIR2 Trial (Asthma Intervention Research 2): Protocol No. 04-02.** Safety and Effectiveness of the Alair System for the Treatment of Asthma: A Multicenter Randomized Clinical Trial (Asthma Intervention Research (AIR2) Trial). Two hundred and ninety seven (297) subjects with severe persistent asthma randomized 2:1 into Treatment (196 subjects) and Sham (101 subjects) groups (United States, Australia, Brazil, Canada, the Netherlands, and United Kingdom). Initiated in October 2005. 12-Month follow-up completed in July 2008. Long-term (5 year) follow-up of Alair-treated subjects ongoing.

  Published: *Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, Fiss E, Olivenstein R, Thomson NC, Niven RM, Pavord ID, Simoff M, et al.* ***Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma. A multicenter, randomized, double-blind, sham-controlled clinical trial.*** *Am J Respir Crit Care Med. 2010; 181:116-124.*

Summaries of these clinical studies can be found in the Investigator's Brochure for this study.

4.0 Objectives with Study Hypotheses

The objective of this study is to evaluate durability of treatment effect and to continue to evaluate the short-term and longer-term safety profile of the Alair System in the United States and Canada in the intended use population (patients 18 years and older with severe persistent asthma) following FDA approval.

Durability of the treatment effect will be evaluated by comparing the proportion of subjects who experience severe exacerbations* during the first year after Alair treatment with the proportion of subjects who experience severe exacerbations during subsequent 12-month periods out to 5 years. Favorable upper 95% confidence limits of the difference in proportion of subjects experiencing severe exacerbations between the subsequent years and the first year will be used to infer a durable treatment effect.

Study Hypothesis: An empirical demonstration of the durability of the treatment effect will be used to show that the proportion of subjects experiencing severe exacerbations in subsequent years compared with the proportion of subjects experiencing severe exacerbations in the first year do not get substantially worse. The primary statistical objective 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 proportion of the first 12-months, 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 formal expression of the hypothesis is as follows:

> Let π_S and π_f be the 12-month probabilities for the period subsequent to the first period and for the first period, respectively. The primary effectiveness endpoint will be demonstrated by rejecting the null hypothesis H_0: $\pi_S \geq \pi_f + \delta$ in favor of H_1: $\pi_S < \pi_f + \delta$ at an alpha of 0.05, using a δ of 0.20 (i.e., 20%).

The test of hypotheses and/or computation of equivalent confidence limits will be based on large-sample confidence interval estimation methods for independent samples.

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* *Severe exacerbation defined as worsening of asthma symptoms requiring use of systemic corticosteroids (tablets, suspension, or injection) (NAEPP Guidelines, 2007).*

For subjects already taking oral corticosteroids on a daily or alternate day basis, a severe exacerbation will be defined as a worsening of asthma symptoms requiring any increase in daily dose of systemic corticosteroids.

For consistency, courses of corticosteroids separated by 1 week or more will be treated as separate severe exacerbations.

Note: This definition of a Severe Exacerbation is different than that used in the AIR2 Trial (Protocol #04-02) where the definition also included the doubling of ICS dose for at least 3 days to treat the worsening of asthma symptoms. The current definition is consistent with, and based on the NAEPP Guidelines, 2007.

The computation of the upper confidence limit (UCL) follows the general formula:

UCL = Point Estimate + z-point * Variance Estimate

where:

- the Point Estimate is derived from the difference in observed proportions for the years being compared;
- the z-point is derived from the standard normal distribution;

and

- the Variance Estimate represents the Standard Error of the Point Estimate. From the available data it is estimated that the Standard Error will be approximately 4%.

The following assumptions are used to derive the 20% non-inferiority margin for the long-term monitoring of the Alair group from the AIR2 Trial (Protocol # 04-02):

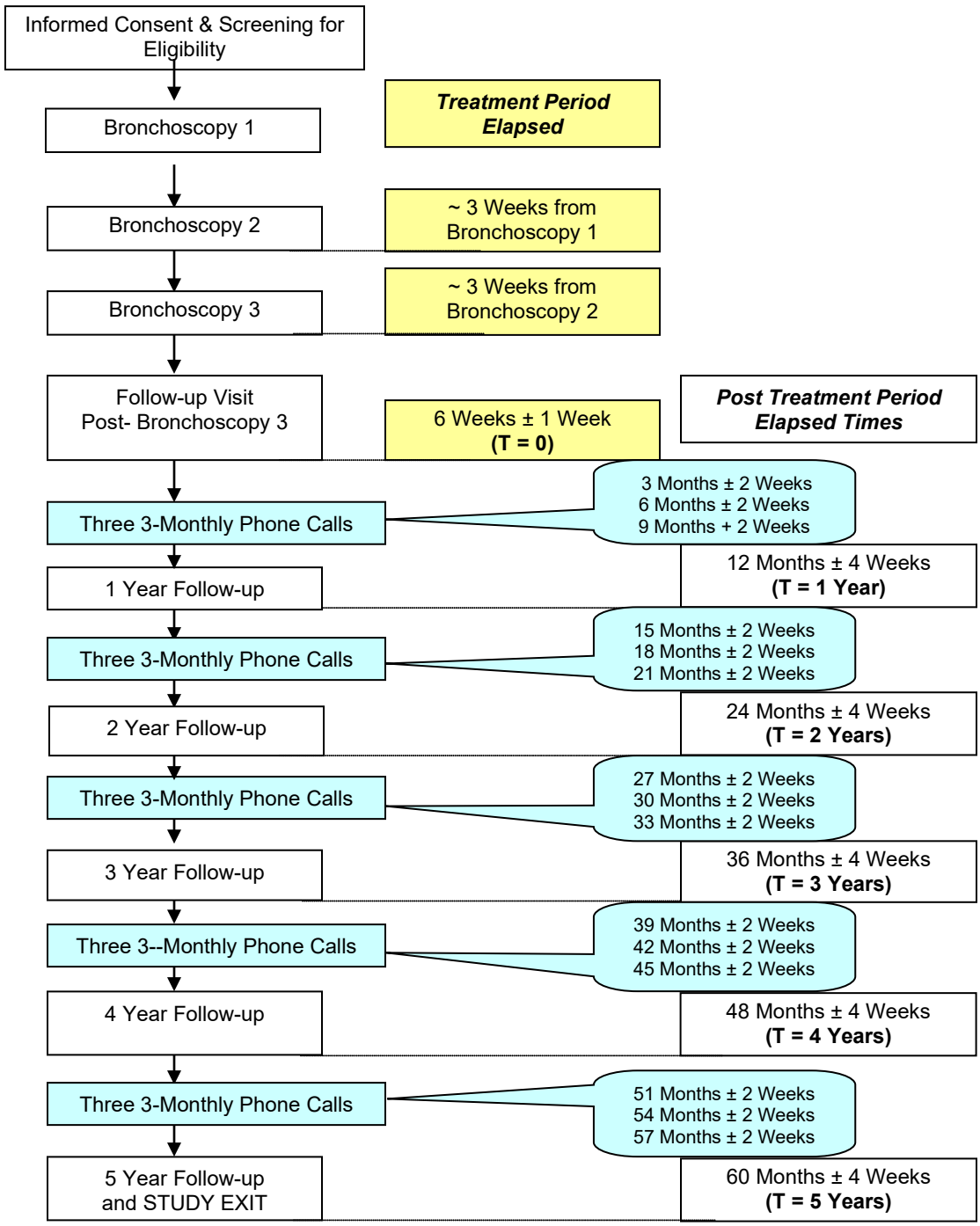
- Approximately 8% due to 2 Standard Errors
- Approximately 12% due to a combination of the following factors:
  - Environmental factors - temperature / humidity / pollution / respiratory infections / allergens
  - Physiological factors - Pulmonary aspergillosis, and development of co-morbid conditions such as obesity, Obstructive Sleep Apnea, rhinitis, sinusitis, gastroesophageal reflux, and stress
  - Changing asthma triggers
  - Patient strict adherence to medications in the absence of more frequent contact by sites
  - Progression of disease

5.0 Study Design

This will be an open-label, single arm study designed to demonstrate durability of the treatment effect and to evaluate the short-term and longer-term safety profile of the Alair System in the United States and Canada in the intended use population (patients 18 years and older with severe persistent asthma).

The schematic in Figure 2 shows the study flow chart.

Figure 2: Study Flow Chart



5.1 Brief Description of the Study

This is a multicenter, open-label, single arm study designed to demonstrate durability of the treatment effect and to evaluate the short-term and longer-term safety profile of the Alair System in the United States and Canada in the intended use population (patients 18 years and older with severe persistent asthma).

The study population consists of subjects with severe asthma who are still symptomatic despite being managed on conventional state-of-the-art therapy of high doses of inhaled corticosteroids (ICS - doses ≥1000µg per day beclomethasone or equivalent) and long-acting β_2-agonists (LABA - doses of ≥80µg per day salmeterol or equivalent).

The study and its required visits and assessments will be carefully discussed with prospective subjects using an Institutional Review Board (IRB) approved Informed Consent form. The Informed Consent form will contain all required essential elements. All subjects will sign an Informed Consent form prior to any procedures being performed to evaluate their eligibility for participation in the study. A Sample Informed Consent form is provided in Appendix C.

All subjects must be on stable maintenance asthma medications for at least 4 weeks before they can be evaluated for participation in the study. Subjects requiring an adjustment of their maintenance asthma medications for the severity of their asthma will enter a 4-week medication stabilization period.

Stability on the appropriate ICS and LABA medication regimen at the time of enrollment is a good indication of the likelihood that this medication regimen can be sustained throughout the study. Changes in a subject's maintenance asthma medication regimen after study entry will confound the data analysis for that subject, therefore this study will not seek to change either the dose, route, frequency, or brand of any maintenance asthma medication a subject is on at study entry (including leukotriene modifiers, theophyllines, etc). During the course of the study, if it is the Investigator's opinion that a subject requires a change in their maintenance asthma medication, this change will be appropriately documented.

Eligible subjects who are enrolled in the study will undergo bronchial thermoplasty over three treatment sessions to allow for a careful and sequential treatment of the entire lung. For each treatment session, subjects will take 50mg of oral prednisone or equivalent, for five days to include the three days before, the day of, and the day after the treatment session (prophylactic indication).

The bronchoscopy procedure will be administered as per the *Alair System Instructions for Use* with local anesthesia and moderate sedation as detailed in Section 7.3.7 below. The treatment sessions will be separated by a follow-up visit at 2 weeks after each bronchoscopy session. During the first session, the right lower lobe (RLL) of the lung will be treated. The right middle lobe will not be treated. During the second treatment session, the left lower lobe (LLL) of the lung will be treated. During the third treatment session, both the right upper lobe (RUL) and the left upper lobe (LUL) including the lingula will be treated.

At the time of the second and third treatment sessions, airways that were treated during the previous treatment session will be carefully examined and any findings will be documented. If any clinically significant findings are observed, the treatment session will be postponed until complete resolution of these findings (see Section 7.3.6). Complete resolution of any

findings must be confirmed and documented in a subject's medical records before subsequent Alair treatments commence.

Bronchial thermoplasty is an "out-patient procedure". Clinical study sites should generally schedule treatments in the morning to allow for post-procedure monitoring of subjects for a minimum of four hours before being released to home. Subjects may be monitored for longer than four hours and, if clinically indicated hospitalized overnight; however, overnight hospitalizations simply for observational reasons will not be considered as an adverse event.

Following each treatment session, subjects will be contacted by telephone on post-treatment Day 1, Day 2, and Day 7. Subjects will be instructed to contact the Investigator or a member of the clinical site staff at each site to report any unusual symptoms at any time following a treatment session.

A follow-up evaluation will be conducted at 6 weeks after the last treatment session. At this time, the 5 year follow-up phase will begin. Subjects will be contacted via phone every 3 months to solicit for adverse events and asthma status. An in-office follow-up evaluation will be performed annually starting after the 6 week evaluation.

Adverse events will be actively solicited by the Investigator or qualified clinical site staff during each contact with the subject.

All assessments to be conducted throughout the course of this study are outlined in Figure 2 and Table 2, and discussed in detail in Section 7.3.2 through 7.3.14.

5.2 Study Groups

This will be an open-label, single-arm study. All subjects who provide informed consent and are eligible for participation based on the inclusion and exclusion criteria will undergo bronchial thermoplasty with the Alair System.

A randomized controlled trial in the United States or Canada would be unethical and extremely difficult to recruit for, because Control group patients with severe persistent asthma would be required to refrain from both the Alair treatment and from other alternative treatment opportunities for a period of 5 years.

5.3 Study Subject Recruitment

All study subjects will be volunteers who meet the Inclusion/Exclusion criteria. Recruitment of study subjects will likely be from the pool of patients attending asthma clinics at the study sites in the United States and Canada. Referrals may also be sought from local physicians/general practitioners in the community who see and treat asthma patients in their practice. A total of 300 subjects will be enrolled in the study with up to 20% of the subjects to be enrolled in Canada.

5.4 Inclusion Criteria

Subjects will be included in the study if they meet the following Inclusion criteria:

1. Subject is an adult between the ages of 18 to 65 years.

2. Subject is able to read, understand, and sign a written Informed Consent to participate in the study and able to comply with the study protocol.

3. Subject has asthma and is taking regular maintenance medication that includes inhaled corticosteroid (ICS) at a dosage greater than 1000µg beclomethasone per day or equivalent, AND long acting β_2-agonist (LABA) at a dosage of ≥80µg per day Salmeterol or equivalent. Subjects may also be on the following medications in addition to the ICS and LABA:
   a. Other asthma medications such as leukotriene modifiers, or anti-IgE, (Subjects on Xolair® must have been on Xolair for greater than 1 year).
   b. Oral corticosteroids (OCS) at a dosage of up to, but not greater than 10mg per day.*.

4. Subject has a pre-bronchodilator FEV_1 of greater than or equal to 60% of predicted.

5. Subject is a non-smoker for 1 year or greater (if former smoker, less than 10 pack years total smoking history).

6. Subject is able to undergo outpatient (same day) bronchoscopy in the opinion of the investigator or per hospital guidelines.

7. Subject has at least 2 days of asthma symptoms in the last 4 weeks.

8. Subject has an AQLQ score during the baseline period of 6.25 or less.

* *NOTE: Subjects on a dosage regimen of 20mg OCS every other day may be included as this is equivalent to an average daily dosage of 10mg.*

5.5 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following Exclusion criteria:

1. Subject is participating in another clinical trial within 6 weeks of the Baseline Period involving respiratory intervention that could affect the outcome measures of this Study.

2. Over the last 7 days of a 4 week medication stable period, subject requirement for rescue medication use other than for prophylactic use for exercise exceeds an average of:
   a. 8 puffs per day of short-acting bronchodilator, or
   b. 4 puffs per day of long-acting rescue bronchodilator, or
   c. 2 nebulizer treatments per day.
   At the discretion of the Principal Investigator, subjects considered as unstable on baseline medications may have medications adjusted and re-evaluated after a 4 week medication stabilization period.

3. Subject has a post-bronchodilator FEV_1 of less than 65%.

4. Subject has a history of life-threatening asthma, defined by past intubation for asthma, or ICU admission for asthma within the prior 2 years.

5. Subject has 3 or more hospitalizations for exacerbations of asthma in the previous year.

6. Subject has had 4 or more infections of lower respiratory tract (LRTI) requiring antibiotics in the past 12 months.

7. Subject has had 4 or more pulses of systemic corticosteroids (tablets, suspension or injection) for asthma symptoms in the past 12 months.

8. Subject has a known sensitivity to medications required to perform bronchoscopy (such as lidocaine, atropine and benzodiazepines).

9. Subject has other respiratory diseases including emphysema, cystic fibrosis, vocal cord dysfunction, mechanical upper airway obstruction, Churg-Strauss syndrome, and allergic bronchopulmonary aspergillosis (asthma, immediate cutaneous reactivity to *A.* fumigatus, total serum IgE of >1000ng/mL, elevated specific IgE and IgG to *A. fumigatus* with or without evidence of central bronchiectasis).

10. Subject has segmental atelectasis, lobar consolidation, significant or unstable pulmonary infiltrate, or pneumothorax, confirmed on x-ray.

11. Subject currently has clinically significant cardiovascular disease, including myocardial infarction, angina, cardiac dysfunction, cardiac dysrhythmia, conduction defect, cardiomyopathy, or stroke.

12. Subject has a known aortic aneurysm.

13. Subject has significant co-morbid illness such as cancer, renal failure, liver disease, or cerebral vascular disease.

14. Subject has uncontrolled hypertension (>200mm Hg systolic or >100mm Hg diastolic pressure).

15. Subject has an implanted electrical stimulation device (e.g., a pacemaker, cardiac defibrillator, or deep nerve or deep brain stimulator).

16. Subject has coagulopathy (INR > 1.5).

17. Subject has any other medical condition that would make them inappropriate for study participation, in the Investigator's opinion.

5.6 Outcomes of Interest

Primary endpoint: The primary endpoint will be the proportion of subjects experiencing severe exacerbations during the subsequent 12-month (for Years 2, 3, 4, and 5) compared to the first 12-month after the Alair treatment.

Note: Severe exacerbation defined as worsening of asthma symptoms requiring use of systemic corticosteroids (tablets, suspension, or injection). For subjects already taking oral corticosteroids on a daily or alternate day basis, a severe exacerbation will be defined as a worsening of asthma symptoms requiring any increase in daily dose of systemic corticosteroids.

For consistency, courses of corticosteroids separated by 1 week or more will be treated as separate severe exacerbations.

Secondary endpoints: 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)

  * A respiratory adverse event is defined as any sign, symptom, illness, clinically significant abnormal laboratory value, or other adverse medical event associated with the "Respiratory System" that appears or worsens in a subject during a clinical study, regardless of whether or not it is considered related to the procedure used as part of the protocol.

- 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 (hospitalizations/ subject/ year and the 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

5.7 Patient Success Criteria

The primary statistical objective 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 proportion of the first 12-months, 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%.

6.0 Statistical Plan

6.1 Statistical Methods

All statistical processing will be performed using SAS® software Version 9.1 or later unless otherwise stated.

6.2 Demographic and Baseline Characteristics

Demographic variables (age, gender, ethnicity, and race), and baseline clinical information (maintenance asthma medication doses, Pre- and Post-BD FEV_1, prior 12 month history of use of systemic corticosteroids (tablets, suspension, or injection) for asthma symptoms, emergency room visits and hospitalizations for respiratory symptoms) will be recorded.

Continuous variables will be summarized with sample size, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized with frequency counts and percentages.

Demographic and baseline clinical information will also be provided separately for the subsets of patients enrolled at sites in the United States and sites in Canada.

6.3 Primary Analysis

Point estimates and 95% confidence intervals for the proportion of subjects experiencing severe exacerbations during each of the 12-month evaluation periods will be provided. Additionally, the upper 95% confidence limit for the difference between the subsequent 12-month proportions and the first 12-month proportion will be calculated; in this analysis, each subsequent 12-month proportion would represent comparisons between the first-year proportion and the second-, third-, fourth-, and fifth-year proportions.

An upper 95% confidence limit of the difference between the subsequent 12-month proportions (for Years 2, 3, 4, and 5) compared to the first 12-month proportion is less than 20% will demonstrate that the proportions are not substantially worse during each of the subsequent evaluation periods.

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. The hypothesis testing (non-inferiority design) will be conducted using the proportions calculated as described above.

Final conclusions regarding the durability of effectiveness (beyond 1 year) will be based on completing the 5 year follow-up of all subjects who are still in the study at that time.

Inferential analysis of the subset of subjects enrolled at sites in the United States or in Canada may lack the statistical power to demonstrate that the proportions are not substantially worse during each of the subsequent evaluation periods. Descriptive statistics for the point estimates introduced above will be presented for each subset, however, the primary endpoint analysis of the upper 95% confidence limit of the difference between the subsequent 12-month proportions (for Years 2, 3, 4, and 5) compared to the first 12-month proportion will not be required for the subsets."

Sensitivity analyses (conducted at 5 years)

- Compare patients who complete the 5 year follow-up with those who are lost to follow-up at 5 years regarding the baseline characteristics including demographics and medical information. The purpose of this analysis is to address whether the missing data observed over the course of study is missing at random and to address the validity of the primary analysis.

- The following three sensitivity analyses will use a test of hypotheses and/or computation of equivalent confidence limits will be based on the statistical methods (formulas) appropriate for matched pairs for proportions noted in Section 2.2 of J. NAM, *"Establishing Equivalence of Two Treatments and Sample Size Requirements in Matched Pairs Design", Biometrics 1997; 53: 1422-1430.*

    - Conduct an adjusted worst-case analysis, which is an intent to treat analysis that imputes missing data using multiple imputations by reasons of loss to follow-up (e.g., due to treatment-related adverse events and/or lack of efficacy; or reasons not related to treatment)

    - Conduct hypothesis testing using the matched pair design, but with multiple imputations.

    - Conduct hypothesis testing using the matched pair design without multiple imputations.

6.4 Secondary Analyses

Descriptive statistics will be performed for the following parameters for each 12-month period starting 6 weeks after the last treatment bronchoscopy and reported as including means and 95% CI:

- 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 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)

- Pre- and post-bronchodilator FEV_1

Descriptive statistics for the subset of subjects enrolled at sites in the United States or in Canada alone will be provided for each of the secondary endpoints, although no conclusions can be drawn from either subset because of the smaller sample sizes.

6.5 Safety Analysis

Adverse events will be reported for the short-term (Treatment Period) and for the long-term (Post-Treatment Period). The Treatment Period will be defined at the Day of 1st procedure bronchoscopy till 6 weeks after the last procedure bronchoscopy. The Post-Treatment Period will begin at the end of the Treatment Period i.e. at beginning at 6 weeks after the last procedure bronchoscopy. Annual visits will be based on a 52 week period beginning at 6 weeks after the last procedure bronchoscopy.

An adverse event is defined as any sign, symptom, illness, clinically significant abnormal laboratory value, or other adverse medical event that appears or worsens in a subject during a clinical study, regardless of whether or not it is considered related to the procedure used as part of the protocol.

All adverse events reported during the study will be listed, documenting course, severity, possible relationship to procedure, and outcome. Verbatim terms will be classified to preferred terms and system organ classes using the MedDRA dictionary. The preferred terms and system organ classes will then be tabulated by the treatment period and each year of follow-up. All reported adverse events will be summarized by the number of subjects reporting adverse events, system organ class, preferred term, severity, duration, and relationship to procedure.

In addition to the complete tabulation of adverse events for all subjects enrolled in the study, adverse events will also be tabulated separately for the subsets of subjects enrolled in sites in the United States and the sites in Canada.

6.6 Study Size and Sampling

Under the assumption that in the population of US subjects treated with the Alair System the proportion of patients that experience severe exacerbations will be 0.33 (33% of subjects) or less (based on data from AIR2 Trial (Protocol #04-02); 30.9%, 95% CI 24.2%, 37.7%), a sample size of 200 is adequate to demonstrate durability of the treatment effect at 5 years post-Alair treatment. Up to 300 subjects (minimum of 250 subjects) will be enrolled to achieve at least 200 evaluable study subjects, accounting for a 20% drop-out rate over 5 years.

nQuery Advisor Version 7.0 was used to form a basis for the sample size estimation. The “Two group test of equivalence in proportions (large equal n’s)” procedure based on a one-sided test at alpha equal to 0.05 and a 20% delta was used to generate the powers presented in Table 1.

Table 1: Sample Size Calculation

Two group test of equivalence in proportions (large equal n's)									**nQuery Advisor 7.0**
	1	2	3	4	5	6	7	8	9
Test significance level, α (one-sided)	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050
Standard proportion, πS	0.330	0.330	0.330	0.330	0.330	0.330	0.330	0.330	0.330
Equivalence limit difference, $\pi_T - \pi_S$, Δ_0	0.200	0.200	0.200	0.200	0.200	0.200	0.200	0.200	0.200
Test expected proportion, π_T	0.330	0.340	0.350	0.360	0.370	0.380	0.390	0.400	0.410
Expected difference, $\pi_T - \pi_S$, Δ_1	0.000	0.010	0.020	0.030	0.040	0.050	0.060	0.070	0.080
Power (%)	99	99	99	98	97	95	92	88	83
n_s	250	250	250	250	250	250	250	250	250
n_T	200	200	200	200	200	200	200	200	200
Ratio: n_T / n_s	0.800	0.800	0.800	0.800	0.800	0.800	0.800	0.800	0.800
$N = n_s + n_T$	450	450	450	450	450	450	450	450	450

A minimum of 80% power was achieved for all situations wherein the subsequent year's assumed proportion of subjects with severe exacerbations was 41% or less.

Because of the length of the follow-up period (5 years following Alair-treatment) it is expected that there will be Loss-to-Follow-up. However, every reasonable effort will be made to retain the subjects in the study over this follow-up period and to limit Loss-to-Follow-up to be less than 20% at the 5 year follow-up (with an average yearly loss <5%).

The study will be conducted at a minimum of 15, and a maximum of 30 centers in the United States and Canada. Investigational centers will include both teaching and non-teaching institutions and will be selected based on criteria that will include geographic location, physician experience with performing bronchoscopy procedures, access to adequate number of patients with severe asthma (either from own practice or through a referral network with allergists), and appropriate personnel resources to adequately execute the study protocol and collect all required data.

6.7 Data collection and Follow-up schedule

The planned study visits are outlined in the Study Flow Chart shown in Figure 2.

All data will be collected using appropriately designed case report forms (CRFs/eCRFs). Information on adverse events, incidences of OCS pulses for worsening of asthma symptoms, emergency room visits for respiratory symptoms, and hospitalizations for respiratory symptoms will be actively solicited by an appropriately qualified member of the clinical study site team during quarterly telephone contacts or at time of in-office visits.

Daily diaries will not be used in this clinical study, and all information solicited from the study subjects will be based on recall since the last contact (maximum recall time of 3 months). Episodes of worsening of asthma symptoms requiring treatment with oral corticosteroids, emergency room visits and hospitalizations for respiratory symptoms are rare events and are readily recalled for immediate past periods of 3 month duration. This approach will be consistent with data collection methodology in the AIR2 Trial.

The following data will be collected at the specified visits/evaluations:

<u>Enrollment</u>

- Medical history (including maintenance asthma medications and history of respiratory infections)
- Occurrence of events in the 12 month period prior to study enrollment
    - Severe exacerbations (pulses of systemic corticosteroids (tablets, suspension, or injection) for asthma symptoms)
    - Emergency room visits for asthma symptoms
    - Hospitalizations for asthma symptoms
- Forced Expiratory Volume in 1 second: FEV_1 (pre- and post-bronchodilator)
- Physical examination (including body weight)
- Chest X-ray (Lateral and PA)
- Asthma Quality of Life Questionnaire (AQLQ)

<u>Treatment Period (Day of 1st bronchoscopy till 6 weeks after 3rd/last bronchoscopy)</u>

- Adverse events
- Emergency room visits for respiratory symptoms
- Hospitalizations for respiratory symptoms
- FEV_1 (pre- and post-bronchodilator)

<u>Phone Contact at every 3 Months between Annual Visits</u>

- Adverse events
- Severe exacerbations
- Maintenance asthma medications
- Emergency room visits for respiratory symptoms
- Hospitalizations for respiratory symptoms

<u>Annual Visits at 1, 2, 3, 4 and 5 years from end of Treatment Period (6 week visit following 3rd/last bronchoscopy)</u>

- Adverse Events
- Severe exacerbations
- Physical examination (including body weight)
- Maintenance asthma medications

- Emergency room visits for respiratory symptoms
- Hospitalizations for respiratory symptoms
- FEV_1 (pre- and post-bronchodilator)

All adverse events will be actively solicited by an appropriately qualified member of the clinical study site team at the time of follow-up evaluations. For the periods between scheduled study visits or telephone contacts, subjects will be encouraged to keep track of any adverse events, pulses of oral corticosteroids for worsening of asthma symptoms, emergency room visits for respiratory symptoms or hospitalizations for respiratory symptoms in a medical event log. Subjects will be trained to contact study site team in the event there is an emergency room visit or hospitalization due to respiratory symptoms.

6.8 Plan to Minimize Loss-to-Follow-up

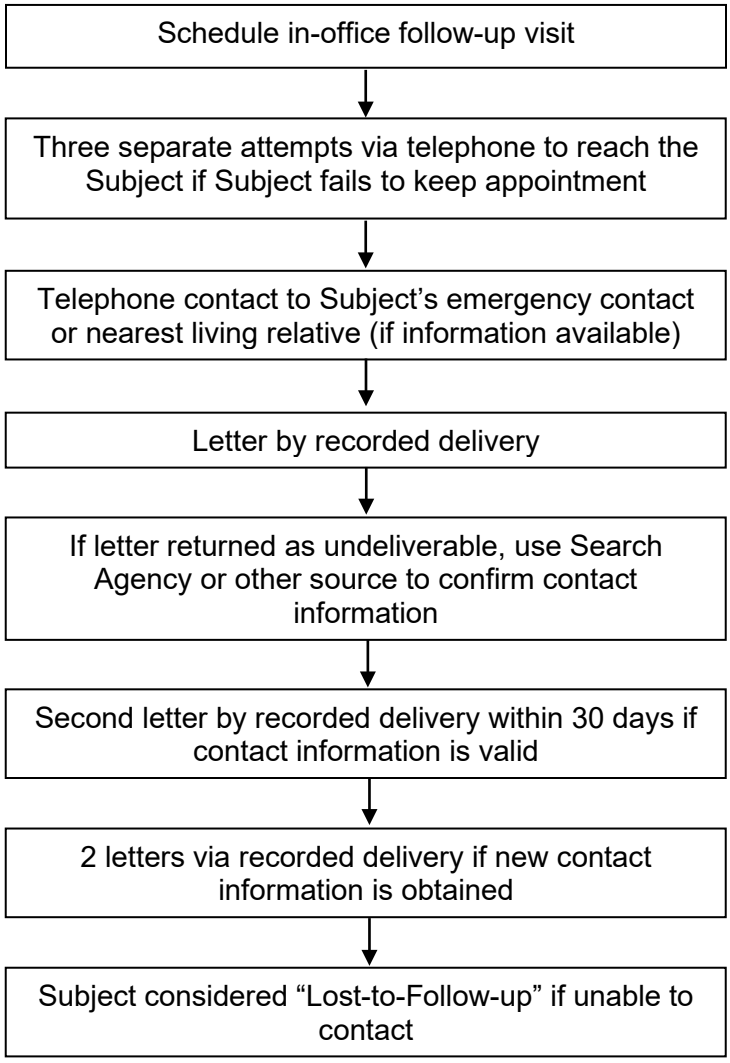
The sample size of up to 300 subjects for this study (minimum of 250) is based on the assumption that over the course of 5 years there will be at least 20% attrition due to Loss-to-Follow-up. All subjects will be offered reimbursement for completing each planned visit. Note that the amount of reimbursement is limited by each Institutional Review Board (IRB).

As part of the informed consent, patients will be asked to agree to follow-up evaluations out to 5 years after Alair treatment. Each subject will be asked to provide an Emergency contact and contact information for mother (if alive) and a nearest living family member who could be used as alternatives to reach the subject. In addition, subject's will be informed that in the event they fail to respond to written communication in the form of letters by recorded delivery, the Site with support from the Sponsor (Asthmatx, Inc.) will enlist the help of a search agency to confirm the subject's contact information.

Sites will be asked to remind subjects that being the first device based procedure for treating asthma, the commitment of the subjects to their participation for the full 5 years is important in understanding all aspects of the Alair treatment.

Figure 3 outlines the steps that will be taken to contact any subject who misses the planned annual follow-up visit so as to ensure adequate follow-up.

Figure 3: Steps to Contact Subjects for Annual Follow-up Visits



In the event that a letter is returned as undeliverable, Asthmatx will enlist the aid of a search agency to confirm the subject's contact information. If existing contact is valid, one more attempt will be made with certified mail within 30 days before the subject is considered as "unable to contact". If new contact information is obtained, contact will be attempted via 2 recorded delivery mails before the subject is considered as "unable to contact". In the event that a subject is Lost-to-Follow-up, their status at the last contact will be reported.

If needed, the Sponsor will offer to cover travel and housing costs for a subject who has relocated to a new city in order for them to return to the clinical study site to complete their annual follow-up evaluations. Alternatively subjects will be allowed to continue follow-up at the closest study site to their new location.

In the event that the subject is unable to complete the annual evaluation during the normal work week (Monday to Friday) because of a change in his/her personal situation, the

Sponsor will work with the site to schedule the evaluation during the weekend days (Saturday or Sunday) provided the subject is agreeable.

Reasons for subject initiated withdrawal from the study will be reported.

An Investigator may withdraw a subject from the study at any time for one or more of the following reasons:

- Subject does not follow instructions given by the Investigator;
- Subject could be harmed by continued participation in the study;
- Subject requires treatment not allowed in the study;
- Subject develops significant other illness such as lung cancer, tuberculosis, emphysema, or heart disease that would compound study validity;
- Subject develops a terminal illness unrelated to their asthma.

7.0 Study Plan

7.1 Test Device

The device being evaluated in this clinical study is the Alair® Bronchial Thermoplasty System (Alair System) (Asthmatx, Inc., Sunnyvale, CA), that consists of the Alair Catheter and the Alair RF Controller.

7.2 Investigator Training

Investigators will be fully trained in the proper use and operation of the Alair System before initiation of any treatments.

- Training will include didactic sessions and hands-on use of the Alair System (using an appropriate anatomical model).
- In addition, on-site training will be provided to the Investigator, Co-Investigators and other study support personnel before the first treatment at each clinical site.
- Trained Asthmatx personnel will be available to provide any additional technical support during the initial treatment sessions performed at a clinical site until the Investigator and his/her staff feel comfortable with the use of the device.

The proctor from Asthmatx will evaluate the success of the training by observing and evaluating the proficiency of the Physician/Investigator in performing the bronchial thermoplasty procedure according to the Directions for Use (DFU).

- If necessary, additional training will be provided.

7.3 Detailed Study Description

An outline of the study design is presented as a Study Flow Chart in Figure 2.

The study procedures and assessments to be performed during the course of the study are described below and outlined in Table 2 and Figure 4.

7.3.1 Informed Consent

- Obtain a signed Informed Consent form from the subject prior to beginning the initial screening, including any necessary medication stabilization.

- Place the original signed Informed Consent form in the Subject Study Binder, and a copy of the signed Informed Consent form in the subject's medical record.

- Provide the subject with a copy of the signed Informed Consent for their records.

- The Informed Consent process (including the initial Informed Consent and any revised Informed Consent forms throughout the duration of the study) should be documented in the subject's study notes and appropriate CRF/eCRF.

7.3.2 Subject Identification Number

- Assign the subject a unique identification number (Subject ID number) at the time of signing the Informed Consent form.

- The subject ID number consists of the Site Number (assigned by the Sponsor, XXXXG), the Study Number (1002), the Subject Number (starting at 01 and increasing sequentially), and a 3 digit subject initials (AAA). For example, subject number 5 at site number XXXXG will be identified as “XXXXG-1002-05-AAA”.

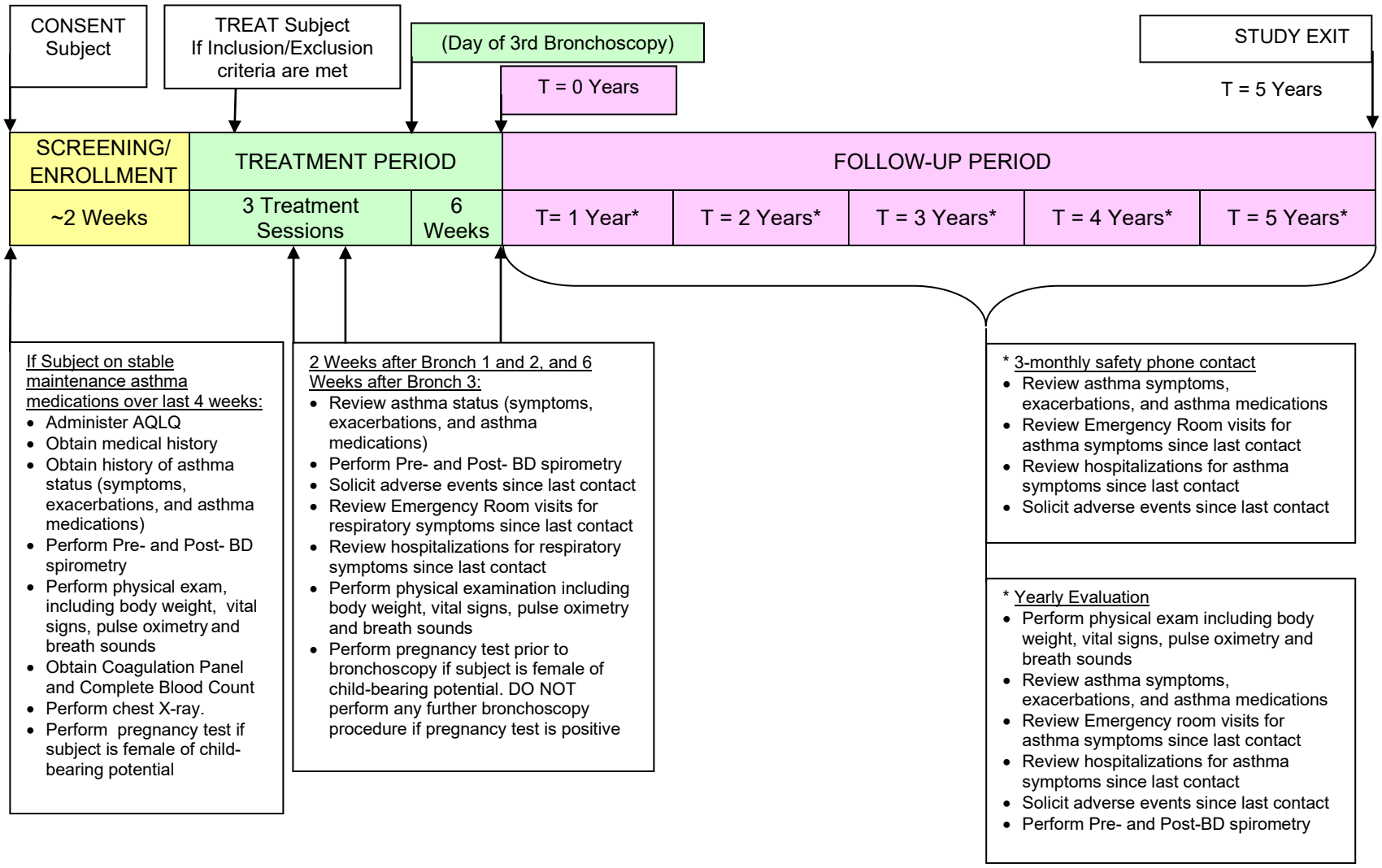
Table 2: Study Procedures and Assessments

Procedure / Assessment	Screening/ Enrollment	1st Bronch.	F/U Visit 1	2nd Bronch.	F/U Visit 2	3rd Bronch.	6-wk F/U Visit **T = 0**	**3-Monthly Safety Phone Calls**	12-mo F/U Visit	**3-Monthly Safety Phone Calls (Yr2 - 5)**	Annual F/U Visits (Yr2 – 5)
Medical History	✓										
AQLQ (Juniper)	✓										
Spirometry[1]	✓	✓	✓	✓	✓	✓	✓		✓		✓
Physical Examination – to include SpO_2	✓	✓	✓	✓	✓	✓	✓		✓		✓
Review of Asthma Symptoms, Exacerbations, Medications	✓		✓		✓		✓	✓	✓	✓	✓
Solicit Adverse Events	✓		✓		✓		✓	✓	✓	✓	✓
Solicit information on Emergency room visits for respiratory symptoms	✓		✓		✓		✓	✓	✓	✓	✓
Solicit information on hospitalizations for respiratory symptoms	✓		✓		✓		✓	✓	✓	✓	✓
Pregnancy Testing	✓	✓[2]		✓[2]		✓[2]					
Chest X-Ray – Lateral & PA	✓										
Blood Coagulation Panel (PT, PTT, INR) and Complete Blood Count (RBC, WBC, platelets)	✓										
Bronchoscopy for BT		✓		✓		✓					

[1] Perform pre-bronchodilator spirometry following a 12-hour abstinence from long-acting β_2-agonist and a 4-hour abstinence from short-acting β_2-agonists, and post-bronchodilator spirometry 15 minutes after the administration of 4 puffs (100µg per puff) of albuterol via a spacer.

[2] Perform pregnancy test prior to initiation of bronchoscopy if subject is a female of child-bearing potential

Figure 4: Chronology of Protocol Required Testing



7.3.3 Evaluations at Enrollment (Baseline)

- Determine whether the subject's maintenance asthma medications are in accordance with conventional therapy utilizing inhaled corticosteroids and long-acting β_2-agonists appropriate for the severity of the Subject's asthma.

  Subjects who require a medication adjustment in order to optimize asthma control must undergo a 4-week medication stabilization period prior to performing enrollment evaluations. If the subject's maintenance asthma medications ARE in accordance with conventional therapy and subject has been on stable asthma medications for at least four weeks:

- Administer Asthma Quality of Life Questionnaire (AQLQ).

- Obtain detailed medical history, to include:
  - Gender
  - Race
  - Date of birth
  - Number of years diagnosed with asthma
  - History of allergies, to include allergy type and the time of year they are susceptible
  - History of respiratory infections in the 2 years prior to the study
  - Other significant illnesses

- Obtain history of asthma symptoms, exacerbations, and asthma medications, to include:
  - Number of emergency room visits for respiratory symptoms over the past 12 months
  - Number of hospitalizations for respiratory symptoms over the past 12 months
  - Number of pulses of systemic corticosteroids (tablet, suspension, or injection) for asthma symptoms over the past 12 months
  - Number of Intensive Care Unit (ICU) admissions for asthma symptoms over lifetime, and timing of each such admission
  - Changes in maintenance asthma medications, if any

- Perform pre-bronchodilator spirometry following a 12-hour abstinence from long-acting β_2-agonist and a 4-hour abstinence from short-acting β_2-agonists.

- Perform post-bronchodilator spirometry 15 minutes after the administration of 4 puffs (100µg per puff) of albuterol via a spacer.

- Perform the following evaluations:
  - Physical examination, including body weight, vital signs, pulse oximetry (SpO_2) and breath sounds.
  - Blood coagulation panel and Complete Blood Count (CBC)
  - Pregnancy test for female subjects of childbearing potential (a positive pregnancy test at this time will disqualify the subject from the study).
  - Obtain Chest X-rays – lateral and posterior anterior (PA) views. Chest X-rays performed within the last 4 months may be used.

- If all entry criteria have been met, enroll the subject and schedule their first bronchoscopy session.

NOTES:

1. *If the subject has an exacerbation during the period of enrollment evaluations that is treated with oral steroids, wait at least 4 weeks following completion of the oral steroids, before proceeding with any further evaluations.*

2. *During the period between enrollment and the entire study period out to 5 years, all subjects should continue to take the same dose, route, and frequency of inhaled corticosteroids, LABA, and other maintenance asthma medications prescribed prior to enrollment. In the instance that medications are adjusted for patient safety, record any deviations from this specified medication usage in the subject's medical chart and on CRF/eCRFs during subsequent follow-up visits.*

Provide the following specific instructions to all subjects that are enrolled in the study:

1. It is important to complete all scheduled study visits and respond to telephone contacts by the research team.

2. It is important to contact the Investigator or the research team if the subject experiences worsening of their asthma symptoms beyond their normal level of symptoms.

3. It is important to seek medical attention between scheduled study visits if necessary.

4. For the periods between scheduled study visits or telephone contacts, subjects should be encouraged to keep track of any adverse events, pulses of oral corticosteroids for worsening of asthma symptoms, emergency room visits for respiratory symptoms or hospitalizations for respiratory symptoms in a diary or log. For any event, subjects' should note the date event occurred, any treatment that was used to address the event, and the date the event was considered resolved. This will aid in an unbiased recall of events.

5. These instructions should be reinforced during each contact with a study subject.

7.3.4 Prior to Performing Bronchial Thermoplasty with the Alair System

- Ensure that subject has not had an asthma exacerbation that was treated with systemic corticosteroids within the last two weeks.

  Do not schedule the treatment session if the subject had an asthma exacerbation requiring systemic corticosteroids within the last 2 weeks and their post-bronchodilator FEV_1 is not back to within 10% of baseline/enrollment levels.

- Ensure that subject has not had a lower respiratory tract infection within the last six weeks.

Do not schedule the treatment session if the subject had a lower respiratory tract infection that resolved within the last 6 weeks.

- Ensure that subject has not had an upper respiratory tract infection within the last one (1) week.

  Do not schedule the treatment session sooner than one (1) week after resolution of symptoms from a recent upper respiratory tract infection.

- Prescribe 5 doses of 50mg each of oral prednisone or equivalent to be taken on the three days prior to treatment, day of treatment, and day after treatment (prophylactic indication).

  Document in subject's study notes and treatment-related CRF/eCRFs; do not add as an additional concomitant medication.

- Schedule the treatment session to allow for required minimum of 4 hours monitoring of subject prior to discharge.

- Subject must continue taking their maintenance asthma medications of inhaled corticosteroids and LABA as prescribed.

- If antibiotics are prescribed for prophylaxis according to institutional policies at the time of the treatment, the antibiotic usage should be noted on the Medication Log for this subject, but this use of antibiotics will NOT trigger the actions called for in Section 8.0 Adverse Events, with regard to infections.

7.3.5 Bronchial Thermoplasty Treatment

Bronchial thermoplasty with the Alair System will be performed in three bronchoscopy sessions, separated by at least 3 weeks. The areas targeted for treatment with the Alair System are the airways distal to the main stem bronchi (beginning at the lobar bronchi, 2nd Weibel generation) down to airways of 3mm in diameter (about the 6th Weibel generation).

- During the first bronchoscopy session, the right lower lobe (RLL) will be treated.

- During the second bronchoscopy session, the left lower lobe (LLL) will be treated.

- During the third bronchoscopy session, both the right upper lobe (RUL) and the left upper lobe (LUL) will be treated.

- The right middle lobe (RML) will not be treated (see Section 7.3.7).

After the first bronchoscopy session and at all subsequent bronchoscopy sessions, carefully conduct a visual bronchoscopic examination of previously treated airways and document any findings. If any clinically significant findings are observed, subsequent bronchoscopy session should be postponed for at least two weeks and until the subject is clinically stable. At the subsequent bronchoscopy the previously abnormal area should be re-inspected. Complete resolution of any findings must be confirmed and documented in the subject's medical records before subsequent Alair treatments commence. If the abnormal findings persist, Investigator should consult with Sponsor to determine whether to proceed with

further treatments or abandon further treatments. In the event that further treatments are not performed, the subject should remain in the study for continued follow-up.

7.3.6 Pre-Procedure Evaluations

- Determine if subject has recently had, or is currently experiencing cold or respiratory symptoms.

  If subject has recently had or is currently experiencing cold or respiratory symptoms, the treatment session must be rescheduled until the subject no longer has these symptoms. Inform subject that the chance of post-procedure side effects increases under these circumstances.

- Verify that the subject has taken the prescribed 50mg oral prednisone or equivalent per day, for the three days prior to, and on the day of treatment session (prophylactic indication).

  If the prescribed prednisone or equivalent was not taken on the three days prior to bronchoscopy, the treatment should be postponed. If the dose of prednisone or equivalent was not taken for the day of the treatment session, an equivalent dose may be given intravenously during the procedure or just after the procedure and prior to release.

- Perform a pregnancy test for female subjects of child bearing potential

  - A positive pregnancy test before the first bronchoscopy session will disqualify the subject from the study.

  - A positive pregnancy test prior to the second bronchoscopy session will result in termination of further bronchoscopy procedures for the subject. However, the subject must be evaluated as per protocol at all planned evaluation visits.

- Perform a post-bronchodilator FEV_1

Postpone treatment session if any of the following conditions apply:

a. Prescribed prednisone or equivalent was not taken on the three days prior to treatment.
b. SpO_2 less than 90% on room air in last 48 hours.
c. Increase in asthma symptoms in last 48 hours requiring more than 4 puffs/day of rescue bronchodilator over normal usage.
d. Subject is less than 2 weeks from completion of a course of oral corticosteroid use for an exacerbation of asthma.
e. Subject's post-bronchodilator FEV_1 is less than 85% of baseline/enrollment level.
f. Subject has an active respiratory infection, active allergic sinusitis, or other clinical instability.
g. Investigator feels for any reason the treatment should be postponed.
h. The absence of a companion or caretaker at home to assist on the day of treatment.

7.3.7 Bronchoscopy Session

If bronchoscopy session is not postponed for any of the above criteria:

- Prepare subject for bronchoscopy per standard hospital protocol.
- Review the treatment plan, including previously treated anatomy (if applicable), identifying targeted anatomy, and choosing the sequence of segments to be treated.
- Administer up to 5 mg albuterol (short-acting bronchodilator), nebulized.
- Administer IV moderate sedation to perform bronchial thermoplasty. During the period of sedation, monitoring should be performed to include at a minimum, SpO_2, heart rate, blood pressure, and ECG. All local institutional policies relevant to moderate sedation should be observed.
- The use of a drying agent such as atropine or glycopyrrolate to reduce secretions is recommended for this procedure.

Criteria for considering termination of a bronchoscopy based on bronchoscopic findings:

a. Airways are unusually edematous or inflamed.
b. Extensive and/or prolonged bronchoconstriction.
c. Airways accessed in a previous treatment session do not appear sufficiently healed.
d. Presence of purulent or abnormally tenacious sputum or mucus plugging.
e. Inability to access airways because of excessive secretions, excessive coughing, or tortuous anatomy.
f. Investigator feels for any reason the treatment should be terminated.

- Perform Bronchial Thermoplasty as follows:
  - Apply the return electrode to subject (lower back suggested).
  - Attach the Alair Catheter to the Alair RF Controller.
  - If the procedure is the second or third bronchoscopy session, carefully examine previously treated airways with the bronchoscope.

    Complete resolution of any findings must be documented before any subsequent Alair treatments commence. Do not treat airways that were treated in a previous treatment session.

- Do not treat the Right Middle Lobe. The right middle lobe is not treated because of the potential theoretical susceptibility of the right middle lobe to transient obstruction as a result of inflammation or edema because of certain anatomical characteristics. This area had not been treated in previous clinical trials of the Alair System and therefore will not be treated here for consistency.

- Advance the bronchoscope to the desired airway and insert the Alair Catheter through the working channel of the bronchoscope. Expand the electrode array to contact the airway wall.

- Activate the RF Controller by pressing the footswitch and deliver RF energy to the target site.

- Collapse the electrode array and reposition the electrode array 5 mm proximally from the previous location. Repeat the delivery of RF energy.

- Continue with treating the length of the airway with contiguous placements and activations of the electrode array.

  NOTE: It is expected that each subject will undergo three treatment sessions. If during the first treatment a subject's airways are noted to be unusually small, tortuous, or of such atypical anatomy that either a safe or a complete procedure cannot be performed, do not proceed with treatment; the subject should be withdrawn from the study.

7.3.8 Post-Bronchoscopy Monitoring and Evaluation

Carefully monitor the subject in the post-procedure recovery area for at least 4 hours as follows:

- Perform at least two assessments of vital signs (heart rate, blood pressure, temperature, respiratory rate, SpO_2): the first within one hour of the treatment; the second just prior to discharge. Perform additional assessments if medically indicated.

- Administer supplemental oxygen if clinically indicated or if SpO_2 falls below 92% (via facemask or nasal cannula). Record the use of supplemental oxygen and reason for administration.

- Assess spirometry and breath sounds at least twice: as soon as the subject has recovered from sedation/anesthesia and just prior to discharge. Perform additional assessments if medically indicated. Record bronchodilators administered during spirometry.

- Document any adverse events (See Section 8.0).

- Document hospital admission if necessary.

Criteria for considering hospital admission post-procedure:

a. Severe or persistent cough at end of monitoring period.
b. Failure of post-bronchodilator FEV_1 to return to within 20% of pre-procedure level at end of monitoring period.
c. Persistent oxygen saturation <90% at end of monitoring period.
d. Persistent tachycardia >130bpm at end of monitoring period.
e. Unexpected altered mental status during or after procedure.
f. Hemoptysis >50ml during 4 hour post-recovery period.
g. Excessive requirement for bronchodilator during monitoring period.
h. The absence of a companion or caretaker at home to assist on the day of treatment.

NOTE: Overnight hospitalizations for observational reasons will not be considered as Serious Adverse Events, but will be tracked as Adverse Events.

Prior to discharge after each bronchoscopy session:

- Remind subject to take 50mg oral prednisone, or equivalent, the day after the treatment session (prophylactic indication).
- Schedule a follow-up evaluation for 2 weeks after each treatment session.
- Instruct subject to contact Investigator or a member of the clinical study staff at the Site if they experience any of the following:
  - Difficulty in breathing.
  - Night awakenings due to asthma symptoms.
  - Changes in maintenance asthma medications.
  - Need to be seen by a physician prior to the next scheduled visit.
  - Any adverse events.
- Record Date and Time of release after the procedure from facility.

7.3.9 Near-Term Follow-up

- Contact subject via telephone on Day 1, Day 2, and Day 7 after the treatment session to assess recovery.
- Remind subject to contact Investigator or a member of the clinical study staff at the Site if they experience any of the following:
  - Difficulty in breathing.
  - Night awakenings due to asthma symptoms.
  - Any changes in maintenance asthma medications.
  - Need to be seen by a physician prior to the next scheduled visit.
  - Any adverse events.

7.3.10 2-Week Follow-up (2 Weeks ± 4 days after Treatment Session 1 and 2)

Examine the subject and perform the following evaluations:

- Focused physical exam including vital signs (heart rate, blood pressure, temperature, respiratory rate, SpO_2) and breath sounds.
- Review asthma symptoms, exacerbations, and asthma medication use.
- Solicit adverse events since last follow-up (See Section 8.0).
- Review Emergency Room visits for respiratory symptoms since last contact.
- Review hospitalizations for respiratory symptoms since last contact.
- Perform physical examination (including body weight).
- Pre-bronchodilator spirometry following a 12-hour abstinence from long-acting β_2-agonist and a 4-hour abstinence from short-acting β_2-agonists

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- Post-bronchodilator spirometry 15 minutes after the administration of 4 puffs (total 400 µg) of albuterol via spacer.
- If a subsequent treatment session is to be completed, see Section 7.3.6 and Section 7.3.7.

7.3.11 6-Week Follow-up (6 Weeks ± 1 Week after last Bronchoscopy Session)

Examine the subject and perform the following evaluations:

- Focused physical exam including body weight, vital signs (heart rate, blood pressure, temperature, respiratory rate, SpO_2) and breath sounds.
- Review asthma symptoms, exacerbations, and asthma medication use.
- Solicit adverse events since last contact.
- Perform pre- and post-bronchodilator spirometry. Pre-bronchodilator spirometry following a 12-hour abstinence from long-acting β_2-agonist and a 4-hour abstinence from short-acting β_2–agonists.
- Review emergency room visits for respiratory symptoms since last contact.
- Review any hospitalizations for respiratory symptoms since last contact.

7.3.12 3-Monthly Follow-up Phone Contact (3 Months ± 2 Weeks, 6 Months ± 2 Weeks, 9 Months ± 2 Weeks, 15 Months ± 2 Weeks, and 18 Months ± 2 Weeks, 21 Months ± 2 Weeks, 27 Months ± 2 Weeks, 30 Months ± 2 Weeks, 33 Months ± 2 Weeks, 39 Months ± 2 Weeks, 42 Months ± 2 Weeks, 45 Months ± 2 Weeks, 51 Months ± 2 Weeks and 54 Months ± 2 Weeks, and 57 Months ± 2 Weeks after 6-Week Follow-up Evaluation)

Perform the following evaluations:

- Review asthma symptoms, exacerbations, and asthma medication use.
- Solicit adverse events since last follow-up (See Section 8.0).
- Review emergency room visits for respiratory symptoms since last contact.
- Review any hospitalizations for respiratory symptoms since last contact.

7.3.13 Yearly Follow-up (12 Months ± 4 Weeks, 24 Months ± 4 Weeks, 36 Months ± 4 Weeks, 48 Months ± 4 Weeks and 60 Months ± 4 Weeks after 6-Week Follow-up Evaluation)

Examine the subject and perform the following evaluations:

- Perform physical exam including body weight, vital signs, pulse oximetry and breath sounds.
- Review asthma symptoms, exacerbations, and asthma medication use.
- Solicit adverse events since last contact.
- Perform pre- and post-bronchodilator spirometry. Pre-bronchodilator spirometry following a 12-hour abstinence from long-acting β_2 -agonist and a 4-hour abstinence from short-acting β_2 –agonists.
- Review emergency room visits for respiratory symptoms since last contact.
- Review any hospitalizations for respiratory symptoms since last contact.

7.3.14 Study Exit

Exit the subject from the study following the successful completion of the 5 year follow-up evaluation.

8.0 Adverse Events

Definition: An adverse event is any sign, symptom, illness, clinically significant abnormal laboratory value, or other adverse medical event that appears or worsens in a subject during a clinical study, regardless of whether or not it is considered related to the procedure used as part of the protocol.

- It is the responsibility of the Investigator to decide when an adverse event has occurred.
- Adverse event information will be collected throughout the study.
- Adverse events will be recorded on the Adverse Event CRF/eCRF by the Investigator or clinical study staff and must include
    - Diagnosis
    - Symptoms
    - Date of onset
    - Date of resolution
    - Severity
    - Relationship to the procedure
- All adverse events will be monitored until they are adequately resolved or stabilized with no further significant change expected.

All Serious Adverse Events or complications must be reported to Clinical Affairs at Asthmatx, Inc. within 3 working days via

Telephone: + 408 419 0100

FAX: + 408 419 0101, or

E-mail: PAS2_Clinical_Safety@bsci.com

For all Serious Adverse Events, reports relating to the subject's subsequent medical follow-up must be submitted to Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

Asthmatx Clinical Affairs will perform real time data review to observe any unanticipated or unforeseen events and to monitor the actual rate of anticipated events. All events will be MedDRA coded and entered into a database for later analyses. This review will occur on an ongoing basis upon event notification.

8.1 Definitions

A. Severe Exacerbation: *Severe exacerbation defined as worsening of asthma symptoms requiring use of systemic corticosteroids (tablets, suspension, or injection) (NAEPP, 2007). For subjects already taking oral corticosteroids on a daily or alternate day basis, a severe exacerbation will be defined as a worsening of asthma symptoms requiring any increase in daily dose of systemic corticosteroids.*

For consistency, courses of corticosteroids separated by 1 week or more will be treated as separate severe exacerbations.

B. Severity of Adverse Events: The following definitions for rating severity of adverse events should be used for this study:

1. **Mild:** Awareness of signs or symptoms, but easily tolerated and transient; causing no loss of time from normal activities; symptoms would not require medication (other than short-acting bronchodilators) or a medical treatment; signs and symptoms are transient.

2. **Moderate:** Marked symptoms and discomfort severe enough to cause moderate interference with subject's usual activities. Symptomatic treatment is possible.

3. **Severe:** Incapacitating with inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical intervention and/or treatment. Hospitalization may be required or prolonged.

The Investigator will determine both the intensity of the adverse event and the event's relationship to Alair treatment. The Data and Safety Monitoring Board (DSMB) will review all respiratory adverse events and other safety endpoint data including hospitalization for respiratory symptom and review procedure/device relationship.

C. Serious Adverse Events (SAE): All adverse events are categorized as Mild, Moderate or Severe (see Section B above). Additionally, if an adverse event meets any of the following criteria, it is also categorized as an SAE when the event is:

- Fatal
- Requires or prolongs hospitalization
- Causes substantial risk of dying at the time of the event (i.e., life-threatening)
- Results in permanent impairment of a body function or permanent damage to a body structure, or
- Requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure
- Results in fetal distress, fetal death or congenital abnormality or birth defect

Note: This categorization for adverse events is independent of the severity rating applied above in Section B.

In the event that a hospital admission is for less than 24 hours, the incidence will be reported as a serious adverse event, but will not be counted as a hospitalization.

D. Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects (21 CFR 812).

All unanticipated adverse device effects must be submitted by the Investigator to the reviewing IRB and Sponsor within 10 working days (see Appendix B).

E. Adverse Event Relationship: The relationship of an Adverse Event to the procedure will be attributed using the following definitions:

1. **Not Related:** No evidence that the timing of the adverse event has a relationship to the procedure performed.

2. **Possibly Related:** The adverse event has a timely relationship to procedure performed. However, a potential alternative etiology may be responsible for the adverse event.

3. **Probably Related:** The adverse event has a timely relationship to study procedure performed and the causative relationship can clearly be established. No potential alternative etiology is apparent.

F. Adverse Event Status: The status of an adverse event shall be determined as per the following definitions:

1. **Resolved:** An adverse event which returns to baseline status.

2. **Resolved with residual effects:** An adverse event which is not expected to return to baseline status.

   Residual effects should be documented in the subject's medical chart and on the Adverse Event CRF/eCRF.

3. **Continuing:** An adverse event which is expected to resolve back to baseline status at some point in the future.

8.2 Antibiotic Use and Respiratory Infections

Every effort will be made to link any antibiotic use directly to respiratory infections. If possible, whenever antibiotics are used for respiratory symptoms (except for prophylaxis at the time of bronchoscopy), the following information should be obtained:

1. Was the subject suspected as having a respiratory infection examined for clinical presentation suggestive of pneumonia, including fever, cough, purulent sputum, etc?
2. Was a chest X-ray performed to confirm infection (and rule out pneumonia)?
3. Was oral temperature recorded? If yes, was it elevated (i.e., above 38^{o}C)?
4. Was a complete blood count with differential obtained?
5. Was sputum gram stain and culture obtained?

If possible, document the following information:

- Which antibiotic were given (dose, time, route).
- Whether the subject was responsive to the antibiotics.
- Was the infection in the upper or lower respiratory tract?

- Which specific areas were affected? In particular, document the relationship of the affected area of the lung to the area that underwent the most recent bronchoscopy procedure; and

- Perform any additional tests that would help to identify the nature of the infection and to assist with the management of the condition.

8.3 Pneumonia

Pneumonia will be diagnosed only if a subject has:

1. Compatible clinical presentation (e.g., fever, cough, purulent sputum, etc.), AND
2. Chest x-ray showing the presence of a new infiltrate consistent with clinical pneumonia.

9.0 Risks and Benefits

9.1 Potential Risks to the Subject

Participation in this study may expose the subject to the following potential risks associated with the device or the procedure:

1. **Bronchoscopy:** With any bronchoscopic procedure, there is the possibility of fever, bleeding, laryngospasm, bronchospasm, irregular heartbeat, shortness of breath, infection, transient infiltrates, pneumonia (*Djukanovic et. al., 1998*), pneumothorax (*Bleeker et al., 1992*) or syncope. In the event that any of these were to occur, the subject will be treated for the condition. Some subjects may experience wheezing, coughing, or shortness of breath during the first few days following a bronchoscopy procedure.

   Bronchoscopy in Subjects with Asthma: Bronchoscopy in patients with asthma has the possibility of precipitating life-threatening (including death) bronchospasm, increased airway reactivity (*Djukanovic et al., 1998; Bleeker et al. 1992*), or atelectasis. Chest pain from a collapse of a small segment of your lung (atelectasis) may occur in less than 1% of patients. The risk of major complications from bronchoscopy is less than 1 in 1000 (*Fulkerson et al., 1984*). Bronchoscopy is frequently performed on asthmatic patients (*Jarjour et al., 1998*) and appropriate safety precautions will be followed. In the unlikely event that any of these risks were to occur, there may be a need for intubation or therapeutic bronchoscopy.

   Bronchial Thermoplasty: The risks of bronchial thermoplasty include the risks associated with bronchoscopy. In addition, the use of energy to heat the airways within the lung could result in injury to other nearby tissue. However, since the temperature of the catheter will be closely monitored throughout the procedure, this is unlikely.

   In the pivotal clinical trial, side effects (occurring within 6 weeks of the procedure) and occurring more frequently in bronchial thermoplasty treated patients than in control patients who had a sham bronchoscopy are listed below:

   Frequent (greater than 5%): Temporary increase in the frequency and worsening of asthma symptoms (shortness of breath, wheeze, cough, productive cough or some combination of these), upper respiratory tract infections, lower respiratory tract infections, chest pain, and headache

   Less common (between 3% and 5%): Sinusitis, bronchitis, collapsed lung, upset stomach, bleeding†, anxiety, fever, influenza, and hypertension

   Rare (between 1% and less than 3%): Pneumonia, bleeding during the procedure, abnormal breath sounds, airway obstruction, acute bronchitis, bronchial spasm, pulmonary congestion, blood-tinged sputum, increased upper airway secretion, and throat inflammation.

   In addition, there is a small possibility (3.4% per procedure) that the temporary worsening of asthma symptoms after a procedure may result in your being admitted to the hospital for management of your asthma symptoms.

The side effects listed above typically happen within one (1) day of the procedure and resolve on average within one (1) week with standard care.

There is a theoretical risk of scarring the airways. We have not seen any scarring or closure of the airways in patients who had the Alair procedure in the earlier research studies.

Subjects may experience a temporary drop in the amount of oxygen in the blood following the procedure. Subjects will be closely monitored immediately after each procedure and, if required, will be given oxygen as well as other medications (steroids) to decrease potential side effects.

2. **Electrocautery:** The Alair System uses radiofrequency (RF) energy (delivered in monopolar mode) similar to that used in electrocautery, but operates at much lower voltage levels than those in typical procedures involving electrocautery. Potential risks of electrocautery include unintended thermal damage to adjacent tissue, worsened asthma, bleeding, infection, and perforation. Application of thermal energy may result in swelling of airways.

   Electrocautery is commonly used in medical procedures and the risks associated with its use are well understood. The Investigators should be familiar with the use of electrocautery equipment and must be trained in the use of the Alair System. An appropriate return electrode must be used as instructed in its product labeling to ensure subject safety. The Alair RF Controller operates in a temperature control mode and has a number of safety algorithms that help prevent unintended thermal damage to adjacent tissue.

Because of the potential interference of monopolar RF energy with electrical signals, subjects with pacemakers and defibrillators will be excluded from participation in the study.

3. **Excess Mucus:** There is a potential for excess mucus production in response to treatment. In general, it is expected that coughing will clear any excess mucus. It is possible that the mucus may, however, become inspissated (thickened) and get stuck in the airway. Inspissated mucus may cause atelectasis and increased chances for pneumonia or infection. In the event that any of these were to occur, there may be a need for intubation, therapeutic bronchoscopy, or treatment with antibiotics.

   All subjects will be instructed to contact their Investigator or a member of the Clinical Study Staff with any breathing or other medical problems that occur during the follow-up period. In the event inspissated mucus is suspected, the subject will be treated as indicated with chest physical therapy at first. Symptomatic subjects with persistent atelectasis will be considered for therapeutic bronchoscopy.

4. **Pneumonia or infection:** There is a risk of developing pneumonia as a result of excess mucus production (as described above) or other theoretical reasons, such as impairment of the ability for the lung to clear mucus.

   During preclinical evaluations of the Alair System, a single case of bronchopneumonia occurred in a dog more than two years after the last treatment. This event was thought to be unrelated to treatment with the Alair System.

5. **Impaired gas exchange:** It is possible that treatment with the Alair System can result in a decrease in the ability of the lungs to exchange gases.

   Based on previous published studies involving bronchoscopy in asthmatic patients, it is believed that patients may experience a transient drop in the amount of oxygen in the blood post treatment (*Spanevello et al., 1998; Van Vyve et al., 1992*). In previous studies with the Alair System, occasional transient decreases in SpO_2 have been noted immediately post treatment, which resolved either spontaneously or with administration of supplemental oxygen during the protocol-specified post-procedure monitoring period.

   Subjects will be monitored closely before, during, and after treatment, to include pulse oximetry. If clinically indicated, supplemental oxygen will be administered. Subjects will not be discharged home if SpO_2 is less than 90% at the end of the post-procedure monitoring, or if there are any ongoing adverse events. In addition, all subjects will be instructed to contact their Investigator or Clinical Study Staff should their condition worsen during follow-up periods.

6. **Moderate Sedation/Anesthesia:** There is a potential risk of developing side effects associated with the use of sedation/anesthesia. The risks depend on the agents and/or gases administered. The most common side effects of these medications include low blood pressure and slow or shallow breathing. These medications also affect memory and most patients either do not remember the procedure at all or only have a vague recollection of it. Although the sedative effects wear off over a few hours, the effect on memory can last all day. Most patients have no after-effects the following day. The risks of anesthesia include postoperative pain, nausea and vomiting, dizziness, drowsiness, shivering, liver toxicity, and/or cardiovascular events.

   Only trained professionals with extensive experience administering local anesthesia with moderate sedation to patients requiring multiple procedures will be responsible for the induction and associated monitoring required for this study. In addition, subjects will undergo extensive monitoring throughout the recovery period, as well after the recovery period if clinically indicated.

The following are potential risks that are associated with the tests required as part of the study conduct:

1. **Pulmonary function tests:** Pulmonary function tests are low risk procedures. They may occasionally cause dizziness and/or slight chest discomfort due to muscle soreness, but these are self-limited.

2. **Chest X-rays:** Subjects will have radiation exposure as a result of the chest X-rays required. The doses of radiation typically used are so small that the risk of these procedures is difficult to measure.

The following risks are associated with the use of certain drugs that are required as part of the study conduct:

3. **Corticosteroids:** All drugs have side effects, and corticosteroids are known to have a number of significant side effects. Corticosteroids frequently are prescribed to help control/manage asthma (*NIH publication No. 97-4051, 2007*). All subjects enrolled in the study will be stabilized on inhaled corticosteroids prior to enrollment. In addition, subjects are administered 50 mg of prednisone or equivalent, for 5 days around the time of each treatment session (prophylactic indication).

4. **Medications required to perform bronchoscopy:** Drugs required for bronchoscopy could include lidocaine, atropine, and one of the benzodiazepines. Although each of these drugs has a number of potentially significant side effects, they are commonly used to perform bronchoscopy (*Djukanovic et al., 1998*).

   Lidocaine toxicity has been described in association with bronchoscopy. At least one death has been reported in the literature as a result of lidocaine toxicity in a research subject who underwent bronchoscopy (*Clinical Trials Advisory Newsletter, 1996*). To minimize the chance of excessive lidocaine use the total dose given during a procedure will be limited to the lower of 600mg or 9mg/kg. Amounts of lidocaine administered will be monitored and recorded. Moderate sedation can be associated with respiratory suppression resulting in hypoxemia and the need for increased supplemental oxygen or the need for intubation with mechanical ventilation. In addition, sedation can result in cardiovascular compromise with hypotension. To minimize these complications, sedation will be given in accordance with moderate sedation protocols applicable at the participating hospitals and administered by trained professionals with experience in conscious sedation and ventilation.

   Subjects with known sensitivity to drugs required to perform bronchoscopy are excluded from study participation. Any subject that experiences a significant side effect for which there is concern will be managed as appropriate, and consideration will be given to canceling any subsequent treatment, if applicable.

5. **Other risks:** The possible short-term risk of the Alair treatment may include acute respiratory failure. The theoretical potential long-term risks may include bronchial stenosis, bronchiectasis, and persistent retained secretions, although these events have not been observed in any subject treated to date, including 16 subjects who are beyond two years post-treatment. There may be additional risks that are unknown at this time that may potentially occur as a result of the Alair treatment of asthma patients.

9.2 Potential Benefits to the Subject

It is possible that a subject will not receive any benefits from treatment with the Alair System. Potential benefits may include less severe bronchoconstriction, reduced need for rescue medications, overall fewer symptoms related to asthma, and improved quality of life.

The following benefits of the Alair treatment have been observed in prior preclinical and clinical studies:

1. In pre-clinical studies in the canine model, treatment with the Alair System has been shown to produce a persistent protective effect against bronchoconstriction invoked via

local application of methacholine chloride to treated airway sites. This effect persisted out to 3 years post-treatment.

In an open-label clinical study involving 16 subjects with mild to severe asthma, there was a significant reduction in airway hyper-responsiveness as measured by methacholine challenge test at three months post-treatment. This reduction in airway hyper-responsiveness was shown to persist out to 24 months. Additionally, the Alair-treated subjects showed a significant improvement in the amPEF and pmPEF, and a significant increase in the number of symptom-free days at 3 months post treatment. (*Cox et al., 2006*)

2. In a multicenter, randomized clinical study involving 109 subjects (55 Alair treated and 54 Control) with moderate to severe-persistent asthma (*Cox et al., 2007*), significant improvements in the following parameters were observed at 3 months post treatment (in subjects on ICS+LABA) with the Alair System:

    - Symptom-free days
    - amPEF
    - pmPEF
    - Use of rescue medication.
    - Number of days when rescue medication was needed
    - Asthma Quality of Life Questionnaire (AQLQ) score

3. In a double-blind, randomized, sham-controlled clinical study (pivotal trial) of bronchial thermoplasty involving 297 subjects (196 Alair treated and 101 Sham-control), patients treated with bronchial thermoplasty had improved asthma-related quality of life out to a year compared to the control (sham-treated) patients (*Castro et al, 2010*). Additionally, when compared to control patients, patients treated with bronchial thermoplasty also experienced the following clinically significant benefits:

    - Reduction in severe asthma exacerbations.
    - Reduction in emergency room visits for respiratory symptoms.
    - Reduction in hospitalizations for respiratory symptoms.
    - Reduction in days lost from work, school, or other daily activities due to asthma symptoms.
    - Reduction in percent of subjects reporting asthma (multiple symptoms) adverse events (combinations of cough, wheeze, productive cough and shortness of breath).

    These benefits were observed during clinical studies where patients continued to take their standard maintenance asthma medications which included combinations of inhaled corticosteroids and long-acting bronchodilators.

One known benefit to subjects participating in this study is the ability to learn more about their asthma, based on the assessments that will be performed throughout the course of the study. In addition, subject will receive education about the monitoring of their disease, as will be required for study participation.

Asthmatx, Inc. will pay all medical costs over the usual costs of treatment associated with study participation.

10.0 Study Monitoring

The Sponsor or its designee will meet with the Investigator prior to the initiation of the study in order to review the adequacy of the patient population, facilities, and equipment with respect to the needs of the study, and to familiarize the Investigator with the protocol.

The Sponsor or its designee will meet with the Investigator at the time enrollment is initiated in order to ensure that subjects are being properly selected, that the methods described in the study protocol are thoroughly understood by the Investigator, and that study data are being correctly recorded.

The Sponsor or its designee will visit the clinical sites periodically during the course of the study to review completed CRF/eCRFs, compare the reported data to source documentation, and resolve any discrepancies.

The Sponsor or its designee will periodically review the data to ensure that the Investigator is in compliance with the Protocol and the Investigator's Agreement. Additionally, telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

11.0 Responsibilities of the Sponsor

The Sponsor of this clinical trial is Boston Scientific (Asthmatx, Inc.) of Sunnyvale, CA, U.S.A. The Sponsor is committed to:

- Conducting this study in compliance with Good Clinical Practices (GCP) Guidelines.
- Protecting the rights, health, safety and welfare of study subjects; the Sponsor is responsible for obtaining and reviewing copies of Institutional Review Board approvals and will verify that appropriate Informed Consent form is obtained.
- Informing the Investigator of any new information about the study that may affect the health, safety or welfare of the subjects, or which may influence their decision to continue participating in the study.
- Providing the Investigator with the Protocol access to the CRF/eCRFs to document the study evaluation variables for each subject entered into the study.
- Providing the statistical analysis and report-writing resources necessary to complete reporting of the study results.
- Ensuring proper clinical site monitoring.
- Selecting qualified Investigators to conduct this study.
- Maintaining copies of correspondence, records of shipment and disposition of devices, adverse device effects, and records related to the signed Investigator agreements, and other records related to the study.
- Providing Investigators with copies of Regulatory approval letters for the study protocol and any protocol amendments.

12.0 Responsibilities of the Principal Investigator

The Principal Investigator (PI) participating in this study must be a licensed physician in his/her country of employment. The PI will affirm by his/her signature on the Investigator's Agreement that he/she will fulfill his/her responsibilities relative to this study.

- Subject Selection
  The PI is responsible for ensuring that all subjects entering the study conform to the subject Inclusion/Exclusion criteria.

- Institutional Review Board (IRB) Approval
  The PI is responsible for obtaining IRB approval from the institution at which he/she shall perform the treatment prior to initiation of the study. The PI is responsible for submitting to the IRB the Protocol, Informed Consent form, and any other additional documentation relevant to the study as required by the IRB for complete review of the study. Written assurance of IRB approval of the Protocol and the Informed Consent form must be provided by the PI to the Sponsor prior to initiation of the study.

  The PI is responsible for ensuring that Regulatory approvals of protocol amendments are provided to their respective IRB if required by the Committee.

- Informed Consent
  The PI is responsible for fully discussing the nature of the study, the possible risks, and the alternative treatments with prospective subjects prior to their participation in the study. The Investigator is responsible for obtaining written Informed Consent from each subject prior to his/her participation in the study. The Informed Consent form must be the same version of the form approved by the IRB. The signed Informed Consent form will be maintained in the subject's medical record, and a copy of the signed Informed Consent form will become an integral part of each case report file retained by the PI. A copy of the signed Informed Consent form must be given to the subject who signed the form.

  A copy of the proposed Informed Consent form for this study is provided as Attachment C to this document.

- Subject Evaluations and Data Reporting
  The PI is responsible for performing the subject evaluations as described in this protocol. Regulations require that the PI maintain information in the subject's medical records (i.e. source documentation) to corroborate data collected on the study CRF/eCRFs.

  All information generated by the subject evaluations is to be transferred from the source documentation and recorded onto CRF/eCRFs provided by the Sponsor. Paper CRFs, if used, should be filled out in blue or black ink, or typewritten. Any necessary corrections should be made by a single strikethrough, initialed, and dated in ink by study site personnel. Correction fluid may not be used. The PI will review, correct as needed, and sign off on the accuracy and completeness of the CRF/eCRF data. Copies of CRF/eCRFs may be printed as needed and are available for review by the Sponsor and monitor. Copies of subject casebooks may be printed for review by authorized regulatory bodies. Original laboratory reports are to be retained by the PI, and the resulting data shall be entered onto the appropriate CRF/eCRFs.

The PI is responsible for submitting reports to the Sponsor and the reviewing IRB as specified in Appendix B of this Protocol.

- Protocol Deviations
  The PI should not deviate from this protocol, unless the study poses unacceptable risks to the health or welfare of the subject.

  The Investigator shall notify the Sponsor and the reviewing IRB of any deviation from the protocol intended to protect the life or physical well being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than five working days after the emergency occurred. Except in such an emergency, prior approval of the Sponsor is required for any deviation from the protocol. Approval from the IRB is required if these changes or deviations are expected to affect the rights, safety or welfare of the subjects.

- Record Retention
  The PI shall maintain all original records as required by local regulation or law. The Sponsor will provide record-retention dates to all Investigators.

- Investigational Device Accountability
  The PI must maintain accurate records of the receipt of all investigational devices shipped by the Sponsor, including the date and lot numbers of devices received. In addition, accurate records must be kept regarding the date and quantities of investigational devices received, dispensed and returned. Information regarding the specific identification numbers for investigation devices used is to be recorded onto the appropriate CRF/eCRF and/or device accountability log for each Subject undergoing the treatment. The PI must assure that study supplies are dispensed only to subjects properly enrolled in the study and under the direct supervision of the PI or Co-Investigators.

  All used and unused investigational supplies, as well as all labeled containers, are to be returned to the Sponsor as soon as practical upon request by the Sponsor or designee, or upon completion of the study. Investigational material accounting procedures must be completed before the study is considered terminated.

13.0 Good Clinical Practice & Regulatory Requirements

- Institutional Review Board Approval
  This study may not be initiated at any site until the local IRB has reviewed the protocol and the Informed Consent documents, and written approval has been submitted to the Sponsor.

- Informed Consent
  Written Informed Consent for the study must be obtained from all subjects who participate in this study prior to their participation.

  A sample of the Informed Consent Form to be used for this study is provided as Appendix C. Clinical sites may revise the form with information that would meaningfully add to the protection of the rights and welfare of patients. Prior to submitting the revised Informed Consent form to the IRB for review, the PI is to receive authorization of the revisions by the Sponsor, who shall review the form to ensure compliance with applicable regulations and inclusion of all essential elements. The IRB at each clinical site will approve the Informed Consent form prior to study initiation. The PI shall submit the written IRB approval along with the final Informed Consent form to the Sponsor.

- Subject Confidentiality
  Subject confidentiality shall be maintained at all times throughout the conduct of this study, and all subject data shall be maintained secure against unauthorized access. Possible review and photocopying of subject records by representatives of Asthmatx, Inc. (Sponsor), United States Food and Drug Administration or other Regulatory agencies could occur. In the event subject data are used for educational, presentation, and/or publication purposes, subject identity will be masked to protect confidentiality.

  Video footage may be taken during the subject's treatment session for educational, presentation, and/or publication purposes. Subject identity will be masked to protect confidentiality in the event video footage is used.

  The U.S. Food and Drug Administration, other Regulatory Agencies, and Asthmatx, Inc., or its representatives are required to maintain the privacy of all records they review in connection with this study.

14.0 Quality Assurance and Control

This study will be conducted according to Good Clinical Practices (GCP), in compliance with the principles enunciated in the Declaration of Helsinki (*World Medical Association Declaration of Helsinki, 2008*), applicable local regulations, and per Asthmatx, Inc., Clinical Department Standard Operating Procedures (SOPs).

Asthmatx, Inc. or its designee will:

- meet with the investigator prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the study protocol

- meet with the investigator at the time enrollment is initiated in order to ensure that subjects are being properly selected, that the methods described in the study protocol are thoroughly understood by the investigator, and that study data are being correctly recorded

- periodically review the data to ensure that the study investigator is in compliance with the protocol and the investigator's agreement

- periodically monitor the sites to ensure that the completed CRFs/eCRFs match the medical records and to resolve any discrepancies

- conduct telephone consultation as necessary during the course of the study to ensure the proper progress and documentation of the study findings

15.0 Reporting Requirements (Interim and Final reports)

Post Approval Study Status Reports will be submitted as per FDA requirements proposed in the "Guidance for Industry and FDA Staff (*Procedures for Handling Post-Approval Studies Imposed by PMA Order; Document issued on: [Level 2, June 15, 2009*]".

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm

An Interim Post-Approval Study Status Report will be submitted every 6 months for the first 2 years of the study and annually, thereafter until study completion, from the PMA approval date. The Final Post-Approval Study Report will be submitted no later than three months after study completion following the 5-year evaluation of all subjects.

The Interim Post-Approval Study Status Reports will include:

- Purpose of the study, including study goals, objectives, and primary and secondary study endpoints
- Patient population being studied
- Begin and end dates of period covered by the report
- Date of database freeze for the interim update
- Date of database closure for the Final Post-Approval Study Report
- Summary of study progress
- Subject accountability
- An explanation for:
  - subjects lost to follow-up, as well as any measure to minimize such future events
  - subject and physician-initiated discontinuations
  - any deaths, including reports from post-mortem examinations
- Summary of safety and/or effectiveness data and an interpretation of study results to date

If necessary:

- A rationale for not meeting the study milestones/timeline specified in the study protocol and a revised study timeline
- A revised reporting schedule (e.g., proposing how frequently interim reports are submitted to FDA) with a rationale for the basis of the revision

16.0 Detailed Timeline

Finalize detailed study outline	December 10, 2009
PMA Supplement with Final Protocol to FDA:	30 days after PMA approval order letter (May 27, 2010)
Submission of Protocol to IRBs:	45 days following approval of the Final Protocol (PMA Supplement) by FDA
Expected date of study initiation:	Within 2 months of IRB approval at a Site that has a signed Clinical Trial Agreement
Expected monthly number of sites with IRB approvals:	One (1) to two (2) per month
Expected date of initiation of subject enrollment:	One to two weeks after study initiation
Expected number of subjects enrolled per month:	Six (6) to ten (10) subjects per month when all 30 planned sites are up and running.
Estimated date of enrollment completion:	Every effort will be made to complete enrollment by December 2014
Interim Reports:	Every 6 months for the first 2 years from the PMA approval date, and annually thereafter until the study is completed.
Projected Study completion and Final Report:	December 2019 (Study completion) June 2020 (Final Report)

17.0 References

1. Bleeker ER, ER McFadden, et al. Editorial - Investigative bronchoscopy in Subjects with asthma and other obstructive pulmonary diseases, whether and when. CHEST 1992; 101(2): 297-298.

2. Bousquet J, Jeffrey P, Busse W, Johnson M, Vignola A. Asthma. From bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med 2000;161:1720-45.

3. Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. Am Rev Respir Dis 1993;147:405-10.

4. Castro M, Smith T, Strunk R. Pathophysiology of Asthma. In: Murphy S, Kelly H, McWilliams B, eds. Pediatric Asthma. New York: Marcel Dekker; 1998:71-115.

5. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, Fiss E, Olivenstein R, Thomson NC, Niven RM, Pavord ID, Simoff M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma. A multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med. 2010; 181:116-124.

6. Cohen L, E X, Horiuchi T, et al. Epithelial cell proliferation contributes to airway remodeling in severe asthma. Am J Res Crit Care Med 2007;176:138-45.

7. Cox G, JD Miller, et al. (2006). "Bronchial thermoplasty for asthma." Am J Respir Crit Care Med. 173(9): 965-969.

8. Cox G, NC Thomson, A Sperb-Rubin, R Niven, P Corris, HC Siersted, R Olivenstein, I Pavord, D McCormack, R Chaudhuri, J Miller, M Laviolette, and The RISA Trial Study Group (2007). “Asthma control during the year after Bronchial Thermoplasty”. N Engl J Med. 356 :1327-1337.

9. Danek CJ, CM Lombard, et al. (2004). "Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs." J Appl Physiol 97(5): 1946-1953.

10. Djukanovic R, R Dahl, et al. Safety of biopsies and bronchoalveolar lavage. Eur Respir J 1998; 11: Suppl 26: 39s-41s.

11. Fredberg JJ, D Inouye, et al. Airway Smooth Muscle, Tidal Stretches, and Dynamically Determined Contractile States. Am J Respir Crit Care Med, 1997; 156: 1752-1759.

12. Fredberg JJ, D Inouye, et al. Perturbed Equilibrium of Myosin Binding in Airway Smooth Muscle and its Implications in Bronchospasm. Am J Respir Crit Care Med, 1999; 159; 959-967.

13. Fulkerson WJ. Current Concepts. Fiberoptic Bronchoscopy. New England Journal of Medicine, 1984; 311:511-5.

14. Fredberg JJ, D Inouye, et al. Perturbed Equilibrium of Myosin Binding in Airway Smooth Muscle and its Implications in Bronchospasm. Am J Respir Crit Care Med, 1999; 159; 959-967.

15. Fulkerson WJ. Current Concepts. Fiberoptic Bronchoscopy. New England Journal of Medicine, 1984; 311:511-5.

16. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2008 Update.

17. James AL, PD Paré, and JC Hogg. The Mechanics of Airway Narrowing in Asthma. Am Rev Respir Dis. 1989; 139: 242-246.

18. Jarjour NN, SP Peters, et al. Investigative use of bronchoscopy in asthma. Am J Respir Crit Care Med 1998; 157: 692-697.

19. King GC, S Eberl, CM Salome, IH Young, and AJ Woolcock. Differences in Airway Closure Between Normal and Asthmatic Subjects Measured with Single-Photon Emission Computed Tomography and Technegas. Am J Respir Crit Care Med 1998; 158: 1900-1906.

20. Miller JD, G Cox, et al. A prospective feasibility study of bronchial thermoplasty in the human airway. CHEST 2005; 127(6): 1999-2006.

21. Nam J. Establishing Equivalence of Two Treatments and Sample Size Requirements in Matched Pairs Design. Biometrics 1997; 53: 1422-1430.

22. NIH Publication No. 97-4051, National Institutes of Health. NAEPP Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007.

23. Pavord ID, G Cox, NC Thomson, AS Rubin, PA Corris, RM Niven, KF Chung, M Laviolette, and the RISA Trial Study Group (2007). “Safety and Efficacy of Bronchial Thermoplasty in Symptomatic, Severe Asthma.” Am J Respir Crit Care Med 176 : 1185–1191.

24. Procedures for Handling Post-Approval Studies Imposed by PMA Order; Document issued on: [Level 2, June 15, 2009]

25. Seow, CY, RR Schellenberg, and PD Paré. Structural and Functional Changes in the Airway Smooth Muscle of Asthmatic Subjects. Am J Respir Crit Care Med 1998; 158: S179-S186.

26. Spanevello A, GB Migliori, et al. Bronchoalveolar lavage causes decrease in PaO2, increase in (A-a) gradient value and bronchoconstriction in asthmatics. Respir Med 1998; 92: 191-197.

27. Van Vyve T, P Chanez, et al. Safety of bronchoalveolar lavage and bronchial biopsies in patients with asthma of variable severity. Am Rev Respir Dis 1992; 146: 116-121.

28. Wilson SR, G Cox, JD Miller, S Lam. Global assessment after bronchial thermoplasty: the patient's perspective. Journal of Outcomes Research 2006; 10: 37-46.

29. Wiggs, BR, CA Hrousis, JM Drazen, and RD Kamm. On the Mechanism of Mucosal Folding in Normal and Asthmatic Airways. J. Applied Physiology. 1997. 83(6): 1814-1821.

30. World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 59th WMA General Assembly, Seoul, October 2008.

APPENDIX A: Summary of Investigator Responsibilities

An Investigator is responsible for:

1. Ensuring that an investigation is conducted in accordance with the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100].

2. Ensuring that an investigation is conducted in accordance with the Helsinki Declaration. [Helsinki Declaration, as most recently amended by the 52nd Annual WMA General Assembly, Edinburgh, Scotland, October 2000, and the note of clarification on Paragraph 29 added by WMA General Assembly, Washington, DC, 2002 and the note of clarification on Paragraph 30 added by WMA General Assembly, Tokyo, 2004.

3. Protecting the rights, safety, and welfare of Subjects under his/her care. [21 CFR 812.100].

4. The control of the treatment material under investigation. [21 CFR 812.140].

5. Ensuring that IRB-approved Informed Consent is obtained for each patient prior to entry into the study. [21 CFR 812.140].

6. Supervising investigational product use and supplying it only to authorized persons. [21 CFR 812.110].

7. Returning to the Sponsor any remaining supply of treatment material upon termination of the Investigator's part of the study. [21 CFR 812.110].

8. Maintaining accurate, complete and current records relating to the investigation. [21 CFR 812.140].

9. Permitting inspections of records by the Sponsor (or Sponsor's designee), and authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation [21 CFR 812.145].

10. Submitting complete, accurate, and timely reports of serious or unanticipated adverse device effects, withdrawal of IRB approval, deviation from the investigational plan, inability to obtain Informed Consent, and study progress and completion. [21 CFR 812.140 and 812.150].

11. Submitting Annual Reports and a Final Report in a timely manner to the IRB. [21 CFR 812.150].

12. Retaining records of the investigation or assigning record custody. [21 CFR 812.140]

APPENDIX A 1: Responsibilities of Investigators (21 CFR 812 Part E and G)

[Code of Federal Regulations]
[Title 21, Volume 8]
[Revised as of April 1, 2009]
[CITE: 21CFR812]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

PART 812 INVESTIGATIONAL DEVICE EXEMPTIONS

Subpart E--Responsibilities of Investigators

Sec. 812.100 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter. Additional responsibilities of investigators are described in subpart G.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8957, Jan. 27, 1981]

Sec. 812.110 Specific responsibilities of investigators.

(a) *Awaiting approval.* An investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval.

(b) *Compliance.* An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

(c) *Supervising device use.* An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it.

(d) *Financial disclosure.* A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the

applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

(e) *Disposing of device.* Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

[45 FR 3751, Jan. 18, 1980, as amended at 63 FR 5253, Feb. 2, 1998]

Sec. 812.119 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted false information either to the sponsor of the investigation or in any required report, the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, or the Center for Drug Evaluation and Research will furnish the investigator written notice of the matter under complaint and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the applicable Center, the disqualification process will be terminated. If an explanation is offered but not accepted by the Center, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is entitled to receive investigational devices.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has deliberately or repeatedly submitted false information either to the sponsor of the investigation or in any required report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing IRB that the investigator is not entitled to receive investigational devices. The notification will provide a statement of basis for such determination.

(c) Each investigational device exemption (IDE) and each cleared or approved application submitted under this part, subpart E of part 807 of this chapter, or part 814 of this chapter containing data reported by an investigator who has been determined to be ineligible to receive investigational devices will be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval or

clearance of any marketing application.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the IDE immediately and notify the sponsor and the reviewing IRB of the determination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 of this chapter on the question of whether the IDE should be reinstated.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued clearance or approval of the marketing application for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval or rescind clearance of the medical device in accordance with the applicable provisions of the act.

(f) An investigator who has been determined to be ineligible to receive investigational devices may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ investigational devices solely in compliance with the provisions of this part and of parts 50 and 56 of this chapter.

[62 FR 12096, Mar. 14, 1997, as amended at 71 FR 76902, Dec. 22, 2006]

Subpart G--Records and Reports

Sec. 812.140 Records.

(a) *Investigator records.* A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

(1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

(2) Records of receipt, use or disposition of a device that relate to:

(i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark.

(ii) The names of all persons who received, used, or disposed of each device.

(iii) Why and how many units of the device have been returned to the

sponsor, repaired, or otherwise disposed of.

(3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:

(i) Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(ii) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

(iii) A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

(4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

(5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

(b) *Sponsor records.* A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

(1) All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.

(2) Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

(3) Signed investigator agreements including the financial disclosure information required to be collected under 812.43(c)(5) in accordance with part 54 of this chapter.

(4) For each investigation subject to 812.2(b)(1) of a device other

than a significant risk device, the records described in paragraph (b)(5) of this section and the following records, consolidated in one location and available for FDA inspection and copying:

(i) The name and intended use of the device and the objectives of the investigation;

(ii) A brief explanation of why the device is not a significant risk device:

(iii) The name and address of each investigator:

(iv) The name and address of each IRB that has reviewed the investigation:

(v) A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and

(vi) Any other information required by FDA.

(5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints and

(6) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

(c) *IRB records.* An IRB shall maintain records in accordance with part 56 of this chapter.

(d) *Retention period.* An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

(e) *Records custody.* An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of 812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58843, Sept. 5, 1980; 46 FR 8957, Jan. 27, 1981; 61 FR 57280, Nov. 5, 1996; 63 FR 5253, Feb. 2, 1998]

Sec. 812.145 Inspections.

(a) *Entry and inspection.* A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

(b) *Records inspection.* A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

(c) *Records identifying subjects.* An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

Sec. 812.150 Reports.

(a) *Investigator reports.* An investigator shall prepare and submit the following complete, accurate, and timely reports:

(1) *Unanticipated adverse device effects.* An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

(2) *Withdrawal of IRB approval.* An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

(3) *Progress.* An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

(4) *Deviations from the investigational plan.* An investigator shall notify the sponsor and the reviewing IRB (see 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required.

(5) *Informed consent.* If an investigator uses a device without obtaining informed consent, the investigator shall report such use to

the sponsor and the reviewing IRB within 5 working days after the use occurs.

(6) *Final report.* An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

(7) *Other.* An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

(b) *Sponsor reports.* A sponsor shall prepare and submit the following complete, accurate, and timely reports:

(1) *Unanticipated adverse device effects.* A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

(2) *Withdrawal of IRB approval.* A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

(3) *Withdrawal of FDA approval.* A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

(4) *Current investigator list.* A sponsor shall submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.

(5) *Progress reports.* At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with 812.36(f) and annual reports in accordance with this section.

(6) *Recall and device disposition.* A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

(7) *Final report.* In the case of a significant risk device, the

sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.

(8) *Informed consent.* A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

(9) *Significant risk device determinations.* If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

(10) *Other.* A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58843, Sept. 5, 1980; 48 FR 15622, Apr. 12, 1983; 62 FR 48948, Sept. 18, 1997]

APPENDIX B: Investigator Reports Required Under an IDE

Under an IDE, the Investigator is required under 21 CFR 812.150 and 21 CFR 812.140 to make the following Reports:

Reports	Submitted To	Comments
Unanticipated Adverse Device Effects	• Reviewing IRB • Sponsor	Within 10 working days of learning of the adverse effect
Withdrawal of IRB Approval	• Sponsor	Within 5 working days of notification
Deviations from the Investigational Plan in an Emergency	• Sponsor • Reviewing IRB	Within 5 working days of occurrence
Informed Consent (Use of a Device prior to obtaining Informed Consent)	• Sponsor • Reviewing IRB	Within 5 working days after use occurs
Progress Report	• Sponsor, Monitor • Reviewing IRB	Regularly and at least yearly
Final Report	• Sponsor • Reviewing IRB	Within 3 months after termination or completion of Study
Records Maintenance Transfer	• FDA	Within 10 working days after transfer occurs
Others as requested by IRB or FDA	• FDA • Reviewing IRB	

APPENDIX C: Sample Informed Consent

Subject ID # □□□□G-1002-□□-AAA

Protocol #10-02

You are being asked to participate as a subject in the research project entitled **Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma**, under the direction of {*Insert principal investigator's name and credentials*}. The sponsor of the study, Boston Scientific Corporation (BSC)is providing funding to {*insert name of institution*} for your enrollment and participation in this study.

WHAT IS THE PURPOSE OF THIS STUDY?

You are being invited to participate in a research study because you have been diagnosed with severe asthma that is not controlled with conventional treatment. This study is designed to evaluate the short- and long-term benefit and safety of a procedure called bronchial thermoplasty (which is performed with the Alair® System) for the treatment of severe persistent asthma. 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. In a recent clinical study lasting one year, bronchial thermoplasty has been shown to reduce asthma attacks and visits to the emergency room for respiratory symptoms, and improve quality of life in patients with severe persistent asthma. It is not known how long this benefit will persist.

The walls of human airways contain a ring of muscle (called 'smooth muscle'). When this smooth muscle contracts the airways are narrowed. In people with asthma, this muscle is thickened and contracts more easily. This causes the airways to narrow and leads to the typical asthma symptoms of chest tightness, breathlessness, wheeze and coughing. The Alair® System uses heat energy to reduce the amount of smooth muscle present in the airways and improves symptoms in patients with asthma.

PREVIOUS EXPERIENCE WITH THE ALAIR® SYSTEM

The Alair® System has been tested in patients with asthma in four clinical studies. Based on the available data, the United States Food and Drug Administration approved the Alair® Bronchial Thermoplasty System 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.

NUMBER OF SUBJECTS PARTICIPATING AND THE DURATION OF YOUR PARTICIPATION

Everyone who takes part in the study will receive the treatment. The anticipated number of subjects involved in the study will be between 250 and 300 at 30 centers across the United States and Canada. Our institution {*insert name of institution*} will enroll up to {*insert number*} subjects. The length of time for your participation is approximately five and a half years.

WHAT WILL THIS STUDY INVOLVE?

Enrollment: If you decide to participate in this Study, and you have not changed your asthma medications for at least 4 weeks, you will undergo evaluations to determine if you qualify to participate in the Study.

You will be required to provide a medical history including a history of your asthma symptoms, asthma attacks, and asthma medications and complete a questionnaire about how asthma affects your quality of life. You will also have a physical examination, lung function tests (breathing tests) and a chest X-ray (if you have not had one done within the last 4 months), and a blood test. If you are a female of child bearing potential, you will be asked to take a pregnancy test at this time and before each treatment session. If you are pregnant before your first treatment you will be withdrawn from the Study. If you become pregnant after your first treatment, further treatments will not be performed while you are pregnant but you may stay in the study for the full five year period.

If you meet all of the Study requirements and decide to take part in the Study, you will be enrolled into the study and undergo the treatment.

Treatment Period: You will undergo 3 separate bronchoscopy procedures each separated by at least three weeks to complete the treatment. During each of the procedures a different part of the lung will be treated. Before each procedure, you will be prescribed oral corticosteroid tablets (50mg prednisone each day for 5 days). You will be required to take one tablet every day for the three days before your procedure, on the day of your procedure, and on the day after your procedure in order to minimize potential side effects from the procedure. This is in addition to your daily-prescribed asthma medications which will continue for the duration of the study.

Bronchoscopy: Bronchoscopy is a commonly performed medical procedure in patients with lung disease. Bronchoscopy involves putting a flexible, thin, tube with a light and camera (bronchoscope) into the airways of your lung through either your nose or mouth. The light and camera allow your doctor to see what she/he is doing in the lungs. To make the procedure more comfortable your nose, throat, and voice box will be numbed with local anesthetic (lidocaine). You may be given an injection to dry up the secretions in your airways. You will be given medications that will induce sleepiness and drowsiness but will still allow you to follow commands – this is called moderate sedation.

Although there will be a tube in your windpipe, it is small enough to allow you to breathe comfortably around it. For your breathing comfort you will be given extra oxygen during the procedure. During the procedure we will apply additional lidocaine into the lungs to reduce cough, though you will probably cough a little as it goes in.

Bronchial Thermoplasty: The Alair® System consists of a thin flexible wire (catheter) with an expandable basket at the tip, and a power source that provides energy. During the procedure the Alair® catheter is passed through the bronchoscope into the lungs and is then used to deliver controlled, focused heat to the airways in your lungs. The wire basket will be heated for up to 10 seconds to a temperature of 65°C at a number of different sites in your airways. Each procedure will typically last between 30 to 60 minutes depending upon the ease of moving the bronchoscope in the different airways.

Once the procedure is completed, the catheter and the bronchoscope will be removed. You will gradually become more alert as the sedation wears off. You will be transferred to an observation area prior to being discharged to go home.

Post-Procedure Monitoring: You will be carefully monitored after each procedure for a minimum of 4 hours by the research study staff. If needed, you will be provided treatment (breathing treatments, medications, oxygen, etc.) after the procedure. At the end of this time, if your breathing, heart rate, blood pressure, level of oxygen in the blood, and lung function tests are near their normal levels, you will be allowed to go home. However, if these values do not return to normal, or you are experiencing other difficulties, you may be admitted to the hospital for additional monitoring overnight.

Follow Up Evaluations: On the first, second and seventh day after each procedure, the Study staff from your doctor's office will contact you to check on how you are feeling and to provide you the dates for your follow-up examination. The follow-up examination will be done approximately 2 weeks after the first and second procedures, and 6 weeks after the third procedure. During this examination, you will receive a physical exam, your asthma symptoms and any emergency room visits or hospitalizations for respiratory symptoms will be reviewed, and a short breathing test to check on your lung function will be performed. Additional procedures may be necessary if the doctor wishes further evaluation. Provided the doctor is satisfied with the findings at this time, you will be ready to continue with your next procedure, which will be scheduled.

You will be evaluated by your doctor in his/her office at 6 weeks after the third (last) treatment procedure. During this visit your asthma symptoms and any emergency room visits or hospitalizations for respiratory symptoms will be reviewed and you will be asked to describe any problems that you may have had since your last contact with the research staff. In addition, a physical exam and lung function tests will be performed. During the periods between scheduled study visits or telephone contacts, you are encouraged to keep track of any problems that you may experience so that they can be accurately described to your doctor. A medical event log will be provided to you during this visit. This will allow your doctor to properly assess your condition.

***Three-monthly telephone calls*.**
Once you have had all your treatments and attended your 6 week follow-up visit, the research staff will contact you every 3 months for the next 5 years by telephone. You will be asked about how well you have been and specifically whether your asthma symptoms have worsened sufficiently that you have needed to take a course of corticosteroids tablets or intravenous infusions. You will be asked about any emergency room visits or hospitalizations for respiratory symptoms since your last contact.

Yearly doctor's office visits.
In addition to the 3-monthly contact calls, you will be evaluated by your doctor in his/her office once every year. During this visit your asthma symptoms and any emergency room visits or hospitalizations for respiratory symptoms will be reviewed and you will be asked to describe any problems that you may have had since your last contact with the research staff. In addition, a physical exam and lung function tests will be performed.

At any time during the course of the study if your asthma symptoms get worse, you must contact your doctor or the Study Coordinator to seek advice and help. The success of this Study depends on you being able to tell us of every occasion (either at the time or when contacted by the study staff) when you have had a new or increased dose of oral steroids, and also being able to attend all of your study visits for the full 5 years. If you move away from where the study is performed, the sponsor will arrange and pay for you to travel to complete your follow-up visits either at your original study site or at another study site if it is close.

Your participation in the Study will be over after you complete your evaluation visit 5 years after your treatment period has finished. At this time you will be exited from the Study. Note that after the treatment, you will continue to take your normal medications for asthma, although your doctor may adjust the dose if necessary.

It is important that you maintain your scheduled appointments for evaluation of your medical condition for the duration of the study. The research staff may ask you to provide contact information for a close family member or friend as an alternative means of contacting you in the event that they cannot reach you. Additionally, if after repeated attempts the research staff is unable to reach you, the research staff reserves the right to contact the family member or fried whose contact information you provided and/or use a third party to locate you in order to determine your medical condition and vital status.

WHAT ARE THE BENEFITS OF BEING IN THIS STUDY?

It is possible that you will not receive any benefit from this treatment or that any benefit you experience may be temporary. There are no guarantees of any results or outcomes. In a double-blind, randomized, sham-controlled clinical study (pivotal trial) of bronchial thermoplasty, patients treated with bronchial thermoplasty had improved asthma-related quality of life out to a year compared to the control (sham-treated) patients. Additionally, when compared to control patients, patients treated with bronchial thermoplasty also experienced the following clinically meaningful benefits:

- Reduction in severe asthma attacks.
- Reduction in emergency room visits for respiratory symptoms.
- Reduction in days lost from work, school, or other daily activities due to asthma symptoms.
- Reduction in percent of subjects reporting multiple asthma adverse events (combinations of cough, wheeze, productive cough and shortness of breath).

These benefits were observed during clinical studies where patients continued to take their standard maintenance asthma medications which included combinations of inhaled corticosteroids and long-acting bronchodilators.

Another potential benefit to you from participation in this Study is that based on the testing and careful observations that will be done throughout the Study, you and your doctor will learn more about your asthma. In addition, you may become better educated about the monitoring of your disease, as required for Study participation.

WHAT ARE THE RISKS OF BEING IN THIS STUDY?

Although all of the risks are not known, as a result of participation in this Study you may experience some risks related to certain tests, medications, and the procedure itself. These risks may include:

Lung Function Testing: Pulmonary function tests are breathing tests. They are low risk procedures however they may occasionally cause slight soreness in the breathing muscles from the effort. Some people get dizzy during such tests, but these feelings are temporary. In order to perform the lung function tests at most visits, you will be asked to stop taking some of your inhalers for up to 12 hours before the test.

Blood Draw / I.V. Needle Insertion: The risks of drawing blood to perform blood tests and IV needle insertion to give you sedation during the bronchoscopy include temporary pain and discomfort from the needle stick, redness or bruising at the site, bleeding, fainting, and lightheadedness.

Chest X-Ray: You will have a chest X-ray before your first procedure which will expose you to radiation. The amount of radiation you will receive from the chest X-ray is equivalent to one week of natural background radiation exposure.

Oral Corticosteroids: Oral corticosteroids will be provided to you during the course of this Study to minimize possible side effects. Corticosteroids are known to have a number of significant side effects with long term use, including osteoporosis, diabetes, high blood pressure, muscle weakness, redistribution of body fat, and others. Short term side-effects may include agitation, a feeling of well being or disruption of your sleep. These short-term side effects wear off quickly once you finish the course. Corticosteroids are used routinely to manage asthma and will be used for only five days around each bronchoscopy.

Moderate Sedation: Medications will be used to make you very drowsy for the procedure. All medications used during bronchoscopy are approved by the FDA (United States Food and Drug Administration, a government agency that regulates approval and use of medications) and Health Canada. The most common side effects of these medications include low blood pressure and slow or shallow breathing. These medications also affect memory and most patients either do not remember the procedure at all or only have a vague recollection of it. Although the sedative effects wear off over a few hours, the effect on memory can last all day. Most patients have no after-effects the following day. Trained medical professionals with extensive experience and expertise will administer these medications and will be responsible for your care during the procedure. Because you may be drowsy, you will need to arrange for someone else to drive you home after each procedure.

Bronchoscopy: Likely side effects of the bronchoscopy (occurring in more than 25% of people) include discomfort (coughing and occasionally gagging) and nosebleed (if the bronchoscope was passed through your nose). Fever or chills may occur in 10-25% of people. Chest pain from a collapse of a small segment of your lung (atelectasis) may occur in less than 1% of people. You may cough up small flecks of blood for 24 hours after the procedure.

More serious complications from the bronchoscopy include collapse of the lung, spasms of the vocal cord and windpipe, pneumonia or bronchitis, and irregular heartbeats. These have been reported but are extremely rare (occurring in less than 1% of people, 1 out of 1000 procedures). Only one death has ever been reported after research bronchoscopy and has not occurred in prior studies using the Alair System. Many thousands of research bronchoscopy procedures have been performed, so the risk of death is extremely remote.

Bronchial Thermoplasty: The risks of bronchial thermoplasty include the risks associated with bronchoscopy. In addition, the use of energy to heat the airways within the lung could result in injury to other nearby tissue. However, since the temperature of the catheter will be closely monitored throughout the procedure and does not exceed 65^{o}C, this is unlikely. No evidence of this has been seen in previous studies of the Alair® System.

In the pivotal clinical trial, side effects (occurring within 6 weeks of the procedure) and occurring more frequently in bronchial thermoplasty treated patients than in control patients who had a sham bronchoscopy are listed below:

Frequent (greater than 5%): Temporary increase in the frequency and worsening of asthma symptoms (shortness of breath, wheeze, cough, productive cough or some combination of these), upper respiratory tract infections, lower respiratory tract infections, chest pain, and headache

Less common (between 3% and 5%): Sinusitis, bronchitis, collapsed lung, upset stomach, bleeding[†], anxiety, fever, influenza, and hypertension

Rare (between 1% and less than 3%): Pneumonia, bleeding during the procedure, abnormal breath sounds, airway obstruction, acute bronchitis, bronchial spasm, pulmonary congestion, blood-tinged sputum, increased upper airway secretion, and throat inflammation.

In addition, there is a small possibility (3.4% per procedure) that the temporary worsening of asthma symptoms after a procedure may result in your being admitted to the hospital for management of your asthma symptoms.

The side effects listed above typically happen within one (1) day of the procedure and resolve on average within one (1) week with standard care.

There is a theoretical risk of scarring the airways. We have not seen any scarring or closure of the airways in patients who had the Alair procedure in the earlier research studies.

You may experience a temporary drop in the amount of oxygen in your blood following the procedure. You will be closely monitored immediately after each procedure and, if required, you will be given oxygen as well as other medications (steroids) to decrease potential side effects.

RISKS IF YOU ARE PREGNANT?

Females: Participation in some parts of this Study may involve risks that are currently unforeseeable to you or to an embryo or fetus if you become pregnant. If you are found to be pregnant, no further treatments will be performed. Once you have had all three treatments, then you may become pregnant if you so wish and there is no risk to any pregnancy.

WHAT ARE THE ALTERNATIVES TO TAKING PART IN THIS STUDY?

You may decline to participate in this Study. The alternative treatment options that are available to you instead of participation in this clinical trial include:

1) Identifying and avoiding or reducing exposure to triggers or things that cause asthma to worsen.
2) Continue or begin taking medications regularly to manage your asthma symptoms. Currently used medications include "Relievers" (bronchodilators) that relax the smooth muscle that surrounds the airway (Short-acting relievers may last 4 - 6 hours and Long-acting relievers may last 8 - 12 hours), and "Controllers" (corticosteroids) that control swelling or inflammation over time. Other medications such as methylxanthines, anticholinergics, leukotriene inhibitors, and IgE inhibitors may be considered when your asthma is still poorly controlled.

There are risks associated with these medications such as increased heart rate, skeletal muscle tremor, low potassium levels, and although uncommon, severe, life-threatening or fatal exacerbation from the use of bronchodilators, and adrenal suppression, thinning of bone, skin thinning and/or bruising, and cataracts from use of corticosteroids. Depending upon the medications that are prescribed, your doctor will explain any associated risks to you.

WILL I BE PAID TO PARTICIPATE IN THIS STUDY?

The cost of the Study and all medical costs over the usual costs of treatment associated with Study participation will be covered by BSC, the Sponsor of this research Study. You will be compensated for your time and participation in this study. The amount that you will receive is proportional to the number of times you attend study visits and respond to study calls / emails. Your compensation will be paid to you at regular intervals during the course of the study. You may be reimbursed for incidental costs such as transportation, parking, and meals on the days of your office visits. The maximum amount approved by the ethics committee that you can be paid during this Study is *{insert maximum compensatable value}*.

WHAT IF I AM INJURED?

If you are physically injured because of any medications given to you or procedure properly performed on you under the plan for this study, *{insert institution name}* will provide you with the appropriate medical treatment, and Asthmatx Inc. will reimburse you for the appropriate medical expenses not covered by your own insurance or health care program. You will be responsible for paying any costs related to illnesses and medical events not associated with being in this study. Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not routinely available. However, you are not waiving any of your legal rights you may have under federal or provincial laws and regulations by participating in this study. Questions about compensation may be directed to the study doctor. If you are injured, please contact *{insert contact details}*.

CONFIDENTIALITY

As a participant in this or any research Study, you have a right to privacy. Your name will be coded and separated or unlinked from all research records associated with this Study. This will protect your identity and preserve anonymity. The Sponsor of this Study (Boston Scientific Corporation) or their designees, the Food and Drug Administration, Health Canada, and other regulatory agencies may review your medical records. Your personal identity will not be disclosed in any document that summarizes or reports the findings from this Study.

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA) AUTHORIZATION

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The Study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What information may be used and given to others? If you choose to be in this Study, the Study doctor will get personal information about you. This may include information

that might identify you. The Study doctor may also get information about your health including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your Study visits
- Information obtained during this research about
- HIV / AIDS
- Hepatitis infection
- Physical exams
- Laboratory, X-ray, and other test results
- Records about any Study drug you received

Who might get this information? Information about your health may be used and given to others by the Study doctor and the research staff. Before the Study doctor sends any information to he/she will carefully unlink your name and other identifiers (such as your address, telephone number, or social security number) from all research records associated with this Study. Instead, the Study doctor will use your initials and assign a code number to the information that is shared with others. This will protect your identity and preserve anonymity. Your coded information may be given to the Sponsor of this research (Boston Scientific Corporation). "BSC" includes any persons or companies that are working for or with BSC, or are owned by BSC. In addition, your coded information may also be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- State of California or other States where Study is conducted
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- The Institutional Review Board (IRB) - a group of independent experts who review this research protocol as required by regulations, in order to protect your interests

Why will this information be used and/or given to others? The coded information about you and your health may be given to others to carry out the research Study. The Sponsor of this research will analyze and evaluate the results of the Study. In addition, The Sponsor or their representatives will be visiting the Investigational Site to follow the progress of the Study and they will be reviewing your information for this purpose.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so that the Sponsor can receive approval from the regulatory agencies to market new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

What if I decide not to give permission to use and give out my health information? By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you decide not to give permission, you will not be able to participate in this research Study.

May I review or copy the information obtained from me or created about me? You have the right to review and copy your health information. However, if you decide to be in

this Study and sign this consent form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission? Yes, but this consent will not stop automatically. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the Study doctor. If you withdraw your permission, you will not be able to continue being in this Study. The mailing address for your Study doctor is:

{insert site PI name and contact address}

When you withdraw your permission, no new health information that might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others? While Asthmatx Inc. and other recipients may understand the importance of protecting the confidentiality of your health information, *{insert institution name}* cannot guarantee the confidentiality of your health information or protect from further disclosures once these recipients receive your health information.

If you are transferred to another facility prior to the end of your participation in this Study, your signature on this document authorizes your Study doctors, the monitors, auditors, and inspectors mentioned above to access your medical records at that other facility. In the rare event that your information is required to be disclosed by law to another entity, neither the Sponsor (BSC), nor the IRB can guarantee that confidentiality of your personal information will be maintained.

PARTICIPATING IN THE STUDY

The procedure to participate in the study begins with your review of the information in this Informed Consent Form. Please take all the time you need to read the information presented in this form, ask questions, and understand the answers. When all your questions have been answered to your satisfaction, if you are still interested in participating in this Study, please sign and date the Authorization page at the end of this form. If you meet all of the study requirements, which will be determined during the screening evaluations, you will be enrolled into the Study.

WITHDRAWAL FROM THE STUDY

Participation in this Study is voluntary. You are free to refuse participation in the Study, or if already enrolled in the Study, to withdraw from the Study at any time and for any reason without fear of penalty. Your refusal to participate or withdraw from the Study will have no impact on your future medical care. You will be told by your doctor(s) of any new information that might affect your condition or influence your willingness to continue participation in this Study.

Additionally, your doctor(s) may decide to terminate your participation in the Study, regardless of your consent, at any time and for any reason. If this were to happen, you will continue to receive the best possible standard treatment. This decision will not affect your future medical care.

QUESTIONS/ CONCERNS

If you have any questions or concerns about the Study, or if you have any breathing or other medical problems at any time during the course of the Study, you may contact {*insert contact name and details*} at any time.

If you have any questions concerning your rights as a research Subject, you may contact the Hospital Ethicist, {*insert contact name and details*} at any time.

AUTHORIZATION / CONSENT

I, _____, therefore certify the following:

a. I have read and understood the details of this research Study and Authorization.

b. My participation in this research Study is voluntary.

c. I give my authorization to use my Protected Health Information for the purposes of this Study, as described above.

d. I agree to participate in this research Study and to comply with all the requirements including, taking my prescribed asthma medication daily, completing all required procedures, and completing all follow-up examination visits as they were explained to me.

e. I voluntarily consent to allow representative(s) of the Sponsor or their designee to be present in the procedure room during my procedure(s) for purpose of observation.

Print Name of Subject	Signature of Subject	Date/Time
Print Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date/Time
Print Name of Principal Investigator	Signature of Principal Investigator	Date

APPENDIX D: Investigator Agreement

Protocol No. 10-02: Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma

Protocol Date: 26APR2012 (Version 3)

By signing this Agreement,

- I signify that I have read the protocol, including all attachments, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

- I signify that I will provide all Study Staff under my supervision copies of the protocol and access to all information provided by Asthmatx, Inc. I will discuss this material with them to ensure they are fully informed about the device and the study.

- I signify that I agree to comply with all responsibilities listed in the Appendices to the Clinical Protocol (Summary of Investigator Responsibilities, Investigator Responsibilities under 21CFR part 812, and Investigator Reports required under an IDE).

- I signify that if required, I will provide the Sponsor a complete list of disclosable financial arrangements and interests in Asthmatx, Inc. in accordance with FDA requirements.

☐ A copy of my curriculum vitae is attached or has been submitted to Sponsor.

Print Name of Principal Investigator	Signature of Principal Investigator	Date
Print Name of Co-Investigator	Signature of Co-Investigator	Date
Print Name of Co-Investigator	Signature of Co-Investigator	Date