(cover page)

Official Title of the Study:

Ten year follow-up of subjects from 3 landmark randomized controlled Bronchial Thermoplasty (BT) Studies

BT 10+ Study

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Ten year follow-up of subjects from 3 landmark randomized controlled Bronchial Thermoplasty (BT) Studies

BT 10+ Study

CLINICAL INVESTIGATION PLAN

BSC Project Number: E7137

National Clinical Trial (NCT) Identification Number 03243292

Sponsored By

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
Version B	**May 31, 2017**	**90702637 Rev.Ver AH**	**Date inserted on protocol**	**Rev/Ver B**	**N/A**	**UK site would not accept protocol without version date**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**1.1 Background**	**Version B**	**Version C**	**Include definition of Bronchiectasis and Bronchial Stenosis**

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**1.3 Conclusion**	**Version B**	**Version C**	**Include Bronchiectasis and Bronchostenosis conclusion sentence.**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**4.1.1 Definition**	**Version B**	**Version C**	**Replace word airway with bronchial**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**9.1.2 Primary Safety Endpoint**	**Version B**	**Version C**	**Replace airway stenosis with bronchial stenosis**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**16.1 Anticipated Adverse Events**	**Version B**	**Version C**	**Add verbiage- Potential device related AEs are described in the DFU**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**16.3 Risk Minimizatio n Action**	**Version B**	**Version C**	**Added verbiage RE: unknown risks of Bronchial Thermoplasty but there is no procedure in the study**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**17.1 Reportable Events by investigation al sites to Boston Scientific**	**Version B**	**Version C**	**Added All fatal Serious Adverse Events**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**17.2 Definition and Classificatio ns**	**Version B**	**Version C**	**Added definitions for: Adverse Device Effects (ADE), Serious Adverse Device Effects (SADE)**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**17.4 Investigator Reporting Requiremen ts**	**Version B**	**Version C**	**Added SAE and AE required timelines to report events**

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**22 Bibliography**	**Version B**	**Version C**	**Added citations #15, 16, 17, 18, 19**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**23.2-1 Definitions**	**Version B**	**Version C**	**Added definitions for Bronchiectasis and Bronchostenosis**
Version C	**Jan 16, 2018**	**90702637 Rev/Ver AH**	**Throughout body of protocol**	**Version B**	**Version C**	**Replace HRCT scan with Volumetric HR CT scan**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**Page 9 & 22 (Table 6.2-1): Key Inclusion Criteria**	**Version C**	**Version D**	**Add language to sentence Subjects who had BT Treatment : applies to previously treated subjects only; does not apply to control/sham subjects)**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**Page 9: Key Inclusion Criteria**	**Version C**	**Version D**	**Control subject : add verbiage after the fifth post-randomization (15 weeks following enrollment) for AIR and RISA subjects and 6 weeks following**

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
						the final sham BT treatment for AIR2 sham subjects visit to match language on page 22:
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**4.1.2 Additional Considerations**	**Version C**	**Version D**	**Remove -who will be blinded to timepoint baseline or 10 year or beyond) RE: independent radiologist**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**Page 1**	**Version C**	**Version D**	**Added NTC Identification Number 03243292**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**8.6 Source Documents**	**Version C**	**Version D**	**Added language RE: Original source documents and certified copies.**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**10.1 Data Collection, Processing, and Review**	**Version C**	**Version D**	**Clarify iMedidata System and Rave software**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**10.2 Data Retention**	**Version C**	**Version D**	**Added language RE: PI responsibility with data collection to be in compliance with regulatory requirements.**

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**14.2.1 Delegation of Responsibility**	**Version C**	**Version D**	**Added language RE: PI delegates tasks, the person has to be trained and be competent to perform assigned tasks. Sub-I cannot be delegated for primary oversight.**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**14.3 Institutional Review Board/Ethics Committee**	**Version C**	**Version D**	**Added language RE: any protocol amendment and ICF must be reviewed and approved by IRB/EC before changes are implemented. IRB/EC determines if participant will need to sign new ICF.**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**14.4 Sponsor Responsibilities**	**Version C**	**Version D**	**Subjects data sent to BSC will be kept confidential by applicable law & regulations. BSC may use data to oversee & improve performance of device.**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**18. Informed Consent**	**Version C**	**Version D**	**Replace word Body with Authority**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**19.1 Premature Termination of the Study**	**Version C**	**Version D**	**BSC delete Corporation, delete administrative and replace with word business.**
Version D	**May 30, 2018**	**90702637 Rev/Ver AH**	**19.2 Termination of Study**	**Version C**	**Version D**	**RE: IRB/EC add word associated,**

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
			Participation by the Investigator or withdrawal of IRB/EC			**add regulatory authority.**

Protocol Synopsis

Ten year follow-up of subjects from 3 randomized controlled Bronchial Thermoplasty (BT) studies **BT 10+ Study**	
Study Objective(s)	To confirm the long-term efficacy and safety of Bronchial Thermoplasty (BT) at 10 years follow-up or beyond in subjects previously enrolled in any of the following Boston Scientific-sponsored, controlled pre-approval studies: AIR, RISA and AIR2.
Test Device	Alair System (Bronchial Thermoplasty): • Alair Controller • Alair Catheter
Study Design	BT 10+ is an international multi-center, prospective follow-up study on subjects who were previously enrolled in any of the following studies: AIR, RISA and AIR2 trials. Subjects who received active BT treatment in any of the 3 trials will be eligible to participate upon achieving a minimum of at least 10 years' time from their last BT treatment's 6-week follow-up. For each of the studies, respective control and sham subjects will also be eligible to participate upon achieving a minimum of at least 10 years' time from 6 weeks after the fifth post-randomization visit (15 weeks following enrollment) for AIR and RISA subjects and 6 weeks following the final sham BT treatment for AIR2 sham subjects.
Planned Number of Subjects	In total, 429 subjects were enrolled in AIR, RISA and AIR2 at 35 investigational sites: 260 BT subjects, 71 control (RISA and AIR) and 98 (AIR2). Only the 22 sites with ≥3 BT subjects who were followed to the 5-year follow-up will be evaluated for participation in the study. These 22 sites enrolled 202 BT, 64 control, and 87 sham subjects. Based on historical loss to follow-up at 5 years for these trials, an attrition of at least 40% is assumed at or beyond 10 year follow-up. This long-term follow-up study is therefore expected to enroll up to 196 subjects: up to 121 BT subjects are expected, up to 32 control (AIR & RISA studies) and up to 43 sham (AIR2 study) subjects. Note: If attrition rates are lower than expected, more than 196 subjects may be enrolled.

Ten year follow-up of subjects from 3 randomized controlled Bronchial Thermoplasty (BT) studies **BT 10+ Study**	
Planned Number of Investigational Sites / Countries	Twenty-two sites in 6 countries that participated in at least one of the AIR, RISA and/or AIR2 clinical trials will be evaluated for participation in this study.
Primary Safety Endpoint(s)	Absence of clinically significant post-treatment respiratory changes, following BT, defined as bronchiectasis or bronchial stenosis, as confirmed by Pulmonary Volumetric HRCT scan at the BT 10+ study visit in those subjects who had a baseline Volumetric HRCT scan in the AIR2 Study.
Primary Effectiveness Endpoint(s)	Durability of the treatment effect by comparing the proportion of subjects who experience severe asthma exacerbations during the first and fifth years after BT treatment with the proportion of subjects who experience severe asthma exacerbations during the 12 month period prior to the BT 10+ study visit. Severe asthma exacerbation is defined as worsening of asthma symptoms requiring use of systemic corticosteroids (tablets, suspension, or injection) (NAEPP Guidelines, 2007). [20]
Additional Endpoints	The following additional endpoints will be evaluated for the 12 month period prior to the BT 10+ study visit and will be compared to the first and fifth years after BT treatment: • Severe asthma exacerbation rates (exacerbations / subject / year) • Emergency room visits for respiratory adverse events (rates of emergency room visits and proportion of subjects with emergency room visits for respiratory adverse events) • Hospitalizations for respiratory adverse events (rates of hospitalizations and proportion of subjects with hospitalizations for respiratory adverse events) • Respiratory Serious Adverse Events (SAEs) (rates of respiratory SAEs, and proportion of subjects with respiratory SAEs)

Ten year follow-up of subjects from 3 randomized controlled Bronchial Thermoplasty (BT) studies **BT 10+ Study**	
Follow-up Schedule	For all participating subjects in the BT 10+ study, subject assessments can occur in one visit or they can be staged to be completed in multiple visits over a 30-day window. The follow-up assessment for this study can take place no earlier than the following: • 10 years after the end of the treatment period (last BT or sham treatment plus 6-weeks) for BT or sham subjects. • 10 years after the end of what was defined as their treatment period for control subjects. The study visit assessments should be completed within 30 days of the subject being consented to the study and will consist of the following: • Chart review and/or subject interview to collect clinical data on chronic sinusitis, GERD, obstructive sleep apnea, respiratory infections, and pulmonary medication usage at and up to the BT 10+ study visit date • Pulmonary Volumetric HRCT scan for subjects from the AIR2 Study • Pulmonary function testing including pre- and post-bronchodilator FEV1 • Lung volumes and diffusion capacity • Subject questionnaires including AQLQ, ACQ, ACT and Subject Satisfaction Survey, EQ5D Questionnaire • Physical assessment • Height and weight • Women of child-bearing potential that were enrolled in the AIR2 study will require a pregnancy test prior to completing the Volumetric HRCT scan. Pregnancy is not an exclusion from the study but any pregnant women will not have the Volumetric HRCT scan. Where available, and in line with local standard of care, the following additional data will be recorded in the database for exploratory analysis: • Allergic skin test or RAST (perennial, seasonal, mold)

Ten year follow-up of subjects from 3 randomized controlled Bronchial Thermoplasty (BT) studies **BT 10+ Study**	
	• Exhaled nitric oxide (eNO) Completion of the BT 10+ study visit will mark the end of subject study participation.
Study Duration	12-Month enrollment period.
Key Inclusion Criteria	• Subjects previously enrolled in AIR, RISA or AIR2 • Subjects who received active BT treatment and had last BT treatment at least 10 years and 6 weeks prior to enrollment (applies to previously treated subjects only; does not apply to control/sham subjects) • Control/Sham subjects with at least 10 years of long-term follow-up from 6 weeks after the fifth post-randomization visit (15 weeks following enrollment) for AIR and RISA subjects and 6 weeks following the final sham BT treatment for AIR2 sham subjects. • Subject is able to read, understand and sign a written Informed Consent to participate in the Study and able to comply with the study requirements
Key Exclusion Criteria	• Severe asthma exacerbation or chest infection in the past 4 weeks. Subject entry into this study should be delayed until free from severe asthma exacerbation or chest infection for a minimum of 4 weeks.
Statistical Methods	
Primary Statistical Hypothesis	No formal hypothesis will be tested. Data will be summarized descriptively with confidence intervals, as appropriate.
Statistical Test Method	Since no formal hypothesis is tested, only descriptive statistics will be used to summarize the primary endpoint.

Table of Contents

2.1. *Table of Figures*

2.2. *Table of Tables*

Introduction

2.3. *Background*

Asthma is a common chronic non-communicable disease that affects as many as 334 million people of all ages in all parts of the world. It is a cause of substantial burden to people, often causing a reduced quality of life, not only due to its physical effects, but also its psychological and social effects. The various estimates of its economic burden, mostly due to productivity loss, are all significant. (The Global Asthma Report 2014). [1]

Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation. Excessive and inappropriate constriction of airway smooth muscle (ASM) is recognized as a predominant feature of asthma. Presently, there is no known cure for asthma. Despite the availability of a number of medications, there remains an unmet medical need for patients with asthma who continue to have symptoms despite optimal medical therapy.

People with asthma can have other concurrent respiratory diseases. Bronchiectasis is common in patients with severe asthma. [15] Patients with both bronchiectasis and asthma have a higher rate of hospitalization due to a severe asthma attack. [17]

Bronchiectasis (BXSIS) is defined by dilation, or ectasia of the airways of the bronchus. The primary clinical manifestation of bronchiectasis is chronic or refractory infection. [18]

Bronchostenosis is seen in asthma patients that have an infection such as a cold. Symptoms include fever, and severe coughing due to attempts to clear secretions. Inability to clear secretions can result in atelectasis. Bronchostenosis is a definite, localized, stricture-like narrowing of a bronchus. [19}

The Alair™ Bronchial Thermoplasty System was developed as a novel system designed to deliver radiofrequency energy to the airways of asthmatic patients. Bronchial thermoplasty (BT) is a non-pharmacologic, bronchoscopic treatment for subjects 18 years and older with severe persistent asthma that is not well controlled with inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA). During the BT procedure, radiofrequency energy is used to heat the airway walls in a controlled manner. The mechanism of action is, in part, a lasting reduction in ASM mass due to the heat produced during the procedure [1-5] The reduction in ASM was associated with the clinical improvement seen in patients undergoing BT. [3, 4]

2.4. *Prior Clinical Trials*

Several randomized controlled clinical trials of BT have been performed in subjects with moderate to severe asthma, such as the AIR2 trial and others. [8-11] In these trials, subjects who underwent BT experienced significantly improved clinical outcomes, including decreased numbers of asthma exacerbations, ER visits and hospitalizations as well as improved quality of life after the procedure. In addition to these randomized controlled trials, open-label studies are needed to confirm the safety and efficacy of BT when performed

in clinical practice compared to clinical outcomes of subjects who participated in previously reported randomized trials of BT. [12, 13]

The pivotal AIR2 ("Asthma Intervention Research 2") trial was a randomized, sham-controlled trial of the BT system in subjects with severe persistent asthma. This trial demonstrated that over a 12-month follow-up period after BT treatment, BT-treated subjects (n=190) experienced clinically relevant improvements in many outcome measures. These improvements persisted through 5 years of follow-up. The detailed methods and results from the AIR2 study are described by Castro et al [14]and Wechsler et al [11].

The Alair system received premarket approval (PMA) from the FDA in April 2010. Subsequently, the "Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma (PAS2)" study was initiated in fulfillment of FDA requirements for PMA approval. PAS2 is an ongoing prospective, open-label, observational, multi-center study. The objectives of the PAS2 study are to evaluate durability of treatment effectiveness in real-world clinical practice and to continue to evaluate the short-term and longer-term safety profile of the Alair System for BT in the United States and Canada in subjects 18 years and older with severe persistent asthma.

2.5. *Conclusion*

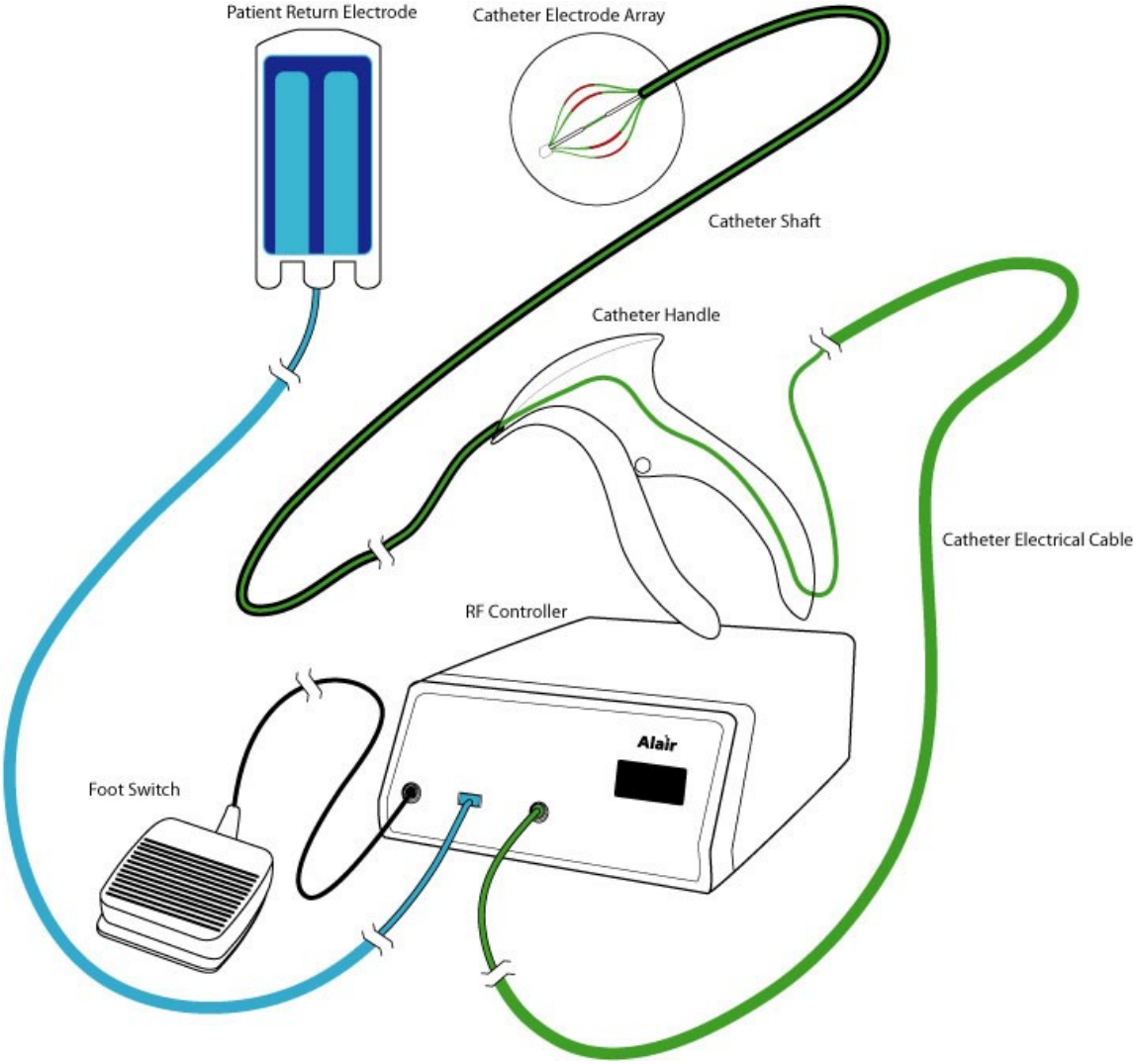
The BT 10+ study will be the first look at BT subjects beyond 5 years. The evaluation of baseline Volumetric HRCT scans from the BT subjects from the AIR2 study and comparison to the 10 year follow-up Volumetric HRCT scan will provide objective safety data to determine if significant post-treatment changes of Bronchiectasis or Bronchostenosis exist

3. Device Description

Bronchial thermoplasty with the Alair System is a non-pharmacologic, device-based treatment option for subjects with asthma. The bronchial thermoplasty procedure with the Alair System involves the delivery of controlled radio frequency (RF) energy to the airway walls as a method for reducing the amount of ASM. The Alair System is designed for treatment of the airways distal to the mainstem bronchi from 10 mm in diameter down to airways of ≥ 3 mm in diameter. These airways normally represent about 80% of the total airways resistance in humans[2]. Bronchial thermoplasty is currently staged in 3 treatment sessions with a different region of the lung being treated during each session (one lower lobe in session 1; the second lower lobe in session 2; and both upper lobes in session 3). Treatment sessions are routinely scheduled at least 3 weeks apart.

The Alair System, shown in **Figure 1**, is comprised of an Alair Catheter, an Alair RF Controller, and accessories.

Error! Reference source not found.**: The Alair System**



3.1. *The Alair Catheter*

The Alair Catheter is a sterile, single-use, disposable device. The purpose of the Catheter is to deliver therapeutic RF energy to the treatment sites in the airway. The Catheter consists of the following key sub-components:

- An electrode array, located at the distal end of the catheter, that contains the electrodes and the temperature sensor (the electrodes make tissue contact and deliver therapeutic RF energy)
- A long flexible catheter shaft that is inserted into the working channel of a flexible bronchoscope
- A handle that is used to expand (open) and relax (closed) the electrode array
- An electrical cable that connects to the RF Controller
- The Catheter is connected to the RF Controller using the catheter receptacle on the RF Controller front panel.

3.2. *Alair RF Controller*

The Alair RF Controller provides temperature-controlled delivery of RF energy to the Alair Catheter. The Controller is reusable and provided non-sterile. It does not come into direct contact with the patient.

3.3. *Alair Accessory Kit*

The Alair System has two accessories, a footswitch and a patient return electrode. The footswitch assembly comprises a commercially available switch, cable, and connector. It connects to the RF Controller front panel and is used to initiate the RF energy delivery. The patient return electrode is used to complete the current path to the RF Controller. The footswitch is provided in the Alair RF Controller Accessory Kit, along with a region-specific power cord and the Operator's Manual. The patient return electrode is a standard, commercially available return electrode, and is not provided by Boston Scientific (BSC).

4. Study Objectives

The objective of this study is to confirm the long-term efficacy and safety of BT at 10 years follow-up or beyond in subjects previously enrolled in any of the following Boston Scientific-sponsored, controlled pre-approval studies; AIR, RISA or AIR2.

5. Study Endpoints

5.1. *Primary Safety Endpoint*

5.1.1. Definition

The safety endpoint is defined as the absence of clinically significant post-treatment changes following BT, defined as bronchiectasis or bronchial stenosis, as confirmed by Pulmonary Volumetric HRCT scan at the BT 10+ study visit in those subjects who also had a baseline Volumetric HRCT scan in the AIR2 Study.

5.1.2. Additional Considerations

Baseline Volumetric HRCT scans were not collected in the AIR and RISA studies. Only the AIR2 study mandated Volumetric HRCT scan at the baseline study visit. Therefore, only AIR2 subjects with available baseline Volumetric HRCT scans will be evaluated for the primary safety endpoint. Volumetric HRCT scans will be collected in both BT and sham subjects at the BT-10+ study visit.

The Volumetric HRCT scans will be reviewed by an independent radiologist qualified to read chest images and a pulmonologist qualified to interpret the radiologist's findings.

Baseline and follow-up HRCT images at 10 years or beyond will be read by an independent pulmonary radiologist. Upon completing this assessment, the radiologist will assess whether

findings in follow-up images were new observations, improvements from baseline or deteriorations from baseline. The radiologist's findings will then be reviewed by an independent pulmonologist who will attribute a clinical significance to each finding based on the subject's information, including lung function and AE profiles, Volumetric HRCT scans at 5 years follow-up (where available) as well as occurrence and timing of respiratory events and severe exacerbations.

A Volumetric HRCT scan protocol will be developed to include guidelines to be followed by the independent reviewers to ascertain whether there are significant post treatment changes, following BT, defined as bronchiectasis or bronchial stenosis.

5.2. *Primary Efficacy Endpoint*

The primary effectiveness endpoint is defined as durability of the treatment effect by comparing the proportion of subjects who experience severe asthma exacerbations during the first and fifth years after BT treatment with the proportion of subjects who experience severe asthma exacerbations during the 12 month period prior to the BT 10+ study visit.

Severe asthma exacerbation is defined as worsening of asthma symptoms requiring use of systemic corticosteroids (tablets, suspension, or injection) (NAEPP Guidelines, 2007). [20]

5.3. *Additional Endpoints*

The following additional endpoints will be evaluated for the 12 month period prior to the BT 10+ study visit and compared to the first and fifth years following BT treatment:

- Severe asthma exacerbation rates (exacerbations / subject / year)
- Emergency room visits for respiratory adverse events (rates of emergency room visits and proportion of subjects with emergency room visits for respiratory adverse events)
- Hospitalizations for respiratory adverse events (rates of hospitalizations and proportion of subjects with hospitalizations for respiratory adverse events)
- Respiratory Serious Adverse Events (SAEs) (rates of respiratory SAEs, and proportion of subjects with respiratory SAEs)

6. Study Design

BT 10+ is an international multi-center, prospective follow-up study on subjects who were enrolled in the AIR, RISA and AIR2 trials.

All subjects who received active BT treatment in the 3 trials will be eligible to participate upon achieving a minimum of at least 10 years' time from their last BT treatment's 6-week follow-up.

For each of the studies, respective control and sham subjects will also be eligible to participate upon achieving a minimum of at least 10 years' time from 6 weeks after the fifth

post-randomization visit (15 weeks following enrollment), for AIR and RISA subjects and 6 weeks following the final sham BT treatment for AIR2 sham subjects.

6.1. *Scale and Duration*

In total, 429 subjects were enrolled in AIR, RISA and AIR2 at 35 investigational sites: 260 BT, 71 control (RISA and AIR) and 98 sham (AIR2) subjects.

Only the 22 sites with ≥3 BT subjects who were followed to the 5-year follow-up will be evaluated for participation in the study.

These 22 sites enrolled 202 BT, 64 control, and 87 sham subjects. Based on historical loss to follow-up at 5 years for these trials, an attrition of at least 40% is assumed at or beyond 10 year follow-up. This long-term follow-up study is therefore expected to enroll up to 196 subjects: up to 121 BT subjects, up to 32 control (AIR & RISA studies) and up to 43 sham (AIR2 study) subjects.

Note: If attrition rates are lower than expected, more than 196 subjects may be enrolled.

6.2. *Treatment and Control*

This is a 10+ years or beyond follow-up study for subjects previously enrolled in the AIR, RISA or AIR2 trials. Subjects that were treated with BT, as well as control and sham subjects will be evaluated for participation in the study.

Sham and control subjects that have undergone BT treatment outside of the respective studies prior to reaching the 10+ year visit will not be analyzed as part of the control/sham group. These subjects will be analyzed as a separate group.

6.3. *Justification for the Study Design*

To date subjects enrolled in clinical studies investigating the safety and efficacy of BT have not been followed beyond 5 years. This study will provide long-term follow-up (10+ years) data of subjects treated with BT as well as sham and control subjects from 3 key randomized controlled studies: AIR, RISA and AIR2 data on the safety of BT and durability of treatment effect at or beyond 10 years post treatment will be collected prospectively from enrolled subjects during a single study visit.

7. Subject Selection

7.1. *Study Population and Eligibility*

The inclusion and exclusion criteria are included in Sections 6.2 and 6.3 below.

7.2. *Inclusion Criteria*

Table 7.2-1: Inclusion Criteria

Clinical Inclusion Criteria	• Subjects previously enrolled in AIR, RISA or AIR2 • Subjects who received active BT treatment and had last BT treatment at least 10 years prior to enrollment (applies to previously treated subjects only; does not apply to control/sham subjects). • Control/Sham subjects with at least 10 years of long-term follow-up from 6 weeks after the fifth post-randomization visit (15 weeks following enrollment) for AIR and RISA subjects and 6 weeks following the final sham BT treatment for AIR2 sham subjects. • Subject is able to read, understand and sign a written Informed Consent to participate in the Study and able to comply with the study requirements

7.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria will be excluded from this clinical study

Table 7.3-1: Exclusion Criteria

Clinical Exclusion Criteria	• Severe asthma exacerbation or chest infection in the past 4 weeks. Subject entry into this study should be delayed until free from severe asthma exacerbation or chest infection for a minimum of 4 weeks.

8. Subject Accountability

8.1. *Point of Enrollment*

The point of enrollment in the study is the date the informed consent form is signed by the subject.

8.2. *Withdrawal*

All subjects enrolled in the study (including those that are withdrawn, voluntarily withdraw, or are lost to follow-up) shall be accounted for and documented. If a subject withdraws from the study, the reason(s) for the withdrawal shall be documented.

8.3. *Enrollment Controls*

As all subjects enrolled in this study will have been subjects from the AIR, RISA or AIR2 trials, all who meet the Inclusion Criteria may be consented and enrolled within the 12-month enrollment period.

9. Study Methods

9.1. *Data Collection*

Data will be collected in line with the endpoints above and according to the schedule contained in Table 8.1-1. All data will be collected using a web-based set of electronic case report forms (eCRFs).

Table 9.1-1: Data Collection

Procedure/Assessment	Enrollment	Study Evaluations
Informed consent process, including informed consent signature date (can be signed and testing completed afterwards on another date or on the same date)	X	
Demographics prior to enrollment		X
Physical assessment, weight, and height		X
Pre-BD FEV_1		X
Post-BD FEV_1		X
Lung volumes		X
Diffusion capacity		X
Lung Volumetric HRCT scan (AIR2 subjects who also had a Volumetric HRCT scan at baseline only)		X
Pulmonary medication use		X
Asthma Quality of Life Questionnaire (AQLQ)		X
Asthma Control Test (ACT)		X
Asthma Control Questionnaire (ACQ)		X
Subject Satisfaction Survey (BT treated subjects only)		X
Subject Productivity Questionnaire		X
Severe asthma exacerbations, respiratory SAEs, hospitalizations for respiratory adverse events, Emergency room visits for respiratory adverse events for 12 month prior to enrollment through study exit		X
Pregnancy test for women of child-bearing potential that were enrolled in AIR2 study prior to completing Volumetric HRCT scan		X
Allergic Skin Test or RAST (perennial, seasonal, mold) (if per local standard of care)		X
Exhaled Nitric Oxide (eNO) (if per local standard of care)		X
Assessment of BT treatment outside of AIR, RISA, or AIR2 studies (control/sham subjects only)		X

9.2. *Study Candidate Screening*

Only subjects who participated in the prior BSC-sponsored BT studies (AIR, RISA, or AIR2) will be screened for enrollment in the BT 10+ study.

Permission will be requested from the respective site Ethics Committee (EC) or Internal Review Board (IRB) to collect cause of death information for AIR, RISA and AIR2 subjects who died after exiting the study.

9.3. *Informed Consent*

Subjects interested in participating in the study will sign an Informed Consent Form prior to study specific tests being performed during the Evaluation Visit.

9.4. *Study Visits*

9.4.1. Study Visit Timing

For all participating subjects in the BT 10+ study, subject assessments can occur in one visit or they can be staged to be completed in multiple visits over a 30-day window. The follow-up assessment for this study can take place no earlier than the following:

- Ten (10) years after the end of the treatment period (last BT or sham treatment plus 6-weeks) for BT or sham subjects.
- Ten (10) years from 6 weeks after the fifth post-randomization visit (15 weeks following enrollment) for the control subjects from the AIR and RISA Studies.

9.4.2. Study Visit Assessments

The following assessments are to be completed:

- Demography
- Medical History for 12 months prior to enrollment
- Collection of clinical data on chronic sinusitis, GERD and Obstructive Sleep Apnea
- Physical Assessment including weight and height
- Assessment of BT treatment outside of AIR, RISA and AIR2 studies (control/sham subjects only)
- Spirometry test to include both Pre and Post BD Forced Expiratory Volume in 1 second: Pre-BD FEV1
- Lung volumes
- Diffusion capacity
- Pulmonary Volumetric HRCT scan (BT treated subjects only)
- Pulmonary medication use

- Asthma Quality of Life Questionnaire (AQLQ)
- Asthma Control Test (ACT)
- Asthma Control Questionnaire (ACQ)
- Subject Satisfaction Survey (BT treated subjects)
- EQ5D Questionnaire
- Respiratory SAEs in the prior 12 months
- Severe asthma exacerbations in the prior 12 months
- Hospitalizations for respiratory adverse events in the prior 12 months
- Emergency room visits for respiratory adverse events in the prior 12 months
- Women of child-bearing potential that were enrolled in the AIR2 study will require a pregnancy test prior to completing the Volumetric HRCT scan. Pregnancy is not an exclusion from the study but any pregnant women will not have the Volumetric HRCT scan.
- Where available:
    - Allergic skin test or RAST (perennial, seasonal, mold)
    - Exhaled nitric oxide (eNO)

9.5. *Study Completion*

Completion of the Evaluations in section 8.4 will mark the end of the subject study participation.

9.6. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in **Error! Reference source not found.**.

Table 9.6-1: Source Documentation Requirements

Requirement	Disposition
Demographic and Physical Exam	Retain at center
Assessment of BT treatment outside of AIR, RISA, and AIR2 studies (control/sham subjects only)	Retain at center
Spirometry test report	Retain at center

Table 9.6-1: Source Documentation Requirements

Requirement	Disposition
Volumetric HRCT scan report (AIR2 subjects who also had a Volumetric HRCT scan at baseline only)	Retain at center
Volumetric HRCT scan (AIR2 subjects who also had a Volumetric HRCT scan at baseline only only)	Send to HRCT Core Lab
Lung volume test report	Retain at center
Diffusion capacity test report	Retain at center
Asthma Quality of Life Questionnaire (AQLQ)	Retain at center
Asthma Control Test (ACT)	Retain at center
Asthma Control Questionnaire (ACQ)	Retain at center
Subject Satisfaction Survey (BT subjects only)	Retain at center
EQ5D Questionnaire	Retain at center
Hospitalization and/or death records as applicable	Retain at center

9.7. *Local Laboratory*

A Core Lab will be utilized for Volumetric HRCT scan imaging repository and archiving for this study.

10. Statistical Considerations

10.1. *Endpoints*

10.1.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as durability of the treatment effect by comparing the proportion of subjects who experience severe asthma exacerbations during the first and fifth year after BT treatment with the proportion of subjects who experience severe asthma exacerbations during the 12 month period prior to the BT 10+ study visit.

Severe asthma exacerbation is defined as worsening of asthma symptoms requiring use of systemic corticosteroids (tablets, suspension, or injection) (NAEPP Guidelines, 2007). [20]

10.1.2. Primary Safety Endpoint

The primary safety endpoint is defined as the absence of clinically significant post-treatment changes following BT, defined as bronchiectasis or bronchial stenosis, as confirmed by Pulmonary Volumetric HRCT scan at the BT 10+ study visit.

10.2. *Hypothesis*

No formal hypothesis will be tested for both the primary effectiveness and safety endpoints since this is an observational study.

10.3. *Sample Size*

Only the 22 sites with ≥3 BT subjects who were followed out to the 5 year follow-up visit will be evaluated for participation in the study. Based on historical loss to follow-up at 5 years for these trials, an attrition rate of at least 40% is expected at or beyond 10 years of follow-up. This long-term follow-up study is therefore expected to enroll up to 121 BT subjects, up to 32 control (AIR & RISA studies) and up to 43 sham (AIR2 study) subjects. Note that if attrition rates are lower than expected, more than 196 subjects may be enrolled.

10.4. *Statistical Methods*

Since no formal hypothesis is tested, only descriptive statistics will be used to summarize the primary effectiveness and safety endpoints.

10.4.1. Analysis Sets

All subjects who signed an informed consent and are enrolled in this study will be included in the Intent to Treat (ITT) analysis set. Since this is a long-term follow-up study using subjects form past studies and involves no treatment, the intention is to analyze data for all subjects enrolled. Thus, no further analysis sets will be required.

10.4.2. Control of Systematic Error/Bias

All subjects who have been evaluated for the inclusion/exclusion criteria and have signed the ICF will be eligible for enrollment in the study. Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving queries in the database.

10.4.3. Number of Subjects per Investigative Site

The intention is to enroll as many subjects as possible from the 3 preceding studies. The number of subjects enrolled for each site in the 3 previous studies is the upper limit for the number of subjects that will be enrolled in this study.

10.4.4. Data Analyses

Descriptive statistics will be presented for all ITT subjects. The mean (± standard deviation) will be used to describe continuous variables with a normal distribution and the median (and interquartile range) will be used to describe continuous variables with a skewed distribution. Frequency tables will be used to summarize discrete variables. Proportions of subjects with adverse events and SAEs will be reported.

Subjects will be analyzed in the following treatment groups:

- BT – subjects who were treated with BT during the AIR, RISA, or AIR2 studies,
- Control/sham – subjects who were treated as control or sham subjects during the AIR, RISA, or AIR2 studies and did not have BT treatment before the BT 10+ study visit, and
- Post-study BT – subjects who were treated as control or sham subjects during the AIR, RISA, or AIR2 studies and had BT treatment before the BT 10+ study visit.

10.4.5. Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early. Informal interim analysis may be conducted for the purpose of submissions of abstracts to major professional meetings.

10.4.6. Subgroup Analyses

There are no planned subgroup analyses.

10.4.7. Justification of Pooling

The analyses will be presented using data pooled across centers. If deemed appropriate, stratified and multivariate analysis techniques, including Chi-square test or logistic regression will be used to assess differences between study centers to justify pooling data across centers.

10.4.8. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analysis will be documented in an amended Statistical Analysis Plan. Changes from the planned statistical methods after performing the analysis will be documented in the clinical study report along with a reason for the deviation.

11. Data Management

11.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC System and will be issued to the site for appropriate response. Site staff will be responsible for resolving queries in the database.

11.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

11.3. *Core Laboratories*

This study requires of a core laboratory for repository and archiving of Volumetric HRCT scan. Appropriate certifications and documentation records are required to be maintained at the site for laboratory and/or vendors.

12. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

13. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

Deviations from the investigational plan, with the reason for the deviation, must be documented and reported to the sponsor using the EDC. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions will be put into place by the sponsor.

14. Device/Equipment Accountability

No device accountability is required for this study.

15. Compliance

15.1. *Statement of Compliance*

This Study will be conducted in accordance with ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. Collection of data in the Study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

15.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan/, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.

- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

15.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated, and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a site, the sub-investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

15.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the ICF will be IRB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

15.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

15.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

16. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, verification will be conducted to ensure that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

17. Potential Risks and Benefits

17.1. *Anticipated Adverse Events*

The following anticipated adverse events (AE) have been identified for this study as risks of the subject's asthma diagnosis. They are not expected to occur at an increased rate or severity due to the subject's participation in this clinical study.

- Severe asthma exacerbations
- Respiratory adverse events
- Potential device related AEs are described in the Alair DFU

17.2. *Risks associated with Participation in the Clinical Study*

The following tests are routinely performed as standard of care for people with asthma:

- 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.
- Volumetric HRCT scan: Study Subjects will have radiation exposure as a result of the Volumetric HRCT scans required. The doses of radiation used typically are so small that the risk of these procedures is difficult to measure.

17.3. *Risk Minimization Actions*

Additional currently unknown long-term risks of bronchial thermoplasty may exist. As this study does not include a bronchial thermoplasty procedure, additional risk from participation in the study is limited to those associated with the study's standard of care assessments (such as HRCT). Risks of standard of care follow-up assessments can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's

physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

Subjects will only be selected if they have participated on one of the previous BT studies.

17.4. *Anticipated Benefits*

There may not be any potential benefit from participating in this study. However, medical science and future subjects may benefit from your participation.

17.5. *Risk to Benefit Rationale*

As a ten-plus year follow-up evaluation of subject previously treated with BT under a separate protocol and separate consent. The only new risks with the trial are those associated with Volumetric HRCT scans and pulmonary function testing. The benefit of, for the first time, evaluating BT and SHAM or control subjects from prior BT studies is anticipated to provide beneficial information to the medical community that outweighs these risks.

18. Safety Reporting

18.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All respiratory Serious Adverse Events
- All fatal Serious Adverse Events
- All respiratory Adverse Events
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the adverse event term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, it should be submitted as an adverse event.

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE (see Table 17.2-1 for AE definitions).

18.2. *Definitions and Classifications*

Adverse event definitions are provided in Table 17.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155and MEDDEV 2.7/3 for clarification purposes.

Table 18.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or intentional abnormal use of the study medical device.

Table 18.2-1: Safety Definitions

Term	Definition
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

18.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study procedure.

Table 18.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Table 18.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

18.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 17.4-1.

Table 18.4-1: Investigator Reporting Requirements for SAEs, AEs and ADEs

Event Classification	Communication Method	Communication Timeline post-market studies** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Serious Adverse Event (respiratory and/or fatal)	Complete AE eCRF page with all available new and updated information.	• Within 10 business days after becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study.
	Provide all relevant source documentation (de-identified) for reported event.	• When documentation is available (recommend within 60 calendar days).

Table 18.4-1: Investigator Reporting Requirements for SAEs, AEs and ADEs

Event Classification	**Communication Method**	**Communication Timeline post-market studies**** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Adverse Event (respiratory)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the procedure.	• In a timely manner (e.g., recommend within 30 business days) after becoming aware of the information. • Reporting required through the end of the study.
Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the procedure.	• In a timely manner (e.g., recommend within 30 business days) after becoming aware of the information. • Reporting required through the end of the study.
	Provide all relevant source documentation (de-identified) for reported event.	
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 2 business days after becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study.
	Provide all relevant source documentation (de-identified) for reported event.	• In a timely manner (e.g., recommend within 30 business days) after becoming aware of the information. • Reporting required through the end of the study

18.5. *Boston Scientific Device Deficiencies*

Since this a 10+ year follow-up study, and there is no device used for this study, device deficiencies will not be collected.

18.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting adverse event information to all participating Principal Investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of SAEs as required by local/regional regulations.

19. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB/EC. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- Ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

20. Suspension or Termination

19.1 Premature Termination of the Study

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

19.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval

Any investigator, or associated IRB/ EC or regulatory authority may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

19.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities

to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

19.4 Criteria for Suspending/Terminating a Study Site

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

21. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The Co-lead investigators are the primary drivers of decisions regarding publication content, review, approval, and submission.

22. Reimbursement and Compensation for Subjects

22.1. *Subject Reimbursement*

There will be no subject compensation for participating in the post-approval study. Subjects can be reimbursed for moderate travel expenses.

22.2. *Compensation for Subject's Health Injury*

Boston Scientific Corporation will purchase an insurance policy to cover the cost of potential health injury for study subjects, and if required by applicable law.

23. Bibliography

1. Marks G, Pearce N, Strachan D, and Asher I. "The Global Burden of Disease Due to Asthma." In: The Global Asthma Report 2014. Auckland, New Zealand: Global Asthma Network, 2014. Pp. 16-21.
2. Chakir J, Haj-Salem I, Gras D, Joubert P, Beaudoin EL, Biardel S, Lampron N, Martel S, Chanez P, Boulet LP, Laviolette M. Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Collagen Deposition in Asthma. *Ann Am Thorac Soc* 2015; **12**: 1612-1618.
3. Pretolani M, Dombret MC, Thabut G, Knap D, Hamidi F, Debray MP, Taille C, Chanez P, Aubier M. Reduction of airway smooth muscle mass by bronchial thermoplasty in patients with severe asthma. *Am J Respir Crit Care Med* 2014; 190: 1452-1454.
4. Pretolani M, Dombret MC, Thabut G, Knap D, Hamidi F, Debray MP, Taille C, Chanez P, Aubier M. Reduction of airway smooth muscle mass by bronchial thermoplasty in patients with severe asthma. *Am J Respir Crit Care Med* 2014; 190: 1452-1454.
5. Pretolani M, Bergqvist A, Thabut G, Dombret MC, Knapp D, Hamidi F, Alavoine L, Taille C, Chanez P, Erjefalt JS, Aubier M. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: clinical and histopathological correlations. *J Allergy Clin Immunol* 2016.
6. Salem IH, Boulet LP, Biardel S, Lampron N, Martel S, Laviolette M, Chakir J. Long-Term Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Reticular Basement Membrane Thickness in Severe Asthma. *Ann Am Thorac Soc* 2016; 13: 1426-1428.
7. Denner DR, Doeing DC, Hogarth DK, Dugan K, Naureckas ET, White SR. Airway Inflammation after Bronchial Thermoplasty for Severe Asthma. *Ann Am Thorac Soc* 2015; 12: 1302-1309.
8. Dombret MC, Alagha K, Boulet LP, Brillet PY, Joos G, Laviolette M, Louis R, Rochat T, Soccal P, Aubier M, Chanez P. Bronchial thermoplasty: a new therapeutic option for the treatment of severe, uncontrolled asthma in adults. *Eur Respir Rev* 2014; 23: 510-518.
9. Castro M, Cox G. Asthma outcomes from bronchial thermoplasty in the AIR2 trial. *Am J Respir Crit Care Med* 2011; **184**: 743-744.
10. Castro M, Rubin A, Laviolette M, Hanania NA, Armstrong B, Cox G. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. *Ann Allergy Asthma Immunol* 2011; **107**: 65-70.
11. 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, Duhamel DR, McEvoy C, Barbers R, Ten Hacken NH, Wechsler ME, Holmes M, Phillips MJ, Erzurum S, Lunn W, Israel E, Jarjour N, Kraft M, Shargill NS, Quiring J, Berry SM, Cox G. 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.

12. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, Fiss E, Olivenstein R, Thomson NC, Niven RM, Pavord ID, Simoff M, Hales JB, McEvoy C, Slebos DJ, Holmes M, Phillips MJ, Erzurum SC, Hanania NA, Sumino K, Kraft M, Cox G, Sterman DH, Hogarth K, Kline JN, Mansur AH, Louie BE, Leeds WM, Barbers RG, Austin JH, Shargill NS, Quiring J, Armstrong B, Castro M. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol* 2013; **132**: 1295-1302.
13. Bicknell S, Chaudhuri R, Lee N, Shepherd M, Spears M, Pitman N, Cameron E, Cowan D, Nixon J, Thompson J, McSharry C, Thomson NC. Effectiveness of bronchial thermoplasty in severe asthma in 'real life' patients compared with those recruited to clinical trials in the same centre. *Ther Adv Respir Dis* 2015; **9**: 267-271.
14. Doeing DC, Mahajan AK, White SR, Naureckas ET, Krishnan JA, Hogarth DK. Safety and feasibility of bronchial thermoplasty in asthma patients with very severe fixed airflow obstruction: a case series. *J Asthma* 2013; **50**: 215-218.13. Castro M, Musani AI, Mayse ML, Shargill NS. Bronchial thermoplasty: a novel technique in the treatment of severe asthma. *Ther Adv Respir Dis* 2010; **4**: 101-116.
15. Dimakou K, Gousiou A, Toumbis M, Kaponi M, Chrysikos S, Thanos L, Triantafillidou C. Investigation of bronchiectasis in severe uncontrolled asthma. *Clinical Respiratory Journal* 2017; May 24. doi: 10.1111/crj.12653. [Epub ahead of print]. PMID: 28544140
16. Luján M, Gallardo X, Amengual MJ, Bosque M, Mirapeix RM, Domingo C. Prevalence of bronchiectasis in asthma according to oral steroid requirement: influence of immunoglobulin levels. *Biomedical Research International* 2013; 2013:109219. doi: 10.1155/2013/109219. Epub 2013 Nov 13.
17. Ozis T, Turktas H. The Impact of Bronchiectasis in Clinical Presentation of Asthma. *Southern Medical Journal* 2007; **100:** 468-471.
18. Robert J. Mason, V. Courtney Broaddus, Thomas R Martin, Talmadge E King, Dean Schraufnagel, John F. Murray, and Jay A. Nadel. Murray and Nadel's Textbook of Respiratory Medicine, 5th Edition. Published by Elsevier Health Sciences (Amsterdam, The Netherlands). 2010.
19. Prickman LE, Moersch HJ. Bronchostenosis complicating allergic and infectious asthma. *Annals of Internal Medicine* 1940; 14(3): 387-392.
20. NHLBI.NIH.gov **Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma – Summary Report 2007. https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/summary-report-2007. Accessed March 22, 2017**

24. Abbreviations and Definitions

24.1. *Abbreviations*

Abbreviations are shown in Table 23.1-1

Table 23.1-1: Abbreviations

Abbreviation/Acronym	Term
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADE	Adverse Device Effects
AIR	Randomized Clinical Trial of the Alair® System for the Bronchial Thermoplasty Treatment of Asthma
AIR2	Safety and Effectiveness of the Alair® System for the Treatment of Asthma: A Multicenter Randomized Clinical Trial (Asthma Intervention Research (AIR2) Trial)
AQLQ	Asthma Quality of Life Questionnaire
AE	Adverse Event
ASM	Airway Smooth Muscle
BSC	Boston Scientific Corp.
BT	Bronchial Thermoplasty
CRF (eCRF)	Case Report Form (electronic Case Report Form)
DFU	Directions for Use
ER	Emergency Room
FEV_1	Forced Expiratory Volume in 1 second: FEV_1 (pre- and post-bronchodilator)
GCP	Good Clinical Practice
HRCT	High Resolution Computed Tomography Scan
ICH	International Council for Harmonization
ICS	Inhaled Corticosteroids
LABA	Long Acting Beta Agonist
PEF	Peak Expiratory Flow
RF	Radio Frequency
RISA	Multicenter Randomized Clinical Trial of Bronchial Thermoplasty with the Alair™ System for the Treatment of Severe Asthma
SADE	Serious Adverse Device Effects
SAE	Serious Adverse Events

24.2. *Definitions*

Terms are defined in Table 23.2-1.

Table 23.2-1: Definitions

Term	Definition
Bronchiectasis	Bronchiectasis is defined by dilation, or ectasia of the airways of the bronchus.
Bronchostenosis	Bronchostenosis is a definite, localized, stricture-like narrowing of a bronchus

Table 23.2-1: Definitions

Term	Definition
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.
Severe Asthma Exacerbation	Severe asthma exacerbation is defined as worsening of asthma symptoms requiring use of systemic corticosteroids (tablets, suspension, or injection) (NAEPP Guidelines, 2007). For subjects already routinely taking systemic corticosteroids, a severe asthma exacerbation is defined as a worsening of asthma symptoms requiring any increase in daily dose of systemic corticosteroids. Note: Short term prophylactic increases in dose around the time of the treatment procedures will not be considered severe asthma exacerbations in the absence of worsening symptoms. For consistency, courses of systemic corticosteroids in excess of baseline separated by 1 week or more will be treated as separate severe asthma exacerbations. All asthma exacerbations (worsening of asthma symptoms) should be recorded as respiratory adverse events termed "asthma aggravated." Asthma exacerbations associated with increases in steroid use as described above will be counted as severe asthma exacerbations.
Severity of Adverse Events	**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 Physician will determine both the intensity of the adverse event and the event's relationship to BT treatment.
Source Data (ISO 14155:2011)	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.
Source Document (ISO 14155:2011)	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.

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25.Appendices

A. 24.1 Asthma Quality of Life Questionnaire (AQLQ) score

B. 24.2 Asthma Control Questionnaire

C. 24.3 Asthma Control Test (ACT) score

D. 24.4 Subject Satisfaction Survey

E. 24.5 Subject EQ5D Questionnaire

Appendix A

Asthma Quality of Life Questionnaire (AQLQ) score

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)

PATIENT ID — — — — — — — — —

SELF-ADMINISTERED

DATE _____

Please complete all questions by circling the number that best describes how you have been during the last 2 weeks as a result of your asthma.

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS IN THESE ACTIVITIES AS A RESULT OF YOUR ASTHMA?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES (tasks you have to do at work*)	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH DISCOMFORT OR DISTRESS HAVE YOU FELT DURING THE LAST 2 WEEKS?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S} PATIENT ID _____

SELF-ADMINISTERED DATE _____

IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH DISCOMFORT OR DISTRESS HAVE YOUR FELT DURING THE LAST 2 WEEKS?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

IN GENERAL HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?		2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?

	Most Not Done		Several Not Done		Very Few Not Done		No Limitation
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)

PATIENT ID — — — — — — — — —

SELF-ADMINISTERED

DATE _____

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVIT!ES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6,8, 10, 12, 14, 16, 18,20,22, 24,29, 30
Activity limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

Appendix B

Asthma Control Questionnaire

ASTHMA CONTROL QUESTIONNAIRE ©

PATIENT ID — — — — — — — —

DATE _____

Page 1 of 2

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you woken by your asthma during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how limited were you in your daily activities because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much shortness of breath did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

ASTHMA CONTROL QUESTIONNAIRE ©

PATIENT ID _____

DATE _____

Page 2

5.	In general, during the past week, how much of the time did you wheeze?	0 1 2 3 4 5 6	Not at all Hardly any of the time A little of the time A moderate amount of the time A lot of the time Most of the time All the time
6.	On average, during the past week, how many puffs/inhalations of short- acting bronchodilator (eg. Ventolin/ Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0 1 2 3 4 5 6	None 1 - 2 puffs/inhalations most days 3 - 4 puffs/inhalations most days 5 - 8 puffs/inhalations most days 9 - 12 puffs/inhalations most days 13 - 16 puffs/inhalations most days More than16 puffs/inhalations most days

To be completed by a member of the clinic staff

7.	FEV_1 pre-bronchodilator: . . . . . . FEV_1 predicted: . . . . . . FEV_1 % predicted: . . . . . . (Record actual values on the dotted Lines and score the FEV_1 % predicted in the next column)	0 1 2 3 4 5 6	> 95 % predicted 95- 90% 89- 80% 79- 70% 69- 60% 59- 50% < 50% predicted

Appendix C

Asthma Control Test (ACT) score

Asthma Control Test™

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an ☒ in the one box that best describes your answer.

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐1	☐2	☐3	☐4	☐5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, or Maxair®)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
☐1	☐2	☐3	☐4	☐5

5. How would you rate your asthma control during the past 4 weeks?

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐1	☐2	☐3	☐4	☐5

Appendix D

Subject Satisfaction Survey

Would subject undergo the Bronchial Thermoplasty procedure if he/she had to do it all over again?

☐ Yes ☐ No

Would subject recommend this treatment to a friend or family member?

☐ Yes ☐ No

Appendix E

Subject EQ5D Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility

- ☐ I have no problems in walking about
- ☐ I have slight problems in walking about
- ☐ I have moderate problems in walking about
- ☐ I have severe problems in walking about
- ☐ I am unable to walk about

Self-Care

- ☐ I have no problems washing or dressing myself
- ☐ I have slight problems washing or dressing myself
- ☐ I have moderate problems washing or dressing myself
- ☐ I have severe problems washing or dressing myself
- ☐ I am unable to wash or dress myself

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

- ☐ I have no problems doing my usual activities
- ☐ I have slight problems doing my usual activities
- ☐ I have moderate problems doing my usual activities
- ☐ I have severe problems doing my usual activities
- ☐ I am unable to do my usual activities

Pain/Discomfort

- ☐ I have no pain or discomfort
- ☐ I have slight pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have severe pain or discomfort
- ☐ I have extreme pain or discomfort

Anxiety/Depression

- ☐ I am not anxious or depressed
- ☐ I am slightly anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am severely anxious or depressed
- ☐ I am extremely anxious or depressed

We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY= ☐☐☐