Washington State Health Care Authority

Health Technology Assessment

Bronchial Thermoplasty for Asthma

Draft Key Questions: Comment & Response

November 19, 2015

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Bronchial Thermoplasty for Asthma

Response to Public Comments on Topic Selection and Draft Key Questions

November 19, 2015

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Response to Public Comments, Topic and Key Questions

Bronchial Thermoplasty for Asthma

Hayes, Inc. is an independent vendor contracted to produce evidence assessment reports for the WA HTA program. For transparency, all comments received during the comments process are included in this response document.

Draft key questions for each WA HTA report are posted online in order to gather public input and any additional evidence to be considered in the evidence review. Since key questions guide the evidence report, WA HTA seeks input on whether the questions are appropriate to address its mandate to gather evidence on safety, efficacy, and cost-effectiveness relevant to coverage determinations. Input about the following is especially helpful:

- Are appropriate populations or indications identified?
- Are appropriate comparators identified?
- Are appropriate patient-oriented outcome measures included?
- Are there special policy or clinical considerations that could affect the review?

Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only. When comments cited evidence, the vendor was encouraged to consider inclusion of this evidence in the report.

This document responds to comments from the following parties:

Topic selection:

- Kelly Shriner (Boston Scientific)
- Rizwana Khan (Multicare Health System, Good Samaritan Hospital)
- Navdeep Rai, M.D., FACP, FCCP (Pulmonary Consultants)
- Catherine Richardson, M.D. (Bronchial Thermoplasty Patient)
- Jiten D. Patel, M.D.
- Jordan Fein, M.D. (Legacy Medical Group)
- Christina Van Wallendael (Boston Scientific)

Key Questions:

- Maria B. Stewart (Boston Scientific)

Table 1 provides a summary of comments with responses.

Table 1. Public Comments on Topic and Key Questions, *Bronchial Thermoplasty for Asthma*

Comment and Source	Response
Comments on Topic	
January 20, 2015 e-mail from Kelly Shriner (Boston Scientific)	
"Thank you for your time earlier today explaining the Washington HTA program. I just want to reiterate the fact that we support the review of bronchial thermoplasty in this process, and hope that a decision is made to proceed with the assessment. I understand there will be an opportunity in the future to provide more information for this review, but I thought I would send a list of the publications on BT in the last 5 years as reference, for your decision of whether or not to conduct this assessment. Please note the recent cost effectiveness paper (Cangelosi et al), in addition to 5 year follow-up in 3 studies (Wechsler, Pavord and Thomson). Finally, you may be interested in knowing that both Healthcare Services Corporation (BCBS TX, IL, OK, NM and MT) and Carefirst BCBS have recently decided to cover BT." Several articles were cited.	Thank you for your comments and for the links to several publications regarding bronchial thermoplasty. The references will be considered for inclusion in the report.
March 3, 2015 e-mail from Rizwana Khan (Multicare Health System, Good Samaritan Hospital)	
"I am a practicing pulmonologist at Multicare - Good Samaritan Hospital. I joined this group in September 2014. Prior to this, I was a practicing pulmonologist at the Lung and Asthma Center of Central WA. I worked there for 5 years. I was introduced to and was very excited about bronchial thermoplasty in 2012. Our group in central WA acquired the equipment and training necessary and between 2012 and 1014, I performed approximately 5 of these procedures on severe persistent asthmatic patients. The results were phenomenal. My patients' asthma exacerbation severity and frequency improved tremendously and they were all thrilled with the results. My only concerns about the procedure are that it is very cumbersome to get insurance approval and we are not able to offer this treatment to so many deserving patients who would benefit tremendously. I believe this would have greatest impact on the younger asthmatics most of whom usually have Medicaid or lack insurance altogether."	Thank you for your comments. We will consider your comment regarding the potential utility of bronchial thermoplasty in younger patients when assessing the impact of patient characteristics on efficacy and safety of the procedure.
March 7, 2015 e-mail from Navdeep Rai, M.D., FACP, FCCP (Pulmonary Consultants)	
"I am a practicing pulmonologist with 21 years of experience, including extensive interventional bronchoscopy. I suspect you have all the literature you need, but I would like to share my experience	Thank you for your comments. We will consider both the short-term and long-

Comment and Source	Response
with this procedure. I have treated 12 pts with bronchial thermoplasty (BT). Eight were through a clinical trial sponsored by the manufacturer, three were with insurance, and one was a cash paying patient. While in the short term patients do experience some exacerbation of asthma, the long term results have been outstanding. Each of these patients was able to reduce their need for medication with dramatic improvement in quality of life. One patient never left her house without a high efficiency face mask. Now she no longer needs the mask and rarely requires use of rescue medicine. To the best of my knowledge all have reduced exacerbation and reduced urgent office/ER visits. I would request your support in further expanding access to this treatment for patients with severe persistent asthma. I would be happy to discuss this further with you."	term effects of bronchial thermoplasty in our assessment.
March 9, 2015 e-mail from Catherine Richardson, M.D. (Bronchial Thermoplasty Patient)	
"I have been asked by Pulmonologist Navdeep Rai, MD to write concerning my experience with Bronchial Thermoplasty. To give you some brief background, I have had asthma for many years, manifested mainly by a persistent hacking cough that was difficult to treat. It became worse and worse over the years, finally requiring medications up to and including subcu Xolair every two weeks. It kept me awake at night for hours on end, unable to sleep due to the cough. Everyone around me knew when I was coming around the corner because they could hear my cough. It was also exacerbated by chemicals, and as I am also a physician, it interfered with work. Breathing in the ubiquitous hand sanitizers could set off a 2 hour long coughing fit. I knew when Dr. Rai started doing thermoplasties, but had some reservations. I looked into it, but kept putting it off until my situation was essentially untenable. Finally after several bouts of pneumonia and the onset of steroid myopathy, (such that I could barely walk up stairs or stand up from a sitting position) I agreed to go ahead. We had a large amount of difficulty getting the procedure approved by Regence. Finally after four months, the last appeal reached a pulmonary physician who understood, and this forced them to pay the approximately $15,000 the 3 total procedures cost. I was very lucky in this respect. The procedures were not difficult, but as predicted I did have a few days of discomfort and shortness of breath after each. The last was in December of 2013. It took a few months after that for me to realize how much better I had gradually become. I no longer have horrible asthma exacerbations with every little hint of an upper respiratory infection. I have not had any need for steroids. We started weaning medications. It has been over 5 months since I had the last Xolair. I have stopped	Thank you for your comments.

Comment and Source	Response
supplemental inhaled steroids, although I still use Advair. I rarely need inhaled bronchodilators to control symptoms. I have stopped using montelukast recently, and have tolerated that. I can sleep without having to take cough suppressants or something such as ambien just to be able to sleep at night. To say the procedure has changed my life is an understatement. I can travel again without being worried about getting back in time for the next xolair injection. I can sleep again without medications. As above, I am weaning off most of the medications which I was dependent on. Most of all, as far as the health insurance industry is concerned, they no longer need to bear the expense of several thousand dollars a month just for the xolair, and I do not have to pay the high copays that went along with it. I assume that this study is being done to try and bring the various health insurers in the state into being consistent with whether this procedure is paid for. I cannot speak for others, as I have never been in touch with anyone else who has had it done, but I believe it is has been highly successful for me, with minimal risk. I would recommend it for anyone with refractory asthma. If you have any questions for me, please do not hesitate to contact me."	
E-mail from Jiten D. Patel, M.D.	
"I am writing a summary of my patients experience and outcomes with Bronchial Thermoplasty (BT). To date, I have completed the most BT's in Washington's Inland Northwest. I am providing a descriptive overview of my clinic outcomes following treatment with Bronchial Thermoplasty. My 2.5 years of experience with this salvage/heroic therapy has been very successful. For the sake of transparency, I have discharged one patient for medical noncompliance, (after 1.2 years follow- -up) and have had one patient demise unrelated to Asthma or the treatment with BT (natural death). 1 patient was denied BT despite insurance coverage due to clinic no---shows (surrogate of poor compliance). In addition, I have no financial relationship with the BT proprietor or Boston Scientific. All patients treated had completed a thorough pre--evaluation including history, review of outside records, physical examination and diagnostic workup that would include an IgE level, limited RAST, pre/post treatment pulmonary function testing and an imaging study (CT chest or CXR, pending symptom complex). All were non--- smokers and greater than 40 years of age. In addition, patients were managed with standard of care per NAEPP guidelines with step up therapy with a minimum of	Thank you for your comments.

Comment and Source	Response
a Leukotriene inhibitor, high dose inhaled corticosteroid in combination with a long acting beta agonist. Salvage/heroic therapy included 2 patients on methotrexate, 3 on theophylline for greater than 2 years, 1 with history of gold treatments and 2 patients with Xolair (Omalizumab) infusions (twice monthly for > 1 year). In general, prior to treatment daily symptoms required rescue therapy in ALL patients > 5-8/daily, had been on chronic prednisone therapy or had at minimum 3 courses of high doses steroids in 12 months or 2 bursts in 6 months. All reported nocturnal awakening > 3 X week and had a health care encounter related to asthma symptoms at minimum 1-2 X monthly in the preceding period. Flow patterns remained obstructive per ATS criteria and varied from mild to very severe obstructive patterns and accordingly, had a preserved or supra---normal DLCO uncorrected for hemoglobin. Median ACT scores were < 12. 32% of my patients had been intubated within 10 years prior to clinic encounter that was related to an asthma exacerbation. 52% of patients had atopic asthma. The Post BT treatment(s) period encompassed 3 outpatient therapeutic visits with a moderate sedation and clinic re---evaluations at 3, 6, 9 and 12 months. Firstly, there were NO complications to be reported including pneumothoraxes, pulmonary hemorrhage, respiratory failure, and further No hospitalizations. Obstructive flow patterns remained similar to pre---treatment evaluation (< 10% variability), but symptoms dramatically improved measured by ACT scores. ACT scores at 3 & 6 months post treatment > 16. All patients reported feeling better daily with less shortness of breath, cough and wheeze and need for rescue therapy. 1 patient was hospitalized at month 4 for an asthma exacerbation related to Influenza A infection. 1 patient had > 3 ER/Urgent care visits after month 9 related to nocturnal cough, wheeze and subsequent dyspnea (this patient was later found to have severe erosive esophagitis). No patients were hospitalized with---in 12 months post treatment follow---up. 30% of patients had reported prednisone burst(s) after 9 months. All atopic---asthmatic patients suffered from concurrent postnasal drip and/or allergic rhinitis. ALL patients remained compliant with anti---reflux medications post treatment up to 12 months. 1 patient remains resistant psychologically to discontinuing theophylline (1/3 patients). 2 cohort patients on Methotrexate remain off and later Xolair patients have discontinued infusions.	

Comment and Source	Response
Conclusions: 1. Severe Asthma is a very heterogeneous disease 2. BT should only be utilized for heroic/salvage therapy in select compliant patients. 3. Silent reflux and Post---nasal drip/allergic rhinitis are significant confounders to asthma control. 4. BT is very favorable therapeutic option for a severe asthmatic only. 5. Only select centers and a trained pulmonologist with adequate resources and RN support should offer BT. 6. Potential BT patients must go through a meticulous screening process. 7. BT is not a cure for asthma, but significantly reduces daily/monthly/seasonal undulations in asthma symptoms complex. 8. By nature of reduced clinical encounter(s) through the emergency room and/or urgent care respectably reduce costs to the patient and their insurance and co---payments incurred with Asthma exacerbations. 9. Patients with history of non---compliance are NOT good candidates for BT. 10. BT has been very effective for severely asthmatic patients who have had present day unorthodox salvage therapies including methotrexate, theophylline and GOLD treatments. **11.** 11. BT is not to be used as a preventative therapeutic modality i.e. intermittent, mild, or a moderate patient asthmatic population."	
March 12, 2015 e-mail from Jordan Fein, M.D. (Legacy Medical Group)	
"I am a pulmonologist who treats patients with Bronchial Thermoplasty for uncontrolled severe persistent asthma that has not responded to medical therapy. The referrals I receive from pulmonologists and allergists throughout Washington and Oregon are to evaluate and treat patients with asthma so severe that no other treatment options exist; this subgroup of asthmatics in which "everything has been tried." The overwhelming majority of these patients is on daily systemic corticosteroids, and has repeated emergency department visits and hospitalizations for asthma exacerbations. I have successfully treated 21 patients in the past 3 years. Our patient outcomes data are similar to those of the AIR2 trial that gained FDA approval of the medical device. Following Bronchial Thermoplasty treatment we see significant reduction in exacerbations requiring emergency department visits and hospitalization. Most patients are able to discontinue systemic corticosteroid use and have improved quality of life. The procedure is safe and efficacious, and for some asthmatics the only hope for regaining control over their disease. Bronchial Thermoplasty is	Thank you for your comments.

Comment and Source	Response
covered by many private insurers, Medicare, and Oregon Medicaid. I strongly urge the Washington State Health Care Authority to make this procedure available to patients in WA as well. I welcome any questions about the procedure or our outcomes."	
March 11, 2015 e-mail from Christina Van Wallendael (Boston Scientific)	
"Boston Scientific Corporation appreciates the opportunity to provide comments and data in anticipation of the WA-HCA technology review of Bronchial Thermoplasty. BT is an innovative procedure for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-lasting beta2-agonists. This treatment has been shown to significantly reduce healthcare utilization, presenting an opportunity to improve patient outcomes and quality of life while reducing overall health care costs. BT has been shown to be a safe, effective, and long-lasting treatment option for a well-defined population of adults. Attached, please find a clinical dossier that provides an overview of the current clinical evidence on BT. This document summarized the clinical findings on BT, including long-term safety and effectiveness out to 5 years post-procedure, and it also provides direct links to the published literature. In addition, the following publication addresses the cost-effectiveness of BT from the commercial payer perspective. This one-time treatment quickly becomes cost-effective as cost offsets accrue annually without the need for re-treatment, demonstrated by persistent reduction in health care utilization over time: Cangelosi et al. Cost-effectiveness of bronchial thermoplasty in commercially-insured patients with poorly controlled, severe, persistent asthma. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15(2):357-364. We noted that the proposed title of the Director Selection is "BT in Asthma." BT is specifically indicated for patients who have severe persistent asthma and who remain not well controlled on inhaled corticosteroids and long acting beta agonists (i.e., step 5 or 6 of the NAEPP guidelines). Therefore we would like to respectfully ask that: 1) The scope of the assessment be limited to the use of this procedure in patients with severe persistent asthma (as indicated); and 2) The title of the assessment be revised to read, "BT in Severe Asthma.""	Thank you for your comments and for the review of clinical evidence. We have noted your suggestion regarding limiting the scope to only patients with severe asthma. Because some of the notable available literature enrolled patients that had moderate as well as severe asthma (e.g., Cox et al., 2007), we have extended the scope to include moderate as well as severe asthma. We will consider your comment regarding the severity of asthma and FDA indication when assessing the impact of patient characteristics on efficacy and safety of the procedure.

Comment and Source	Response
An overview of clinical evidence was provided.	
Comments on Draft Key Questions	
November 3, 2015 e-mail from Maria B. Stewart (Boston Scientific)	
"Boston Scientific Corporation appreciates the opportunity to provide comments and responses to the questions posed in the Washington State Health Care Authority's technology assessment of bronchial thermoplasty. Bronchial thermoplasty is an innovative procedure for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting beta2-agonists. This treatment has been shown to significantly reduce healthcare utilization, presenting an opportunity to improve patient outcomes and quality of life while reducing overall health care costs. Bronchial thermoplasty has been shown to be a safe, effective, and long-lasting treatment option for a well-defined population of adults. The comments contained in this letter are intended to address the following questions posed by the Washington State Health Care Authority: 1. What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma? a. Is there clinically meaningful improvement for patients with severe asthma? 2. What are the harms associated with bronchial thermoplasty? 3. Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)? 4. What are the cost implications and cost-effectiveness of bronchial thermoplasty? **Comments regarding clinical background:** Before addressing the key questions detailed by the Health Care Authority, Boston Scientific respectfully requests that the final technology assessment for bronchial thermoplasty be updated to reflect a more accurate description of the procedure, the devices used, and the intended result of the procedure. In its draft Key Questions and Background document for bronchial thermoplasty, the Washington State Health Care Authority states that, *"Bronchial thermoplasty is designed to weaken and partially destroy the smooth muscle that*	Thank you for your comments. We have modified the medical background to more precisely describe the procedure and mechanism of action.

Comment and Source	Response
constricts the airway during asthma attacks." While bronchial thermoplasty is intended to reduce the amount of airway smooth muscle and subsequent muscle-mediated bronchoconstriction, it does not "weaken" the smooth muscle but rather targets and partially eliminates airway smooth muscle. (Please refer to Appendix A for a more detailed discussion of airway responsiveness and airway smooth muscle changes resulting from bronchial thermoplasty as observed out to three years). The Draft Key Questions and Background document goes on to state, *"This procedure relies on a catheter that has an expandable array of electrodes and that has a fiber optic camera, which allows the physician to see inside the lung. After the catheter is threaded into the airway, a wire leading out of the back end of the catheter is attached to a radiofrequency generator and a lever is operated that causes the electrodes to curl into a ball shape around the front end of the catheter. The curved electrodes are held against the bronchial walls and an electrical current is applied to generate heat that destroys the smooth muscle underneath the lining of the bronchial passages."* In actuality, during bronchial thermoplasty, the physician introduces a standard flexible bronchoscope through a patient's nose or mouth, and into the airways of the lung. The bronchoscope, rather than the Alair™ Catheter, facilitates visualization of the airways. There is no fiber optic camera on the Alair Catheter, which is delivered into the airways through the working channel of the bronchoscope. Once the catheter's electrode array has been expanded to come in contact with and fit snugly against the airway wall, the physician activates the catheter to deliver controlled thermal energy from the radiofrequency controller. This controller uses specific safety algorithms, for a maximum of 10 seconds, to heat the airway smooth muscle and cause remodeling resulting in partial loss of airway smooth muscle function and improved asthma control. We appreciate the Washington State Health Care Authority's willingness to consider this more accurate description of the bronchial thermoplasty procedure in its final technology assessment.	

Comment and Source	Response
Comments on Key Question 1: *What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma?* "Clinical effectiveness of bronchial thermoplasty has been demonstrated in several randomized clinical trials, including RISA [1], AIR [2], and AIR2 [3]. The pivotal trial, AIR2, was a randomized, sham controlled, double-blind trial comparing bronchial thermoplasty to a sham procedure (e.g. the medical device analogue to a placebo-controlled trial). In this trial, bronchial thermoplasty was shown to be superior to the sham with regards to the improvement in the integrated AQLQ score relative to baseline (bronchial thermoplasty, 1.35±1.10; sham, 1.16±1.23 (PPS, 96.0% ITT and 97.9% per protocol)). Furthermore there was a statistically significantly greater percentage of bronchial thermoplasty subjects compared to sham that achieved a clinically meaningful improvement in their quality of life, as measured by the improvement of the AQLQ score of equal to or greater than 0.5 (the minimal clinical important difference [MCID] for this tool) (79% percent of bronchial thermoplasty and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (PPS, 99.6%)). Moreover, compared to the sham group, bronchial thermoplasty was associated with significant reductions in asthma-related healthcare utilization events with an 84% reduction in ER/ED visits for respiratory events within the post-treatment period compared to sham (PPS = 99.9%). There was a 32 % reduction in severe exacerbations compared to the sham group (PPS 95.5%) and a 66% reduction in the days lost from school, work or other daily activities due to asthma (1.135 ± 0.361 vs. 3.915 ± 1.553, PPS=99.3%). These are all meaningful and important measures of asthma control in patients with severe persistent asthma. The durability of effectiveness of bronchial thermoplasty has been demonstrated out to 5years, as detailed in the post-approval AIR2 Trial Extension Study [4]. This study was conducted to evaluate the durability of effectiveness of bronchial thermoplasty beyond one year and the long-term safety of the procedure out to 5 years post-treatment in bronchial thermoplasty-treated subjects from the AIR2 Trial. The AIR2 Trial demonstrated that compared to the Sham group, fewer subjects in the bronchial thermoplasty group had severe exacerbations in the year following bronchial thermoplasty. The AIR2 Extension Study used a non-inferiority design to show that the proportion of	Thank you for your comments. The references cited will be considered for inclusion in the report.

Comment and Source	Response
subjects in the bronchial thermoplasty group experiencing severe exacerbations in subsequent years (years 2 to 5) does not worsen, when compared with the proportion of subjects experiencing severe exacerbations for the first year. Subject retention was very high for a study of this complexity and lengthy follow-up with 162 of the 190 subjects (85%) who underwent bronchial thermoplasty treatment in the AIR2 Trial having fully completed the 5-year follow-up. While the main purpose of this study was to assess long term (5-year) durability of clinical effectiveness and demonstrate similar long-term safety in a cohort of subjects who underwent bronchial thermoplasty, a limitation of this study is the lack of sham-control group beyond one year. Collecting meaningful 5-year study data without confounding would have required maintaining the study blind for the entire 5-year period in both groups and this was felt to be unethical in this study population. Maintaining sham subjects in the follow-up study after breaking the blind and requiring them to continue the same treatment regimen despite poor control was deemed similarly unethical and impractical – likely resulting in poor subject retention and leading to further difficulty in study result interpretation. Because of these concerns, the sham group exited the study at the end of the first year and was not followed in the long-term extension study. Key Findings from the AIR2 5-Year Follow-Up Study Included: • The proportion of bronchial thermoplasty-treated subjects experiencing severe exacerbations in Year 1 after bronchial thermoplasty (N.B. demonstrated statistically less – superior – than Sham within Year 1) was maintained out to 5 years. o The upper 95% confidence limit of the difference in proportions in each year minus Year 1 remained below the pre-specified non-inferiority margin of 20%. • Compared to the 12 months prior to bronchial thermoplasty treatment, the following results were observed: o 44% average decrease over 5 years in proportion of bronchial thermoplasty-treated subjects having severe exacerbations o 48% average decrease over 5 years in severe exacerbation event rates (events/subject/year) o 78% average decrease over 5 years in bronchial thermoplasty-treated subjects	

Comment and Source	Response
having ER visits o 88% average decrease over 5 years in ER visit event rates (events/subject/year) • Reduction in the proportion of bronchial thermoplasty-treated subjects having emergency room (ER) visits for respiratory symptoms seen in Year 1 after bronchial thermoplasty (N.B. demonstrated statistically less – superior – than Sham within Year 1) was maintained out to 5 years. • No increase in hospitalizations, general respiratory adverse events or asthma symptoms over the course of 5 years post-bronchial thermoplasty. • No clinically significant change in FEV1 over 5 years. • At 5 years post-bronchial thermoplasty a post net-beneficial reduction in inhaled corticosteroid (ICS) dose was observed. 28% of subjects reduced their daily ICS dose by 50% or more compared to 5% of subjects who increased their daily ICS dose by 50% or more. o Average 18% reduction in daily ICS dose • Comparison of HRCT images at Baseline and at 5 years post-bronchial thermoplasty showed no structural changes in the airways due to bronchial thermoplasty that were of clinical significance. In the earlier AIR randomized clinical study and the associated AIR extension study [5, 6], bronchial thermoplasty was compared to a standard of care control group. The AIR Trial demonstrated that the mean rate of mild exacerbations, as compared with baseline, was reduced in the bronchial thermoplasty group but was unchanged in the control group (change in frequency per subject per week, –0.16±0.37 (improvement) vs. 0.04±0.29 (worsening); P=0.005). At 12 months, there were significantly greater improvements in the bronchial thermoplasty group than in the control group in the morning peak expiratory flow (39.3±48.7 vs. 8.5±44.2 liters per minute), scores on the AQLQ (1.3±1.0 vs. 0.6±1.1) and ACQ (reduction, 1.2±1.0 vs. 0.5±1.0), the percentage of symptom-free days (40.6±39.7 vs. 17.0±37.9), and symptom scores (reduction, 1.9±2.1 vs. 0.7±2.5) while fewer puffs of rescue medication were required. Similar results were observed within the Research in Severe Asthma (RISA) study and RISA extension study, which examined a cohort of patients that could be considered more severe than the then	

Comment and Source	Response
contemporaneous AIR Trial [7, 8]. Within RISA, it was observed that bronchial thermoplasty was associated with a significant improvement versus control in rescue medication use (22.6 ± 40.1 vs. -1.5 ± 11.7 puffs per week p<0.05), prebronchodilator FEV1% predicted (14.9 ± 17.4 vs. –0.94 ± 22.3%, P = 0.04), and Asthma Control Questionnaire (ACQ) scores (- 1.04 ± 1.03 vs. - 0.13 ± 1.00, P = 0.02). Improvements in rescue medication use and ACQ scores remained significantly different from those of controls at 52 weeks. Based on the available data from these RCTs, bronchial thermoplasty is now included in several recent severe asthma treatment guidelines as an add-on therapy for the effective clinical management of patients with severe asthma who are poorly controlled despite being on optimal doses of inhaled corticosteroids and long-acting beta agonists, including the British Thoracic Society (bronchial thermoplasty) [9], the Global Initiative for Asthma (GINA) [10]. The earlier European Respiratory Society (ERS) / American Respiratory Society (ATS) guidelines for the management of severe asthma, which were published in 2013 [11] and did not consider the five year follow-up data described above recommended the use bronchial thermoplasty in IRB approved settings, however more recent guidelines have superseded these recommendations, including the 2014 GINA guidelines and the guidelines published by the Assembly on Interventional Pulmonology of the South African Thoracic Society [12]. Key professional specialty societies and patient advocacy groups including the American College of Chest Physicians (ACCP - CHEST) and the American College of Allergy, Asthma, and Immunology (ACAAI) have also published position statements supporting bronchial thermoplasty as a treatment option based on their conclusion that scientific literature supports bronchial thermoplasty as a therapeutic consideration for some carefully chosen patients with severe asthma (see list and links below): • American College of Asthma, Allergy and Immunology (ACAAI): http://college.acaai.org/Pages/Statement_on_Bronchial_Thermoplasty.aspx • American College of Chest Physicians (CHEST): http://www.chestnet.org/Guidelines-and-Resources/Health-Policy/Position-Papers • Asthma & Allergy Foundation of America (AAFA): http://www.aafa.org/display.cfm?id=8&sub=104&cont=864	

Comment and Source	Response
• INTERASMA (Global Asthma Association): http://www.interasma.org/images/manifesto3.pdf • Allergy & Asthma Network (AAN): http://www.allergyasthmanetwork.org/education/asthma/treatment-and-medications/bronchial-thermoplasty/ Finally, in 2011, the California Technology Assessment Forum (CTAF) reviewed bronchial thermoplasty and concluded that all 5 criteria were met in support of the safety, efficacy and long-term positive health outcomes of bronchial thermoplasty in patients 18 years or older with severe asthma [13]. The CTAF assessment stated, "It is recommended that use of bronchial thermoplasty for the treatment of severe, refractory asthma meets CTAF TA Criterion 1 through 5 for safety, effectiveness and improvement in net health outcomes." The ATS testified in support of this conclusion on October 19, 2011."	
Comments on Key Question 1a: *Is there clinically meaningful improvement for patients with severe asthma?* "Yes. In the AIR2 trial, the proportion of patients with a clinically meaningfully difference in their AQLQ (an asthma-specific quality of life metric) was statistically significantly more likely to be improved compared to sham. This improvement relative to sham suggests meaningful clinical benefit of bronchial thermoplasty. For example, a statistically significantly greater percentage of bronchial thermoplasty subjects compared to sham showed clinically meaningful improvement in their quality of life, as measured by the AQLQ (79% percent of bronchial thermoplasty and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (PPS, 99.6%)). This improvement in asthma control is echoed in the healthcare utilization differences between those subjects within the AIR2 trial treated with bronchial thermoplasty, compared to those treated with sham procedures. Within AIR2, there was observed an 84% reduction in ER/ED visits for respiratory events within the post-treatment period compared to sham (PPS = 99.9%). In addition, a 32% reduction in severe exacerbations was observed relative to those exacerbations observed in the sham group (PPS 95.5%). According to Elizabeth Juniper, MSCP, MSc, the developer of the AQLQ instrument, in a memo discussing the interpretation of AQLQ in the AIR2 trial [Appendix B], "Based on published literature	Thank you for your comments. The references cited will be considered for inclusion in the report.

Comment and Source	Response
to date, I am not aware of any other therapy for severe asthma that has demonstrated this degree of clinically meaningful benefit between groups (measured by the proportion of patients benefiting from the treatment) as compared to optimal standard of care."	
Comments on Key Question 2: What are the harms associated with bronchial thermoplasty? "Bronchial thermoplasty is associated with a transient increase in respiratory related adverse events in the peri-procedural period. These adverse events include but are not limited to airway irritation, temporary worsening of asthma symptoms (wheezing, chest discomfort, cough, and chest pain), and upper respiratory tract infections. The majority of these complications occur within 1 day of the procedure and typically resolve within 1 week with standard of care. During the AIR2 Trial, 8.4% of the BT group required hospitalizations for respiratory symptoms, compared with 2.0% in the sham group. All of these events resolved with standard therapy. The hospitalization incidence rate was 3.4% per bronchoscopy (note that each patient undergoes 3 bronchoscopic procedures). After these peri-procedural complications, the types and rates of adverse events observed during the AIR2 Trial were similar between the BT and sham groups. A notable difference is that a lower occurrence of asthma symptoms (worsening of shortness of breath, wheeze, cough, productive cough, or some combination of these) was reported in the post-treatment period within the BT group than the sham group. Consistent with this observation was a 32% reduction in severe exacerbations requiring treatment with oral corticosteroids and an 84% risk reduction in ER/ED visits for respiratory symptoms among the BT group compared to sham. Boston Scientific is aware of three patient deaths reported since the Alair™ Bronchial Thermoplasty System received pre-market approval from the US Food and Drug Administration in 2010. All three events were thoroughly investigated and Medical Device Reports (MDRs) were filed with the FDA. In all three cases, bronchial thermoplasty was not conclusively identified as being solely causative in these deaths. Other adverse events reported to the US Food and Drug Administration's MAUDE database are in line with potential adverse events described in the Alair Bronchial Thermoplasty System's Directions for Use."	Thank you for your comments. The references cited will be considered for inclusion in the report.
Comments on Key Question 3: Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)? "Bronchial thermoplasty is indicated for patients at Step 5 of the Global GINA guidelines [14]. These	Thank you for your comments.

Comment and Source	Response
patients are among the most severe asthma patients whose asthma is not well-controlled with inhaled corticosteroids and another controller medication such as long-acting beta-agonists (LABAs), their short-acting analogues (SABAs), or long-acting anti-muscarinic agents (LAMAs). Published peer-reviewed data to date does not predict which patients will respond best to bronchial thermoplasty. However, it should be noted that within the AIR2 trial, 79% of those patients within the bronchial thermoplasty cohort responded positively to treatment, as defined by an improvement in AQLQ score of at least 0.5. This is reinforced by a recent abstract presented at the annual meeting of the American Thoracic Society in May 2015 [15], in which it was shown that those patients with a AQLQ improvement of at least 0.5 consistently experienced 8 fewer ER visits at each of years of the five years of follow-up and the difference of the averages across these five years was statistically significantly different (p=0.03), suggesting that the AQLQ response is predictive of reductions in future healthcare utilization. This analysis notes differences in baseline AQLQ score between responders and non-responders, with responders having had higher baseline AQLQ scores (p<0.001)."	
Comments on Key Question 3: ***Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)?*** "As of January 1, 2016, Medicare will reimburse hospitals at a national average rate of $3,066 per bronchial thermoplasty procedure, for an average total of approximately $9,198 for the entire (three) series of required bronchial thermoplasty procedures. Physicians will be reimbursed approximately $217 for single lobe procedures and $227 for multi-lobe procedures, for an average total of approximately $651-$681 for the entire series of required bronchial thermoplasty procedures. Cost implications for private payers may differ and can vary provider to provider based on proprietary negotiated payments between payers and providers. Two recently-published cost effectiveness publications estimate the value of bronchial thermoplasty when considering the impact of reduction in utilization of health care resources in the post-procedure period. In the 2015 analysis by Cangelosi et al [16], the authors found that over a 5-year time horizon, providing bronchial thermoplasty to patients would be mildly cost-increasing but was estimated to provide significant gains in quality of life. The cost-per-QALY, a measure of a particular treatment's value was estimated to be at least $5,495/QALY.	Thank you for your comments. The references cited will be considered for inclusion in the report.

Comment and Source	Response
A more recent publication by Zein et al [17] using similar methodology but with different parameters for patient healthcare utilization (i.e. mathematically a less-severe patient population that was estimated to require less healthcare utilization without bronchial thermoplasty) and a longer time horizon of 10 years found the estimated cost-per-QALY to be approximately $29,821/QALY. Note that in each of these cases, the estimated cost-per-QALY falls well below (N.B. is more favorable than) the commonly cited cost-effectiveness threshold of $50,000/QALY. This suggests that the value of bronchial thermoplasty – when considering the constellation of evidence regarding costs, benefits, and marginally increased peri-procedural adverse events – is sufficient to recommend bronchial thermoplasty.”	

From: Shriner, Kelly kelly.Shriner@bsci.com Sent: Tue 1/20/2015 10:46 AM
To: HCA ST Health Tech Assessment Prog
Cc:
Subject: bronchial thermoplasty

Josh:

Thank you for your time earlier today explaining the Washington HTA program. I just want to re-iterate the fact that we support the review of bronchial thermoplasty in this process, and hope that a decision is made to proceed with the assessment.

I understand there will be an opportunity in the future to provide more information for this review, but I thought I would send a list of the publications on BT in the last 5 years as reference, for your decision of whether or not to conduct this assessment. Please note the recent cost effectiveness paper (Cangelosi et al), in addition to 5 year follow-up in 3 studies (Wechsler, Pavord and Thomson). Finally, you may be interested in knowing that both Healthcare Services Corporation (BCBS TX, IL, OK, NM and MT) and Carefirst BCBS have recently decided to cover BT.

References:

1. Cangelosi M, et al., Cost–effectiveness of bronchial thermoplasty in commercially-insured patients with poorly controlled, severe, persistent asthma, Expert Rev Pharmacoecon Outcomes Res. 2014 Nov 1:1-8. Epub Nov 2014. http://informahealthcare.com/doi/abs/10.1586/14737167.2015.978292
2. Wechsler ME, et al., Bronchial Thermoplasty: Long-Term Safety and Effectiveness in Patients with Severe Persistent Asthma. J Allergy Clin Immunol. 2013 Dec;132(6):1295-1302.e3. doi: 10.1016/j.jaci.2013.08.009. Epub 2013 Aug 30. http://www.jacionline.org/article/S0091-6749(13)01268-2/fulltext
3. Pavord ID, et al; Safety of Bronchial Thermoplasty in Patients with Severe Refractory Asthma. Ann Allergy Asthma Immunol. 2013 Nov;111(5):402-7. doi: 10.1016/j.anai.2013.05.002. Epub 2013 Jun 13. http://digitalreprints.elsevier.com/t/66735
4. Thomson N, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) Trial. BMC Pulmonary Medicine 2011, 11:8. www.biomedcentral.com/content/pdf/1471-2466-11-8.pdf
5. Castro M, et al. Persistence of Effectiveness of Bronchial Thermoplasty in Patients with Severe Asthma. *Annals of Allergy, Asthma & Immunology*, 2011 Jul;107(1):65-70. http://www.cenveomobile.com/issue/35148

Thank you for your consideration. We look forward to observing and commenting on your assessment process.

Kelly

Kelly M Shriner, Director, Health Economics & Reimbursement
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[redacted]

From: Rizwana Khan <Rizwana.Khan@multicare.org>
Sent: Tuesday, March 03, 2015 10:44 AM
To: HCA ST Health Tech Assessment Prog
Subject: Bronchial thermoplasty

Follow Up Flag: Follow up
Flag Status: Completed

Hello,

I am a practicing pulmonologist at Multicare - Good Samarrtan Hospital. I joined this group in September 2014.

Prior to this, I was a practicing pulmonogist at the Lung and Asthma Center of Cenral WA. I worked there for 5 years. I was introduced to and was very excited about bronchial thermoplasty in 2012. Our group in central WA acquired the equipment and training necessary and between 2012 and 1014, I performed approximately 5 of these procedures on severe persistant asthmatic patients. The results were phenomenal. My patients asthma exacerbation severity and frequency improved tremendousy and they were all thrilled with the results.

My only concerns about the procedure are that it is very cumbersome to get insurance approval and we are not able to offer this treatment to so many deserving patients who would benefit tremendously.
I believe this would have greatest impact on the younger asthmatics most of whom usually have Medicaid or lack insurance altogether.

Please feel free to contact me with any qusetions.

Regards,
Rizwana Khan
Multicare Pulmonary Specialists
[redacted]

[redacted]

From: Navdeep Rai <nsrai@pulmonaryconsultants.org>
Sent: Saturday, March 07, 2015 6:07 PM
To: HCA ST Health Tech Assessment Prog
Subject: Experience with bronchial thermoplasty

Follow Up Flag: Follow up
Flag Status: Completed

Dear Members of the HCA,

I am a practicing pulmonologist with 21 years of experience, including extensive interventional bronchoscopy. I suspect you have all the literature you need, but I would like to share my experience with this procedure.

I have treated 12 pts with bronchial thermoplasty (BT). Eight were through a clinical trial sponsored by the manufacturer, three were with insurance, and one was a cash paying patient.

While in the short term patients do experience some exacerbation of asthma, the long term results have been outstanding. Each of these patients was able to reduce their need for medication with dramatic improvement in quality of life. One patient never left her house without a high efficiency face mask. Now she no longer needs the mask and rarely requires use of recuse medicine. To the best of my knowledge all have reduced exacerbation and reduced urgent office/ER visits.

I would request your support in further expanding access to this treatment for patients with severe persistent asthma. I would be happy to discuss this further with you.

Navdeep S Rai, MD FACP, FCCP
Pulmonary Consultants, PLLC
[redacted]

[redacted]

[redacted]

From: Catherine Richardson <ca_richardson@earthlink.net>
Sent: Monday, March 09, 2015 12:23 AM
To: HCA ST Health Tech Assessment Prog
Cc: nsrai@pulmonaryconsultants.org
Subject: Bronchial Thermoplasty

Follow Up Flag: Follow up
Flag Status: Completed

To
Washington State Health Care Authority
Health Technology Assessment Program

I have been asked by Pulmonologist Navdeep Rai, MD to write concerning my experience with Bronchial Thermoplasty.

To give you some brief background, I have had asthma for many years, manifested mainly by a persistent hacking cough that was difficult to treat. It became worse and worse over the years, finally requiring medications up to and including subcu Xolair every two weeks. It kept me awake at night for hours on end, unable to sleep due to the cough. Everyone around me knew when I was coming around the corner because they could hear my cough. It was also exacerbated by chemicals, and as I am also a physician, it interfered with work. Breathing in the ubiquitous hand sanitizers could set off a 2 hour long coughing fit.

I knew when Dr. Rai started doing thermoplasties, but had some reservations. I looked into it, but kept putting it off until my situation was essentially untenable.
Finally after several bouts of pneumonia and the onset of steroid myopathy, (such that I could barely walk up stairs or stand up from a sitting position) I agreed to go ahead.
We had a large amount of difficulty getting the procedure approved by Regence. Finally after four months, the last appeal reached a pulmonary physician who understood, and this forced them to pay the approximately $15,000 the 3 total procedures cost. I was very lucky in this respect.

The procedures were not difficult, but as predicted I did have a few days of discomfort and shortness of breath after each. The last was in December of 2013. it took a few months after that for me to realize how much better I had gradually become. I no longer have horrible asthma exacerbations with every little hint of an upper respiratory infection. I have not had any need for steroids. We started weaning medications. It has been over 5 months since I had the last Xolair. I have stopped supplemental inhaled steroids, although I still use Advair. I rarely need inhaled bronchodilators to control symptoms. I have stopped using montelukast recently, and have tolerated that. I can sleep without having to take cough suppressants or something such as ambien just to be able to sleep at night.

To say the procedure has changed my life is an understatement. I can travel again without being worried about getting back in time for the next xolair injection. I can sleep again without medications. As above, I am weaning off most of the medications which I was dependent on. Most of all, as far as the health insurance industry is concerned, they no longer need to bear the expense of several thousand dollars a month just for the xolair, and I do not have to pay the high co-pays that went along with it.

I assume that this study is being done to try and bring the various health insurers in the state into being consistent with whether this procedure is paid for. I cannot speak for others, as I have never been in touch with anyone else who has had it done, but I believe it is has been highly successful for me, with minimal risk. I would recommend it for anyone with refractory asthma.

If you have any questions for me, please do not hesitate to contact me.

Catherine A. Richardson, MD

ca_richardson@earthlink.net
[redacted]

[redacted]

I am writing a summary of my patients experience and outcomes with Bronchial Thermoplasty (BT). To date, I have completed the most BT's in Washington's Inland Northwest. I am providing a descriptive overview of my clinic outcomes following treatment with Bronchial Thermoplasty. My 2.5 years of experience with this salvage/heroic therapy has been very successful. For the sake of transparency, I have discharged one patient for medical noncompliance, (after 1.2 years follow-up) and have had one patient demise **unrelated** to Asthma or the treatment with BT (natural death). 1 patient was denied BT despite insurance coverage due to clinic no-shows (surrogate of poor compliance). In addition, I have **no financial relationship** with the BT proprietor or Boston Scientific.

All patients treated had completed a thorough pre-evaluation including history, review of outside records, physical examination and diagnostic workup that would include an IgE level, limited RAST, pre/post treatment pulmonary function testing and an imaging study (CT chest or CXR, pending symptom complex). All were non-smokers and greater than 40 years of age. In addition, patients were managed with standard of care per **NAEPP guidelines** with *step up therapy* with a minimum of a Leukotriene inhibitor, high dose inhaled corticosteroid in combination with a long acting beta agonist.

Salvage/heroic therapy included 2 patients on methotrexate, 3 on theophylline for greater then 2 years, 1 with history of gold treatments and 2 patients with Xolair (Omalizumab) infusions (twice monthly for > 1 year).

In general, **prior** to treatment daily symptoms required rescue therapy in ALL patients > 5-8/daily, had been on chronic prednisone therapy or had at minimum 3 courses of high doses steroids in 12 months or 2 bursts in 6 months. All reported nocturnal awakening > 3 X week and had a health care encounter related to asthma symptoms at minimum 1-2 X monthly in the preceding period. Flow patterns remained obstructive per ATS criteria and varied from mild to very severe obstructive patterns and accordingly, had a preserved or supra-normal DLCO uncorrected for hemoglobin. Median ACT scores was < 12. 32% of my patients had been intubated within 10 years prior to clinic encounter that was related to an asthma exacerbation. 52% of patients had atopic asthma.

The Post BT treatment(s) period encompassed 3 outpatient therapeutic visits with a moderate sedation and clinic re-evaluations at 3, 6, 9 and 12 months. Firstly, there were NO complications to be reported including pneumothoraces, pulmonary hemorrhage, respiratory failure, and further no hospitalizations. Obstructive flow patterns remained similar to pre-treatment evaluation (< 10% variability), but symptoms dramatically improved measured by ACT scores. ACT scores at 3 & 6 months post treatment > 16. All patients reported feeling better daily with less shortness of breath, cough and wheeze and need for rescue therapy. 1 patient was hospitalized at month 4 for an Asthma exacerbation related to Influenza A infection. 1 patient had > 3 ER/Urgent care visits after month 9 related to nocturnal cough,

wheeze and subsequent dyspnea (this patient was later found to have severe erosive esophagitis). No patients were hospitalized with-in 12 months post treatment follow-up. 30% of patients had reported prednisone burst(s) after 9 months. All atopic-asthmatic patients suffered from concurrent postnasal drip and/or allergic rhinitis. ALL patients remained compliant with anti-reflux medications post treatment up to 12 months. 1 patient remains resistant psychologically to discontinuing theophylline (1/3 patients). 2 cohort patients on Methotrexate remain off and later Xolair patients have discontinued infusions.

Conclusions:

1. Severe Asthma is a very heterogeneous disease
2. BT should only be utilized for heroic/salvage therapy in select compliant patients.
3. Silent reflux and Post-nasal drip/allergic rhinitis are significant confounders to asthma control.
4. BT is very favorable therapeutic option for a **severe** asthmatic only.
5. Only select centers and a trained pulmonologist with adequate resources and RN support should offer BT.
6. Potential BT patients must go through a meticulous screening process.
7. BT is **not a cure** for asthma, but significantly reduces daily/monthly/seasonal undulations in asthma symptoms complex.
8. By nature of reduced clinical encounter(s) through the emergency room and/or urgent care respectably reduce costs to the patient and their insurance and co-payments incurred with Asthma exacerbations.
9. Patients with history of non-compliance are NOT good candidates for BT.
10. BT has been **very effective** for severely asthmatic patients who have had present day *unorthodox* salvage therapies including methotrexate, theophylline and GOLD treatments.
11. BT is **not** to be used as a preventative therapeutic modality i.e. intermittent, mild, or a moderate patient asthmatic population.

If there are questions or queries, please feel free to call and/or page me directly.
Please do not release my email or personal information to public resources.
Best,

Jiten D. Patel MD
[redacted]

[redacted]

From: Fein, Jordan D :LMG Pulmonologist <JFEIN@LHS.ORG>
Sent: Thursday, March 12, 2015 3:53 PM
To: HCA ST Health Tech Assessment Prog
Subject: Health Technology Assessment: Bronchial Themoplasty

Follow Up Flag: Follow up
Flag Status: Flagged

HTAP Reviewers:

I am a pulmonologist who treats patients with Bronchial Thermoplasty for uncontrolled severe persistent asthma that has not responded to medical therapy. The referrals I receive from pulmonologists and allergists throughout Washington and Oregon are to evaluate and treat patients with asthma so severe that no other treatment options exist; this a subgroup of asthmatics in which "everything has been tried." The overwhelming majority of these patients are on daily systemic corticosteroids, and have repeated emergency department visits and hospitalizations for asthma exacerbations. I have successfully treated 21 patients in the past 3 years. Our patient outcomes data are similar to those of the AIR2 trial that gained FDA approval of the medical device. Following Bronchial Thermoplasty treatment we see significant reduction in exacerbations requiring emergency department visits and hospitalization. Most patients are able to discontinue systemic corticosteroid use and have improved quality of life. The procedure is safe and efficacious, and for some asthmatics the only hope for regaining control over their disease. Bronchial Thermoplasty is covered by many private insurers, Medicare, and Oregon Medicaid. I strongly urge the Washington State Health Care Authority to make this procedure available to patients in WA as well. I welcome any questions about the procedure or our outcomes.

Thank you,

Jordan Fein, MD

Jordan D. Fein, MD|Medical Director Legacy Thoracic Oncology and Interventional Pulmonology|Legacy Medical Group Specialties Division of Pulmonary, Critical Care, and Sleep Medicine|2222 NW Lovejoy Street, Ste. 411|Portland, OR 97210|(503) 413-5702|Fax (503) 413-6499| jfein@lhs.org

Corporate Headquarters
100 Boston Scientific Way
Marlborough, MA 01752

March 11, 2015

SUBMITTED ELECTRONICALLY

Dear Mr. Morse:

Boston Scientific Corporation appreciates the opportunity to provide comments and data in anticipation of the Washington State Health Care Authority's technology review of Bronchial Thermoplasty.

Bronchial thermoplasty is an innovative procedure for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting beta2-agonists. This treatment has been shown to significantly reduce healthcare utilization, presenting an opportunity to improve patient outcomes and quality of life while reducing overall health care costs. Bronchial thermoplasty has been shown to be a safe, effective, and long-lasting treatment option for a well-defined population of adults.

Attached, please find a clinical dossier that provides an overview of the current clinical evidence on bronchial thermoplasty. This document summarizes the clinical findings on BT, including long-term safety and effectiveness out to 5 years post-procedure, and it also provides direct links to the published literature.

In addition, the following publication addresses the cost-effectiveness of bronchial thermoplasty from the commercial payer perspective. This one-time treatment quickly becomes cost-effective as cost offsets accrue annually without the need for re-treatment, demonstrated by persistent reduction in healthcare utilization over time:

> Cangelosi M, et al., Cost–effectiveness of bronchial thermoplasty in commercially-insured patients with poorly controlled, severe, persistent asthma, Expert Rev Pharmacoecon Outcomes Res. 2014 Nov 1:1-8. Epub Nov 2014. http://informahealthcare.com/doi/abs/10.1586/14737167.2015.978292

We noted that the proposed title of the Director Selection is "Bronchial Thermoplasty in Asthma." Bronchial thermoplasty is specifically indicated for patients who have severe persistent asthma and who remain not well controlled on inhaled corticosteroids and long acting beta agonists (i.e. step 5 or 6 of the NAEPP guidelines). Therefore we would like to respectfully ask that: 1) the scope of the assessment be limited to the use of this procedure in patients with severe persistent asthma (as indicated); and 2) the title of the assessment be revised to read, "Bronchial Thermoplasty in Severe Asthma."

Please do not hesitate to contact me if you have any questions or need any additional information.

Thank you in advance for your consideration.

Best regards,

[redacted]

Christina Van Wallendael
Senior Field Reimbursement Manager
Boston Scientific Endoscopy

Corporate Headquarters
100 Boston Scientific Way
Marlborough, MA 01752

November 3, 2015

SUBMITTED ELECTRONICALLY

Dear Sir or Madame:

Boston Scientific Corporation appreciates the opportunity to provide comments and responses to the questions posed in the Washington State Health Care Authority's technology assessment of bronchial thermoplasty.

Bronchial thermoplasty is an innovative procedure for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting beta2-agonists. This treatment has been shown to significantly reduce healthcare utilization, presenting an opportunity to improve patient outcomes and quality of life while reducing overall health care costs. Bronchial thermoplasty has been shown to be a safe, effective, and long-lasting treatment option for a well-defined population of adults.

The comments contained in this letter are intended to address the following questions posed by the Washington State Health Care Authority:

1. What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma?

    a. Is there clinically meaningful improvement for patients with severe asthma?

2. What are the harms associated with bronchial thermoplasty?

3. Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)?

4. What are the cost implications and cost-effectiveness of bronchial thermoplasty?

Before addressing the key questions detailed by the Health Care Authority, Boston Scientific respectfully requests that the final technology assessment for bronchial thermoplasty be updated to reflect a more accurate description of the procedure, the devices used, and the intended result of the procedure. In its draft Key Questions and Background document for bronchial thermoplasty, the Washington State Health Care Authority states that,

> "*Bronchial thermoplasty is designed to weaken and partially destroy the smooth muscle that constricts the airway during asthma attacks.*"

While bronchial thermoplasty is intended to reduce the amount of airway smooth muscle and subsequent muscle-mediated bronchoconstriction, it does not "weaken" the smooth muscle but rather targets and partially eliminates airway smooth muscle. (Please refer to Appendix A for a more detailed discussion of airway responsiveness and airway smooth muscle changes resulting from bronchial thermoplasty as observed out to three years).

The Draft Key Questions and Background document goes on to state,

> *"This procedure relies on a catheter that has an expandable array of electrodes and that has a fiber optic camera, which allows the physician to see inside the lung. After the catheter is threaded into the airway, a wire leading out of the back end of the catheter is attached to a radiofrequency generator and a lever is operated that causes the electrodes to curl into a ball shape around the front end of the catheter. The curved electrodes are held against the bronchial walls and an electrical current is applied to generate heat that destroys the smooth muscle underneath the lining of the bronchial passages."*

In actuality, during bronchial thermoplasty, the physician introduces a standard flexible bronchoscope through a patient's nose or mouth, and into the airways of the lung. The bronchoscope, rather than the Alair™ Catheter, facilitates visualization of the airways. There is no fiber optic camera on the Alair Catheter, which is delivered into the airways through the working channel of the bronchoscope. Once the catheter's electrode array has been expanded to come in contact with and fit snugly against the airway wall, the physician activates the catheter to deliver controlled thermal energy from the radiofrequency controller. This controller uses specific safety algorithms, for a maximum of 10 seconds, to heat the airway smooth muscle and cause remodeling resulting in partial loss of airway smooth muscle function and improved asthma control.

We appreciate the Washington State Health Care Authority's willingness to consider this more accurate description of the bronchial thermoplasty procedure in its final technology assessment.

Responses to Key Questions

1. What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma?

Clinical effectiveness of bronchial thermoplasty has been demonstrated in several randomized clinical trials, including RISA [1], AIR [2], and AIR2 [3]. .

The pivotal trial, AIR2, was a randomized, sham controlled, double-blind trial comparing bronchial thermoplasty to a sham procedure (e.g. the medical device analogue to a placebo-controlled trial). In this trial, bronchial thermoplasty was shown to be superior to the sham with regards to the improvement in the integrated AQLQ score relative to baseline (bronchial thermoplasty, 1.35±1.10; sham, 1.16±1.23 (PPS, 96.0% ITT and 97.9% per protocol)).

Furthermore there was a statistically significantly greater percentage of bronchial thermoplasty subjects compared to sham that achieved a clinically meaningful improvement in their quality of life, as measured by the improvement of the AQLQ score of equal to or greater than 0.5 (the minimal clinical important difference [MCID] for this tool) (79% percent of bronchial thermoplasty and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (PPS, 99.6%)).

Moreover, compared to the sham group, bronchial thermoplasty was associated with significant reductions in asthma-related healthcare utilization events with an 84% reduction in ER/ED visits for respiratory events within the post-treatment period compared to sham (PPS = 99.9%). There was a 32 % reduction in severe exacerbations compared to the sham group (PPS 95.5%) and a 66% reduction in the days lost from school, work or other daily activities due to asthma (1.135 ± 0.361 vs. 3.915 ± 1.553, PPS=99.3%). These are all meaningful and important measures of asthma control in patients with severe persistent asthma.

The durability of effectiveness of bronchial thermoplasty has been demonstrated out to 5years, as detailed in the post-approval AIR2 Trial Extension Study [4]. This study was conducted to evaluate the durability of effectiveness of bronchial thermoplasty beyond one year and the long-term safety of the procedure out to 5 years post-treatment in bronchial thermoplasty-treated subjects from the AIR2 Trial. The AIR2 Trial demonstrated that compared to the Sham group, fewer subjects in the bronchial thermoplasty group had severe exacerbations in the year following bronchial thermoplasty. The AIR2 Extension Study used a non-inferiority design to show that the proportion of subjects in the bronchial thermoplasty group experiencing severe exacerbations in subsequent years (years 2 to 5) does not worsen, when compared with the proportion of subjects experiencing severe exacerbations for the first year. Subject retention was very high for a study of this complexity and lengthy follow-up with 162 of the 190 subjects (85%) who underwent bronchial thermoplasty treatment in the AIR2 Trial having fully completed the 5-year follow-up.

While the main purpose of this study was to assess long term (5-year) durability of clinical effectiveness and demonstrate similar long-term safety in a cohort of subjects who underwent bronchial thermoplasty, a limitation of this study is the lack of sham-control group beyond one year. Collecting meaningful 5-year study data without confounding would have required maintaining the study blind for the entire 5-year period in both groups and this was felt to be unethical in this study population. Maintaining sham subjects in the follow-up study after breaking the blind and requiring them to continue the same treatment regimen despite poor control was deemed similarly unethical and impractical – likely resulting in poor subject retention and leading to further difficulty in study result interpretation. Because of these

concerns, the sham group exited the study at the end of the first year and was not followed in the long-term extension study.[1]

Key Findings from the AIR2 5-Year Follow-Up Study Included:

- The proportion of bronchial thermoplasty-treated subjects experiencing severe exacerbations in Year 1 after bronchial thermoplasty (N.B. demonstrated statistically less – superior – than Sham within Year 1) was maintained out to 5 years.
    - The upper 95% confidence limit of the difference in proportions in each year minus Year 1 remained below the pre-specified non-inferiority margin of 20%.
- Compared to the 12 months prior to bronchial thermoplasty treatment, the following results were observed:
    - 44% average decrease over 5 years in proportion of bronchial thermoplasty-treated subjects having severe exacerbations
    - 48% average decrease over 5 years in severe exacerbation event rates (events/subject/year)
    - 78% average decrease over 5 years in bronchial thermoplasty-treated subjects having ER visits
    - 88% average decrease over 5 years in ER visit event rates (events/subject/year)
- Reduction in the proportion of bronchial thermoplasty-treated subjects having emergency room (ER) visits for respiratory symptoms seen in Year 1 after bronchial thermoplasty (N.B. demonstrated statistically less – superior – than Sham within Year 1) was maintained out to 5 years.
- No increase in hospitalizations, general respiratory adverse events or asthma symptoms over the course of 5 years post-bronchial thermoplasty.
- No clinically significant change in FEV1 over 5 years.
- At 5 years post-bronchial thermoplasty a post net-beneficial reduction in inhaled corticosteroid (ICS) dose was observed. 28% of subjects reduced their daily ICS dose by 50% or more compared to 5% of subjects who increased their daily ICS dose by 50% or more.
    - Average 18% reduction in daily ICS dose
- Comparison of HRCT images at Baseline and at 5 years post-bronchial thermoplasty showed no structural changes in the airways due to bronchial thermoplasty that were of clinical significance.

[1] It should be noted that among severe asthma patients not receiving BT, it has been demonstrated in a published peer-reviewed retrospective analysis of payers' claims that the rate of asthma exacerbations remains elevated, in spite of non-BT treatment. (Schatz M, et al. Asthma exacerbation rates in adults are unchanged over a 5-year period despite high-intensity therapy. J Allergy Clin Immunol Pract. 2014 Sep-Oct;2(5):570-4). Thus it may be inferred that the experience of the Sham cohort within the AIR2 trial may have similarly continued to have an elevated rate of exacerbation relative to the rate of exacerbations observed within the BT-treated cohort.

In the earlier AIR randomized clinical study and the associated AIR extension study [5, 6], bronchial thermoplasty was compared to a standard of care control group. The AIR Trial demonstrated that the mean rate of mild exacerbations, as compared with baseline, was reduced in the bronchial thermoplasty group but was unchanged in the control group (change in frequency per subject per week, –0.16±0.37 (improvement) vs. 0.04±0.29 (worsening); P=0.005). At 12 months, there were significantly greater improvements in the bronchial thermoplasty group than in the control group in the morning peak expiratory flow (39.3±48.7 vs. 8.5±44.2 liters per minute), scores on the AQLQ (1.3±1.0 vs. 0.6±1.1) and ACQ (reduction, 1.2±1.0 vs. 0.5±1.0), the percentage of symptom-free days (40.6±39.7 vs. 17.0±37.9), and symptom scores (reduction, 1.9±2.1 vs. 0.7±2.5) while fewer puffs of rescue medication were required.

Similar results were observed within the Research in Severe Asthma (RISA) study and RISA extension study, which examined a cohort of patients that could be considered more severe than the then contemporaneous AIR Trial [7, 8]. Within RISA, it was observed that bronchial thermoplasty was associated with a significant improvement versus control in rescue medication use (22.6 ± 40.1 vs. -1.5 ± 11.7 puffs per week $p<0.05$), prebronchodilator FEV_1% predicted (14.9 ± 17.4 vs. –0.94 ± 22.3%, P = 0.04), and Asthma Control Questionnaire (ACQ) scores (-1.04 ± 1.03 vs. - 0.13 ± 1.00, P = 0.02). Improvements in rescue medication use and ACQ scores remained significantly different from those of controls at 52 weeks.

Based on the available data from these RCTs, bronchial thermoplasty is now included in several recent severe asthma treatment guidelines as an add-on therapy for the effective clinical management of patients with severe asthma who are poorly controlled despite being on optimal doses of inhaled corticosteroids and long-acting beta agonists, including the British Thoracic Society (bronchial thermoplasty) [9], the Global Initiative for Asthma (GINA) [10]. The earlier European Respiratory Society (ERS) / American Respiratory Society (ATS) guidelines for the management of severe asthma, which were published in 2013 [11] and did not consider the five year follow-up data described above recommended the use bronchial thermoplasty in IRB approved settings, however more recent guidelines have superseded these recommendations, including the 2014 GINA guidelines and the guidelines published by the Assembly on Interventional Pulmonology of the South African Thoracic Society [12]. ,

Key professional specialty societies and patient advocacy groups including the American College of Chest Physicians (ACCP - CHEST) and the American College of Allergy, Asthma, and Immunology (ACAAI) have also published position statements supporting bronchial thermoplasty as a treatment option based on their conclusion that scientific literature supports bronchial thermoplasty as a therapeutic consideration for some carefully chosen patients with severe asthma (see list and links below):

- American College of Asthma, Allergy and Immunology (ACAAI): http://college.acaai.org/Pages/Statement_on_Bronchial_Thermoplasty.aspx

- American College of Chest Physicians (CHEST): http://www.chestnet.org/Guidelines-and-Resources/Health-Policy/Position-Papers
- Asthma & Allergy Foundation of America (AAFA): http://www.aafa.org/display.cfm?id=8&sub=104&cont=864
- INTERASMA (Global Asthma Association): http://www.interasma.org/images/manifesto3.pdf
- Allergy & Asthma Network (AAN): http://www.allergyasthmanetwork.org/education/asthma/treatment-and-medications/bronchial-thermoplasty/

Finally, in 2011, the California Technology Assessment Forum (CTAF) reviewed bronchial thermoplasty and concluded that all 5 criteria were met in support of the safety, efficacy and long-term positive health outcomes of bronchial thermoplasty in patients 18 years or older with severe asthma [13]. The CTAF assessment stated, **"It is recommended that use of bronchial thermoplasty for the treatment of severe, refractory asthma meets CTAF TA Criterion 1 through 5 for safety, effectiveness and improvement in net health outcomes."** The ATS testified in support of this conclusion on October 19, 2011.

a. Is there clinically meaningful improvement for patients with severe asthma?

Yes. In the AIR2 trial, the proportion of patients with a clinically meaningfully difference in their AQLQ (an asthma-specific quality of life metric) was statistically significantly more likely to be improved compared to sham. This improvement relative to sham suggests meaningful clinical benefit of bronchial thermoplasty. For example, a statistically significantly greater percentage of bronchial thermoplasty subjects compared to sham showed clinically meaningful improvement in their quality of life, as measured by the AQLQ (79% percent of bronchial thermoplasty and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (PPS, 99.6%)).

This improvement in asthma control is echoed in the healthcare utilization differences between those subjects within the AIR2 trial treated with bronchial thermoplasty, compared to those treated with sham procedures. Within AIR2, there was observed an 84% reduction in ER/ED visits for respiratory events within the post-treatment period compared to sham (PPS = 99.9%). In addition, a 32% reduction in severe exacerbations was observed relative to those exacerbations observed in the sham group (PPS 95.5%).

According to Elizabeth Juniper, MSCP, MSc, the developer of the AQLQ instrument, in a memo discussing the interpretation of AQLQ in the AIR2 trial [Appendix B], **"Based on published literature to date, I am not aware of any other therapy for severe asthma that has demonstrated this degree of clinically meaningful benefit between groups (measured by the proportion of patients benefiting from the treatment) as compared to optimal standard of care."**

2. What are the harms associated with bronchial thermoplasty?

Bronchial thermoplasty is associated with a transient increase in respiratory related adverse events in the peri-procedural period. These adverse events include but are not limited to airway irritation, temporary worsening of asthma symptoms (wheezing, chest discomfort, cough, and chest pain), and upper respiratory tract infections. The majority of these complications occur within 1 day of the procedure and typically resolve within 1 week with standard of care. During the AIR2 Trial, 8.4% of the BT group required hospitalizations for respiratory symptoms, compared with 2.0% in the sham group. All of these events resolved with standard therapy. The hospitalization incidence rate was 3.4% per bronchoscopy (note that each patient undergoes 3 bronchoscopic procedures).

After these peri-procedural complications, the types and rates of adverse events observed during the AIR2 Trial were similar between the BT and sham groups. A notable difference is that a lower occurrence of asthma symptoms (worsening of shortness of breath, wheeze, cough, productive cough, or some combination of these) was reported in the post-treatment period within the BT group than the sham group. Consistent with this observation was a 32% reduction in severe exacerbations requiring treatment with oral corticosteroids and an 84% risk reduction in ER/ED visits for respiratory symptoms among the BT group compared to sham.

Boston Scientific is aware of three patient deaths reported since the Alair™ Bronchial Thermoplasty System received pre-market approval from the US Food and Drug Administration in 2010. All three events were thoroughly investigated and Medical Device Reports (MDRs) were filed with the FDA. In all three cases, bronchial thermoplasty was not conclusively identified as being solely causative in these deaths. Other adverse events reported to the US Food and Drug Administration's MAUDE database are in line with potential adverse events described in the Alair Bronchial Thermoplasty System's Directions for Use.

3. Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)?

Bronchial thermoplasty is indicated for patients at Step 5 of the Global GINA guidelines [14]. These patients are among the most severe asthma patients whose asthma is not well-controlled with inhaled corticosteroids and another controller medication such as long-acting beta-agonists (LABAs), their short-acting analogues (SABAs), or long-acting anti-muscarinic agents (LAMAs).

Published peer-reviewed data to date does not predict which patients will respond best to bronchial thermoplasty. However, it should be noted that within the AIR2 trial, 79% of those patients within the bronchial thermoplasty cohort responded positively to treatment, as defined by an improvement in AQLQ score of at least 0.5. This is reinforced by a recent abstract presented at the annual meeting of the American Thoracic Society in May 2015 [15], in which it was shown that those patients with a AQLQ improvement of at least 0.5 consistently experienced

fewer ER visits at each of years of the five years of follow-up and the difference of the averages across these five years was statistically significantly different ($p=0.03$), suggesting that the AQLQ response is predictive of reductions in future healthcare utilization. This analysis notes differences in baseline AQLQ score between responders and non-responders, with responders having had higher baseline AQLQ scores ($p<0.001$).

4. What are the cost implications and cost-effectiveness of bronchial thermoplasty?

As of January 1, 2016, Medicare will reimburse hospitals at a national average rate of $3,066 per bronchial thermoplasty procedure, for an average total of approximately $9,198 for the entire (three) series of required bronchial thermoplasty procedures. Physicians will be reimbursed approximately $217 for single lobe procedures and $227 for multi-lobe procedures, for an average total of approximately $651-$681 for the entire series of required bronchial thermoplasty procedures. Cost implications for private payers may differ and can vary provider to provider based on proprietary negotiated payments between payers and providers.

Two recently-published cost effectiveness publications estimate the value of bronchial thermoplasty when considering the impact of reduction in utilization of health care resources in the post-procedure period. In the 2015 analysis by Cangelosi et al [16], the authors found that over a 5-year time horizon, providing bronchial thermoplasty to patients would be mildly cost-increasing but was estimated to provide significant gains in quality of life. The cost-per-QALY, a measure of a particular treatment's value was estimated to be at least $5,495/QALY.

A more recent publication by Zein et al [17] using similar methodology but with different parameters for patient healthcare utilization (i.e. mathematically a less-severe patient population that was estimated to require less healthcare utilization without bronchial thermoplasty) and a longer time horizon of 10 years found the estimated cost-per-QALY to be approximately $29,821/QALY.

Note that in each of these cases, the estimated cost-per-QALY falls well below (N.B. is more favorable than) the commonly cited cost-effectiveness threshold of $50,000/QALY. This suggests that the value of bronchial thermoplasty – when considering the constellation of evidence regarding costs, benefits, and marginally increased peri-procedural adverse events – is sufficient to recommend bronchial thermoplasty.

Closing

Thank you for your consideration of these responses to the Washington State Health Care Authority's Key Questions regarding bronchial thermoplasty. Please do not hesitate to contact me should you have any questions or need clarification.

Sincerely,

Maria B. Stewart
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Appendix A: Summary of FindingsRegarding Airway Responsiveness and Airway Smooth Muscle Changes Resulting from Bronchial Thermoplasty

From Danek, CJ, et al, "Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs." Journal of Applied Physiology 2004; 97: 1946-1953:

Physiologic effects:

- Airway smooth muscle was reduced.
- Histology obronchial thermoplastyained at 12 weeks after the procedure demonstrated the epithelial layer returned to normal.
- Histology obronchial thermoplastyained at 3 years after the procedure did not show any evidence of intraluminal scarring, and appeared similar to the earlier findings at 12 weeks.
- Demonstrated significant reduction in airway responsiveness to local methacholine challenge, an established tool for constricting airway smooth muscle.

Durability:

- Persistence in the reduction of airway smooth muscle out to 3 years.
- Persistence in the reduction in airway hyperresponsiveness out to 3 years.

Mechanism:

- The reduction in airway hyperresponsiveness was found to be correlated to the reduction in airway smooth muscle.

Recent independently conducted human studies have borne out these original observations relating to the effect of bronchial thermoplasty on airway smooth muscle.and

Documented Reduction in Anatomical Smooth Muscle:

- Bronchial thermoplasty decreased airway smooth muscle from 12.9 ± 1.2% to 4.6 ± 0.8% [Dyrda, P; Tazzeo, T; DoHarris, L; e. al. "Acute Response of Airway Muscle to Extreme Temperature Includes Disruption of Actin-Myosin Interaction." Am J Respir Cell Mol Biol. Pp.213-221. April 2010.].
- Bronchial thermoplasty decreased airway smooth muscle from 20.25% ± 4.12% to 7.28% ± 3.2% [Pretolani, M; Dombret, M-C; Knap, D; e. al. "Reduction of Airway Smooth Muscle Mass by Bronchial Thermoplasty in Patients with Severe Asthma". Am J Resp & Crit Care Med. Pp.1452-1454. Dec. 2014.].
- Bronchial thermoplasty decreased airway smooth muscle from 20.8% ± 4.9% to 10.6% ± 9.54% [Bergqvist, A; Pretolani, M; Taille, C; e. al. "Selective Structural Changes of Bronchial Thermoplasty in the Treatment of Severe Uncontrolled Asthma". Am J Respir Crit Care Med pp. A4171. May 2015.].

Improved Asthma Control:

- Over 1 year after treatment, the number of severe exacerbations and doses of inhaled corticosteroids were decreased ($p<0.02$) and asthma control was improved ($p\leq0.02$). [Chakir, J; Haj-Salem, I; Gas, D; e. al. “Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Collagen Deposition in Asthma.” Ann Am Thorac Soc. 2015 September (Epub ahead of print)].

Appendix B: Internal Communication from Juniper EF. Interpretation of the AQLQ Score Change and its Application in the AIR2 Trial. December 18, 2008.

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December 18, 2008

Interpretation of the AQLQ Score Change and its Application in the AIR2 Trial

The Asthma Quality of Life Questionnaire (AQLQ) was developed to assess areas of quality of life impairment that are important to adult asthmatic patients. The questionnaire was designed to be responsive to within-subject change (Juniper 1992). The questionnaire was further validated for a within-subject change in score of 0.5 as representing the minimal important difference (MID) (Juniper 1994). This score was very similar for both improvement and deterioration. The Minimal Important Difference is defined as the smallest change in treatment that a patient considers important and would justify a change in treatment (in the absence of undue side effects and excessive costs).

The method for determining whether between-treatment differences in AQLQ scores can be considered clinically important have been published by Guyatt et all (1998). The method uses the proportion of patients who improve and deteriorate by the MID (+0.5 and –0.5) in the two treatment groups. Thus any abnormality in distribution may be taken into account.

Based on my review of the AQLQ data from the AIR2 Trial, I consider that an analysis that includes both subjects who improved by ≥0.5 and subjects who deteriorated by ≤ -0.5 is appropriate to fully utilize the power of the AQLQ and identify the true benefit of the Alair treatment. The following analysis provides this perspective.

Figure 1 illustrates the % of subjects in both groups who improved, i.e. achieved an AQLQ score change of ≥ 0.5; Figure 2 illustrates the % of subjects in both groups who deteriorated, i.e. had an AQLQ score change of ≤ -0.5. The Intent to Treat (ITT) population includes all patients that received at least one bronchoscopy, and the Per Protocol (PP) population includes all patients with complete Alair treatments and complete follow-up, at 6, 9, and 12 months.

First, let us consider responders in the AIR2 Trial using the per protocol data (PP)

81% of patients showed a clinically important improvement when treated with the Alair System whereas only 63% of the sham group benefited. In contrast, 7% of the sham group had a clinically important deterioration compared to only 3% in the Alair System treated patients.

Therefore, the net percentage of patients who had a benefit (% improving - % deteriorating) in the Alair group was 78% and the net benefit in the sham group was reduced to 56%. Taking this one step further, the difference in true benefit between Alair and sham was 22% (78% - 56%). This means that 22% of patients would benefit in a clinically meaningful way from Alair compared with if they had received the sham treatment.

Table 1 shows the difference in the proportion of patients that benefitted from the Alair procedure.

Based on published literature to date, I am not aware of any other therapy for severe asthma that has demonstrated this degree of clinically meaningful benefit between groups (measured by the proportion of patients benefitting from the treatment) as compared to optimal standard of care.

Figure 1: Improvements in Integrated AQLQ Score

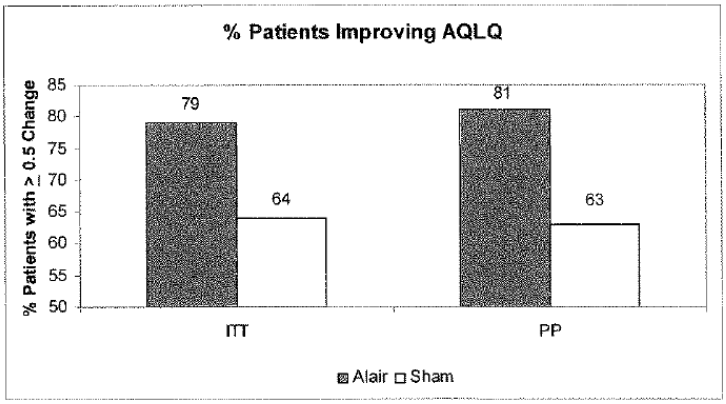

Figure 2: Declines in Integrated AQLQ Score

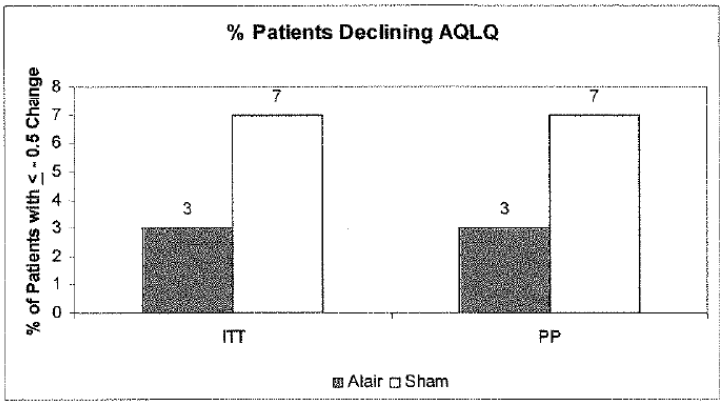

Table 1: Net Proportion of Patients That Benefit from Alair over Sham

AQLQ Score	Group	% ≥ 0.5 (Increase)	% Increase over Sham[1]	% ≤ -0.5 (Deterioration)	% With Net Increase[2]	Proportion that benefitted[3]	% Increase over Sham[4]
Intent-to-Treat Population	Alair	79	15	3	76	19	33%
	Sham	64		7	57		
Per Protocol Population	Alair	81	18	3	78	22	39%
	Sham	63		7	56		

[1] The difference between Alair and Sham in the % of patients with ≥ 0.5 improvement
[2] The difference in % of patients with ≥ 0.5 improvement and ≤ 0.5 deterioration
[3] The difference between Alair and Sham in the % of patients with a net improvement.
[4] Proportion that benefitted divided by % of Sham patients with net improvement.

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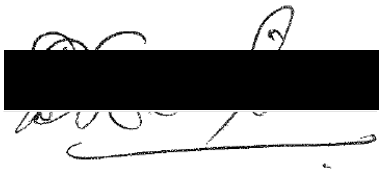

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