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Bronchial Thermoplasty – Long Term Safety and Effectiveness in Severe Persistent Asthma

Michael E. Wechsler, M.D.[1], **Michel Laviolette, M.D.**[2], **Adalberto S. Rubin, M.D.**[3], **Jussara Fiterman, M.D.**[4], **Jose R. Lapa e Silva, M.D.**[5], **Pallav L. Shah, M.D.**[6], **Elie Fiss, M.D.**[7], **Ronald Olivenstein, M.D.**[8], **Neil C. Thomson, M.D.**[9], **Robert M. Niven, M.D.**[10], **Ian D. Pavord, M.D.**[11], **Michael Simoff, M.D.**[12], **Jeff B. Hales, M.D.**[13], **Charlene McEvoy, M.D.**[14], **Dirk-Jan Slebos, M.D.**[15], **Mark Holmes, M.D.**[16], **Martin J. Phillips, M.D.**[17], **Serpil C. Erzurum, M.D.**[18], **Nicola A. Hanania, M.D.**[19], **Kaharu Sumino, M.D.**[20], **Monica Kraft, M.D.**[21], **Gerard Cox, M.B.**[22], **Daniel H. Sterman, M.D.**[23], **Kyle Hogarth, M.D.**[24], **Joel N. Kline, M.D.**[25], **Adel H. Mansur, M.D.**[26], **Brian E. Louie, M.D.**[27], **William M. Leeds, M.D.**[28], **Richard G. Barbers, M.D.**[29], **John H.M. Austin, M.D.**[30], **Narinder S. Shargill, Ph.D.**[31], **John Quiring, Ph.D.**[32], **Brian Armstrong, M.S.**[32], and **Mario Castro, M.D.**[20] **for the AIR2 Trial Study Group***

Michel Laviolette: Michel.Laviolette@fmed.ulaval.ca; Adalberto S. Rubin: arubin@terra.com.br; Jussara Fiterman: fiterman@pucrs.br; Jose R. Lapa e Silva: Jrlapa.ntg@terra.com.br; Pallav L. Shah: pallav.shah@ic.ac.uk; Elie Fiss: eliefiss@uol.com.br; Ronald Olivenstein: Ronald.Olivenstein@mcgill.ca; Neil C. Thomson: Neil.Thomson@glasgow.ac.uk; Robert M. Niven: robert.niven@uhsm.nhs.uk; Ian D. Pavord: ian.pavord@uhl-tr.nhs.uk; Michael Simoff: msimoff1@hfhs.org; Jeff B. Hales: jhales@pmaofnova.com; Charlene McEvoy: Charlene.E.McEvoy@HealthPartners.com; Dirk-Jan Slebos: d.j.slebos@umcg.nl; Mark Holmes: mark.holmes@health.sa.gov.au; Martin J. Phillips: Martin.Phillips@health.wa.gov.au; Serpil C. Erzurum: erzurus@ccf.org; Nicola A. Hanania: Hanania@bcm.tmc.edu; Kaharu Sumino: KSUMINO@DOM.wustl.edu; Monica Kraft: monica.kraft@duke.edu; Gerard Cox: coxp@mcmaster.ca; Daniel H. Sterman: sterman@mail.med.upenn.edu; Kyle Hogarth: dhogarth@uchicago.edu; Joel N. Kline: Joel-kline@uiowa.edu; Adel H. Mansur: Adel.mansur@heartofengland.nhs.uk; Brian E. Louie: Brian.Louie@swedish.org; William M. Leeds: dr.leeds@psakansas.com; Richard G. Barbers: barbers@usc.edu; John H.M. Austin: jha3@columbia.edu; Narinder S. Shargill: Narinder.shargill@bsci.com; John Quiring: jquiring@qstconsultations.com; Brian Armstrong: barmstrong@qstconsultations.com; Mario Castro: castrom@wustl.edu

[1]Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO [2]IUCPQ (Hôpital Laval), Laval University, Quebec, Canada [3]Irmandade Santa Casa de Misericórdia da Porto Alegre, Porto Alegre [4]Hospital São Lucas da PUCRS, Porto Alegre, Brazil [5]Hospital Universitário Clementino Fraga Filho, Rio de Janeiro, Brazil [6]Chelsea & Westminster Hospital NHS Foundation Trust, London, United Kingdom [7]Faculdade de Medicina do ABC, Santo Andrė, Sao Paulo, Brazil [8]Montreal Chest Institute, Montreal, Quebec, Canada [9]Gartnavel General Hospital, University of Glasgow, Glasgow, United Kingdom [10]MAHSC, The University of Manchester and University Hospital of South Manchester, Manchester, United Kingdom [11]Glenfield General Hospital, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom [12]Henry Ford Medical Center, Detroit, Michigan [13]Pulmonary and Medical Associate of

Correspondence and requests for reprints should be addressed to: Michael E Wechsler, MD, National Jewish Health, Division of Pulmonary, Critical Care and Sleep Medicine, 1400 Jackson St, Denver, CO 80206, Tel: (303) 398 1085, mikewechsler@gmail.com.
*A list of the members of the AIR2 Trial Study Group can be found at the end of this article.

Northern Virginia, Arlington, Virginia [14]HealthPartners Specialty Center, St. Paul, Minnesota [15]Department of Pulmonary Diseases, Universtair Medisch Centrum, Groningen, the Netherlands [16]Respiratory Clinical Trials Unit, Royal Adelaide Hospital, Adelaide, Australia [17]Western Australia Lung Research, Sir Charles Gairdner Hospital, Perth, Australia [18]Department of Pulmonary and Critical Care Medicine, Cleveland Clinic, Cleveland, Ohio [19]Baylor College of Medicine, Houston, Texas [20]Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri [21]Duke University Medical Center, Durham, North Carolina [22]St. Joseph's Healthcare, McMaster University, Hamilton, Ontario, Canada [23]University of Pennsylvania Health System, Philadelphia, Pennsylvania [24]Department of Pulmonary and Critical Care Medicine, University of Chicago, Chicago, Illinois [25]University of Iowa, Iowa City, Iowa [26]Birmingham Heartlands Hospital, Respiratory Unit, University of Birmingham, Birmingham, United Kingdom [27]Section of Thoracic and Foregut Surgery, Swedish Medical Center, Seattle, Seattle, WA [28]Veritas Clinical Specialties, Topeka, Kansas [29]Division of Pulmonary and Critical Care Medicine, Keck School of Medicine of the Universityof Southern California, Los Angeles, California [30]Division of Radiology, Columbia University Medical Center, New York, New York [31]Boston Scientific Corporation, Sunnyvale, California [32]QST Consultations Ltd, Allendale, Michigan

Abstract

Background—Bronchial thermoplasty (BT) has previously been shown to improve asthma control out to 2 years in patients with severe persistent asthma.

Objective—To assess effectiveness and safety of BT in asthma patients 5 years post therapy.

Methods—BT-treated subjects from the Asthma Intervention Research 2 (AIR2) Trial (ClinicalTrials.gov NCT01350414) were evaluated annually for 5 years to assess long-term safety of BT and durability of treatment effect. Outcomes assessed post-BT included severe exacerbations, adverse events, healthcare utilization, spirometry data, and high resolution computed tomography (HRCT) scans.

Results—162/190 BT-treated subjects (85.3%) from the AIR2 Trial completed 5 years of follow-up. The proportion of subjects experiencing severe exacerbations and Emergency Room visits, and the rates of events in each of years 1 to 5 remained low and were less than those observed in the 12 months prior to BT treatment (average 5 year reduction in proportions: 44% for exacerbations and 78% for ER visits). Respiratory adverse events and respiratory-related hospitalizations remained unchanged in Years 2 through 5 as compared to the first year after BT. Pre-BD FEV_1 values remained stable between years 1 and 5 after BT, despite a 17% reduction in average daily inhaled corticosteroid dose. HRCT scans from baseline to 5 years after BT showed no structural abnormalities that could be attributed to BT.

Conclusions—These data demonstrate the 5-year durability of the benefits of BT with regard to both asthma control (based on maintained reduction in severe exacerbations and ER visits for respiratory symptoms) and safety. BT has become an important addition to our treatment armamentarium and should be considered for patients with severe persistent asthma who remain symptomatic despite taking ICS (inhaled corticosteroids) and LABA (long-acting-β_2-agonists).

Keywords

Bronchial thermoplasty; asthma; Bronchoscopic procedure; Alair System; asthma exacerbation

Introduction

Over 23 million people in the United States suffer from asthma[1, 2]. Approximately 5% of patients have severe persistent asthma and continue to experience asthma symptoms despite treatment with current state-of-the-art medications[3]. Poorly controlled and "not-well controlled" asthma remain a significant social and economic burden,[2, 4] and lead to increased healthcare utilization with negative impacts on patients' quality of life.

Bronchial Thermoplasty (BT) is a non-pharmacologic treatment for asthma that has been shown to result in significant improvements in a number of asthma control measures in three randomized clinical trials in patients with moderate-to-severe, persistent asthma[5-7]. The Asthma Intervention Research 2 (AIR2) Trial, a double-blind, sham-controlled, randomized clinical trial of BT in patients with severe asthma, showed a 32% reduction in severe exacerbations, an 84% reduction in emergency room (ER) visits due to respiratory symptoms, a 73% reduction in hospitalizations for respiratory symptoms, and a 66% reduction in time lost from work/school/other daily activities due to asthma symptoms compared to a sham-treated group in the year following the BT treatment period (day of first BT procedure until 6 weeks after the last bronchoscopy, approximately 12 weeks)[7]. We previously reported safety out to 5 years in moderate-to-severe persistent asthma through extended follow-up of 45/52 BT-treated subjects (86.5%) in the AIR Trial[8]. Safety and durability of the treatment effect (reduced severe exacerbations and ER visits for respiratory symptoms) were previously reported out to 2 years post-BT in subjects with severe persistent asthma in the AIR2 Trial[9]. We now describe the long-term safety and durability of BT out to 5 years post-treatment in 162/190 subjects from the AIR2 Trial.

Methods

Study procedures

BT group subjects in the AIR2 Trial were followed to 5 years. The study population and design of the AIR2 Trial have been published[7]. Data that were collected during the 5-year follow-up and episodes of severe exacerbations were analyzed using a non-inferiority approach to demonstrate that the benefit of BT in the year after the procedure was maintained in each of the subsequent years out to 5 years (ClinicalTrials.gov number, NCT01350414).

Upon completion of the Year 1 evaluation in the AIR2 Trial, subjects in the BT group were instructed to maintain their use of controller medications (unless changes were medically indicated as determined by the investigator) and were contacted via telephone every 3 months. Information on adverse events (AEs – defined as any sign, symptom, illness, clinically significant abnormal laboratory value, or other adverse medical event that appeared or worsened in a patient during the clinical study, regardless of whether or not it is

considered related to the procedure used as part of the protocol), hospitalizations, ER visits for respiratory symptoms, and new or increased dosages of oral corticosteroids (OCS) for worsening of asthma symptoms were collected via a specific set of questions. An in-office evaluation was performed annually at Years 2, 3, 4, and 5 at which time the same questions as above were posed and a physical examination and pre- and post-bronchodilator spirometry were performed. Severe exacerbations, ER visits, and hospitalizations for the year prior to BT were subject-reported. One-hundred (100) subjects in the BT group who had a HRCT scan at baseline and Year 1 underwent repeat HRCT scan at Years 3 and 5.

Evaluation Periods

In order to facilitate a comparison of the durability of treatment effect over matched periods of time, the post-treatment evaluation period for the purposes of these analyses consisted of 52 week windows beginning at 6 weeks after the last BT bronchoscopy. An additional analysis of the annualized rate of exacerbations and emergency room visits beginning at the time of randomization, including the three bronchoscopies, was also performed.

Evaluation of HRCT

Baseline and Year 5 follow-up HRCT images for 93 evaluable pairs were read by an independent pulmonary radiologist who was blinded to time point (Baseline or Year 5) (J.H.M.A, over 33 years of thoracic CT experience). Upon completing this assessment, the radiologist was unblinded and assessed whether findings in follow-up images were new observations, improvements from baseline, or deteriorations from baseline. The radiologist's findings were reviewed by an independent pulmonologist (N.N.J, 24 years of pulmonology experience) who attributed a clinical significance to each finding based on subject information including lung function and AE profiles, as well as occurrence and timing of respiratory events and severe exacerbations.

Statistical Analyses

All statistical processing was performed using SAS® software Version 9.1.

Severe Exacerbations—Point estimates and 95% confidence intervals for the proportion of subjects (number of subjects with events over the total number of subjects evaluated in the period) experiencing severe exacerbations during each of the 12-month evaluation periods were calculated. The definition of severe exacerbations was derived from the definition originally utilized in the parent trial[7] and consisted of treatment with oral or intravenous corticosteroids, OR a doubling of the baseline inhaled corticosteroid [ICS] dose for at least 3 days, OR any temporary increase in the dosage of OCS for subjects taking maintenance OCS at entry into the AIR2 Trial. Additionally, the upper 95% confidence limit for the difference in proportions between 12-month follow-up periods and the first year was calculated. A non-inferiority margin of 20% was used to demonstrate that the proportions were not substantially worse during each of the subsequent evaluation periods (i.e. the upper 95% confidence limit for the difference in proportions is less than 20%). The number of subjects who completed follow-up visits for each particular year was used as the denominator to calculate the proportions of subjects with severe exacerbations during each

year. No imputations were made for missing data. A subject that terminated during the follow-up was still counted in those years that the subject provided data.

Hospitalizations and ER Visits for respiratory symptoms—Descriptive statistics with 95% CI were tabulated for the event rates (events/subject/year) and the proportions of subjects experiencing respiratory adverse events, ER visits for respiratory symptoms, and hospitalizations for respiratory symptoms for each 12-month period starting 6 weeks after the last treatment bronchoscopy.

Maintenance medications—Changes in the ICS dose from baseline to Year 5 were analyzed with the Sign test. Medication change was defined as an increase or decrease of 50% or more in daily dosage.

Sub-Group Analyses—Responder analysis based on improvements in the Asthma Quality of Life Questionnaire (AQLQ) scores at Year 1 following BT in this group showed that 79% of the subjects achieved a minimally important difference (MID) of 0.5 or more. In the absence of a control group during the long-term follow-up, key parameters were evaluated for the responders (subjects achieving an AQLQ score change of ≥0.5) and non-responders (subjects not achieving an AQLQ score change of ≥0.5).

Ethics

Written, informed consent was obtained from all participating subjects after the AIR2 Trial was approved by the Institutional Review Boards/Ethics Committees at each participating institution. The study was conducted in accordance with the principles of the Declaration of Helsinki (2004[10], 2008[11]).

Results

Of the 190 subjects who underwent BT treatment in the AIR2 Trial, 162 subjects (85.3%) completed the 5 year follow-up. The number of BT subjects completing annual follow-up at Years 1, 2, 3, 4, and 5 was 181, 165, 162, 159, and 162, respectively. Twenty-eight (28) BT subjects (14.7%) did not complete the Year 5 evaluation (18 were lost to follow-up, 4 were withdrawn by the investigators (terminal illness: 1; non-compliance with physician instructions: 3), 5 were withdrawn for nonmedical reasons, and 1 died in a motor vehicle accident). Four subjects missed the Year 4 visit, but remained in the study.

Demographics and Clinical Characteristics

The baseline demographics and clinical characteristics of the 190 subjects enrolled in the BT group in the AIR2 Trial, the 162 subjects completing follow-up at 5 years, and the 28 subjects who did not complete follow-up at 5 years are summarized in Table 1. There was no difference in baseline characteristics between the subjects completing the 5 year follow-up compared to the subjects not completing follow-up at 5 years, or the original cohort of 190 subjects at enrollment, except for age, with the cohort not completing follow up at year 5 being younger (p=0.019). At Baseline, 32% of the subjects were not-well controlled and

68% were poorly controlled according to the NAEPP EPR-3 (2007) guidelines despite their maintenance asthma medication.

Treatment Parameters

The average number of activations (± standard error of the mean) for the 3 treatment procedures were 44 ± 1.2 (Procedure 1, right lower lobe), 47 ± 1.2 (Procedure 2, left lower lobe), and 60 ± 1.6 (Procedure 3, both right and left upper lobes) with coverage of all accessible airways between 3 and 10mm in diameter. For the 162 patients that completed follow up at 5 years, the total number of activations for the 3 procedures was 151.

Severe Exacerbations

The proportion of subjects experiencing severe exacerbations (>97% of which were based on systemic corticosteroid administration) in each of Years 1 to 5 are shown in Figure 1A with the period constituting Year 1 beginning at 6 weeks after the last BT bronchoscopy. The proportion of subjects having severe exacerbations in each subsequent year (Years 2, 3, 4, and 5) compared to the first year after BT were not significantly different. In addition, the reduction in proportion of subjects experiencing severe exacerbations in the year following BT (30.9%) compared to the 12 months before BT (51.6%) was maintained for the entire 5 year follow up period with an average decrease of 44% over this period. Matched pairs analysis comparing the 162 subjects completing the Year 5 evaluations to the same group in previous years showed similar proportion of subjects having a severe exacerbation in Years 1-5 (30.9%, 23.5%, 34.0%, 36.4%, and 21.6%, respectively), representing a persistent reduction compared to the 12 months before BT when 53.1% of subjects experienced one or more exacerbations. The decrease in severe exacerbation rates that was achieved in the post-treatment period following BT in Year 1 was maintained out to 5 years (Figure 1B). Compared to the 12 months prior to BT treatment, the average reduction over 5 years in the rate of severe exacerbations was 48%. The upper 95% confidence limit for the difference in percentages for Years 2, 3, 4, and 5 compared to Year 1 (Subsequent Year – Year 1) was 0.5, 11.3, 14.0, and -1.6, respectively. All were less than the pre-defined non-inferiority margin of 20%. The rates of severe exacerbation during Years 2 through 5 were also low when compared to the annualized exacerbation rate during the approximately 64-week “Year 1” period that included both the treatment period (approximately 12-week period from the first bronchoscopy until 6 weeks after the third bronchoscopy) and post-treatment period (52-week period beginning 6 weeks after the last bronchoscopy) (online supplement, Figure 1).

There was no difference in the average proportion of subjects experiencing severe exacerbations over 5 years between subjects reporting seasonal allergy (29.3%) versus those with no allergies (29.5%). On average, patients with both FEV_1 60-70% predicted as well as those with FEV_1 >70% predicted had sustained improvements in exacerbations over the 5 year period (data not shown).

Safety

The proportions of subjects having ER visits for respiratory symptoms and the yearly rates of ER visits over the 5 years after BT are shown in Figures 1C and 1D, respectively. The

decrease in the proportion of subjects experiencing ER visits for respiratory symptoms that was achieved following BT in Year 1 was maintained out to 5 years. Compared to the 12 months before BT, the average reduction over the 5 years in proportion of subjects having ER visits for respiratory symptoms was 78%. The decrease in rates of ER visits that was achieved following BT in Year 1 was maintained out to 5 years (Figure 1D). Compared to the 12 months prior to BT treatment, the average reduction over 5 years in the rate of ER visits was 88%. The rates of ER visits during Years 2 through 5 were lower when compared to the annualized rate of the approximately 64-week Year 1 period that included both the treatment period (approximately 12-week period from the first bronchoscopy until 6 weeks after the third bronchoscopy) and post-treatment period (52-week period beginning 6 weeks after the last bronchoscopy)-(online supplement, Figure 1).

The proportion of subjects experiencing any respiratory AEs, asthma (multiple symptoms) AEs, and hospitalizations for respiratory symptoms did not increase over 5 years (online supplement Table 1). The reduction in respiratory adverse events and asthma (multiple symptoms) adverse events that was observed at one year persisted through the 5 years of follow-up, with no increase in rate from years 1 through 5 (online supplement Table 1). Respiratory adverse events that occurred at an incidence rate of ≥3.0% of subjects in any of the years 1 through 5 included sinusitis, asthma (multiple symptoms), bronchitis, cough, lower respiratory tract infections, influenza, nasopharyngitis, pneumonia, rhinitis, upper respiratory tract infections, and wheezing. There were no incidences of pneumothorax, intubation/mechanical ventilation, cardiac arrhythmias, or death as a result of BT treatment over the 5 years of follow-up. The proportion of subjects experiencing hospitalization and the rate of hospitalization for respiratory symptoms was low at baseline and remained unchanged over the 5 years after BT.

Lung Function

The percent predicted pre-bronchodilator FEV_1 values remained unchanged over the 5 years after BT and bronchodilator responsiveness was maintained over the 5 years after BT (Figure 2).

Maintenance Medication Changes

At baseline, 116 of the 162 subjects (72%) who completed evaluations at 5 years were prescribed 2 maintenance asthma medications (i.e. high dose ICS (>1000μg beclomethasone equivalent) + LABA), and 45 of the 162 subjects (28%) were prescribed 3 or more maintenance asthma medications. At 5 years following BT, 27% of subjects (44/162) had decreases of 50% or more of their ICS maintenance medications, with half of this group (21/162) having reduced their daily ICS dose to equal to or less than 500 μg/day beclomethasone equivalent. Nine of the 162 subjects (5%) subjects had an increase of 50% or greater of their ICS maintenance medications. Of those subjects with changes in ICS doses of 50% or greater, significantly more subjects had a decrease compared to those with an increase ($p<0.001$). There was an overall reduction of 17% in the average ICS dose at 5 years. Twenty of the 162 subjects (12%) were completely weaned off LABA, 9% (15/162) were weaned off ICS and LABA maintenance medications, and 7% (12/162) were no longer taking any maintenance asthma medications.

High Resolution Computed Tomography

Of the 93 evaluable HRCT pairs at Year 5, 82% showed either no radiological changes or improvement from baseline. At 5 years post-BT as compared to baseline, 71% of the HRCT pairs showed no radiologic changes of clinical significance. A similar proportion of subjects had improvements or deteriorations of clinical significance (improvements in 14% and deteriorations in 15%) and represented predominantly changes in gas trapping, bronchial wall thickening, or consolidation. Over the 5 year period, 3 subjects (3%) were noted to have increased or new bronchiectasis: one involved worsening of pre-existing bronchiectasis; one with mild bronchiectasis in two lobes, including the right middle lobe that had not been treated with BT; and one subject with newly identified bronchiectasis by HRCT at 3 years. Unfortunately, no 5 year HRCT for this subject was obtained, but the subject was clinically stable. There was no evidence of bronchial stricture, bronchiolitis obliterans or new pulmonary emphysema in any of the HRCT pairs evaluated at Year 5.

Sub-Group Analyses

The event rates (events/subject/year) averaged over Years 2 through 5 were higher in the non-responders compared to the responders: severe exacerbations, 0.720 versus 0.389; respiratory AEs, 1.487 versus 1.012; asthma (multiple symptoms) AEs, 0.745 versus 0.376; ER visits for respiratory symptoms, 0.214 versus 0.068; and hospitalizations for respiratory symptoms, 0.079 versus 0.051, respectively (online supplement Table 2).

Discussion

In this study, we examined the long-term follow-up of patients that underwent BT in the AIR2 Trial[7] via an open-label observation of post-therapy events. Previously published data have demonstrated the persistent benefits of BT out to 2 years in patients with severe persistent asthma[9]. This study demonstrates an improvement in asthma control as measured by a maintained reduction in the proportion of subjects experiencing severe exacerbations that persists out to at least 5 years post-BT. There was minimal loss to follow up with 85.3% of subjects completing the evaluations at Year 5. A 44% average reduction in the proportion of subjects experiencing severe exacerbations over a 5-year period may be associated with a substantial reduction in the use of systemic corticosteroids in these patients and provide a meaningful improvement in quality of life.

Consistent with the persistent reduction in severe exacerbations, the data also demonstrate a persistent reduction in ER visits for respiratory symptoms, with an average decrease in the proportion of subjects with ER visits over 5 years of 78% compared to the 12 months before BT. The absence of an increase in respiratory AEs and asthma (multiple symptoms) AEs over a 5 year period provides further support for the long-term effectiveness of BT. These improvements with BT were noted in the presence of reduced use of maintenance medications. Collectively, these data raise the possibility that BT may be a disease modifying therapy. Further work will be needed to test this intriguing hypothesis.

The safety of BT over the long-term is supported by the absence of any decline in lung function (no deterioration of FEV_1), the lack of increase from the low baseline rate of

hospitalizations, and the absence of any significant structural changes in the airways (from HRCT review) over the course of 5 years of follow-up. These data confirm the previously established safety profile[6-9, 12-14].

The potential for a transient increase in AEs (including severe exacerbations) around the time of BT procedures compared with sham-control subjects[7] should be considered in seeking to achieve a sustained improvement in asthma control defined by maintained reduction in severe exacerbations and ER visits out to at least 5 years following BT. The long-term benefits of BT, including a reduction in severe exacerbations and ER visits reported here, are consistent with the stated goals of asthma control as defined by the National Asthma Education and Prevention Program (NAEPP)[15]. Unlike other currently available therapies for asthma, BT appears to provide long term (years) asthma control for many patients following a one-time treatment comprising three procedures. Physicians must consider these short-term risks of the procedure along with the long-term safety and efficacy described here to assess the appropriateness of this therapy for their individual patients.

Follow-up out to 5 years in this large cohort of severe asthma subjects treated with BT addresses many concerns previously expressed regarding long-term safety of this novel therapy. Furthermore, the stable lung function as assessed by FEV_1 over 5 years and the absence of any unexpected structural alterations in HRCT scans in 93 matched HRCT pairs from subjects with severe asthma evaluated at 5 years is reassuring and consistent with findings previously reported in subjects with mild to moderate asthma following BT[12]. The observed radiological improvements or deteriorations of gas trapping, bronchial wall thickening, or consolidation at 5 years following BT represent findings that are commonly associated with severe asthma and are often temporary and transient in nature[16, 17], and have been shown in cross-sectional surveys to correlate with indicators of airway obstruction by spirometry and lung volume measurements[18]. The 3 cases of bronchiectasis are of particular interest; one had existing bronchiectasis which would currently be considered a contraindication to BT treatment, the second case developed bronchiectasis in the lingula and the untreated right middle lobe making a cause and effect relationship with BT treatment unlikely. The third case represents the only case of bronchiectasis that is theoretically possibly related to BT treatment within the study population. Gupta et al[19] have previously reported a baseline prevalence of bronchiectasis in asthma of ∼31% when compared to healthy controls (∼12.5%), so it is not clear in the present cases if the development of bronchiectasis is due to the underlying severe asthma or BT. The approximate incidence of less than 0.2% per annum in the present study is reassuring and suggests that BT does not cause bronchiectasis. While the main purpose of this study was to assess long term (5-year) durability and safety follow-up in a cohort of patients who underwent BT, as in other long term studies of therapies for severe asthma, a limitation of this study is the lack of sham-control group beyond one year, including the lack of HRCT scans for the sham-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 treatment and sham groups and this was felt to be unethical in this study population. On the other hand, maintaining sham patients in the follow-up study after breaking the blind and requiring them to continue the same treatment regimen despite poor control was deemed neither ethical nor practical and likely to result in poor patient retention, thus leading to

further difficulty in study result interpretation due to missing data and confounding. 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

While comparison to historical controls has not been possible due to the lack of studies with long-term (greater than one year) follow-up of patients with severe asthma on current standard-of-care therapy, one potential approach to address this in the present study was to compare the outcomes of those subjects who improved post-BT and those that did not improve. The analysis of the data for responders and non-responders following BT treatment (based on an AQLQ score improvement of ≥0.5 (responders) and <0.5 (non-responders)) provided insight into the subsequent course of these two groups and is consistent with previously published literature suggesting AQLQ is linked with healthcare utilization[20]; over the 5 years of follow-up, severe exacerbation rates, respiratory AE rates, asthma (multiple symptoms) AE rates, and rates of ER visits and hospitalizations for respiratory symptoms remained higher in the non-responders compared to the responders.

Despite the absence of the sham-control group comparison at 5 years, the present data are meaningful as the benefits in the BT group demonstrated in the first year after BT were maintained at 5 years. The effects of BT that were reported for the first year after the treatment were based on a mean of 151 total number of activations for the full treatment[7] and were not different for the 162 subjects that completed follow-up at 5 years. It has not been possible to demonstrate a dose response that defines a minimal number of activations that may be necessary for producing an effect at one year. The intent of bronchial thermoplasty remains to treat all accessible airways reachable by the bronchoscope and therefore activations will vary by patient airway anatomy.

The question of phenotyping to define responders cannot be addressed from the present data as assessments of exhaled nitrous oxide (FeNO), sputum eosinophils, or other biomarkers were not performed at baseline as part of the AIR2 Trial. However, there was no difference in outcomes based on the subjects' self-reported allergy status (allergic versus non-allergic). Describing the phenotypes that benefit most from this therapy remains an area of considerable interest. BT may benefit a heterogeneous group of patients with severe asthma who remain symptomatic despite standard care. These patients are identified at Steps 5 or 6 of the NAEPP guidelines[15] by the need for high dose inhaled corticosteroids and long-acting beta-agonists but who are still experiencing break through asthma symptoms. Although patients in this study were reasonably stable (i.e. FEV_1>60%, no more than 3 hospitalizations in the prior year and 8 or fewer puffs of rescue medications per day on average) and able to undergo bronchoscopy, the experience of the patients with severe refractory asthma in the RISA Trial[5] (i.e. no limit on previous hospitalizations or rescue medication use) provides assurance that more severe patients may also benefit from BT.

These data demonstrate that BT is an effective and safe therapy. The improvements in asthma control in the post-treatment period at one year based on reduction in severe exacerbations and ER visits compared to the Sham control group[7] are maintained for at least 5 years in the BT group of patients with severe persistent asthma. A single BT treatment comprising 3 procedures provides long-term benefit to at least 5 years. Whether BT is a

disease-modifying therapy will depend upon results of future appropriately designed clinical studies. BT has become an important addition to our treatment armamentarium for patients with severe persistent asthma who remain symptomatic despite taking ICS and LABA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Author contributions

Dr. Wechsler had full access to the data and vouches for the integrity of the data and the accuracy of the data analysis, including adverse events.

Dr. M.E. Wechsler: contributed to the acquisition and interpretation of the data, writing and critical revision of the article for important intellectual content, and final approval of the version to be published.

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Dr. M Simoff: In the past 3 years MS has been involved in the Lung Cancer Guidelines, 3rd edition, by the American College of Chest Physicians as a Chapter Editor, all relationships for research, consulting, and advisory boards has been reviewed regularly by the American College of Chest Physicians. He is on the Medical Advisory Board for Varian Medical with all honorarium donated to charitable organizations as per agreements with the American College of Chest Physicians. Industry sponsored grants have come from Boston Scientific – Asthmatx, for ongoing work in bronchial thermoplasty, and is part of a grant from Varian Medical for $100,000.00 analyzing tissue samples in radiation therapy treated lung cancer patients for molecular markers, which suggest improved result. No other conflict to report.

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Mr. B Armstrong: BA is an employee of QST Consultations which was paid more than $100,001 from Asthmatx/Boston Scientific in consultancy fees.

Dr. M Castro: MC reported consultancies with Schering, Asthmatx, Genentech, IPS, Pulmogen, and Sanofi-Aventis; grants pending from American Lung Association, Asthmatx, Amgen, Ception, Genentech, MedImmune, Merck, Novartis, GlaxoSmithKline, and Sanofi-Aventis; lecture fees from Boehringer, Pfizer, Merck, GlaxoSmithKline, Genentech, Asthmatx; and royalties from Elsevier.

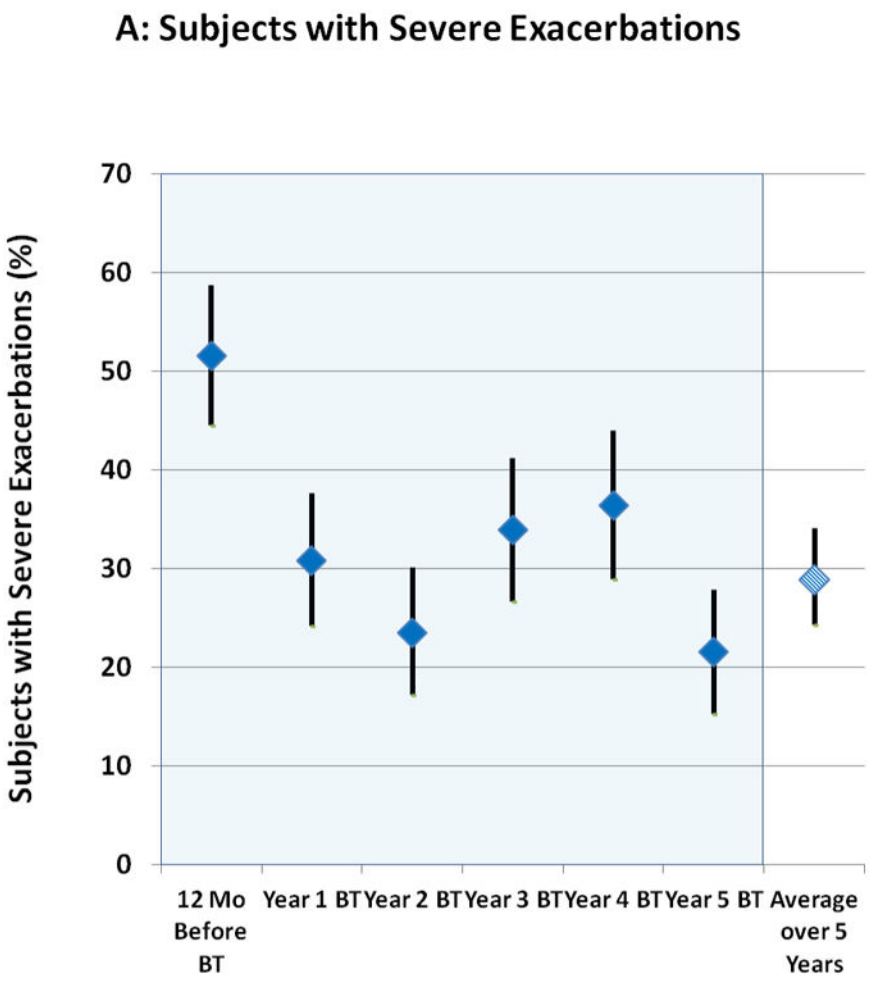
Abbreviations List

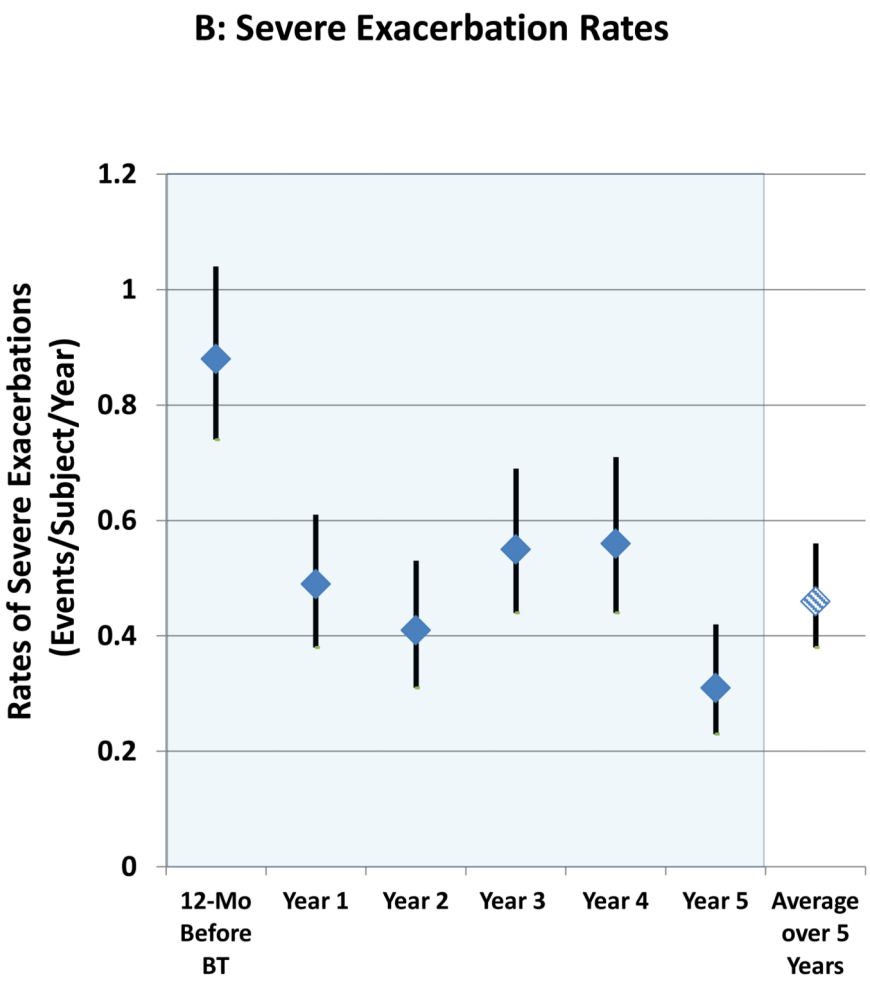
AEA	Adverse Event

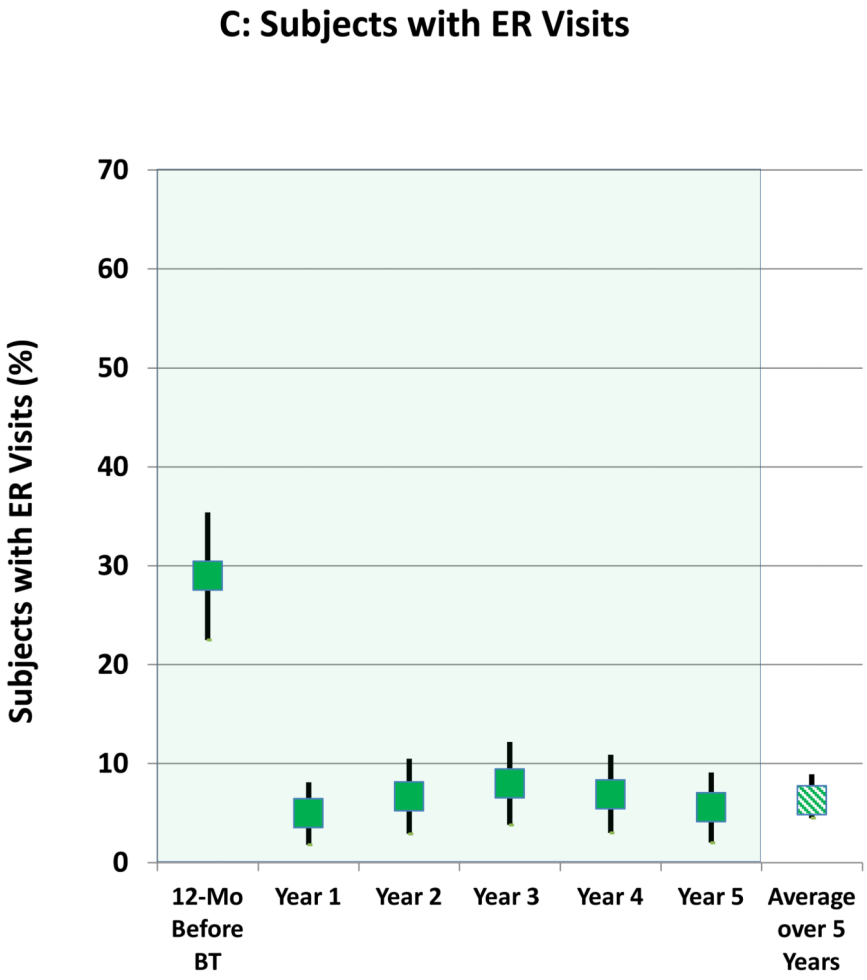
AIR2	Asthma Intervention Research 2
AQLQ	Asthma Quality of Life Questionnaire
BD	Bronchodilator
BT	Bronchial Thermoplasty
CI	Confidence Interval
ER	Emergency Room
FEV_1	Forced Expiratory Volume in 1 second
HRCT	High Resolution Computed Tomography
ICS	Inhaled Corticosteroid
LABA	Long-acting beta-agonist
MID	Minimal Important Difference
PEF	Peak Expiratory Flow
OCS	Oral Corticosteroids

Clinical Implications

With 5 years of data demonstrating safety and durability of effect, bronchial thermoplasty should be considered for severe persistent asthma patients who remain symptomatic despite taking inhaled corticosteroids and long-acting-β_2-agonists.







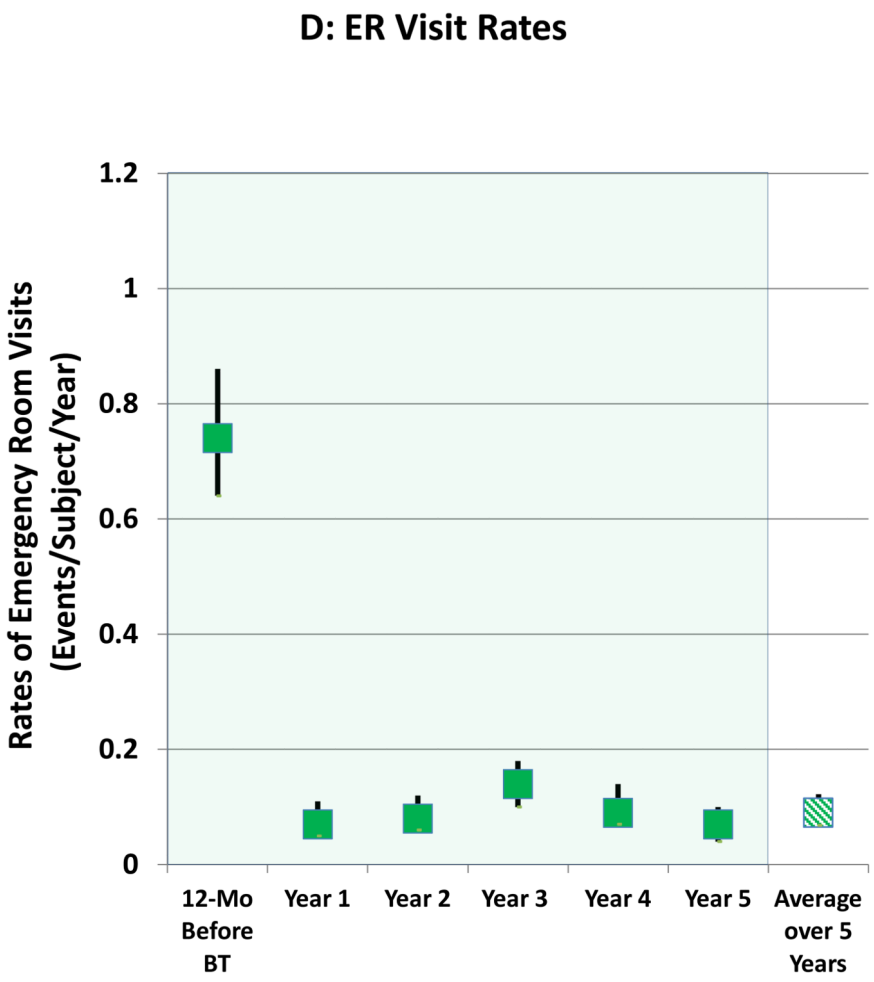


Figure 1. Severe Exacerbations and Emergency Room Visits In the 5 Years Following BT

A: Proportion of subjects with severe exacerbations; B: Severe exacerbation rates; C: Proportion of subjects with Emergency Room visits for respiratory symptoms; D: Emergency Room visit rates. Values are point estimates with 95% upper and lower CIs. The 365 day period constituting Year 1 began at 6 weeks after the last BT bronchoscopy.

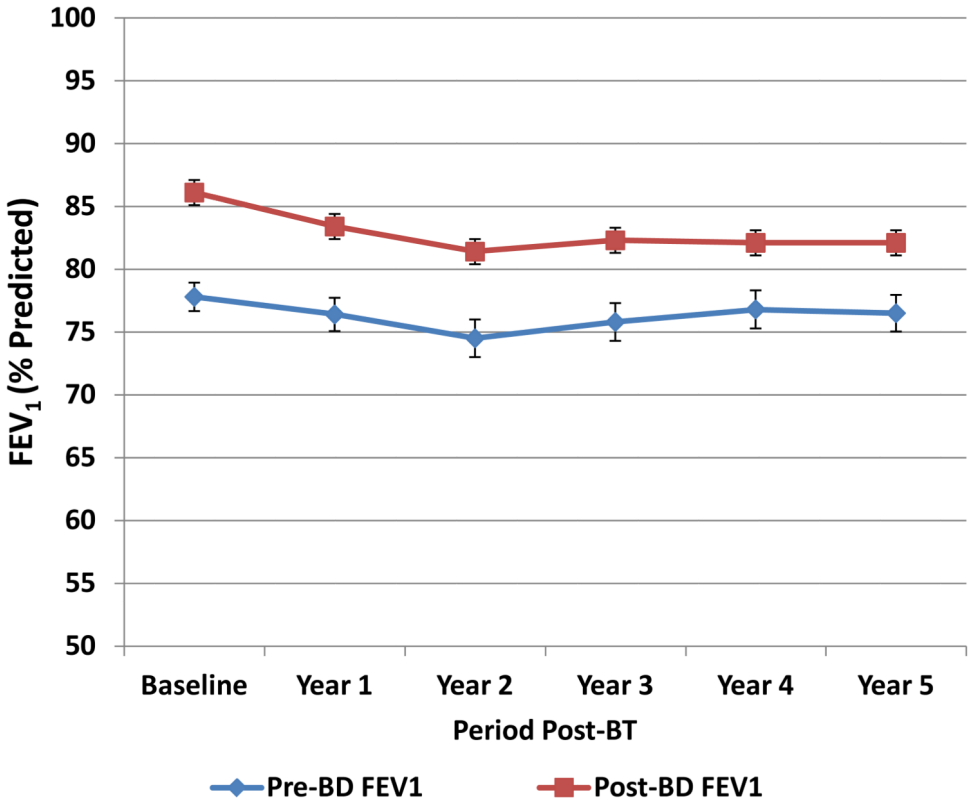


Figure 2. Pre- and Post-bronchodilator FEV_1 over 5 Years (% Predicted)

Percent predicted pre- and post-bronchodilator FEV_1 values (mean ± SEM) for subjects completing follow-up during each year. The percent predicted pre-bronchodilator FEV_1 values remained unchanged over the 5 years after BT and bronchodilator responsiveness was maintained over the 5 years after BT.

Table 1
Demographics and Clinical Characteristics

	All BT Subjects at Baseline (n= 190)	BT Subjects completing 5 Year Follow-up (n= 162)	BT Subjects Not completing 5 Year Follow-up (n= 28)
Age (years)	40.7 ± 11.9	41.5 ± 11.8	35.8 ± 11.3[d]
Gender	Male: 81 (42.6%) Female: 109 (57.4%)	Male: 68 (42.0%) Female: 94 (58.0%)	Male: 13 (46.4%) Female: 15 (63.6%)
Race			
Caucasian	151 (79.5%)	134 (82.7%)	17 (60.7%)
African American/Black	19 (10.0%)	13 (8.0%)	6 (21.4%)
Hispanic	6 (3.2%)	4 (2.5%)	2 (7.1%)
Asian	4 (2.1%)	3 (1.9%)	1 (3.6%)
Other	10 (5.3%)	8 (4.9%)	2 (7.1%)
Weight (kg)	81.7 ± 18.4	81.4 ±17.1	83.4 ± 24.6
ICS Dose (μg)[a]	1960.7 ± 745.2	1958.9 ±757.9	1900 ± 551.6
LABA Dose (μg)[b]	116.8 ± 34.4	120.8 ± 47.7	108.9 ± 23.8
Symptom-Free Days (%)	16.4 ± 24.0	16.1 ± 24.1	18.4 ± 24.1
Asthma Control Questionnaire (ACQ) Score	2.1 ± 0.87	2.1 ± 0.84	2.3 ± 1.02
Asthma Quality of Life Questionnaire (AQLQ) Score	4.30 ± 1.17	4.32 ± 1.17	4.23 ± 1.16
Emergency Room Visits for Respiratory Symptoms in prior 12 months [c] No. Events (No. Subjects)	141 (55)	115 (47)	26 (8)
Hospitalizations for Respiratory Symptoms in prior 12 months [c] No. Events (No. Subjects)	10 (8)	10 (8)	0 (0)
Seasonal allergies (n[%])[c]			
Yes	103 (54.5%)	85 (52.8%)	18 (64.3%)
No	86 (45.5%)	76 (47.2%)	10 (35.7%)
Lung Function Measures			
Pre-bronchodilator FEV_1	77.8 ± 15.65	77.8 ± 15.84	78.0 ± 14.75
Post-bronchodilator FEV_1	86.1 ± 15.76	85.9 ± 15.83	87.1 ± 15.57
Morning PEF (L/min)	383.8 ± 104.3	380.9 ± 106.0	400.7 ± 93.8
Methacholine PC_{20} (mg/ml) Geometric mean [range]	0.27 [0.22, 0.34]	0.27 [0.21, 0.35]	0.29 [0.15, 0.54]

Definition of abbreviations: BT = Bronchial Thermoplasty; ICS = Inhaled Corticosteroid; LABA = Long-Acting β_2-Agonist; PEF = Peak Expiratory Flow; FEV_1 = Forced Expiratory Volume in 1 second Values are mean ± SD except when indicated otherwise.

[a] Beclomethasone or equivalent;

[b] Salmeterol or equivalent;

[c] Patient reported;

[d] p=0.019 comparing subjects completing 5 year follow-up versus subjects not completing 5 year follow-up (t-test)