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Bronchial Thermoplasty in Patients With Severe Asthma at 5 Years: The Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma Study

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Bronchial Thermoplasty in Severe Asthmatics At 5 Years: The PAS2 Study

Running Head: Bronchial Thermoplasty in Severe Asthmatics

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Dr. Chupp was a member of the Boston Scientific Corporation speaker's bureau during the conduct of the study, was an asthma clinical trial investigator, advisory board consultant, and speakers' bureau member for GlaxoSmithKline, AstraZeneca, Genentech, Sanofi-Genzyme, Regeneron, Amgen, and Boehringer Ingelheim and was an asthma advisory board member for Teva Pharmaceuticals. Dr. Kline reports grants from Boston Scientific Corporation during the conduct of this study. Dr. Khatri reports grants from Boston Scientific during the conduct of the study. Dr. McEvoy reports grants from Boston Scientific Corporation and grants from AstraZeneca during the conduct of the study, as well as grants from National Institutes of Health (US), grants from Department of Defense (US), grants from GlaxoSmithKline, grants from PCORI, grants from COPD Foundation, and personal fees from Respirtech (A Phillips Company), all outside the submitted work. Dr. Silvestri has nothing to disclose. Dr. Shifren reports grants from Boston Scientific during the conduct of the study and personal fees from Genentech and Boehringer Ingelheim, both outside the submitted work. Dr. Castro received university grant funding from the National Institutes of Health, the American Lung Association, and PCORI, and received pharmaceutical grant funding from AstraZeneca, GlaxoSmithKline,

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Data Sharing Statement: The data and study protocol for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/en-US/data-sharing-requests.html). For questions related to Boston Scientific Data Sharing Requests contact ClinicalSolutions@bsci.com.

Key Words: Severe asthma, bronchial thermoplasty, asthma subgroups, severe exacerbations, corticosteroid exposure

ABBREVIATIONS

AE	Adverse event
AIR	Asthma Intervention Research
AIR2	Asthma Intervention Research 2
AQLQ	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
BL	Baseline
BMI	Body mass index
BT	Bronchial thermoplasty
Eos	Eosinophils
ED	Emergency department
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GLM	Generalized linear model
ICS	Inhaled corticosteroids
LABA	Long-acting β-agonist
mL	milliliters
NAEPP	National Asthma Education and Prevention Program
Neu	Neutrophils
Norm	Normal
OCS	Oral corticosteroids

PAS2	Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma
Pre-Br	Pre-bronchodilator
RCT	Randomized controlled trial
RISA	Research in Severe Asthma
μg	micrograms
μL	microliters

ABSTRACT

Background: Bronchial thermoplasty is a device-based treatment for subjects ≥18 years with severe asthma poorly controlled with inhaled corticosteroids and long-acting beta-agonists. The Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (PAS2) study collected data on severe asthmatics undergoing this procedure.

Research Question: What are the 5-year efficacy and safety results in severe asthmatics who have undergone bronchial thermoplasty?

Study Design and Methods: This was a prospective, open-label, observational, multi-center study conducted in the United States and Canada. Subjects aged 18-65, taking inhaled corticosteroids ≥1000μg/day (beclomethasone or equivalent) and long-acting β-agonists ≥80μg/day (salmeterol or equivalent) were included. Severe exacerbations, hospitalization, emergency department visits, and medication usage were evaluated for the 12 months prior to and at years 1-5 post-treatment. Spirometry was evaluated at baseline and at years 1-5 post-treatment.

Results: 284 subjects were enrolled at 27 centers; 227 subjects (80%) completed 5 years of follow-up. By year 5 post-treatment, the proportion of subjects with severe exacerbations, emergency department visits, and hospitalizations was 42.7%, 7.9%, and 4.8%, respectively, compared to 77.8%, 29.4%, and 16.1% in the 12 months prior to treatment. The proportion of subjects on maintenance oral corticosteroids decreased from 19.4% at baseline to 9.7% at 5 years. Analyses of subgroups based on baseline clinical and biomarker characteristics revealed a statistically significant clinical improvement among all subgroups.

Interpretation: Five years after treatment, subjects experienced decreases in severe exacerbations, hospitalizations, emergency department visits and corticosteroid exposure. All subgroups demonstrated clinically significant improvement, suggesting that bronchial thermoplasty improves asthma control in different asthma phenotypes.

Clinical Trial Registry: http://www.clinicaltrials.gov, NCT01350336

Asthma is a chronic disease of the airways characterized by airway inflammation, excess mucus production, airway hyperresponsiveness, and variable airflow obstruction. Ten percent of patients have severe, poorly controlled disease despite optimal medical therapy. These patients account for more than 80% of asthma-related healthcare costs.[1-3]

Bronchial thermoplasty (BT) is the only FDA-approved procedure for the treatment of asthma. It is indicated for patients ≥18 years with severe persistent asthma not well controlled with inhaled corticosteroids (ICS) and long-acting bronchodilators (LABA). BT employs radiofrequency energy to heat the airway walls in a controlled manner. The mechanism of action is attributed to a reduction in airway smooth muscle (ASM) mass after the procedure[4-9]. Reduction in ASM has been associated with clinical improvement seen in patients undergoing BT[5,6]. Other structural and immunohistological changes after BT, including reduction in reticular basement membrane thickness, reduction in collagen type I deposition, and changes in neuroendocrine cells, may also contribute to clinical improvement[4,6,10,11].

Several randomized controlled clinical trials (RCT) of BT have been carried out in subjects with moderate to severe asthma – including the AIR, RISA, and AIR2 studies[12-15]. These studies demonstrated improvements in asthma control following BT, including decreased numbers of asthma exacerbations, ED visits, and hospitalizations. In addition, subjects experienced improved quality of life as measured by Asthma Quality of Life Questionnaire (AQLQ) scores[15]. These improvements persisted for at least 5 years and side effects were minimal[14]. Nevertheless, data obtained from prospective studies with more clinically realistic eligibility criteria than those defined by previous RCTs can provide reassurance that these results can be duplicated in clinical practice, which often includes subjects with more severe disease.

Following FDA approval in 2010, the "Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma (PAS2)" study was initiated. An interim analysis of data from the first 190 PAS2 subjects confirmed previous reports that BT is safe and effective[16]. Although the PAS2 subjects were sicker than those in the AIR2 trial (94.7% of PAS2 subjects vs. 82.1% of AIR2 subjects were classified as severe asthmatics based on the ERS/ATS guidelines), the results from these 190 PAS2 subjects were comparable to those from the 190 BT subjects studied in AIR2. PAS2 subjects had reduced rates of exacerbations, hospitalizations and ED visits at 3 years post-BT compared to the 12 months prior to BT, indicating a consistent and durable treatment effect. This analysis also showed, for the first time, that patients sustainably reduced asthma medication post-BT, including complete discontinuation of maintenance oral corticosteroids (OCS) in a significant proportion of subjects.

Here, we describe the clinical outcomes over five years following BT for the full cohort of 284 PAS2 subjects. Analyses of subgroups based on baseline clinical and biomarker characteristics were also performed to investigate potential correlations with responses to BT.

METHODS

Study Design

The PAS2 study design has been previously published[16]. PAS2 was a prospective, open-label, observational, multi-center clinical study (NCT01350336; clinicaltrials.gov) to investigate the 5-year efficacy and safety of BT. The study was approved by the Ethics committee at each participating site and all subjects signed an informed consent form prior to participation. The last subject exited the study in November 2019 after completing the 5-year follow-up visit.

Study Subjects

Between 2011 and 2014, PAS2 enrolled subjects between 18-65 years whose asthma was inadequately controlled despite optimized treatment with high ICS and LABA doses (ICS ≥1000 μg/day [beclomethasone or equivalent] and LABA ≥80 μg/day [salmeterol or equivalent]). Subjects were allowed asthma medications in addition to ICS and LABA/SABA (short-acting beta-agonists), including OCS and/or omalizumab. Subjects diagnosed with other severe respiratory diseases were excluded. Other eligibility criteria for PAS2 have been previously described[16].

Treatment

BT treatments were administered using the Alair™ Bronchial Thermoplasty System (Boston Scientific, Marlborough, MA) per FDA labeling by the investigators as previously described[14,15].

Follow-up

PAS2 subjects were evaluated 2 weeks following each of the first 2 BT procedures and 6 weeks after the third (the end of the treatment period). Subjects were scheduled to be seen at annual in-person visits for 5 years after the BT treatments and by phone every 3 months between visits.

Outcome Measures

The primary objective of PAS2 was to demonstrate the durability of treatment effect after BT. Severe asthma exacerbations, ED visits, and hospitalizations for respiratory symptoms during the 5 years after BT were compared to the respiratory events which occurred during the 12-month period prior to BT. Severe exacerbations were defined as a worsening of asthma symptoms requiring the use of systemic corticosteroids (tablets, suspension, or injection; for further details,

see **Supplementary Methods 1**)[17]. Other outcome measures used in PAS2 have been previously described[16].

Adverse Event Monitoring

Adverse events were collected peri-procedurally (defined as the period beginning on the day of the first BT procedure and ending 6 weeks after the last BT procedure) and at each follow-up visit in the post-treatment period. For further description of how adverse events were defined, see **Supplementary Methods 1**.

Statistical Analyses

Baseline demographics, clinical characteristics, and outcomes were summarized with sample size, mean, standard deviation, minimum and maximum for continuous variables and with proportions (numerator over denominator) for binary variables. To compare proportions, counts of events, and doses between baseline and years 1-5, the Fisher's exact test, negative binomial test and t-test were used, respectively. For the subgroup analyses, a generalized linear model (GLM) with binomial or negative binomial error distribution was fit with factors of the subgroup, time and interaction of subgroup and time; if the interaction had a p-value<0.10, contrasts of time within subgroup and subgroup within time were performed to explore differences. SAS version 9.4 was used for all analyses.

RESULTS

Baseline demographics and clinical characteristics

Of 284 subjects enrolled, 279 (mean age 45.7±11.6 years) underwent BT as previously described[16], and 227 (81%) subjects completed 5 years of follow-up (**Supplementary Figure 1)**.

Subjects were 64.5% female with mean body mass index (BMI) 32.2±7.5 kg/m^2, and were 84% Caucasian, 9% black or African heritage, and 7% from other racial groups. Subjects had mean AQLQ score of 4.03±1.28, had asthma diagnosis on average 25.2 years prior to BT, and based on the ERS/ATS Guidelines for Severe Asthma[18], 95% of subjects were considered severe asthmatics (**Table 1)**.

Baseline demographics were similar between the 227 subjects followed for 5 years and the 52 subjects who were not. A larger proportion of the subjects not followed for 5 years experienced severe exacerbations (92.3% vs. 74.4%), ED visits (51.9% vs. 24.2%), and hospitalizations (30.8% vs. 12.8%) during the 12 months before BT compared to the 227 subjects followed for 5 years (**Table 2**). This indicates that the subjects who dropped out of the PAS2 study may have had more severe disease and thus some subjects with the most severe asthma were not included in the analysis.

Severe asthma exacerbations, ED visits, and hospitalizations

During the 12 months prior to BT, 77.8% of subjects experienced at least one severe exacerbation, compared to 50.4% after 1 year, 46.8% after 2 years, 47.0.% after 3 years, 44.2% after 4 years, and 42.7% after 5 years of follow-up (77.8% vs. 50.4%, 46.8%, 47.0%, 44.2%, and 42.7%, $p<0.001$) (**Table 1 and Figure 1**). There was also a significant reduction in the rate of

severe exacerbations from baseline (1.61 exacerbations/subject) to 5 years (0.72 exacerbations/subject; p<0.001). There were 61.8% (68/110) subjects with ≤1 severe exacerbations during the 12 months prior to BT who experienced ≤1 severe exacerbation per year following BT treatment compared to 35.0% (41/117) subjects with ≥2 severe exacerbations during the 12 months prior to BT (**Table 3**).

The proportion of subjects with ED visits significantly decreased from 29.4% during the 12 months prior to BT to 18.3%, 14.7%, 13.0%, 11.7%, and 7.9% during Years 1 through 5, respectively, after BT (p< 0.001) (**Figure 1**). ED visit rates were also reduced from 0.54 ED visits/subject in the 12 months prior to BT to 0.13 ED visits/subject in Year 5 (p=0.0002). A decrease in hospitalizations was also observed after BT (**Figure 1**); 16.1% of subjects were hospitalized for asthma in the year prior to BT, but during Years 1-5, only 8.0%, 7.5%, 7.3%, 3.3%, and 4.8%, respectively, were hospitalized (p=0.0003). Annual hospitalization rates fell from 0.22 hospitalizations/subject at baseline to 0.06 hospitalizations/subject at Year 5 after BT (p=0.0012).

The PAS2 data confirms reductions in these outcomes demonstrated in the AIR2 study (**Figure 1)**.

Spirometry

Spirometry was performed at baseline and at yearly follow-up visits for all subjects. BT did not alter spirometric parameters as reported in previous studies[6,14,19,20] (**Supplementary Figure 2**).

Medication usage

PAS2 subjects reduced asthma maintenance medications. Notably, clinical improvements were accompanied by a reduction in corticosteroid exposure. The mean daily ICS dose of 2272 μg/day (beclomethasone or equivalent) at baseline was sustainably reduced to 1928 μg/day, by Year 5 post-BT (**Table 4**).

The percentage of subjects using biologic medications for asthma control remained relatively constant (15.8%-18.5%) over the course of the study (**Table 4**). At baseline, omalizumab was used exclusively. In subsequent years, some subjects began using mepolizumab, benralizumab, and reslizumab as these monoclonal antibodies were introduced (**Table 4)**.

Additionally, 54 (54/279: 19.4%) subjects were taking maintenance OCS at the baseline visit. After BT treatment, 10.7%, 10.2%, 10.0%, 8.1%, and 9.7% of subjects were taking maintenance OCS at the 1-5-year follow-up visits, respectively (**Table 4**). Twenty-two (42%) of the 54 subjects taking OCS at baseline discontinued OCS after BT (**Figure 2**), and only 6 of these 22 subjects then used a biologic. The proportion of subjects with severe exacerbations among those 22 fell from 95.5% at baseline to 50.0% at Year 5 following BT treatment (**Figure 2**). In these subjects BT not only reduced OCS exposure, but also severe exacerbations, ED visits and hospitalizations.

Clinical improvements in the 32 subjects who continued taking OCS medications after BT were similar. In this case, 18/32 subjects also used a biologic for asthma maintenance. The proportion of the 32 subjects experiencing severe exacerbations was reduced from 93.8% at baseline to 51.9% at Year 5 after BT. These reductions in the proportion of subjects experiencing severe exacerbations were comparable to subjects who never used maintenance OCS (73.3%

experienced severe exacerbations at baseline vs. 42.7% at Year 5 after BT), even though patients using maintenance OCS may have had more severe disease at baseline (**Figure 2**).

Only 9 subjects who were not taking OCS at baseline began taking these medications for asthma control after BT. These patients did not experience a reduction in severe exacerbations.

Adverse Events

Bronchoscopic procedures can worsen asthma-related symptoms in the short term and induce other complications in severe asthmatics[21-23]. While the percentage of subjects with peri-procedural respiratory serious AEs (requiring hospitalization or prolongation of hospitalization) during the treatment phase was 14.7% (**Table 5**), respiratory serious AEs were reduced during the post-treatment phase to 9.4% during Year 1 after BT and to 4.7% during Year 5 after BT. During this study, 4 deaths, all unrelated to BT, occurred. Two males, aged 50 and 55 years, died of cardiac arrest. The 55-year-old male was found unresponsive (pulseless and asystolic) at home approximately 3 years after the third BT procedure. The 50-year-old male died of cardiac arrest shortly after completing the third BT treatment. A 57-year-old female subject died of myocardial infarction approximately two years after the final BT treatment after cardiac catheterization/stenting for severe arterial stenoses failed. A 53-year-old male died approximately 3 years after his last BT procedure of unknown causes. This subject had severe obstructive sleep apnea and died in his sleep; no autopsy was performed.

Subgroup analysis

We analyzed subgroups of subjects to see if BT was effective in reducing severe exacerbations, ED visits, and hospitalizations. Subgroups included: gender, age (<40 and ≥40 years), BMI (<30 and ≥30 kg/m^2), baseline AQLQ (<4.0 and ≥4.0), baseline OCS use (yes and no), baseline

omalizumab use (yes and no), and complete activations (≤140 and >140). We also analyzed subgroups based on baseline pre-bronchodilator FEV_1/FVC (≤70% and >70%), and bronchodilator reversibility (fixed or reversible)[24], as well as baseline blood counts of eosinophils (≤150 and >150 cells/μL), neutrophils (≤5000 and >5000 cells/μL), and both eosinophils and neutrophils (both eosinophils ≤150 cells/μL and neutrophils ≤5000 cells/μL and at least one of eosinophils >150 cells/μL or neutrophils >5000 cells/μL)[25-27].

Our analysis indicated there was a significant decrease in severe exacerbations, ED visits, and hospitalizations over time for all sets of subgroups (**Figure 3, Supplemental Table 1, Supplemental Figure 3; for more detail see Supplemental Results 1**), showing that all examined subgroups of subjects benefitted from BT.

For subgroups based on blood eosinophil and neutrophil counts, significant differences in the percentages of subjects experiencing hospitalizations and severe exacerbations after BT were observed in the subgroups based on baseline blood eosinophil and neutrophil counts, respectively. There were no differences in subgroups based on both baseline blood eosinophil and neutrophil counts (**Figure 4**). Subjects with eosinophil counts of ≤150 cells/μL had consistently higher percentages of subjects experiencing hospitalizations than subjects with eosinophil counts >150 cells/μL in the 12 months before and in the years following BT treatment. Subjects with neutrophil counts ≤5000 cells/μL had consistently lower percentages of severe exacerbations than subjects with neutrophil counts >5000 cells/μL in the years following BT treatment, but not during the 12 months before BT. (**Figure 4, middle** and **bottom**).

DISCUSSION

With 284 patients enrolled, PAS2 is the largest study to date designed to evaluate the effectiveness and safety of BT and the durability of treatment effect in subjects with poorly controlled asthma despite treatment with the current standard of care. Previous clinical trials of BT (AIR, AIR2, and RISA) have shown that the procedure is safe and effective, but subjects enrolled in these clinical trials may not be representative of the most severe asthma cases considered for BT in clinical practice. For example, the AIR2 RCT excluded patients with insulin-dependent diabetes, interstitial lung disease, chronic sinus disease, obstructive sleep apnea, and other common comorbidities found in asthmatics, but the PAS2 study allowed participation of subjects with these conditions. Recent publications have reported on BT in more severe asthmatics that were older and had worse baseline lung function and quality of life[4,6-8,28]. The data indicated a clinical improvement post-BT in these subjects as well as acceptable rates of adverse events. Additionally, Chaudhuri et. al. recently reported that the clinical improvements following BT can last for 10 or more years after treatment in some subjects[29]. PAS2 adds to the body of evidence demonstrating the long-term safety and effectiveness of BT outside the setting of RCTs.

While PAS2 is a single-arm study, the findings are important and confirm previously published interim results in this population[16], indicating that clinically relevant improvements in asthma control (particularly significant reductions in severe exacerbations) are sustainable to 5 years of follow-up.

The severe asthmatics in PAS2 had relatively well-preserved pulmonary function (FEV_1 in the 75-80% range)[30]. Asthmatics, particularly those with severe asthma, experience a progressive

decline in lung function as measured by FEV_1 with time (22.5-50 mL/year). Subjects who experience more severe exacerbations per year tend to exhibit a more rapid decline in FEV_1[30-33]. As in previous publications[14-16], there is no significant decline in FEV_1 and FVC out to 5 years following BT, highlighting the long-term safety of the BT procedure.

In PAS2, 14.7% of subjects experienced procedure-related SAEs during the treatment period. This was slightly higher than in previously reported trials of BT[14,34], perhaps due to enrollment of subjects with more severe asthma and more comorbidities in PAS2. The most common peri-procedural respiratory SAE was asthma aggravation (77.8%), due in part to the length of the bronchoscopic procedure required and/or the thermal injury sustained during the procedure. While hospitalization was required for all peri-procedural respiratory SAEs, intubation and/or mechanical ventilation was reported in only 4 cases, 2 due to hemoptysis. One occurred one week after the second BT treatment; the subject was intubated, underwent bronchoscopy to suction a blood clot, and had the third BT treatment. The second occurred one month after the third BT procedure; the subject was intubated, an embolization procedure was performed, and the subject completed follow-up. A third subject experienced vocal cord spasm 30 minutes after the first BT treatment and required intubation until the spasm resolved; the subject recovered but did not undergo further BT treatments. The last subject experienced an asthma exacerbation requiring intubation in the ED one day after the second BT treatment; the subject recovered and completed the third BT treatment, but withdrew before the 3-year follow-up.

PAS2 subjects were able to reduce exposure to corticosteroid medications, particularly OCS, after BT. Forty-two percent of subjects on OCS were able to completely discontinue them after BT treatment while simultaneously improving asthma control. This is encouraging, as daily use of OCS is associated with significant side effects and negative impact on quality of life[35]. This

suggests that BT should be considered as a treatment option for patients who are taking systemic corticosteroids and are experiencing or concerned about these side effects[36].

Although we were unable to identify a specific subgroup of patients in which BT was most effective using baseline data, it is important to note that BT was effective in all subgroups, including subjects with both fixed and reversible airways and both high and low eosinophil counts. Interestingly, patients with low blood eosinophil counts responded favorably to BT, suggesting that BT can be considered as a treatment option for patients that are not candidates for a biologic therapy[37,38].

One limitation of the PAS2 study was that it did not include a sham or control group, and the effect of closer follow-up of patients in the setting of a clinical study on potential medication reductions and improvement in asthma control cannot be ruled out. Another limitation is that, as in all open-label extension studies, the subjects who were not followed for the entire 5-year period tended to be more severe asthmatics with worse prognosis, which introduced bias. While changes in quality-of-life scores (AQLQ) would have been useful to present, AQLQ scores were only collected at baseline in PAS2 and we were unable to analyze the effect BT had them. The PAS2 subjects were heterogeneous in terms of asthma phenotype, and the subgroup analysis based on asthma phenotype was post-hoc and based on counts of blood eosinophils and neutrophils taken at baseline for a subset of subjects. However, it has been hypothesized that sputum cellular profiles may be a more accurate measure of the type of inflammation occurring in the airways, as blood counts of eosinophils and neutrophils may not always correlate perfectly with sputum cellular profiles[37]. This limited our ability to accurately phenotype the subjects. Studies in which asthma phenotype is more clearly defined are required to determine whether certain types of asthma respond better to BT. Finally, as we did not compare responses after BT

to responses to biologics, it is not known whether the response to biologics in this study population would have been more pronounced than the response to BT. It is possible that since biologics selectively target pro-inflammatory pathways, and BT largely acts on processes involved in airway remodeling, the two treatments could be complementary in severe asthmatics with evidence of both airway inflammation and airway remodeling. We did observe that BT was safe and improved clinical outcomes regardless of whether or not biologic medications, including those targeting IL5, were initiated after treatment (data not shown); however, we recognize that the PAS2 study was not controlled and that the asthma treatment landscape is shifting, which is a challenge for all trials involving this disease.

INTERPRETATION

Five years after treatment, PAS2 subjects experienced decreases in severe exacerbations, hospitalizations, ED visits and corticosteroid exposure. Subgroup analyses suggested that BT improves asthma control in different asthma phenotypes. BT may be a valuable add-on therapy for the treatment of severe asthma. It may also be a treatment option for severe asthmatics who do not qualify for biologic therapy.

TAKE-HOME POINTS

Study Question: What are the 5-year efficacy and safety outcomes in severe asthmatics who have undergone bronchial thermoplasty?

Results: Out of 284 subjects enrolled in the PAS2 study, 227 subjects (80%) completed 5 years of follow-up. By year 5 post-treatment, the proportion of these subjects with severe exacerbations, emergency department visits, and hospitalizations was 42.7%, 7.9%, and 4.8%, respectively, compared to 77.8%, 29.4%, and 16.1% in the 12 months prior to treatment. The

proportion of subjects on maintenance oral corticosteroids decreased from 19.4% at baseline to 9.7% at 5 years. Subgroup analyses based on baseline clinical and biomarker characteristics revealed a statistically significant clinical improvement among all subgroups, including those based on eosinophil and neutrophil counts.

Interpretation: Five years after treatment, subjects experienced decreases in severe exacerbations, hospitalizations, emergency department visits and corticosteroid exposure, indicating clinically relevant improvements in asthma control. The subgroup analyses performed indicate BT may be a valuable add-on therapy for the treatment of subjects with severe asthma including those on OCS and omalizumab. BT may also be a treatment option for severe asthmatics who cannot use or do not qualify for biologic therapy for asthma, such as those with non-eosinophilic disease.

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REFERENCES

1. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. *J Allergy Clin Immunol.* 2011;127(1):145-152.
2. Smith DH, Malone DC, Lawson KA, Okamoto LJ, Battista C, Saunders WB. A national estimate of the economic costs of asthma. *Am J Respir Crit Care Med.* 1997;156(3 Pt 1):787-793.
3. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med.* 2009;9:24.
4. Chakir J, Haj-Salem I, Gras D, et al. Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Collagen Deposition in Asthma. *Ann Am Thorac Soc.* 2015;12(11):1612-1618.
5. Pretolani M, Dombret MC, Thabut G, et al. Reduction of airway smooth muscle mass by bronchial thermoplasty in patients with severe asthma. *Am J Respir Crit Care Med.* 2014;190(12):1452-1454.
6. Pretolani M, Bergqvist A, Thabut G, et al. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: clinical and histopathological correlations. *J Allergy Clin Immunol.* 2016.
7. Salem IH, Boulet LP, Biardel S, et al. Long-Term Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Reticular Basement Membrane Thickness in Severe Asthma. *Ann Am Thorac Soc.* 2016;13(8):1426-1428.
8. Denner DR, Doeing DC, Hogarth DK, Dugan K, Naureckas ET, White SR. Airway Inflammation after Bronchial Thermoplasty for Severe Asthma. *Ann Am Thorac Soc.* 2015;12(9):1302-1309.

9. Goorsenberg AWM, d'Hooghe JNS, Srikanthan K, et al. Bronchial Thermoplasty Induced Airway Smooth Muscle Reduction and Clinical Response in Severe Asthma. The TASMA Randomized Trial. *Am J Respir Crit Care Med.* 2021;203(2):175-184.

10. Dombret MC, Alagha K, Boulet LP, et al. Bronchial thermoplasty: a new therapeutic option for the treatment of severe, uncontrolled asthma in adults. *Eur Respir Rev.* 2014;23(134):510-518.

11. Sun Q, Liu L, Wang H, et al. Constitutive high expression of protein arginine methyltransferase 1 in asthmatic airway smooth muscle cells is caused by reduced microRNA-19a expression and leads to enhanced remodeling. *J Allergy Clin Immunol.* 2017;140(2):510-524 e513.

12. Castro M, Cox G. Asthma outcomes from bronchial thermoplasty in the AIR2 trial. *Am J Respir Crit Care Med.* 2011;184(6):743-744.

13. Castro M, Rubin A, Laviolette M, Hanania NA, Armstrong B, Cox G. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. *Ann Allergy Asthma Immunol.* 2011;107(1):65-70.

14. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med.* 2010;181(2):116-124.

15. Wechsler ME, Laviolette M, Rubin AS, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol.* 2013;132(6):1295-1302.

16. Chupp G, Laviolette M, Cohn L, et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. *Eur Respir J.* 2017;50(2).

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

18. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J.* 2014;43(2):343-373.

19. Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med.* 2007;356(13):1327-1337.

20. Wilhelm CP, Chipps BE. Bronchial thermoplasty: a review of the evidence. *Ann Allergy Asthma Immunol.* 2016;116(2):92-98.

21. Pratt S. Anesthesia for bronchoscopy. In: Ernst A, ed. *Introduction to Bronchoscopy*. New York: Cambridge University Press; 2009:59-60.

22. Waxman A. Flexible bronchoscopy: indications, contraindications, and consent. In: Ernst A, ed. *Introduction to Bronchoscopy*. New York: Cambridge University Press; 2009.

23. de Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. *Eur Respir J.* 2002;20(5):1271-1276.

24. Langton D, Ing A, Fielding D, Wang W, Plummer V, Thien F. Bronchodilator responsiveness as a predictor of success for bronchial thermoplasty. *Respirology.* 2018.

25. Nadif R, Siroux V, Boudier A, et al. Blood granulocyte patterns as predictors of asthma phenotypes in adults from the EGEA study. *Eur Respir J.* 2016;48(4):1040-1051.

26. Nadif R, Siroux V, Oryszczyn MP, et al. Heterogeneity of asthma according to blood inflammatory patterns. *Thorax.* 2009;64(5):374-380.

27. Zhang XY, Simpson JL, Powell H, et al. Full blood count parameters for the detection of asthma inflammatory phenotypes. *Clin Exp Allergy.* 2014;44(9):1137-1145.

28. Burn J, Sims AJ, Keltie K, et al. Procedural and short-term safety of bronchial thermoplasty in clinical practice: evidence from a national registry and Hospital Episode Statistics. *Journal of Asthma.* 2017:1-8.

29. Chaudhuri R, Rubin A, Sumino K, et al. Safety and effectiveness of bronchial thermoplasty after 10 years in patients with persistent asthma (BT10+): a follow-up of three randomised controlled trials. *Lancet Respir Med.* 2021.

30. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med.* 1998;339(17):1194-1200.

31. Matsunaga K, Ichikawa T, Oka A, et al. Changes in forced expiratory volume in 1 second over time in patients with controlled asthma at baseline. *Respir Med.* 2014;108(7):976-982.

32. Ortega H, Yancey SW, Keene ON, Gunsoy NB, Albers FC, Howarth PH. Asthma Exacerbations Associated with Lung Function Decline in Patients with Severe Eosinophilic Asthma. *J Allergy Clin Immunol Pract.* 2018.

33. Calhoun WJ, Haselkorn T, Miller DP, Omachi TA. Asthma exacerbations and lung function in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol.* 2015;136(4):1125-1127 e1124.

34. Laviolette M, Pavord I, Thomson N, et al. Safety of bronchial thermoplasty out to 5 years in patients with severe refractory asthma: Research in severe asthma (RISA) trial. *European Respiratory Journal.* 2011;38.

35. Nguyen VQ, Ulrik CS. Measures to reduce maintenance therapy with oral corticosteroid in adults with severe asthma. *Allergy Asthma Proc.* 2016;37(6):125-139.

36. Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ Prim Care Respir Med.* 2015;25:15026.

37. Carr TF, Zeki AA, Kraft M. Eosinophilic and Noneosinophilic Asthma. *Am J Respir Crit Care Med.* 2018;197(1):22-37.

38. Katial RK, Bensch GW, Busse WW, et al. Changing Paradigms in the Treatment of Severe Asthma: The Role of Biologic Therapies. *J Allergy Clin Immunol Pract.* 2017;5(2S):S1-S14.

FIGURE LEGENDS

Figure 1. Percent of subjects experiencing severe exacerbations, ED visits, and hospitalizations (top panel) and the rates of these events (# events/subject, bottom panel) out to 5 years after BT. Results from the AIR2 randomized controlled trial are shown for comparison; note that the definition of "severe exacerbation" differed between the AIR2 trial and the PAS2 study. Abbreviations: ED, emergency department.

Figure 2. Clinical outcomes for different patterns of maintenance oral corticosteroid usage in PAS2 subjects. Abbreviations: BL, baseline; BT, bronchial thermoplasty; ED, emergency department; OCS, oral corticosteroid.

Figure 3. Subgroup analyses of major endpoints after BT for: male vs. female subjects (top left), subjects aged ≤40 years vs. subjects aged ≥41 years (top right), subjects with BMI ≤30 vs. subjects with BMI >30 (middle left), subjects with baseline AQLQ scores ≤4.0 or less vs. subjects with baseline AQLQ scores >4.0 (middle right), subjects not using OCS at baseline vs. subjects using OCS at baseline (bottom left), and subjects not using omalizumab at baseline vs. subjects using omalizumab at baseline (bottom right). Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; BL, baseline; BMI, body mass index; ED, emergency department; OCS, oral corticosteroids; Oma, omalizumab; yrs, years.

Figure 4. Subgroup analyses of major endpoints after BT by baseline blood eosinophil counts (middle right), baseline blood neutrophil counts (bottom left), and for subjects with paucigranulocytic asthma (low blood eosinophil/low blood neutrophil) vs. those with high blood eosinophil or high blood neutrophil counts (bottom right). Abbreviations: eos, eosinophils; ED, emergency department; neu, neutrophils.

TABLES

Table 1. Baseline Demographics and Characteristics – All Treated Subjects (N=279)

		PAS2 (N=279)[1]
Demographics		
Age (years)		45.7±11.6
Female		64.5% (180)
Body Mass Index [kg/m^2]		32.2±7.5
Race / Ethnicity		
Caucasian		83.9% (234)
Black, of African heritage		9.0% (25)
Hispanic or Latino		2.9% (8)
Asian		1.4% (4)
American Indian or Alaska native		1.1% (3)
Other		1.8% (5)
Baseline Medication usage		
ICS Dose (µg/day; beclomethasone or equivalent)		2272±787 (278)
LABA Dose (µg/day; salmeterol or equivalent)		105.3±4063 (278)
SABA (puffs/day)		2.4±1.5 (264)
Other Asthma Medications		
OCS (prednisone or equivalent)		19.4% (54)
Dose (mg/day)		8.8±2.8 (52)
Methylxanthines		5.0% (14)
Leukotriene Modifiers		49.5% (138)
Omalizumab		15.8% (44)
Other		26.2% (73)
Quality of Life Measurement		
AQLQ		4.03±1.28
ERS/ATS Guidelines on Severe Asthma[2]		
Severe Asthmatics		95.0% (265)
Spirometry: FEV_1		
% predicted:	Pre-BD	80.4±13.7
	Post-BD	85.8±13.6
Measured (L):	Pre-BD	2.57±0.65
	Post-BD	2.74±0.66
Spirometry: FVC		
% predicted:	Pre-BD	91.1±13.1

		PAS2 (N=279)[1]
	Post-BD	94.6±12.9
Measured (L):	Pre-BD	3.66±0.90
	Post-BD	3.79±0.92
Spirometry: FEV_1/FVC		
Pre-BD		70.9±9.6
Post-BD		72.9±9.7
Blood Lab (cells/μL)		
Eosinophils		285.6±262.1 (264)
Basophils		44.3±43.2 (264)
Neutrophils		5026±1956 (263)
Lymphocytes		2150±663 (264)
Monocytes		581.5±198.4 (264)
Medical History		
Years since asthma diagnosis		25.2±14.9
12 Months prior to BT: % Subjects		
Severe Exacerbations		77.8% (217)
Hospitalizations for asthma		16.1% (45)
ED visits for asthma		29.4% (82)
12 Months prior to BT: # Events/Subject		
Severe Exacerbations		1.61±1.12
Hospitalizations for asthma		0.22±0.53
ED visits for asthma		0.54±1.20

Abbreviations: ATS, American Thoracic Society; AQLQ, Asthma Quality of Life Questionnaire; BD, bronchodilator; BT, bronchial thermoplasty; ED, emergency department; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; OCS, oral corticosteroids; SABA, short-acting β-agonists; SE, severe exacerbation.

[1] – Numbers are: mean ± standard deviation (sample size if <279) or % (x) or % (x/N) if sample size <279

[2] – Based on ERS/ATS Guidelines for Severe Asthma, and due to the limitations of the PAS2 data, we have defined subjects as having Severe Asthma if one of the following is true:

- ICS≥2000 μg/day beclomethasone or equivalent and either LABA or Leukotriene Modifier usage, or
- ≥2 SE in 12 months prior to first BT treatment, or
- ≥1 hospitalization in 12 months prior to first BT treatment, or
- post-BD FEV_1<80% and FEV_1/FVC<0.7.

Table 2. Baseline Demographics and Characteristics – Comparison of Terminated Subjects and Subjects Followed for 5 Years

Variable	Terminated Subjects (N = 52)	Subjects Followed for 5 Years (N = 227)	p-value
Age (yr)	42.50±11.89 (52)	46.44±11.46 (227)	0.027
Female	71.2% (37/52)	63.0% (143/227)	0.27
Ethnicity and Race			
American Indian or Alaska native	1.9% (1/52)	0.9% (2/227)	0.51
Asian	0.0% (0/52)	1.8% (4/227)	0.34
Black, of African heritage	7.7% (4/52)	9.3% (21/227)	0.72
Caucasian	80.8% (42/52)	84.6% (192/227)	0.50
Hispanic or Latino	5.8% (3/52)	2.2% (5/227)	0.16
Other	3.8% (2/52)	1.3% (3/227)	0.22
BMI (kg/m^2)	33.21±7.71 (52)	31.97±7.40 (227)	0.28
Medication usage			
ICS Dose (μg/day)	2141.15±798.01 (52)	2302.03±783.66 (226)	0.18
LABA Dose (μg/day)	104.12±42.01 (52)	105.90±40.00 (225)	0.82
Short-acting beta agonists (puffs/day)	2.29±1.22 (48)	2.38±1.58 (216)	0.73
Other Asthma Medications			
OCS	25.0% (13/52)	18.1% (41/227)	0.25
Dose (mg/day)	10.00±2.04 (13)	8.35±2.89 (39)	0.062
Methylxanthines	3.8% (2/52)	5.3% (12/227)	0.67
Leukotriene Modifiers	53.8% (28/52)	48.5% (110/227)	0.66
Omalizumab	13.5% (7/52)	16.3% (37/227)	0.61
Other	44.2% (23/52)	39.2% (89/227)	0.24
Any of the above maintenance medications	80.8% (42/52)	74.4% (169/227)	0.34
Other measures			
AQLQ	3.63±1.25 (52)	4.12±1.27 (227)	0.013
FEV_1			
Pre-bronchodialator			
Measured value (liters)	2.63±0.62 (52)	2.55±0.65 (227)	0.47
% predicted	82.91±12.74 (52)	79.82±13.91 (227)	0.14
Post-bronchodialator			
Measured value (liters)	2.83±0.64 (52)	2.72±0.67 (227)	0.26
% predicted	89.49±12.41 (52)	84.93±13.80 (227)	0.03
Length of time diagnosed with asthma (years)	24.94±16.87 (52)	25.29±14.45 (227)	0.88
Former Smoker	13.5% (7/52)	18.9% (43/227)	
Hospitalizations for asthma in the 12 months prior to study entry			
% subjects with hospitalizations	30.8% (16/52)	12.8% (29/227)	0.0015
# hospitalizations	0.44±0.73 (52)	0.16±0.46 (227)	0.0005

Variable	Terminated Subjects (N = 52)	Subjects Followed for 5 Years (N = 227)	p-value
ED visits for asthma in the 12 months prior to study entry			
% subjects with ED visits	51.9% (27/52)	24.2% (55/227)	< 0.0001
# ED visits	0.96±1.25 (52)	0.44±1.16 (227)	0.0047
Pulses of oral/IV steriods for asthma in the 12 months prior to study entry			
% subjects with pulses of oral/IV steriods	92.3% (48/52)	74.4% (169/227)	0.0052
# pulses of oral/IV steriods	2.02±0.94 (52)	1.52±1.13 (227)	0.0034

Table 3. Control of severe exacerbations for subjects with 0, ≤1, and ≥2 severe exacerbations 12 months prior to BT treatment (for the 227 subjects with a 5-year follow-up).

	5-year subjects with ≤1 SEs in 12 months prior to BT	5-year subjects with ≥2 SEs in 12 months prior to BT
0 or 1 SEs for each year from years 1 to 5	61.8% (68/110)	35.0% (41/117)
≥2 SEs in at least one year from years 1 to 5	38.2% (42/110)	65.0% (76/117)

SE, severe exacerbation

Table 4. Medication Usage in PAS2 Subjects.

	Baseline (N=279)	1 Year (N=261)	2 Years (N=244)	3 Years (N=239)	4 Years (N=221)	5 Years (N=227)
ICS Dose (μg/day)	2272±787 (278)	2080±933 (253)	1910±1004 (234)	1979±1065 (225)	1926±1180 (207)	1928±1200 (206)
LABA Dose (μg/day)	105.3±40.6 (278)	106.8±77.1 (247)	98.8±45.2 (222)	102.9±83.5 (216)	109.3±105.4 (196)	101.7±77.8 (198)
SABA (puffs/day)	2.4±1.5 (264)	2.4±1.5 (246)	2.4±1.6 (233)	2.4±1.6 (227)	2.4±1.7 (210)	2.4±1.6 (213)
OCS	19.4% (54/279)	10.7% (28/261)	10.2% (25/244)	10.0% (24/239)	8.1% (18/221)	9.7% (22/227)
Dose (mg/day)	8.8±2.8 (52)	8.3±3.0 (26)	12.8±6.8 (25)	12.6±8.8 (23)	13.0±6.6 (17)	11.3±5.8 (21)
Methylxanthines	5.0% (14/279)	3.8% (10/261)	5.3% (13/244)	5.9% (14/239)	4.5% (10/221)	4.4% (10/227)
Leukotriene Modifiers	49.5% (138/279)	48.3% (126/261)	45.9% (112/244)	46.9% (112/239)	47.5% (105/221)	44.9% (102/227)
Any biologic	15.8% (44/279)	15.3% (40/261)	14.8% (36/244)	17.2% (41/239)	19.9% (44/221)	18.5% (42/227)
Omalizumab	15.8% (44/279)	14.9% (39/261)	14.3% (35/244)	14.6% (35/239)	13.1% (29/221)	10.6% (24/227)
Mepolizumab	0.0% (0/279)	0.4% (1/261)	0.0% (0/244)	2.1% (5/239)	5.9% (13/221)	6.6% (15/227)
Benralizumab	0.0% (0/279)	0.0% (0/261)	0.4% (1/244)	0.4% (1/239)	0.9% (2/221)	0.9% (2/227)
Reslizumab	0.0% (0/279)	0.0% (0/261)	0.0% (0/244)	0.0% (0/239)	0.0% (0/221)	0.4% (1/227)
Other asthma-related medications (anticholinergics, mast cell stabilizers)	26.2% (73/279)	28.4% (74/261)	28.3% (69/244)	31.0% (74/239)	34.4% (76/221)	33.5% (76/227)

Numbers are: mean ± standard deviation (sample size) or % (x/N)

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β-agonist; OCS, oral corticosteroids; SABA, short-acting β-agonists

Table 5. Respiratory-related adverse events in PAS2 Subjects

	# Subjects	Total # Events	Subject with ≥1 event [n (%)]	Events / Subject
Respiratory-related SAEs				
Treatment phase [a]	279	63	41 (14.7%)	0.23
Year 1 Post-treatment [b]	276	39	26 (9.4%)	0.14
Year 2 Post-treatment [b]	262	29	25 (9.5%)	0.11
Year 3 Post-treatment [b]	250	25	17 (6.8%)	0.10
Year 4 Post-treatment [b]	240	15	10 (4.2%)	0.06
Year 5 Post-treatment [b]	235	13	11 (4.7%)	0.06
Respiratory-related AEs				
Treatment phase [a]	279	815	233 (83.5%)	2.92
Year 1 Post-treatment [b]	276	470	184 (66.7%)	1.70
Year 2 Post-treatment [b]	262	397	165 (63.0%)	1.52
Year 3 Post-treatment [b]	250	321	155 (62.0%)	1.28
Year 4 Post-treatment [b]	240	324	141 (58.8%)	1.35
Year 5 Post-treatment [b]	235	287	133 (56.6%)	1.22

[a] The treatment period is from first bronchoscopy to 6 weeks after last bronchoscopy. Yearly periods are 365 days times the number of years after the treatment period.

[b] Subjects that have completed a 6-week follow-up visit at least 42 days after last bronchoscopy or any annual follow-up visit or started an AE at least 42 days after last bronchoscopy.

Abbreviations: AE, adverse event; SAE, serious adverse event

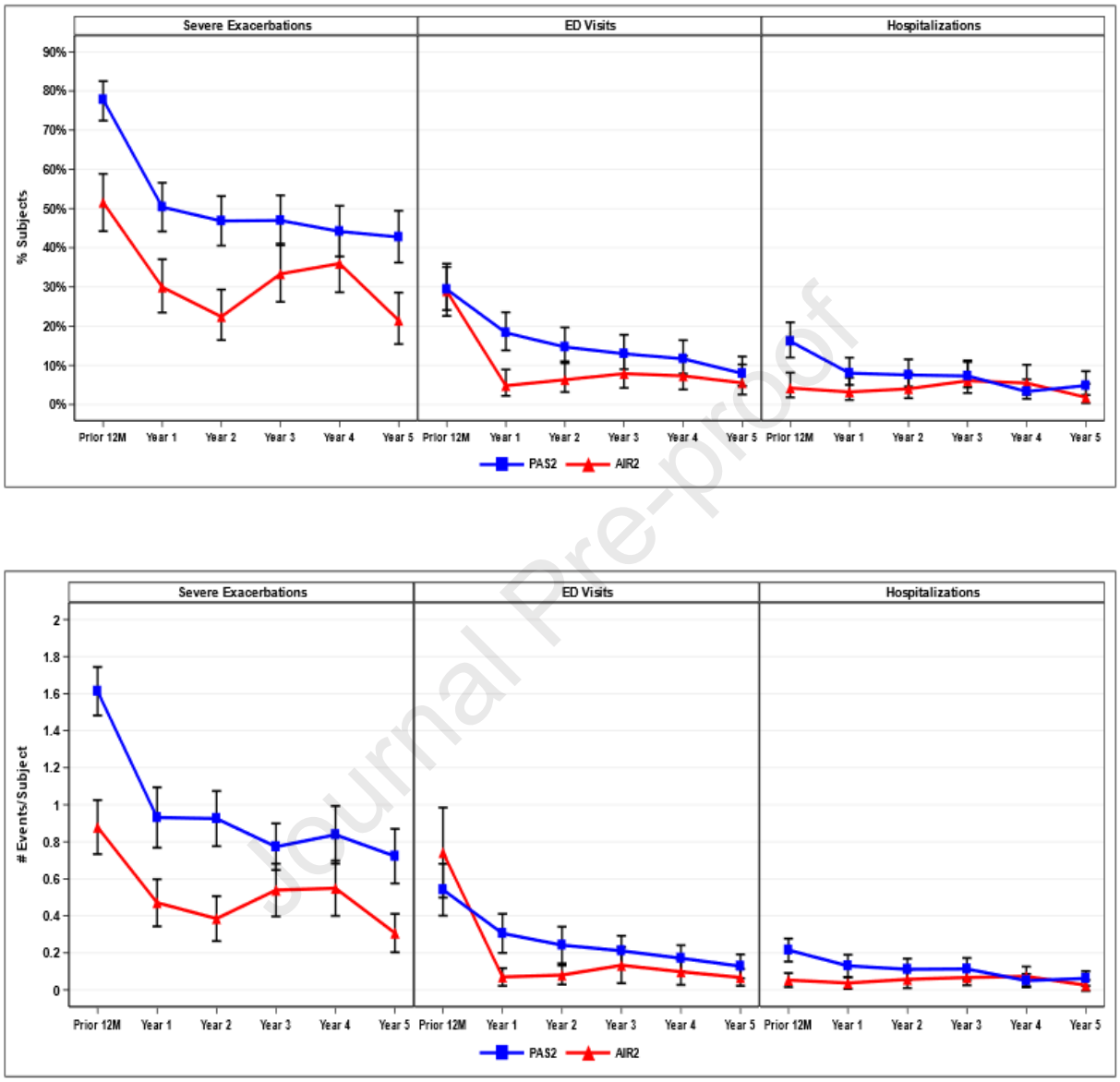

Figure 1

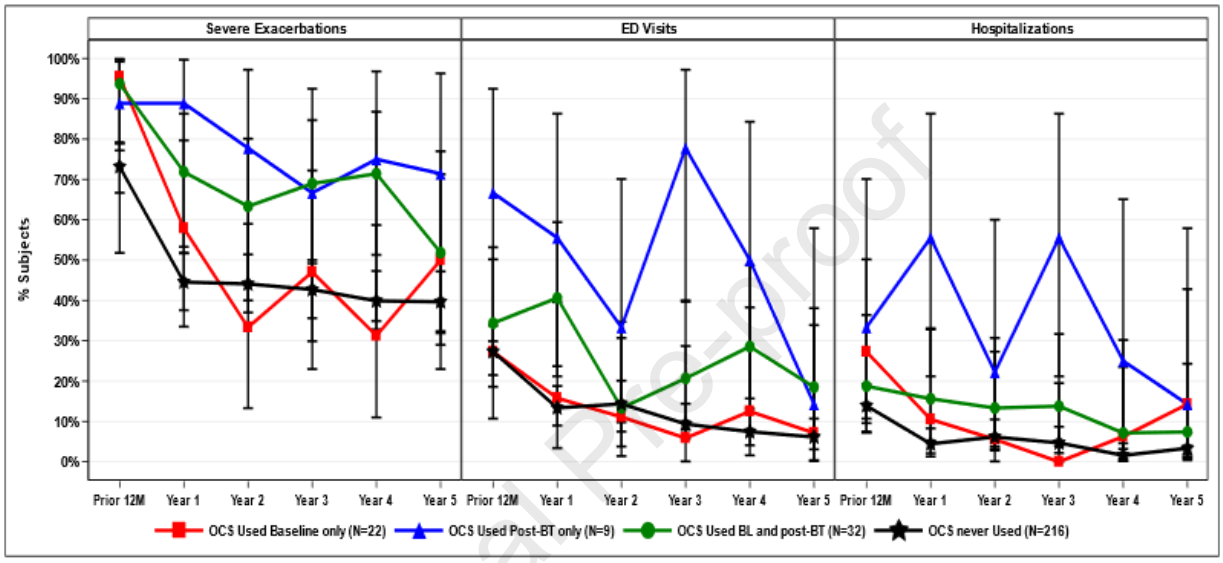

Figure 2

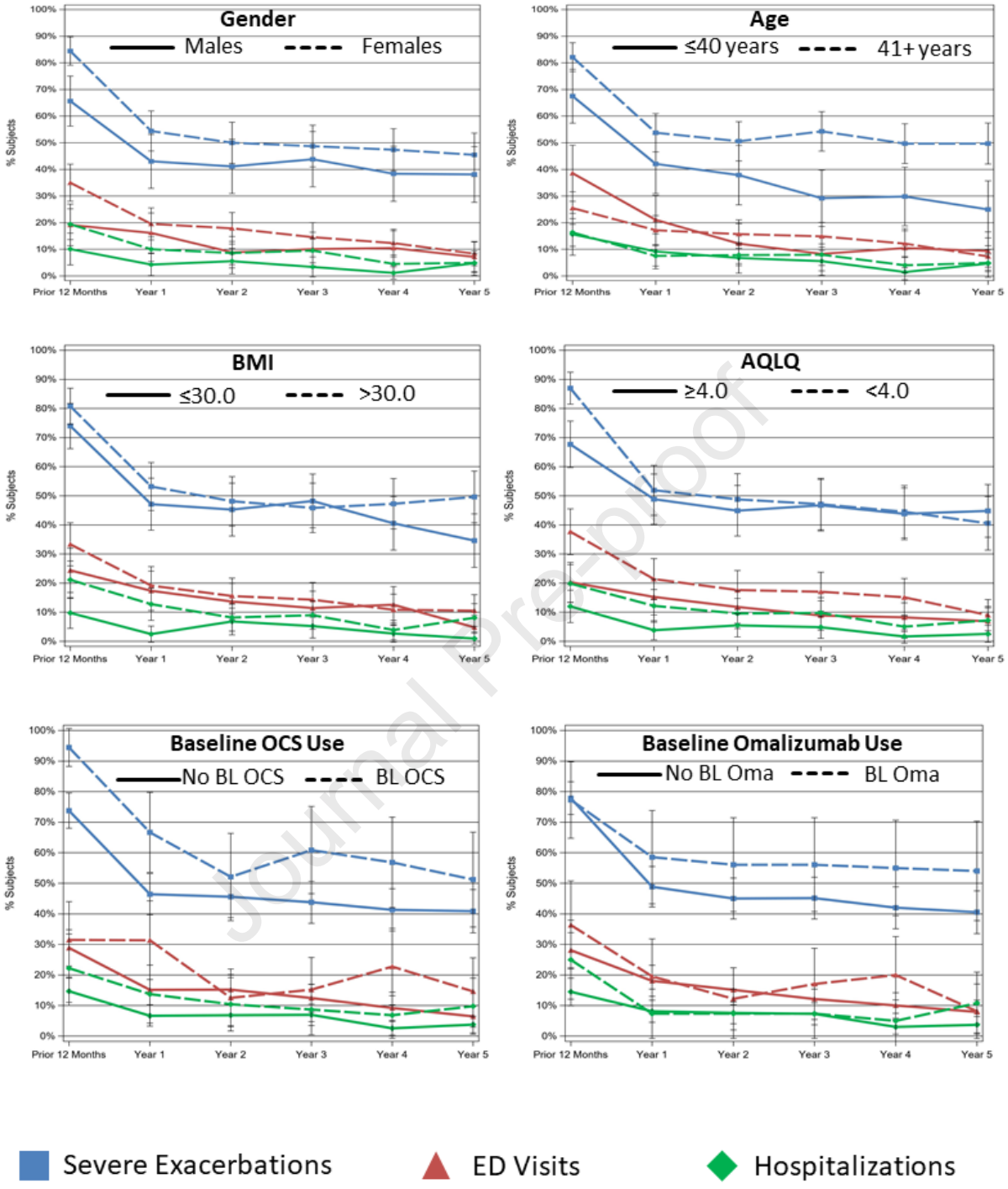

Figure 3

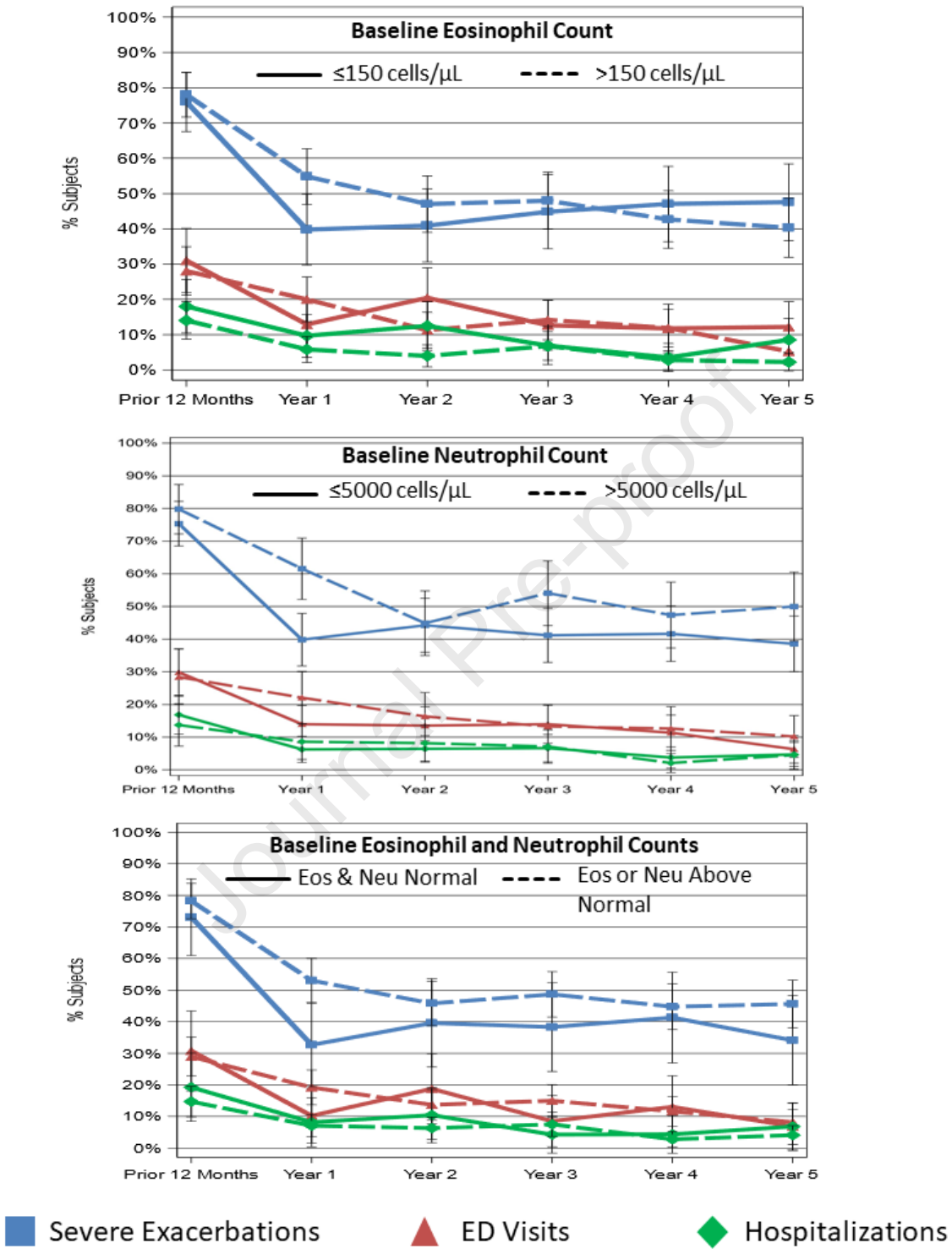
Baseline Eosinophil Count
≤150 cells/µL
>150 cells/µL
% Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Prior 12 Months
Year 1
Year 2
Year 3
Year 4
Year 5
Baseline Neutrophil Count
≤5000 cells/µL
>5000 cells/µL
% Subjects
Prior 12 Months
Year 1
Year 2
Year 3
Year 4
Year 5
Baseline Eosinophil and Neutrophil Counts
Eos & Neu Normal
Eos or Neu Above Normal
% Subjects
Prior 12 Months
Year 1
Year 2
Year 3
Year 4
Year 5
Severe Exacerbations
ED Visits
Hospitalizations

Figure 4