CHEST

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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BACKGROUND: Bronchial thermoplasty is a device-based treatment for subjects ≥ 18 years of age 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 patients with severe asthma undergoing this procedure.

RESEARCH QUESTION: What are the 5-year efficacy and safety results in patients with severe asthma who have undergone bronchial thermoplasty?

STUDY DESIGN AND METHODS: This was a prospective, open-label, observational, multicenter study conducted in the United States and Canada. Subjects 18 to 65 years of age who were taking inhaled corticosteroids ≥ 1,000 μg/d (beclomethasone or equivalent) and long-acting beta-agonists ≥ 80 μg/d (salmeterol or equivalent) were included. Severe exacerbations, hospitalization, ED visits, and medication usage were evaluated for the 12 months prior to and at years 1 through 5 posttreatment. Spirometry was evaluated at baseline and at years 1 through 5 posttreatment.

RESULTS: A total of 284 subjects were enrolled at 27 centers; 227 subjects (80%) completed 5 years of follow-up. By year 5 posttreatment, the proportion of subjects with severe exacerbations, ED visits, and hospitalizations was 42.7%, 7.9%, and 4.8%, respectively, compared with 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, ED visits, and corticosteroid exposure. All subgroups demonstrated clinically significant improvement, suggesting that bronchial thermoplasty improves asthma control in different asthma phenotypes.

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KEY WORDS: asthma subgroups; bronchial thermoplasty; corticosteroid exposure; severe asthma; severe exacerbations

ABBREVIATIONS: AIR = Asthma Intervention Research; AIR2 = Asthma Intervention Research 2; AQLQ = Asthma Quality of Life Questionnaire; BT = bronchial thermoplasty; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; OCS = oral corticosteroid; PAS2 = Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma; RCT = randomized controlled trial

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Take-home Points

Study Question: What are the 5-year efficacy and safety outcomes in people with severe asthma who have undergone bronchial thermoplasty (BT)?

Results: Out of 284 subjects enrolled in the Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma, 227 subjects (80%) completed 5 years of follow-up. By year 5 posttreatment, the proportion of these subjects with severe exacerbations, ED visits, and hospitalizations was 42.7%, 7.9%, and 4.8%, respectively, compared with 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, ED 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 oral corticosteroids and omalizumab. BT may also be a treatment option for people with severe asthma who cannot use or do not qualify for biological therapy for asthma (eg, those with noneosinophilic disease).

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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 > 80% of asthma-related health care costs.[1-3]

Bronchial thermoplasty (BT) is the only Food and Drug Administration-approved procedure for the treatment of asthma. It is indicated for patients ≥ 18 years of age with severe persistent asthma not well controlled with inhaled corticosteroids (ICSs) and long-acting beta-agonists (LABAs). BT uses radiofrequency energy to heat the airway walls in a controlled manner. The mechanism of action is attributed to a reduction in airway smooth muscle mass after the procedure.[4-9] Reduction in airway smooth muscle has been associated with clinical improvement seen in patients undergoing BT.[5,6] Other structural and immunohistologic 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 trials (RCTs) of BT have been carried out in subjects with moderate to severe asthma, including the Asthma Intervention Research (AIR), Research in Severe Asthma (RISA), and Asthma Intervention Research 2 (AIR2) studies.[12-15] These studies demonstrated improvements in asthma control after 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.

After Food and Drug Administration approval in 2010, the Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma (PAS2) 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 with severe asthma based on the European Respiratory Society/American Thoracic Society

guidelines), the results from these 190 PAS2 subjects were comparable with 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 with 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 (OCSs) in a significant proportion of subjects.

Here, we describe the clinical outcomes over 5 years after 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.

Study Design and Methods

Study Design

The PAS2 study design has been previously published.[16] PAS2 was a prospective, open-label, observational, multicenter clinical study 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 and 65 years of age whose asthma was inadequately controlled despite optimized treatment with high ICS and LABA doses (ICSs $\geq$ 1,000 µg/d [beclomethasone or equivalent] and LABAs $\geq$ 80 µg/d [salmeterol or equivalent]). Subjects were allowed asthma medications in addition to ICSs and LABAs/short-acting beta-agonists, including OCSs 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) per Food and Drug Administration labeling by the investigators as previously described.[14,15]

Follow-up

PAS2 subjects were evaluated 2 weeks after 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 with 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 in e-Appendix 1).[17] Other outcome measures used in PAS2 have been previously described.[16]

Adverse Event Monitoring

Adverse events were collected periprocedurally (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 posttreatment period. For further description of how adverse events were defined, see Supplementary Methods 1 in e-Appendix 1.

Statistical Analyses

Baseline demographics, clinical characteristics, and outcomes were summarized with sample size, mean, SD, 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 through 5, the Fisher exact test, negative binomial test, and Student t test were used, respectively. For the subgroup analyses, a generalized linear model 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 $P < .10$, contrasts of time within subgroup and subgroup within time were performed to explore differences. SAS version 9.4 (SAS Institute) was used for all analyses.

Results

Baseline Demographics and Clinical Characteristics

Of 284 subjects enrolled, 279 (mean age, 45.7 $\pm$ 11.6 years) underwent BT as previously described,[16] and 227 (81%) subjects completed 5 years of follow-up (e-Fig 1).

Subjects were 64.5% female with a mean BMI of 32.2 $\pm$ 7.5 kg/m^2 and were 84% White, 9% Black or African heritage, and 7% from other racial groups. Subjects had a mean AQLQ score of 4.03 $\pm$ 1.28, had asthma diagnosis on average 25.2 years prior to BT, and based on the European Respiratory Society/American Thoracic Society Guidelines for Severe Asthma,[18] 95% of subjects were considered to have severe asthma (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 with the 227 subjects followed for 5 years, respectively (Table 2). This indicates that the subjects who dropped out of PAS2 may have had more

TABLE 1] Baseline Demographics and Characteristics of All Treated Subjects (N = 279)

Variable	Value
Demographics	
Age, y	45.7 ± 11.6
Female	64.5 (180)
BMI, kg/m^2	32.2 ± 7.5
Race/ethnicity	
White	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 (beclomethasone or equivalent), μg/d (n = 278)	2,272 ± 787
LABA dose (salmeterol or equivalent), μg/d (n = 278)	105.3 ± 40.6
SABA, puffs/d (n = 264)	2.4 ± 1.5
Other asthma medications	
OCS (prednisone or equivalent)	19.4 (54)
Dose, mg/d (n = 52)	8.8 ± 2.8
Methylxanthines	5.0 (14)
Leukotriene modifiers	53.0 (148)
Omalizumab	15.8 (44)
Other	26.2 (73)
Quality of life measurement	
AQLQ	4.03 ± 1.28
ERS/ATS guidelines on severe asthma[a]	
People with severe asthma	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
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 laboratory tests, cells/μL	
Eosinophil count (n = 264)	285.6 ± 262.1
Basophil count (n = 264)	44.3 ± 43.2
Neutrophil count (n = 263)	5,026 ± 1,956
Lymphocyte count (n = 264)	2,150 ± 663
Monocyte count (n = 264)	581.5 ± 198.4
Medical history	
Years since asthma diagnosis	25.2 ± 14.9
12 mo prior to BT, % subjects with	
Severe exacerbations	77.8 (217)
Hospitalizations for asthma	16.1 (45)
ED visits for asthma	29.4 (82)
12 mo prior to BT, No. of events/subject	
Severe exacerbations	1.61 ± 1.12
Hospitalizations for asthma	0.22 ± 0.53
ED visits for asthma	0.54 ± 1.20

Values are mean ± SD or % (No. of patients). AQLQ = Asthma Quality of Life Questionnaire; ATS = American Thoracic Society; BD = bronchodilator; BT = bronchial thermoplasty; ERS = European Respiratory Society; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; OCS = oral corticosteroid; SABA = short-acting beta-agonist.

[a]Based on ERS/ATS guidelines for severe asthma, and because of the limitations of the Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma data, we defined subjects as having severe asthma if one of the following is true: (A) ICSs ≥ 2,000 μg/d beclomethasone or equivalent and either LABA or leukotriene modifier usage, (2) two or more severe exacerbations in 12 mo prior to first BT treatment, (3) one or more hospitalizations in 12 mo prior to first BT treatment, or (4) post-BD FEV_1 < 80% and FEV_1/FVC < 0.7.

severe disease; therefore, 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 with 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 ($P < .001$) (Fig 1, Table 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; $P < .001$). There were 61.8% of subjects (68/110) with 1 or fewer severe exacerbations during the 12 months prior to BT who experienced 1 or fewer severe exacerbations per year after BT treatment compared with 35.0% of subjects (41/117) with 2 or more 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

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, y	42.50 ± 11.89	46.44 ± 11.46	.027
Female	71.2 (37)	63.0 (143)	.27
Ethnicity and race			
American Indian or Alaska native	1.9 (1)	0.9 (2)	.51
Asian	0.0 (0)	1.8 (4)	.34
Black, of African heritage	7.7 (4)	9.3 (21)	.72
White	80.8 (42)	84.6 (192)	.50
Hispanic or Latino	5.8 (3)	2.2 (5)	.16
Other	3.8 (2)	1.3 (3)	.22
BMI, kg/m^2	33.21 ± 7.71	31.97 ± 7.40	.28
Medication usage			
ICS dose, μg/d	2,141 ± 798	2,302 ± 784 (n = 226)	.18
LABA dose, μg/d	104.1 ± 42.0	105.5 ± 40.3 (n = 226)	.82
Short-acting beta agonists, puffs/d	2.29 ± 1.22 (n = 48)	2.38 ± 1.58 (n = 216)	.73
Other asthma medications			
OCS	25.0 (13)	18.1 (41)	.25
Dose, mg/d	10.00 ± 2.04 (n = 13)	8.35 ± 2.89 (n = 39)	.062
Methylxanthines	3.8 (2)	5.3 (12)	.67
Leukotriene modifiers	55.8 (29)	52.4 (119)	.66
Omalizumab	13.5 (7)	16.3 (37)	.61
Other	32.7 (17)	24.7 (56)	.24
Any of the aforementioned maintenance medications	80.8 (42)	74.4 (169)	.34
Other measures			
AQLQ	3.63 ± 1.25	4.12 ± 1.27	.013
FEV_1			
Prebronchodialator			
Measured value, L	2.63 ± 0.62	2.55 ± 0.65	.47
% predicted	82.91 ± 12.74	79.82 ± 13.91	.14
Postbronchodialator			
Measured value, L	2.83 ± 0.64	2.72 ± 0.67	.26
% predicted	89.49 ± 12.41	84.93 ± 13.80	.03
Length of time diagnosed with asthma, y	24.94 ± 16.87	25.29 ± 14.45	.88
Former smoker	13.5 (7)	18.9 (43)	
Hospitalizations for asthma in the 12 mo prior to study entry			
Subjects with hospitalizations	30.8 (16)	12.8 (29)	.0015
No. of hospitalizations	0.44 ± 0.73	0.16 ± 0.46	.0005
ED visits for asthma in the 12 mo prior to study entry			
Subjects with ED visits	51.9 (27)	24.2 (55)	< .0001
No. of ED visits	0.96 ± 1.25	0.44 ± 1.16	.0047
Pulses of oral/IV steriods for asthma in the 12 mo prior to study entry			
Subjects with pulses of oral/IV steriods	92.3 (48)	74.4 (169)	.0052
No. of pulses of oral/IV steriods	2.02 ± 0.94	1.52 ± 1.13	.0034

Values are mean ± SD, % (No.), or as otherwise indicated. AQLQ = Asthma Quality of Life Questionnaire; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; OCS = oral corticosteroid.

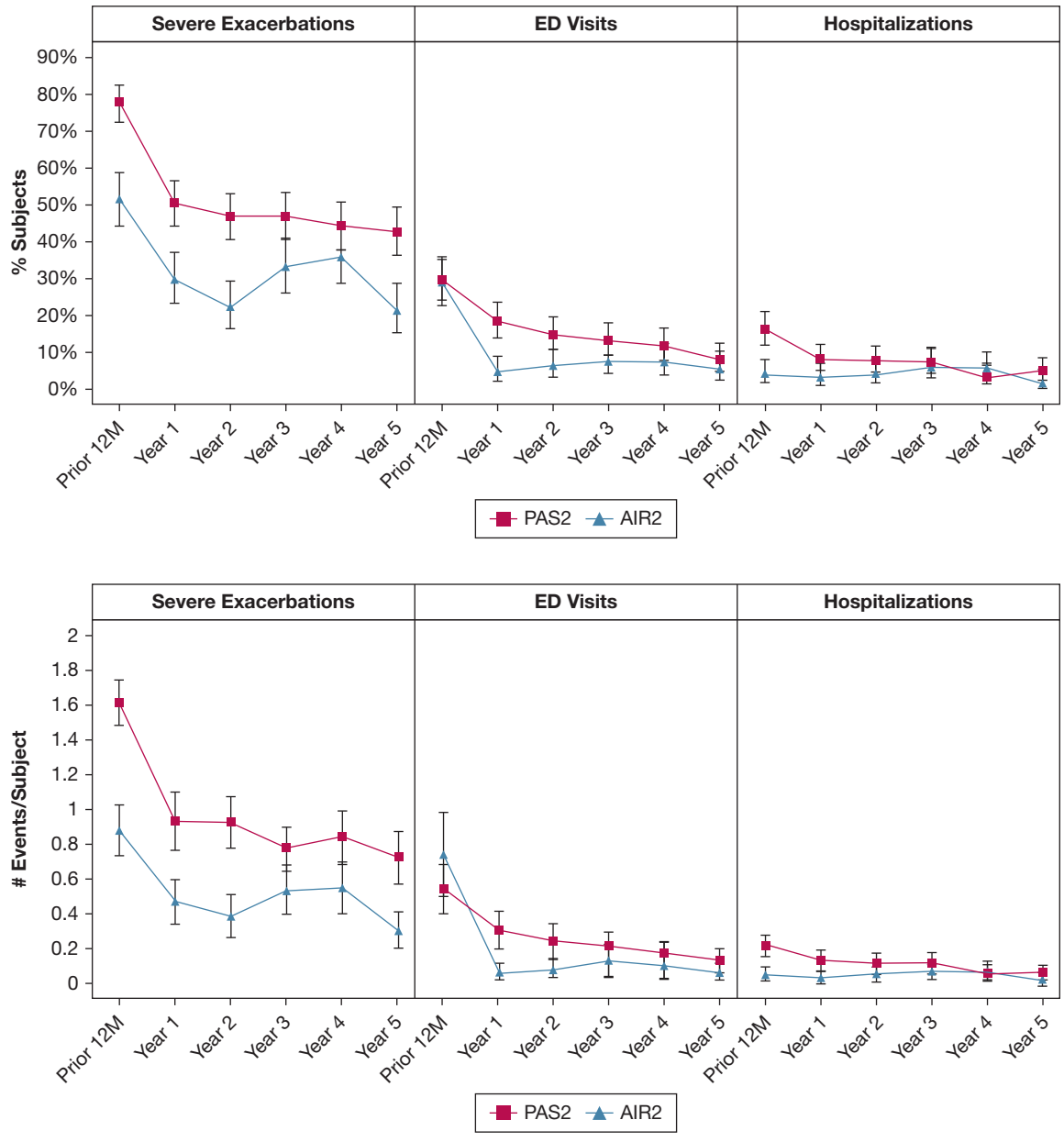

Figure 1 – *A, Percent of subjects experiencing severe exacerbations, ED visits, and hospitalizations and (B) the rates of these events (No. of events/subject) out to 5 years after bronchial thermoplasty. Results from the AIR2 randomized controlled trial are shown for comparison; the definition of severe exacerbation differed between the AIR2 trial and PAS2. AIR2 = Asthma Intervention Research 2; PAS2 = Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma.*

years 1 through 5, respectively, after BT ($P < .001$) (Fig 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 ($P = .0002$). A decrease in hospitalizations was also observed after BT (Fig 1); 16.1% of subjects were hospitalized for asthma in the year prior to BT, but during years 1 through 5, only 8.0%, 7.5%, 7.3%, 3.3%, and 4.8%, respectively, were hospitalized ($P = .0003$). Annual hospitalization rates fell from 0.22 hospitalizations/subject at baseline to 0.06 hospitalizations/subject at year 5 after BT ($P = .0012$).

The PAS2 data confirms reductions in these outcomes demonstrated in the AIR2 study (Fig 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] (e-Fig 2).

TABLE 3] Control of Severe Exacerbations for Subjects 12 Months Prior to Bronchial Thermoplasty Treatment

Subjects With:	5-y Subjects With ≤ 1 SEs in 12 mo Prior to BT (n = 110)	5-y Subjects With ≥ 2 SEs in 12 mo Prior to BT (n = 117)
0 or 1 SEs for each year from years 1 to 5	61.8 (68)	35.0 (41)
≥ 2 SEs in at least 1 y from years 1 to 5	38.2 (42)	65.0 (76)

Subjects included the 227 patients with a 5-year follow-up. Values are % (No.). SE, severe exacerbation.

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 2,272 μg/d (beclomethasone or equivalent) at baseline was sustainably reduced to 1,928 μg/d by year 5 post-BT (Table 4).

The percentage of subjects using biological 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 of 279 subjects (19.4%) were taking maintenance OCSs at the baseline visit. After BT treatment, 10.7%, 10.2%, 10.0%, 8.1%, and 9.7% of subjects were taking maintenance OCSs at the 1- to 5-year follow-up visits, respectively (Table 4). Twenty-two of the 54 subjects (42%) taking OCSs at baseline discontinued OCSs after BT (Fig 2), and only six of these 22 subjects then used a biological medication. The proportion of subjects with severe exacerbations among those 22 fell from 95.5% at baseline to 50.0% at year 5 after BT treatment (Fig 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 of 32 subjects also used a biological medication 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 with subjects who never used maintenance OCSs (73.3% experienced severe exacerbations at baseline vs 42.7% at year 5 after BT), even though patients using maintenance OCSs may have had more severe disease at baseline (Fig 2).

Only nine subjects who were not taking OCSs 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 people with severe asthma.[21-23] Although the percentage of subjects with periprocedural respiratory serious adverse events (requiring hospitalization or prolongation of hospitalization) during the treatment phase was 14.7% (Table 5), respiratory serious adverse events were reduced during the posttreatment phase to 9.4% during year 1 after BT and to 4.7% during year 5 after BT. During this study, four deaths, all unrelated to BT, occurred. Two men, 50 and 55 years of age, died of cardiac arrest. The 55-year-old man was found unresponsive (pulseless and asystolic) at home approximately 3 years after the third BT procedure. The 50-year-old man died of cardiac arrest shortly after completing the third BT treatment. A 57-year-old woman died of myocardial infarction approximately 2 years after the final BT treatment after cardiac catheterization/stenting for severe arterial stenoses failed. A 53-year-old man died approximately 3 years after his last BT procedure of unknown causes. This subject had severe OSA 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 the following: sex, age (< 40 and ≥ 40 years), BMI (< 30 and ≥ 30 kg/m^2), baseline AQLQ score (< 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 prebronchodilator FEV_1/FVC (≤ 70% and > 70%), and bronchodilator reversibility (fixed or reversible),[24] and baseline blood

TABLE 4] Medication Usage in Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma Subjects

Variable	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/d)	2,272 ± 787 (n = 278)	2,080 ± 933 (n = 253)	1,910 ± 1,004 (n = 234)	1,979 ± 1,065 (n = 225)	1, 926 ± 1,180 (n = 207)	1,928 ± 1,200 (n = 206)
LABA dose (μg/d)	105.3 ± 40.6 (n = 278)	106.8 ± 77.1 (n = 247)	98.8 ± 45.2 (n = 222)	102.9 ± 83.5 (n = 216)	109.3 ± 105.4 (n = 196)	101.7 ± 77.8 (n = 198)
SABA (puffs/d)	2.4 ± 1.5 (n = 264)	2.4 ± 1.5 (n = 246)	2.4 ± 1.6 (n = 233)	2.4 ± 1.6 (n = 227)	2.4 ± 1.7 (n = 210)	2.4 ± 1.6 (n = 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/d)	8.8 ± 2.8 (n = 52)	8.3 ± 3.0 (n = 26)	12.8 ± 6.8 (n = 25)	12.6 ± 8.8 (n = 23)	13.0 ± 6.6 (n = 17)	11.3 ± 5.8 (n = 21)
Methylxanthines	5.0 (14)	3.8 (10)	5.3 (13)	5.9 (14)	4.5 (10)	4.4% (10)
Leukotriene modifiers	53.0 (148)	51.7 (135)	49.6 (121)	50.2 (120)	51.1 (113)	48.5 (110)
Any biological medication	15.8 (44)	15.3 (40)	14.8 (36)	17.2 (41)	19.9 (44)	18.5 (42)
Omalizumab	15.8 (44)	14.9 (39)	14.3 (35)	14.6 (35)	13.1 (29)	10.6 (24)
Mepolizumab	0.0 (0)	0.4 (1)	0.0 (0)	2.1 (5)	5.9 (13)	6.6 (15)
Benralizumab	0.0 (0)	0.0 (0)	0.4 (1)	0.4 (1)	0.9 (2)	0.9 (2)
Reslizumab	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.4 (1)
Other asthma-related medications (anticholinergics, mast cell stabilizers)	26.2 (73)	28.4 (74)	28.3 (69)	31.0 (74)	34.4 (76)	33.5 (76)

Values are mean ± SD or % (No.). ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; OCS = oral corticosteroid; SABA = short-acting beta-agonist.

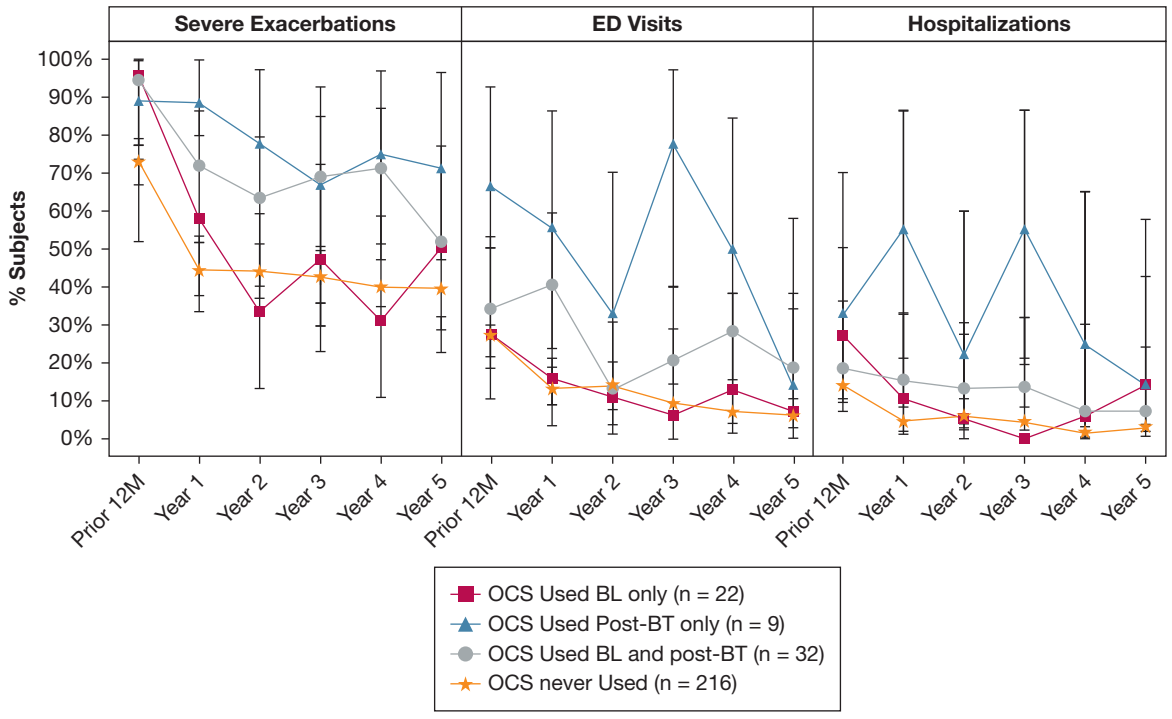

Figure 2 – *Clinical outcomes for different patterns of maintenance OCS usage in Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma subjects. BL = baseline; BT = bronchial thermoplasty; OCS = oral corticosteroid.*

counts of eosinophils (≤ 150 and > 150 cells/μL), neutrophils (≤ 5,000 and > 5,000 cells/μL), and both eosinophils and neutrophils (both eosinophils ≤ 150 cells/μL and neutrophils ≤ 5,000 cells/μL and at least one of eosinophils > 150 cells/μL or neutrophils > 5,000 cells/μL).[25-27]

TABLE 5] Respiratory-Related Adverse Events in Post-FDA Approval Clinical Trial Evaluating BT in Severe Persistent Asthma Subjects

Variable	No. of Subjects	Total No. of Events	Subjects With ≥ 1 Event, No. (%)	Events/Subject
Respiratory-related SAEs				
Treatment phase[a]	279	63	41 (14.7)	0.23
Year 1 posttreatment[b]	276	39	26 (9.4)	0.14
Year 2 posttreatment[b]	262	29	25 (9.5)	0.11
Year 3 posttreatment[b]	250	25	17 (6.8)	0.10
Year 4 posttreatment[b]	240	15	10 (4.2)	0.06
Year 5 posttreatment[b]	235	13	11 (4.7)	0.06
Respiratory-related AEs				
Treatment phase[a]	279	815	233 (83.5)	2.92
Year 1 posttreatment[b]	276	470	184 (66.7)	1.70
Year 2 posttreatment[b]	262	397	165 (63.0)	1.52
Year 3 posttreatment[b]	250	321	155 (62.0)	1.28
Year 4 posttreatment[b]	240	324	141 (58.8)	1.35
Year 5 posttreatment[b]	235	287	133 (56.6)	1.22

AE = adverse event; SAE = serious adverse event.
[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.

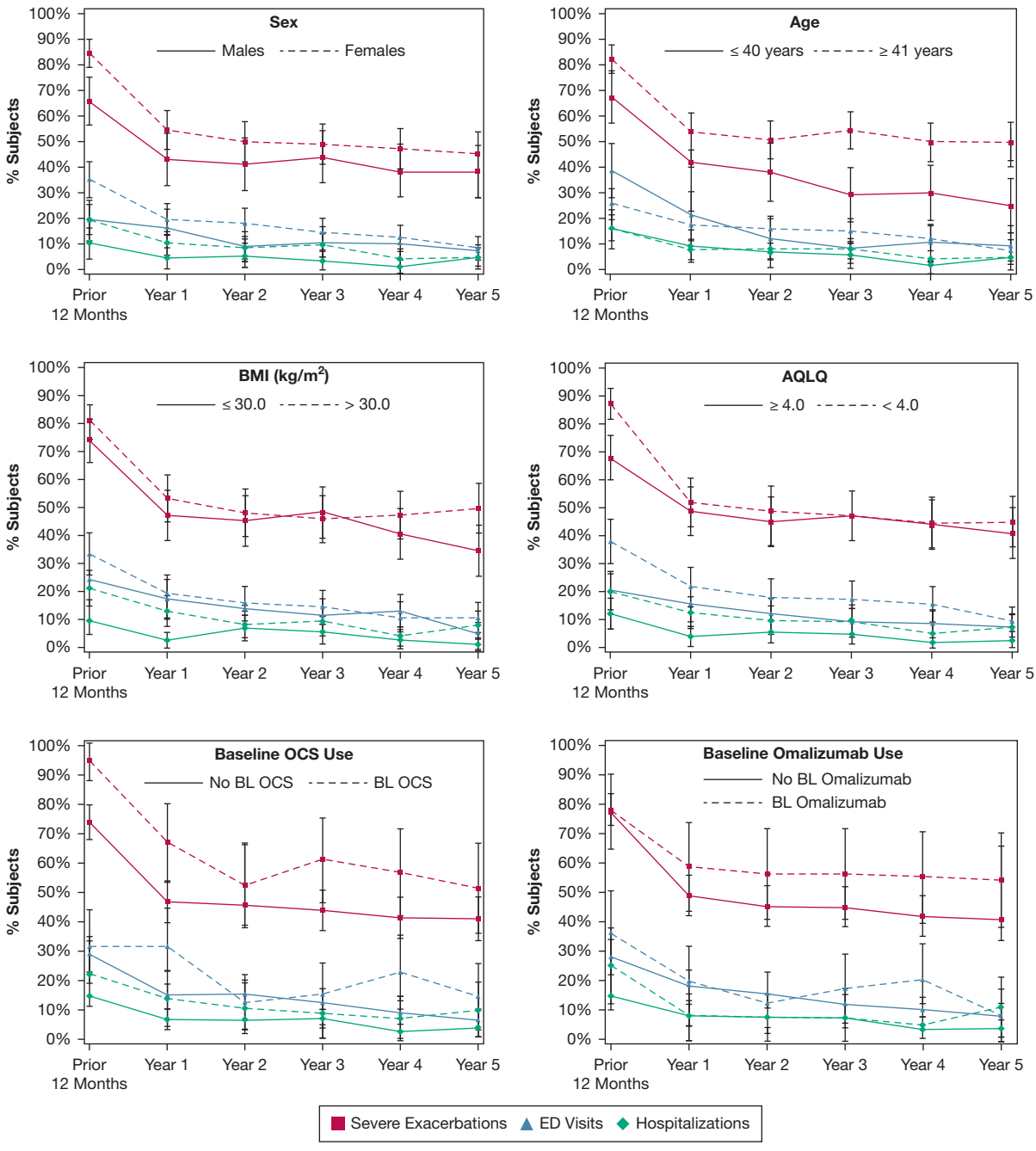

Figure 3 – *A-F, Subgroup analyses of major end points after bronchial thermoplasty for (A) male vs female subjects, (B) subjects ≤ 40 vs ≥ 41 years of age, (C) subjects with BMI ≤ 30 vs > 30 kg/m², (D) subjects with baseline AQLQ scores ≤ 4.0 vs > 4.0, (E) subjects not using OCSs at baseline vs subjects using OCS at baseline, and (F) subjects not using Oma at baseline vs subjects using Oma at baseline. AQLQ = Asthma Quality of Life Questionnaire; BL = baseline; OCS = oral corticosteroid; Oma = omalizumab.*

Our analysis indicated there was a significant decrease in severe exacerbations, ED visits, and hospitalizations over time for all sets of subgroups (e-Fig 3, e-Table 1, Fig 3; for more detail see Supplemental Results 1 in e-Appendix 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

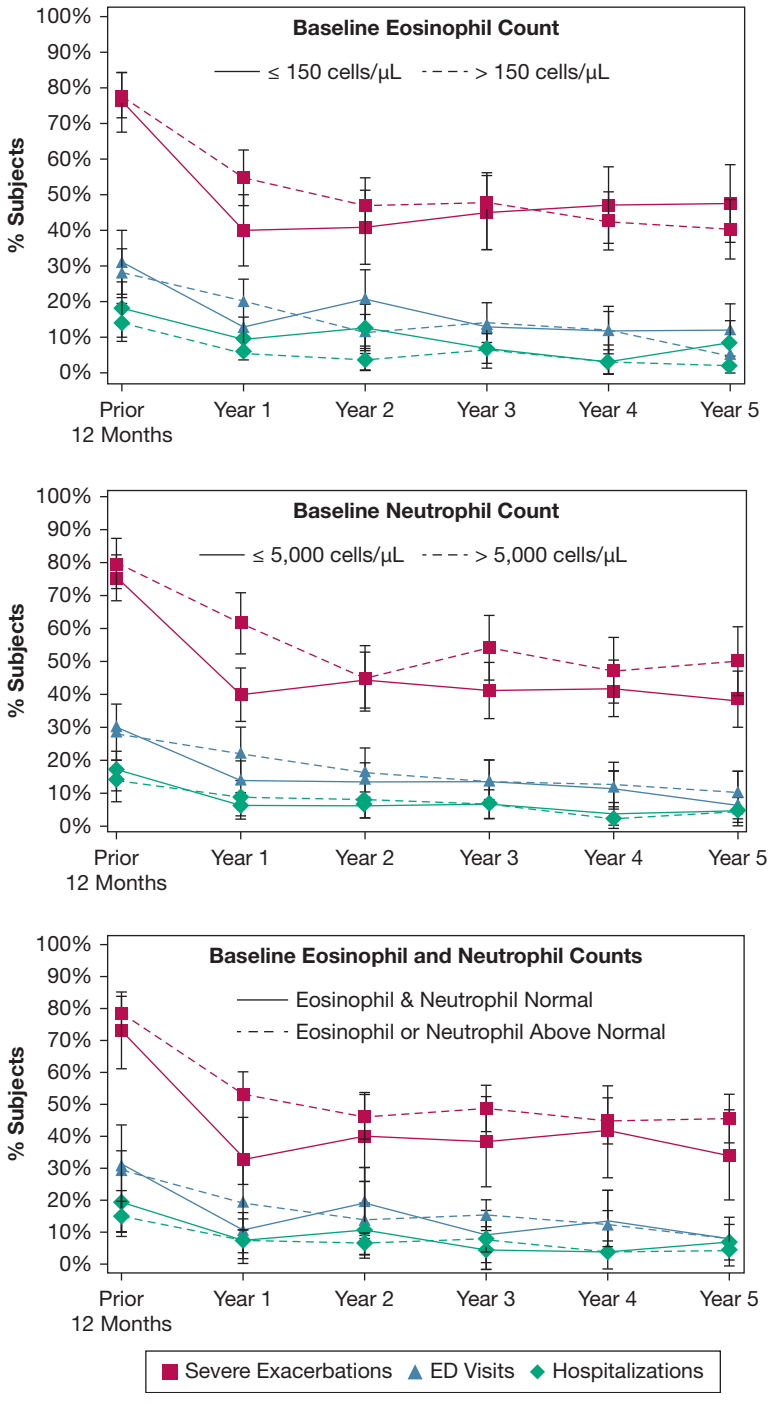

Figure 4 – *A-C, Subgroup analyses of major endpoints after bronchial thermoplasty by baseline blood eosinophil counts (A), baseline blood neutrophil counts (B), and for subjects with paucigranulocytic asthma (low blood eosinophil count/low blood neutrophil count) vs those with high blood eosinophil or high blood neutrophil counts (C).*

subgroups based on both baseline blood eosinophil and neutrophil counts (Fig 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 after BT treatment. Subjects with neutrophil counts ≤ 5,000 cells/μL had consistently lower percentages of severe exacerbations than subjects with neutrophil counts > 5,000 cells/μL in the years after BT treatment, but not during the 12 months before BT (Figs 4B, 4C).

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 Research in Severe Asthma [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, OSA, and other common comorbidities found in people with asthma, but the PAS2 allowed participation of subjects with these conditions. Publications have reported on BT in people with more severe asthma that were older and had worse baseline lung function and quality of life.[4,6-8,28] These data indicated a clinical improvement post-BT in these subjects and acceptable rates of adverse events. Additionally, Chaudhuri et al[29] recently reported that the clinical improvements after BT can last for $\geq$ 10 years after treatment in some subjects. PAS2 adds to the body of evidence demonstrating the long-term safety and effectiveness of BT outside the setting of RCTs.

Although 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 people with severe asthma in PAS2 had relatively well-preserved pulmonary function (FEV_1 in the 75%-80% range).[30] People with asthma, particularly those with severe asthma, experience a progressive decline in lung function as measured by FEV_1 with time (22.5-50 mL/y). Subjects who experience more severe exacerbations per year tend to exhibit a more rapid decline in FEV_1.[30-33] As shown in previous publications,[14-16] there is no significant decline in FEV_1 and FVC up to 5 years after BT, highlighting the long-term safety of the BT procedure.

In PAS2, 14.7% of subjects experienced procedure-related serious adverse events during the treatment period. This was slightly higher than in previously reported trials of BT,[14,34] perhaps because of enrollment of subjects with more severe asthma and more comorbidities in PAS2. The most common periprocedural respiratory serious adverse event 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. Although hospitalization was required for all periprocedural respiratory serious adverse events, intubation and/or mechanical ventilation was reported in only four cases, two because of hemoptysis. One occurred 1 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 1 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 min 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 1 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 OCSs, after BT. Forty-two percent of subjects on OCSs were able to completely discontinue them after BT treatment while simultaneously improving asthma control. This is encouraging because daily use of OCSs 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, 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 biological 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 people with more severe asthma with worse prognosis, which introduced bias. Although 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 because 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, because we did not compare responses after BT to responses to biological medications, it is not known whether the response to biological medications in this study population would have been more pronounced than the response to BT. It is possible that because biological medications selectively target proinflammatory pathways, and BT largely acts on processes involved in airway remodeling, the two treatments could be complementary in people with severe asthma 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 biological medications, including those targeting IL-5, 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 people with severe asthma who do not qualify for biological therapy.

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Author contributions: G. C. is the guarantor of the manuscript; he had full access to the data from the study at all times and takes responsibility for the integrity of all data and analyses. M. C., M. S., D. K. H., and M. L. contributed to study design. All authors followed-up study participants. E. A. M. performed the data analysis. G. M. G. was trial manager. G. C., J. N. K., E. A. M., and J. L. O. wrote the first draft of the manuscript. G. C., J. N. K., E. A. M., J. L. O., and M. L. wrote the final draft of the manuscript. All authors approved the final version of the manuscript.

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Additional information: The e-Appendix, e-Figures, and e-Table can be found in the Supplemental Materials section of the online article. 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.

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