



# Safety and effectiveness of bronchial thermoplasty after 10 years in patients with persistent asthma (BT10+): a follow-up of three randomised controlled trials

Rekha Chaudhuri, Adalberto Rubin, Kaharu Sumino, Jose Roberto Lapa e Silva, Robert Niven, Salman Siddiqui, Karin Klooster, Charlene McEvoy, Pallav L Shah, Michael Simoff, Sumita Khatri, Richard Barbers, G Mark Grubb, Edmund A McMullen, Jennifer L Olson, Michel Laviolette, on behalf of the BT10+ Study Group\*

## Summary

**Background** Bronchial thermoplasty is an endoscopic treatment for uncontrolled asthma. Previous randomised clinical trials have shown that bronchial thermoplasty reduces severe exacerbations in people with asthma. However, the long-term efficacy and safety of bronchial thermoplasty beyond 5 years is unknown. The BT10+ study aimed to investigate the efficacy and safety of bronchial thermoplasty after 10 or more years of follow-up.

**Methods** BT10+ was an international, multicentre, follow-up study of participants who were previously enrolled in the AIR, RISA, and AIR2 trials and who had 10 or more years of follow-up since bronchial thermoplasty treatment. Data on patient demographics, quality of life, lung function, CT scans (AIR2 participants only), severe exacerbations, and health-care use during the previous year were collected at the BT10+ 10-year outcomes study visit. The primary effectiveness endpoint was durability of the thermoplasty treatment effect, determined by comparing the proportion of participants who had severe exacerbations during the first and fifth years after bronchial thermoplasty treatment with the proportion of participants who had severe exacerbations during the 12-month period before the BT10+ visit. The primary safety endpoint was the absence of clinically significant post-treatment respiratory image changes after bronchial thermoplasty, defined as bronchiectasis or bronchial stenosis as confirmed by pulmonary volumetric high-resolution CT scan at the BT10+ visit (AIR2 participants only). All analyses were done on an intention-to-treat basis. The trial is registered with ClinicalTrials.gov, NCT03243292. The last patient was enrolled on Dec 11, 2018. The last patient completed follow-up on Jan 10, 2019.

**Findings** The BT10+ study enrolled 192 (45%) of the 429 participants who were enrolled in the AIR, RISA, and AIR2 trials. The BT10+ participants comprised 136 who received bronchial thermoplasty (52% of the 260 participants who received bronchial thermoplasty in the original trials), and 56 sham or control participants (33% of 169 from the original trials). 18 (32%) sham or control participants received bronchial thermoplasty after the previous trials concluded. The participants included in BT10+ were followed for 10·8–15·6 years (median 12·1 years) post-treatment. Baseline characteristics were similar between participants enrolled in BT10+ and those not enrolled. Participants treated with bronchial thermoplasty had similar proportions of severe exacerbations at the BT10+ visit (34 [25%] of 136 participants) compared with 1 year (33 [24%] of 135 participants; difference 0·6%, 95% CI –9·7 to 10·8) and 5 years (28 [22%] of 130 participants; difference 3·5%, –6·7% to 13·6) after treatment. Quality of life measurements and spirometry were similar between year 1, year 5, and the BT10+ visit. At the BT10+ study visit, pulmonary high-resolution CT scans from AIR2 participants treated with bronchial thermoplasty showed that 13 (13%) of 97 participants had bronchiectasis. When compared with baseline high-resolution CT scans, six (7%) of 89 participants treated with bronchial thermoplasty who did not have bronchiectasis at baseline had developed bronchiectasis after treatment (5 classified as mild, 1 classified as moderate). Participants treated with bronchial thermoplasty after the original study and participants in the sham or control group also had reductions in severe exacerbations at the BT10+ visit compared with baseline.

**Interpretation** Our findings suggest that efficacy of bronchial thermoplasty is sustained for 10 years or more, with an acceptable safety profile. Therefore, bronchial thermoplasty is a long-acting therapeutic option for patients with asthma that remains uncontrolled despite optimised medical treatment.

**Funding** Boston Scientific.

**Copyright** ©2021 Elsevier Ltd. All rights reserved.

## Introduction

Asthma affects around 334 million people worldwide, leading to reduced quality of life and substantial economic burden.<sup>1</sup> Some asthmatics have persistent

symptoms and exacerbations despite optimal medical therapy.

Excessive constriction and hypertrophy of airway smooth muscle contributes to bronchial hyper-responsiveness

*Lancet Respir Med* 2021

Published Online

January 29, 2021

[https://doi.org/10.1016/S2213-2600\(20\)30408-2](https://doi.org/10.1016/S2213-2600(20)30408-2)

See Online/Comment

[https://doi.org/10.1016/S2213-2600\(20\)30456-2](https://doi.org/10.1016/S2213-2600(20)30456-2)

\*Members are listed in the

appendix (pp 3–4)

Asthma/COPD Clinical Research

Centre, Gartnavel General

Hospital, Glasgow, UK

(Prof R Chaudhuri MD); Institute

of Infection, Immunity, and

Inflammation, University of

Glasgow, Glasgow, UK

(Prof R Chaudhuri); Department

of Pulmonary Medicine, Santa

Casa of Porto Alegre Hospital,

Federal University of Health

Ciencias of Porto Alegre

(UFCSA), Porto Alegre, Brazil

(Prof A Rubin MD); Department

of Medicine, Division of

Pulmonary and Critical Care

Medicine, Washington

University School of Medicine,

St Louis, MO, USA

(K Sumino MD); Department of

Medicine, Division of Infectious

Diseases, Hospital Universitário

Clementino Fraga Filho,

Rio de Janeiro, Brazil

(Prof J R Lapa e Silva MD);

Manchester Academic Health

Science Centre, The University

of Manchester and Manchester

Foundation Trust, Manchester,

UK (R Niven MD); University of

Leicester, College of Life

Sciences, Department of

Respiratory Sciences, NIHR

Biomedical Research Centre

(Respiratory Theme), Leicester,

UK (Prof S Siddiqui MD); Faculty

of Medical Sciences, Groningen

Research Institute for Asthma

and COPD, University of

Groningen, University Medical

Center Groningen, Groningen,

Netherlands (K Klooster PhD);

HealthPartners Specialty

Center—Lung and Sleep Health,

St Paul, MN, USA

(C McEvoy MD); Department of

Respiratory Medicine, Chelsea and Westminster Hospital, London, UK (Prof P L Shah MD); National Heart & Lung Institute, Imperial College, London, UK (Prof P L Shah); Division of Pulmonary and Critical Care Medicine, Henry Ford Hospital, Detroit, MI, USA (M Simoff MD); Asthma Center, Cleveland Clinic Foundation, Cleveland, OH, USA (S Khatri MD); Department of Clinical Medicine, Division of Pulmonary and Critical Care Medicine, Keck School of Medicine of USC, University of Southern California Hospital, Los Angeles, CA, USA (Prof R Barbers MD); Boston Scientific Corporation, Marlborough, MA, USA (G Mark Grubb RN, E A McMullen MMath, J L Olson PhD); Institut Universitaire de cardiologie et de pneumologie, Université Laval, Québec, QC, Canada (Prof M Laviolette MD)

Correspondence to: Prof Rekha Chaudhuri, Asthma/COPD Clinical Research Centre, Gartnavel General Hospital, Glasgow G12 0YN, UK rekha.chaudhuri@ggc.scot.nhs.uk

See Online for appendix

## Research in context

### Evidence before this study

Bronchial thermoplasty is the only US Food and Drug Administration-approved non-pharmacological procedure for the treatment of patients aged 18 years and older with severe persistent asthma that is not well controlled with inhaled corticosteroids and long-acting  $\beta$ -agonists. During the bronchial thermoplasty procedure, radiofrequency energy is used to heat the airway walls in a controlled manner. Pretolani and colleagues attributed the mechanism of action to a lasting reduction in airway smooth muscle mass and airway nerve endings after the procedure, as well as downstream mechanical and physiological actions resulting from these reductions. We searched MEDLINE between Jan 1, 1990, and Jan 1, 2020, for clinical trials involving bronchial thermoplasty for asthma, using the search terms “bronchial thermoplasty”, “asthma”, and “clinical trial”. The search was limited to publications in English. Our search retrieved several good quality results. Three previous randomised trials (AIR, RISA, and AIR2) investigating the safety and efficacy of bronchial thermoplasty showed that participants undergoing the procedure had improvements in asthma control up to 5 years after treatment, as indicated by decreased numbers of asthma exacerbations, hospital emergency department visits, and admissions to hospital, as well as improved quality of life as measured by Asthma Quality of Life Questionnaire scores. Additionally, the PAS2 study is an ongoing, prospective, multicentre, observational study designed to investigate the safety and efficacy of bronchial thermoplasty outside the confines of a randomised trial, and

interim results from this study indicated that, while the PAS2 study enrolled participants with more severe asthma than the AIR2 trial, participants had reductions in severe exacerbations and lower health-care service use compared with the 12 months before enrolment in PAS2. However, data on long-term (more than 5 years) safety and efficacy of bronchial thermoplasty are lacking, and studies designed to address this are needed.

### Added value of this study

To our knowledge, the BT10+ study is the first to follow up a large group of participants treated with bronchial thermoplasty beyond 5 years. The study was designed to follow participants from the RISA, AIR, and AIR2 trials for 10 years or more after treatment to evaluate the long-term durability of the improvements in asthma control seen in previous studies. The study was also designed to address long-term safety concerns associated with bronchial thermoplasty, such as diminution of treatment effect and the development of bronchiectasis. We showed that, in participants from the AIR, RISA, and AIR2 trials, the efficacy of bronchial thermoplasty was sustained over 10 years.

### Implications of all the available evidence

Long-term (>10 years) evidence suggests that bronchial thermoplasty is a safe and effective non-pharmacological therapy for asthma, and can be considered as a treatment option for patients whose asthma remains uncontrolled despite optimised medical therapy.

and airflow obstruction. Bronchial thermoplasty is a non-pharmacological, bronchoscopic, catheter-based treatment approved for patients aged 18 years and older with severe persistent asthma that is not well controlled with long-acting  $\beta$ -agonists and inhaled corticosteroids. During the bronchial thermoplasty procedure, radiofrequency energy is used to heat the airway walls in a controlled manner,<sup>2</sup> which leads to a reduction in airway smooth muscle mass and bronchial nerve endings.<sup>3-7</sup>

Three randomised clinical trials of bronchial thermoplasty have been done in participants with moderate to severe asthma: the Asthma Intervention Research (AIR) trial,<sup>8</sup> the Asthma Intervention Research-2 (AIR2) trial,<sup>9-12</sup> and the Research in Severe Asthma (RISA) trial.<sup>13</sup> In these trials, participants who underwent bronchial thermoplasty had significantly improved clinical outcomes, including decreased numbers of severe asthma exacerbations, hospital emergency department visits, and admissions to hospital, as well as improved quality of life after the procedure. These trials showed that improvements in asthma control after bronchial thermoplasty persisted for 5 years.

To our knowledge, the BT10+ study is the first to follow up participants treated with bronchial thermoplasty

beyond 5 years. The study followed up participants from the previous randomised trial for 10 or more years after bronchial thermoplasty treatment to evaluate the long-term durability of improvements in asthma control and to address long term concerns, such as diminution of treatment effect and development of bronchiectasis.

## Methods

### Study design and participants

The BT10+ study was an international, multicentre, prospective, follow-up study of participants who were enrolled in the AIR, RISA, and AIR2 trials. BT10+ began enrolment on Dec 11, 2017, at 16 hospitals in the USA, the UK, Canada, Brazil, and the Netherlands that had enrolled three or more bronchial thermoplasty participants from the previous trials (figure 1). The study was approved by the ethics committees at each participating hospital and all participants signed written informed consent.

An enrolment requirement of BT10+ was previous participation in the AIR,<sup>8</sup> AIR2,<sup>9-12</sup> or RISA trials.<sup>13</sup> Participants from the previous trials were contacted by the enrolling sites to determine if they were interested in participating in the BT10+ study. Participants who underwent bronchial thermoplasty treatment in these trials at least 10 years ago were invited to participate.

Control or sham treated participants from the previous trials were also invited; the enrolment requirement for the control or sham participants in BT10+ was also participation in one of the previous trials as a control or sham participant. The control group in the AIR and RISA studies received standard asthma therapy, as per the local standard of treatment practice at each clinical site. Sham participants from the AIR2 trial underwent bronchoscopy procedures identical to those performed in bronchial thermoplasty participants with an inactive bronchial thermoplasty catheter. Control and sham participants were enrolled in the BT10+ study regardless of whether they received bronchial thermoplasty treatment after their participation in the original studies but before their enrolment in BT10+. Enrolment was delayed by 4 weeks if participants had a severe exacerbation or chest infection. A full description of the inclusion and exclusion criteria for the BT10+ study can be found in the study protocol online.

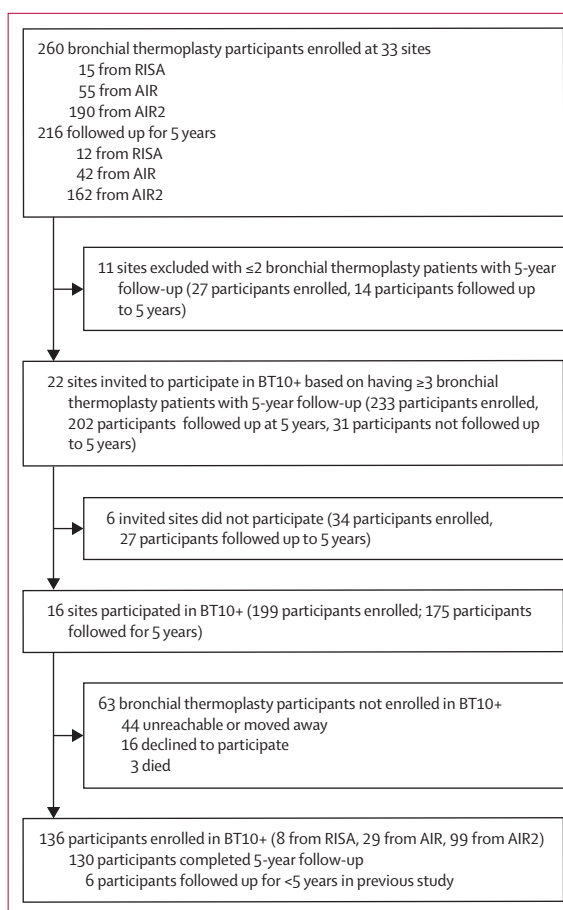
The inclusion and exclusion criteria for the original AIR,<sup>8,14</sup> RISA,<sup>13</sup> and AIR2<sup>11</sup> trials were previously published; for a brief summary of the enrolment criteria for each of these trials see the appendix (p 5).

### Procedures

Bronchial thermoplasty participants in the previous trials were followed up for 5 years after bronchial thermoplasty treatment and control or sham participants were followed up for 1 year. Historical data from AIR, RISA, and AIR2 were used for analysis of outcomes during years 1–5; data from the BT10+ visit were used for analysis of 10-year outcomes. Participants underwent the following assessments: medical history, review of clinical notes to collect data on comorbidities, exacerbations, and pulmonary medication use before and at the BT10+ visit, chest high-resolution CT (AIR2 participants, as only AIR2 participants underwent CT imaging at baseline), pre-bronchodilator and post-bronchodilator spirometry, lung volumes and diffusion capacity measurements, participant questionnaires (Asthma Quality of Life Questionnaire [AQLQ] and Asthma Control Questionnaire [ACQ]), satisfaction survey, and physical examination by a physician. These assessments were completed in a single visit or within 30 days.

### Outcomes

The primary effectiveness endpoint in the BT10+ study was durability of the thermoplasty treatment effect, determined by comparing the proportion of participants who had severe exacerbations during the first and fifth years after bronchial thermoplasty treatment with the proportion of participants who had severe exacerbations during the 12-month period before the BT10+ visit. Severe exacerbations were defined as a self-reported worsening of asthma symptoms requiring the use of systemic corticosteroids or an increase in the dose of maintenance systemic corticosteroids as defined



**Figure 1: Trial profile**

Participants who received bronchial thermoplasty in previous studies and enrolled in BT10+ are included in the figure. In addition, 56 control or sham participants were also enrolled in BT10+, of whom 18 received bronchial thermoplasty after participation in AIR, RISA, or AIR2, and 38 participants were not treated (received no bronchial thermoplasty treatment).

in the National Asthma Education and Prevention Program Guidelines.<sup>15</sup>

The primary safety endpoint of the BT10+ study was the absence of clinically significant post-treatment respiratory image changes after bronchial thermoplasty, defined as bronchiectasis or bronchial stenosis as confirmed by pulmonary volumetric high-resolution CT at the BT10+ visit for AIR2 participants. Each high-resolution CT scan was read by independent, treatment-masked core laboratory staff (BioClinica; London, UK), including a radiologist qualified to read chest images and a pulmonologist qualified to interpret the radiologist's findings. Specifically, the radiologist and pulmonologist diagnosed bronchiectasis based on morphological criteria on thin-section CT scans, including bronchial dilatation with respect to the accompanying pulmonary artery (signet ring sign), lack of tapering of bronchi, and identification of bronchi within 1 cm of the pleural surface, as defined in the Fleischner Society Glossary of Terms for Thoracic Imaging.<sup>16</sup> This same core laboratory

For the study protocol see [https://clinicaltrials.gov/ProvidedDocs/92/NCT03243292/Prot\\_000.pdf](https://clinicaltrials.gov/ProvidedDocs/92/NCT03243292/Prot_000.pdf)

	Control or sham with no post-study bronchial thermoplasty (n=38)	Control or sham with post-study bronchial thermoplasty (n=18)	Bronchial thermoplasty (n=136)
Age (years)	54.4 (11.8)	54.2 (8.9)	53.6 (11.4)
Sex			
Female	19 (50%)	7 (39%)	82 (60%)
Male	19 (50%)	11 (61%)	54 (40%)
Weight (kg)	80.4 (19.1)	96.5 (14.0)	83.7 (19.8)
Height (cm)	167.7 (11.3)	166.6 (8.8)	165.2 (9.1)
Body-mass index (kg/m <sup>2</sup> )	28.5 (5.7)	34.9 (5.2)	30.6 (6.5)
Meet current European Respiratory Society and American Thoracic Society Guidelines for Severe Asthma*	26 (68%)	13 (72%)	103 (76%)
FEV <sub>1</sub>			
Pre-bronchodilator, % predicted	74.4 (17.4)	73.4 (17.1)	72.9 (19.4)
Post-bronchodilator, % predicted	80.7 (16.3)	80.1 (15.2)	79.4 (18.5)
Pre-bronchodilator, measured (L)	2.3 (0.8)	2.3 (0.8)	2.2 (0.8)
Post-bronchodilator, measured (L)	2.5 (0.8)	2.5 (0.8)	2.4 (0.7)
Forced vital capacity			
Pre-bronchodilator, % predicted	93.2 (16.4)	87.7 (14.1)	90.2 (15.1)
Post-bronchodilator, % predicted	97.8 (16.3)	93.2 (11.8)	96.5 (14.3)
Pre-bronchodilator, measured (L)	4.0 (1.1)	3.7 (1.0)	3.7 (0.9)
Post-bronchodilator, measured (L)	4.2 (1.1)	3.9 (1.0)	4.0 (0.9)
Residual volume, % predicted	121.2 (41.8)	121.2 (21.2)	120.9 (34.6)
Total lung capacity, % predicted	102.1 (14.7)	101.8 (13.0)	105.1 (14.0)

Data are mean (SD) or n (%). \*Defined as those who take 2000 µg or more inhaled corticosteroids per day and long-acting β-agonists or leukotriene modifiers or two or more severe exacerbations in the 12 months before the first bronchial thermoplasty treatment, or had one or more admissions to hospital for asthma in the 12 months before the first bronchial thermoplasty treatment, or who had post-bronchodilator FEV<sub>1</sub> less than 80% and FEV<sub>1</sub>/forced vital capacity ratio less than 0.7.<sup>18</sup>

**Table 1: Baseline demographics and results of tests at BT10+ study visit**

was used in the AIR2 trial and, to allow comparison, the scans were done and read as in the AIR2 trial.

Additional endpoints were severe exacerbation rates (exacerbations per participant per year), hospital emergency department visits and hospital admissions for asthma, and respiratory-related serious adverse events, defined as any respiratory-related adverse events that were life-threatening, led to hospital treatment or prolonged admission to hospital, disability, or death. Post-hoc comparisons were done between pre-treatment and post-treatment measurements to investigate the efficacy of bronchial thermoplasty in this current cohort. Although severe exacerbations were recorded before treatment only for AIR2 participants, comparisons with post-treatment severe exacerbations included all BT10+ participants.

### Statistical analysis

All analyses were done on an intention-to-treat basis. Baseline demographics, medical history, outcomes, and adverse events were summarised with sample size, mean, and SD for continuous variables and percentages

for binary variables. Comparisons of severe exacerbations, hospital emergency department visits, and admissions to hospital counts between time periods were based on a repeated measures analysis that controlled for participants (as random effects) over time with negative binomial errors. For the bronchial thermoplasty participants, post-hoc analyses were done to compare the proportions of participants with severe exacerbations, hospital emergency department visits, and admissions to hospital for several pairs of mutually exclusive subgroups. The subgroups analysed were sex (male vs female), age (<40 years vs ≥40 years), body-mass index (<30 kg/m<sup>2</sup> vs ≥30 kg/m<sup>2</sup>), baseline AQLQ (≤4.0 vs >4.0), baseline ACQ (≤1.5 vs >1.5), baseline post-bronchodilator FEV<sub>1</sub> % predicted (≤75% vs >75%), baseline pre-bronchodilator FEV<sub>1</sub>/forced vital capacity ratio (≤70% vs >70%), bronchodilator reversibility (reversible vs fixed), and number of complete thermoplasty activations (≤140 vs >140).<sup>17</sup> A repeated measures analysis consisting of a generalised linear mixed model with binomial error were fitted with factors of subgroup, time, and interaction of subgroup and time with participants treated as random effects. For interactions with p<0.10, time periods for each subgroup and subgroups within time periods were investigated. SAS version 9.4 was used for all analyses.

The trial is registered with ClinicalTrials.gov, NCT03243292. The last patient was enrolled on Dec 11, 2018. The last patient completed follow-up on Jan 10, 2019.

### Role of the funding source

The funder of the study participated in study design, data analysis, data interpretation, and writing of the report. Sites collected the data and the funder provided an electronic data capture system for data entry. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

429 participants were enrolled in the AIR, RISA, and AIR2 trials (260 treated with bronchial thermoplasty and 169 treated with control or sham) at 33 clinical sites. 22 sites with three or more participants treated with bronchial thermoplasty with 5 years of follow-up were invited to participate in the BT10+ study. Six invited sites did not participate. The 16 participating sites enrolled 199 participants treated with bronchial thermoplasty in the previous three trials, of which 63 participants were not enrolled in BT10+ (44 participants moved or were unreachable, 16 declined to participate, and three died). Thus, 136 participants treated with bronchial thermoplasty participated in the BT10+ study (figure 1). Additionally, 56 control or sham participants were enrolled, of whom 18 received bronchial thermoplasty after participation in AIR, RISA, or AIR2, and 38 participants received no bronchial thermoplasty treatment (control or sham not treated with bronchial

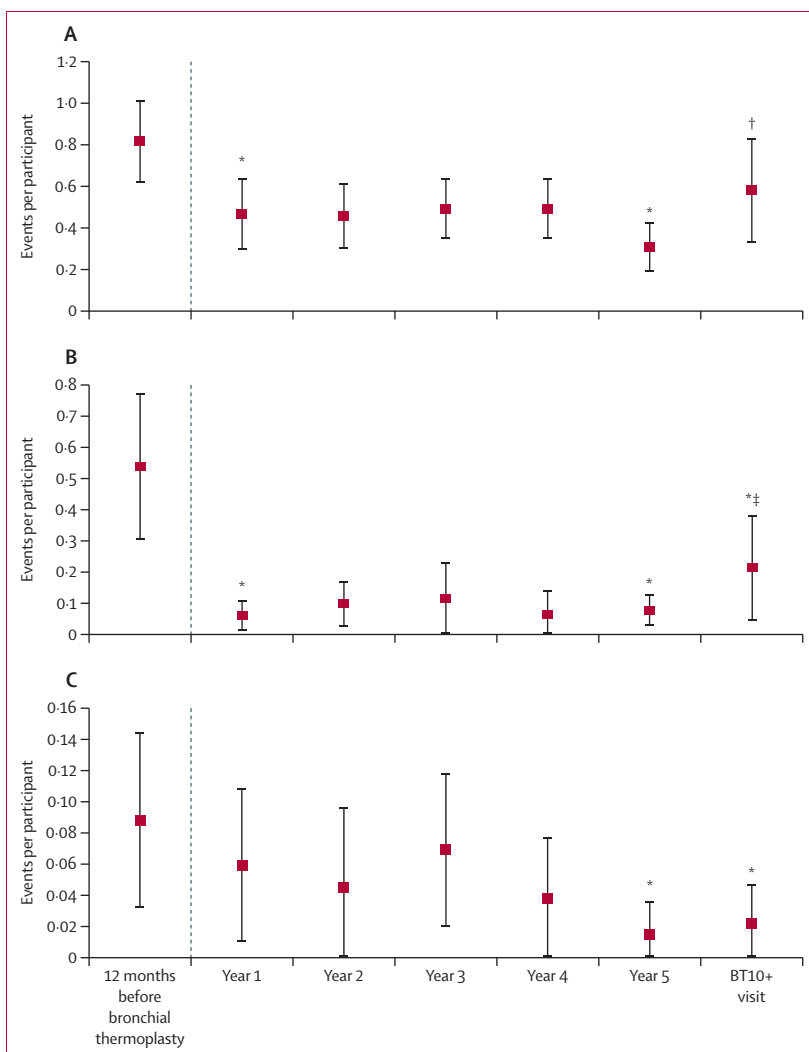


thermoplasty). The 192 patients included in BT10+ were followed for 10.8–15.6 years (12.1 median) post-treatment. Table 1 lists the demographic and assessments from the BT10+ visit for each group of participants. There were no clinically relevant differences in baseline characteristics between participants enrolled and not enrolled in the BT10+ study (appendix p 7).

The most common comorbidities were gastro-oesophageal reflux disease and hypertension in all three groups (appendix p 10). Maintenance oral corticosteroid use was reported in seven (5%) of 136 participants treated with bronchial thermoplasty, and ten (7%) of 136 participants treated with bronchial thermoplasty received biological medications. Maintenance oral corticosteroid use was reported in one (3%) of 38 control or sham participants not treated with bronchial thermoplasty, and biological medications in three (8%) of 38 control or sham participants not treated with bronchial thermoplasty.

In the 12 months before the BT10+ visit, 34 (25%, 95% CI 18.0 to 33.1) of 136 participants treated with bronchial thermoplasty had severe exacerbations (15 participants had one severe exacerbation, ten had two severe exacerbations, and nine had three or more severe exacerbations). These severe exacerbation proportions were similar to those for bronchial thermoplasty participants during the first year after treatment (33 of 135 participants; 24%, 95% CI 17.5 to 32.6; difference 0.6%, 95% CI -9.7 to 10.8) and during year 5 after treatment (28 of 130 participants; 22%, 14.8 to 29.6; difference 3.5%, -6.7 to 13.6); however, proportions were smaller compared with AIR2 bronchial thermoplasty participants 12 months before treatment (50 of 99 participants; 51%, 40.3 to 60.7; difference -25.5%, -37.8 to -13.3). Participants treated with bronchial thermoplasty included in BT10+ had 0.82 (95% CI 0.62 to 1.02) severe exacerbations per participant (AIR2 data only) 12 months before bronchial thermoplasty treatment compared with 0.47 (0.29 to 0.64) severe exacerbations per participant during the first year after bronchial thermoplasty (difference -0.35, 95% CI -0.61 to -0.09;  $p=0.012$ ) and 0.31 (0.19 to 0.43) severe exacerbations per participant during year 5 after bronchial thermoplasty (-0.51, -0.73 to -0.29;  $p<0.0001$ ), both of which were significantly reduced compared with 12 months before bronchial thermoplasty. During the 12 months before the BT10+ visit, there were 0.58 (95% CI 0.33 to 0.83) severe exacerbations per participant, which was significantly more than during year 5 after bronchial thermoplasty treatment (difference 0.27, 95% CI 0.01 to 0.56;  $p=0.044$ ) but not significantly different from year 1 after bronchial thermoplasty treatment (difference 0.11, -0.19 to 0.42;  $p=0.43$ ; figure 2A). Thus, reductions in both the proportion of participants with severe exacerbations after bronchial thermoplasty and the number of severe exacerbations per participant appear to be sustained for 10 years or more after treatment.

There was also a reduction in severe exacerbations in the control or sham participants not treated with bronchial thermoplasty, who had 0.96 (95% CI 0.53–1.39) severe exacerbations per participant in the 12 months before control or sham treatment, 0.39 (0.19–0.60) severe exacerbations per participant during year 1 after treatment, and 0.82 (0.32–1.32) severe exacerbations per participant during the 12 months before the BT10+ study visit. In the 12 months before control or sham treatment, 12 (50%, 95% CI 29.1–70.9) of 24 AIR2 control or sham participants not treated with bronchial thermoplasty had severe exacerbations compared with 12 (32%, 17.5–48.7) of 38 control or sham participants not treated with bronchial thermoplasty at year 1 after treatment and 14 (37%, 21.8–54.0) of 38 during the



**Figure 2: Severe asthma exacerbations in participants treated with bronchial thermoplasty (A), hospital emergency department visits (B), and admissions to hospital for asthma (C) in the BT10+ study**  
Datapoints represent mean and 95% CIs. In part A, only participants previously enrolled in AIR2 are analysed at 12 months before treatment as this information was not collected in the RISA and AIR trials. \*Significantly lower than 12 months before bronchial thermoplasty ( $p<0.05$ ). †Significantly higher than year 5 ( $p<0.05$ ), but not significantly different from 12 months before bronchial thermoplasty and year 1. ‡Significantly higher than years 1 and 5 ( $p<0.05$ ).

12 months before the BT10+ visit (eight participants had one severe exacerbation, three had two severe exacerbations, and three had three or more severe exacerbations). However, in the 24 sham participants from the AIR2 trial who had baseline, 1 year, and 10 year data, there was no change in the rate of severe exacerbations over time.

A reduction in hospital emergency department visits for asthma was also observed. During the 12 months before treatment, bronchial thermoplasty participants experienced 0.54 (95% CI 0.30 to 0.77) hospital emergency department visits per participant compared with 0.06 (0.01 to 0.11) hospital emergency department visits per participant during year 1 after bronchial thermoplasty, 0.08 (0.03 to 0.13) hospital emergency department visits per participant during year 5 after bronchial thermoplasty, and 0.21 (0.04 to 0.38) hospital emergency department visits per participant during the 12 months before the BT10+ visit. Compared with the 12 months before bronchial thermoplasty, the number of hospital emergency department visits per participant was lower at year 1 after bronchial thermoplasty, (difference  $-0.48$ , 95% CI  $-0.72$  to  $-0.24$ ;  $p < 0.0001$ ), year 5 after bronchial thermoplasty ( $-0.46$ ,  $-0.71$  to  $-0.21$ ;  $p < 0.0001$ ), and during the 12 months before the BT10+ visit ( $-0.32$ ,  $-0.61$  to  $-0.03$ ;  $p = 0.031$ ); however, the rate of hospital emergency department visits was significantly higher during the 12 months before the BT10+ visit than during year 1 (0.15, 95% CI 0.02 to 0.29;  $p = 0.026$ ) and year 5 (0.14, 0.02 to 0.26;  $p = 0.024$ ) after bronchial thermoplasty (figure 2B). The proportion of participants with hospital emergency department visits was also reduced after bronchial thermoplasty. During the 12 months before bronchial thermoplasty, 33 (24%, 95% CI 17.3% to 32.4%) of 136 participants visited a hospital emergency department for asthma symptoms. During year 1, year 5, and the 12 months before the BT10+ visit, the proportions of participants treated with bronchial thermoplasty who visited a hospital emergency department because of asthma symptoms were six (4%, 95% CI 1.6 to 9.4) of 135, nine (7%, 3.2 to 12.7) of 130, and 14 (10%, 5.7 to 16.7) of 136, respectively.

A reduction in hospital emergency department visits was also observed in control or sham participants not treated with bronchial thermoplasty. In the 12 months before control or sham treatment, participants had 0.34 (95% CI 0.07–0.61) hospital emergency department visits per participant, which reduced to 0.05 (0.00–0.12) visits per participant during year 1 after control or sham treatment and 0.08 (0.00–0.17) visits per participant during the 12 months before the BT10+ visit. The proportion of control or sham participants not treated with bronchial thermoplasty who visited a hospital emergency department for asthma symptoms after treatment reduced from seven (18%, 95% CI 7.7–34.3) of 38 participants in the 12 months before control or sham treatment, to two (5%, 0.6–17.7) of 38 participants at year 1 after treatment and 3 (8%, 1.7–21.4)

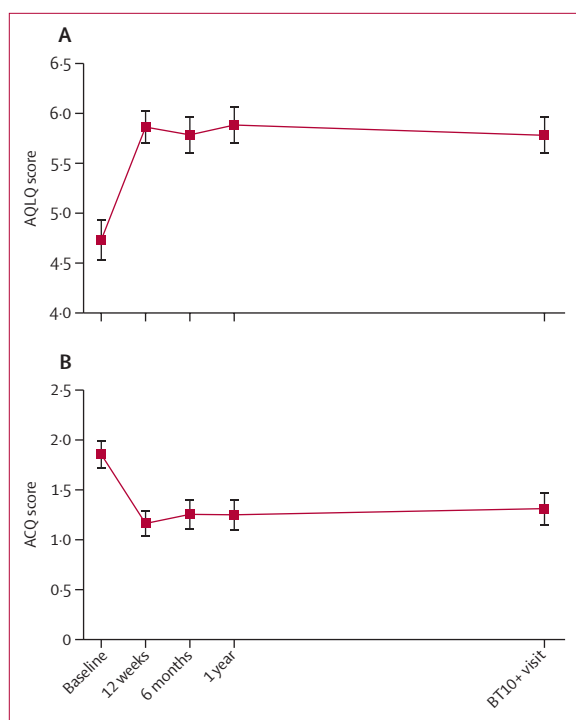
of 38 participants during the 12 months before the BT10+ visit.

Similarly, a reduction in admissions to hospital for asthma was seen. During the 12 months before bronchial thermoplasty treatment, the rate of admissions to hospital for asthma in the bronchial thermoplasty group was 0.09 (95% CI 0.03 to 0.14) admissions to hospital per participant, which reduced to 0.06 (0.01 to 0.11) admissions to hospital per participant during year 1 after bronchial thermoplasty, 0.02 (0.00 to 0.04) admissions to hospital per participant during year 5, and 0.02 (0.00 to 0.05) admissions to hospital per participant during the 12 months before the BT10+ visit. Compared to the 12 months before bronchial thermoplasty, the rates of admissions to hospital for asthma were lower at year 5 (difference  $-0.07$ , 95% CI  $-0.13$  to  $-0.01$ ;  $p = 0.022$ ) and during the 12 months before the BT10+ visit ( $-0.07$ ,  $-0.13$  to  $-0.01$ ;  $p = 0.016$ ; figure 2C). During follow-up, a reduction in the proportion of participants treated with bronchial thermoplasty being admitted to hospital for asthma was observed. During the 12 months before bronchial thermoplasty treatment, ten (7%, 95% CI 3.6–13.1) of 136 participants treated with bronchial thermoplasty were admitted to hospital. During year 1, year 5, and the 12 months before the BT10+ visit, the proportion of participants treated with bronchial thermoplasty who were admitted to hospital for asthma was six (4%, 95% CI 1.6–9.4) of 135 participants, two (2%, 0.2–5.4) of 130 participants, and three (2%, 0.5–6.3) of 136 participants, respectively.

Although three (8%, 95% CI 1.7–21.4) of 38 control or sham participants not treated with bronchial thermoplasty were admitted to hospital for asthma (0.08 admissions to hospital per participant, 95% CI 0.00–0.17) in the 12 months before control or sham treatment, no admissions to hospital occurred during either year 1 after treatment or during the 12 months before the BT10+ visit.

Spirometry was done at baseline and yearly until year 5 after treatment as part of the previous studies and at the BT10+ visit. Bronchial thermoplasty treatment did not affect either pre-bronchodilator or post-bronchodilator FEV<sub>1</sub> (appendix pp 14–15).

Mean AQLQ scores increased from 4.73 (SD 1.21; 95% CI 4.53–4.94) to 5.86 (0.98; 5.69–6.03) by 12 weeks after bronchial thermoplasty, and this improvement was sustained for 10 years or more after treatment (5.78, SD 1.11; 95% CI 5.59–5.97; figure 3). Similarly, ACQ scores dropped from 1.86 (SD 0.85; 95% CI 1.71–2.00) to 1.17 (0.76; 1.04–1.29) by 12 weeks after bronchial thermoplasty, and improvements in these scores also persisted for 10 years or more (1.31, SD 1.00; 95% CI 1.15–1.48). Participants also completed a patient satisfaction survey. 122 (90%, 95% CI 83.3–94.3) of 136 patients treated with bronchial thermoplasty stated they would undergo the procedure again and



**Figure 3:** AQLQ (A) and ACQ (B) scores over time in participants treated with bronchial thermoplasty

Datapoints represent mean and 95% CIs.

130 (96%, 90.6–98.4) of 136 stated they would recommend bronchial thermoplasty to a friend or family member.

At baseline, seven (7%, 95% CI 3.0–14.4) of 96 AIR2 participants treated with bronchial thermoplasty had bronchiectasis (table 2). At the BT10+ study visit, 13 (13%, 95% CI 7.3–21.8) of 97 participants had bronchiectasis. Six (7%, 95% CI 2.5–14.1) of 89 participants treated with bronchial thermoplasty who did not have bronchiectasis at baseline developed bronchiectasis after treatment. All but one instance of bronchiectasis was classified as mild; one case was classified as moderate. Clinical symptoms of bronchiectasis (chronic cough, increased sputum, and recurrent infections) were not present in these participants.

At baseline, 3 (14%, 95% CI 3.0–36.3) of 21 AIR2 sham participants had bronchiectasis, and at the BT10+ visit, two (10%, 1.2–30.4) of 21 had evidence of bronchiectasis (table 2). None of the sham participants developed bronchiectasis after sham treatment.

We analysed several pairs of mutually exclusive subgroups of participants treated with bronchial thermoplasty using a generalised linear mixed model to see if bronchial thermoplasty was effective in reducing the proportion of participants with severe exacerbations, hospital emergency department visits, and admissions to hospital over time and to see if there were any differences between the subgroup pairs. For severe exacerbations and hospital emergency department visits,

	Sham (n=24)	Bronchial thermoplasty (n=99)
Bronchiectasis observed at baseline	3/21 (14%; 3.0–36.3)	7/96 (7%; 3.0–14.4)
Bronchiectasis observed at BT10+ visit	2/21 (10%; 1.2–30.4)	13/97 (13%; 7.3–21.8)
Bronchiectasis observed at BT10+ visit and not baseline	0/18 (0; 0–18.5)	6/89 (7%; 2.5–14.1)

Data are n/N (%; 95% CI). Sham participants receiving bronchial thermoplasty after participation in the AIR2 study were excluded. Baseline high-resolution CT information for one AIR2 bronchial thermoplasty participant was missing but this participant had a high-resolution CT at the BT10+ study visit.

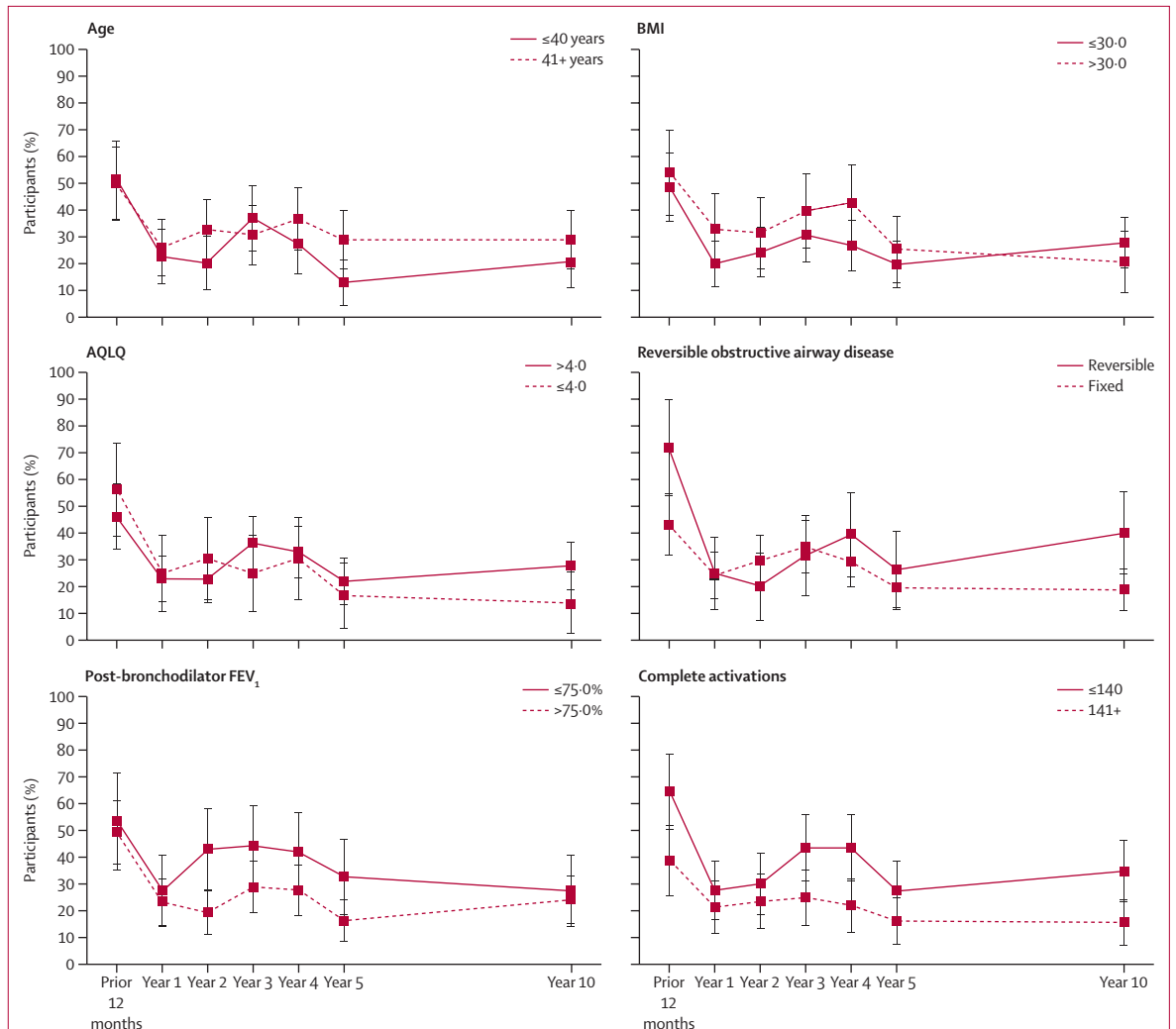
**Table 2: Results of high-resolution pulmonary CT at the BT10+ study visit (AIR2 participants only)**

our analysis showed there was a significant decrease in both outcome measures over time for all sets of subgroups (figure 4; appendix pp 12, 16), and nearly all subgroups of participants treated with bronchial thermoplasty benefited (appendix p 6).

Based on a composite definition of a bronchial thermoplasty responder (participants with neither severe exacerbations nor admissions to hospital for asthma in the year before the BT10+ study and taking neither maintenance corticosteroids nor monoclonal antibodies at the BT10+ visit), 93 (68%) of 136 participants treated with bronchial thermoplasty were responders in this post-hoc analysis. Within the subgroups, younger participants had a higher proportion of responders than older participants (51 [76%] of 67 participants aged  $\leq 40$  years vs 42 [61%] of 69 participants aged  $> 40$  years), participants with lower baseline AQLQ responded more often than those with higher baseline AQLQ (30 [83%] of 36 participants with score  $\leq 4$  vs 62 [64%] of 97 participants with score  $> 4$  [baseline AQLQ data were missing for three participants]), and participants with higher post-bronchodilator FEV<sub>1</sub> had more responders than those with lower post-bronchodilator FEV<sub>1</sub> (25 [57%] of 44 participants with baseline post-bronchodilator FEV<sub>1</sub> % predicted  $\leq 75$  vs 68 [74%] of 92 participants with baseline post-bronchodilator FEV<sub>1</sub> % predicted  $> 75$ ). Additionally, there were more responders with fixed (70 [73%] of 96 participants) versus reversible (23 [58%] of 40 participants) obstructive airway disease, and participants with more treatment activations responded more often (40 [61%] of 66 participants for  $\leq 140$  complete activations vs 53 [76%] of 70 participants for  $> 140$  complete activations).

There were no adverse events after patients consented to the BT10+ study. Respiratory events in the year before the BT10+ visit are included in table 3 and the appendix (p 17). These events were not thought to be associated with bronchial thermoplasty by the study investigators.

Two deaths occurred during the previous studies, and both were unrelated to bronchial thermoplasty. One participant treated with bronchial thermoplasty in the AIR2 study died in a motor vehicle accident, and one patient treated with bronchial thermoplasty in the RISA study died of acute intoxication with  $\gamma$ -hydroxybutyrate. Two additional participants treated with bronchial thermoplasty died after the previous studies completed



**Figure 4:** Subgroup responder analyses of severe asthma exacerbations after bronchial thermoplasty for participants aged  $\leq 40$  years vs  $\geq 41$  years, participants with BMI  $\leq 30$  kg/m<sup>2</sup> or vs  $> 30$  kg/m<sup>2</sup>, participants with AQLQ scores  $> 4$  vs  $\leq 4$ , participants with reversible vs fixed obstructive airway disease, participants with post-bronchodilator FEV<sub>1</sub>  $\leq 75\%$  vs  $> 75\%$ , and participants receiving  $\leq 140$  activations vs  $\geq 141$  activations. AQLQ=Asthma Quality of Life Questionnaire. BMI=body-mass index.

(neither related to the bronchial thermoplasty procedure). One participant treated with bronchial thermoplasty in the RISA study died from pneumonia and one participant treated with bronchial thermoplasty in the AIR2 study died from metastasis of primary renal cancer.

No control or sham group participants died during the AIR, RISA, and AIR2 trials. However, one AIR2 participant treated with the sham procedure died after the study, with an unspecified violent death.

## Discussion

Previous randomised trials have shown that bronchial thermoplasty significantly improved quality of life scores, including AQLQ and ACQ, and decreased severe exacerbations, hospital emergency department visits, and admissions to hospital. These improvements were observed up to 5 years after bronchial thermoplasty. The

BT10+ study shows that participants treated with bronchial thermoplasty had sustainable improvements in severe exacerbations and other health-care use outcomes for 10 or more years of follow-up. At the BT10+ study visit, the rates of severe exacerbations and hospital emergency department visits were higher compared with data collected at year 5, but the positive effect compared with baseline was sustained, as was the improvement in AQLQ and ACQ up to 10 years.

The BT10+ study found that participants in the control group had decreases in severe exacerbations, hospital emergency department visits, and admissions to hospital. This placebo effect has been reported for other studies, including the AIR2 trial,<sup>12</sup> but we believe that a placebo effect is unlikely to last for 10 years or more. In the BT10+ study, we were able to regain contact with only 56 (33%) of 169 control or sham group participants and



18 of these received bronchial thermoplasty after their original study. However, the small number of control or sham group participants does not fully explain the effect seen in this study, which might be within the natural variation of asthma, but this aspect needs further investigation.

In BT10+, FEV<sub>1</sub> remained relatively consistent over time. People with severe asthma have a progressive decline of 22.5–50 mL per year in FEV<sub>1</sub><sup>19–23</sup> (appendix pp 14–15), and the measured FEV<sub>1</sub> in participants treated with bronchial thermoplasty from AIR, RISA, and AIR2 suggests FEV<sub>1</sub> might not have declined as rapidly as would be expected in participants not receiving this treatment.

Because the previous randomised trials were not designed to capture the data required to predict responses to bronchial thermoplasty, we were unable to do an analysis to identify likely responders to bronchial thermoplasty. However, our subgroup analysis showed that all groups of several mutually exclusive subsets of patients had a reduction in severe exacerbations, hospital emergency department visits, and admissions to hospital from the time of bronchial thermoplasty treatment to the most recent BT10+ study. It is encouraging to find that a variety of patients benefit from bronchial thermoplasty, although the sample size in this study did not allow us to show differences between groups for most factors. However, there seemed to be an improvement in outcomes for patients with more than 140 activations over the three bronchial thermoplasty treatments compared with patients with 140 or fewer activations, and there was a better response for those younger than 40 years compared with those older than 40 years, those with higher baseline post-bronchodilator FEV<sub>1</sub> and those with poorer baseline asthma quality of life scores.

The question of whether bronchial thermoplasty induces clinically significant respiratory changes, such as bronchiectasis, over the long term has not been addressed. High-resolution CT scans from BT10+ participants revealed that although none of the sham participants developed bronchiectasis during the time period between high-resolution CT scans, six (7%) participants treated with bronchial thermoplasty appeared to develop bronchiectasis over the same time period. This bronchiectasis was mostly mild and might not necessarily be attributable to bronchial thermoplasty treatment. An alternative explanation for the slight increase in participants with bronchiectasis at the BT10+ study visit could be related to improvements in both CT hardware and image processing algorithms developed over the past decade that could result in better detection of mild bronchiectasis compared with older images. When baseline high-resolution CT was done on AIR2 patients, the scans consisted of interval slices rather than volume high-resolution CT. Thus, comparison of airway volumes between the BT10+ and baseline scans is not possible. Finally, several studies have shown that airway dilation, often transient, can be observed after bronchial thermoplasty, and this is associated with reduced

	Control or sham (n=38)		Bronchial thermoplasty (n=136)	
	Events*	Participants with event	Events*	Participants with event
Total	5	5 (13%)	35	29 (21%)
Infections and infestations	1	1 (3%)	1	1 (1%)
Bronchitis	0	0	1	1 (1%)
Respiratory tract infection	1	1 (3%)	0	0
Investigations	0	0	1	1 (1%)
Abnormal CT scan	0	0	1	1 (1%)
Respiratory, thoracic, and mediastinal disorders	4	4 (11%)	33	28 (21%)
Asthma	0	0	1	1 (1%)
Atelectasis	0	0	2	1 (1%)
Bronchial wall thickening	0	0	1	1 (1%)
Bronchiectasis	3	3 (8%)	20	20 (15%)
Interstitial lung disease	0	0	1	1 (1%)
Pulmonary fibrosis	0	0	1	1 (1%)
Pulmonary hypertension	0	0	1	1 (1%)
Pulmonary mass	1	1 (3%)	5	5 (4%)
Respiratory tract inflammation	0	0	1	1 (1%)

Data are n or n (%). There were no participant deaths in the year before the BT10+ study visit. Two bronchial thermoplasty participant deaths occurred during the previous studies and two additional bronchial thermoplasty participants died after year 5 of the previous study but before enrolment in the BT10+ study (none were related to the bronchial thermoplasty procedure). One sham participant from AIR2 died after the AIR2 study but before the BT10+ study visit due to unspecified violent death. \*Events numbers are the total episodes of each type of event among all participants.

**Table 3: Adverse events during the 12 months before the BT10+ study visit**

airway resistance and improved asthma symptoms.<sup>24–26</sup> It is possible that we are observing this phenomenon in a delayed fashion in a small number of scans in the BT10+ study rather than the development of true bronchiectasis, particularly since the BT10+ investigators have noted that these participants did not display any clinically relevant symptoms of bronchiectasis.

The BT10+ study has several other important limitations. First, because of the length of time between participation in the three original trials and BT10+, several participants from the original trials were lost to follow-up and could not be enrolled in the BT10+ study. Although our findings suggest that there were no clinically relevant differences in demographics and characteristics between participants who were enrolled in BT10+ and those who were not, it is possible that selection bias might have occurred. Additionally, the reporting of results pertaining to severe exacerbations was based on patient recollection supported by case note reviews by investigators, similar to the methodology used for baseline data from the original trials. Bronchial thermoplasty is only recommended for use in patients with severe asthma, and although most participants in the BT10+ study were considered to have severe asthma based on European Respiratory Society and American Thoracic Society Guidelines for Severe Asthma,<sup>18</sup> 26% of participants did not fulfill these criteria. Thus, the improvements in asthma control seen in the BT10+ study population should be interpreted with caution and might

not be applicable to patients with the most severe asthma who are seen in clinical practice. Finally, this study was funded by the manufacturer of the bronchial thermoplasty system and three of the listed authors are full-time employees of the manufacturer, which could potentially lead to a perceived conflict of interest.

In conclusion, the data from the BT10+ study indicate that the efficacy of bronchial thermoplasty is sustained for 10 or more years and that bronchial thermoplasty has an acceptable safety profile. This suggests that bronchial thermoplasty is an effective non-pharmacological therapy for patients with asthma, particularly for those whose asthma remains uncontrolled despite optimised medical therapy and for those who do not qualify for or respond adequately to biologicals.

#### Contributors

RC, CM, GMG, and EAM contributed to study design. All authors followed up study participants. EAM did the data analysis. GMG was trial manager. RC, GMG, EAM, JLO, and ML wrote the first draft of the manuscript. RC, GMG, EAM, JLO, and ML wrote the final draft of the manuscript. All authors approved the final version of the manuscript.

#### Declaration of interests

RC reports research grants from AstraZeneca, fees for advisory board meetings from GlaxoSmithKline, AstraZeneca, Novartis, Teva, and Chiesi, speaker fees from Novartis, AstraZeneca and GlaxoSmithKline, and conference travel support from AstraZeneca and Napp Pharmaceuticals. AR reports receipt of personal fees from Novartis, GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, and Sanofi. JRL reports grants from Boston Scientific. RN reports the receipt of grants and personal fees from Boston Scientific. SS reports personal fees from Chiesi, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, ERT Medical, Owlstone Medical, Roche, and Mundipharma. CM reports grants from Boston Scientific. PLS reports personal fees for lectures and consultancy from Boston Scientific and sponsorship to Imperial College for a bronchoscopy course from ERBE, Cook Medical, Medtronic, Boston Scientific, Broncus, Nuvaria, Pulmonx, Olympus, and PneumRX/BTG. MS reports personal fees from Intuitive Surgical and Gongwin Biopharm. SK reports grants from Boston Scientific. GMG, EAM, and JLO are full-time employees of the study sponsor (Boston Scientific Corporation). ML reports personal fees from Boston Scientific and GlaxoSmithKline. All other authors report no competing interests.

#### Data sharing

For the **Boston Scientific Data Sharing Policy** see <https://www.bostonscientific.com/en-US/data-sharing-requests.html>

The data and study protocol for this clinical trial can be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy. For questions related to Boston Scientific Data Sharing Requests contact [clinicalolutions@bsci.com](mailto:clinicalolutions@bsci.com).

#### Acknowledgments

We thank Frances Nolan for her contributions to the management of the BT10+ study.

#### References

- Marks G, Pearce N, Strachan D, Asher I. The global burden of disease due to asthma. The Global Asthma Report. Auckland: Global Asthma Network, 2014.
- Bonta PI, Chanez P, Annema JT, Shah PL, Niven R. Bronchial thermoplasty in severe asthma: best practice recommendations from an expert panel. *Respiration* 2018; **95**: 289–300.
- 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**: 1612–18.
- 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**: 1426–28.
- Bergqvist A, Pretolani M, Taille C, et al. Selective structural changes of bronchial thermoplasty in the treatment of severe uncontrolled asthma. *Am J Respir Crit Care Med* 2015; **201**: A4171.
- Pretolani M, Bergqvist A, Thabut G, et al. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: clinical and histopathologic correlations. *J Allergy Clin Immunol* 2017; **139**: 1176–85.
- 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**: 1452–54.
- 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**: 510–18.
- Castro M, Cox G. Asthma outcomes from bronchial thermoplasty in the AIR2 trial. *Am J Respir Crit Care Med* 2011; **184**: 743–44.
- Castro M, Rubin A, Laviolette M, Hanania NA, Armstrong B, Cox G. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. *Ann Allergy Asthma Immunol* 2011; **107**: 65–70.
- 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**: 116–24.
- 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**: 1295–302.
- Pavord I. 5-year safety of bronchial thermoplasty demonstrated in patients with severe refractory asthma: research in severe asthma (RISA) trial. *Am J Respir Crit Care Med* 2011; **183**: A6382.
- Thomson NC, Rubin AS, Niven RM, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. *BMC Pulm Med* 2011; **11**: 8.
- National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda: National Institutes of Health, 2007.
- Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; **246**: 697–722.
- Langton D, Sha J, Ing A, Fielding D, Thien F, Plummer V. Bronchial thermoplasty: activations predict response. *Respir Res* 2017; **18**: 134.
- 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**: 343–73.
- Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 1987; **70**: 171–79.
- 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**: 1194–200.
- O'Byrne P, Fabbri LM, Pavord ID, Papi A, Petruzzelli S, Lange P. Asthma progression and mortality: the role of inhaled corticosteroids. *Eur Respir J* 2019; **54**: 1900491.
- Ulrik CS, Lange P. Decline of lung function in adults with bronchial asthma. *Am J Respir Crit Care Med* 1994; **150**: 629–34.
- Cibella F, Cuttitta G, Bellia V, et al. Lung function decline in bronchial asthma. *Chest* 2002; **122**: 1944–48.
- d'Hooghe JNS, van den Berk IAH, Annema JT, Bonta PI. Acute radiological abnormalities after bronchial thermoplasty: a prospective cohort trial. *Respiration* 2017; **94**: 258–62.
- Qiu M, Lai Z, Wei S, et al. Bronchiectasis after bronchial thermoplasty. *J Thorac Dis* 2018; **10**: E721–26.
- Menzella F, Lusuardi M, Galeone C, Montanari G, Cavazza A, Facciolo N. Heat-induced necrosis after bronchial thermoplasty: a new concern? *Allergy Asthma Clin Immunol* 2018; **14**: 25.