Bronchial Thermoplasty Global Registry (BTGR): 2-year results

Alfons Torrego, Felix J Herth, Ana M Munoz-Fernandez, Luis Puente, Nicola Facciolongo, Stephen Bicknell, Mauro Novali, Stefano Gasparini, Martina Bonifazi, Keertan Dheda, Felipe Andreo, Praha Votruba, David Langton, Javier Flandes, David Fielding, Peter I Bonta, Dirk Skowasch, Christian Schulz, Kaid Darwiche, Edmund McMullen, G. Mark Grubb, Robert Niven

ABSTRACT

Objectives Bronchial thermoplasty (BT) is a device-based treatment for subjects ≥18 years with severe asthma not well controlled with inhaled corticosteroids and long-acting beta-agonists. The Bronchial Thermoplasty Global Registry (BTGR) collected real-world data on subjects undergoing this procedure.

Design The BTGR is an all-comer, prospective, open-label, multicentre study enrolling adult subjects indicated for and treated with BT.

Setting Eighteen centres in Spain, Italy, Germany, the UK, the Netherlands, the Czech Republic, South Africa and Australia.

Participants One hundred fifty-seven subjects aged 18 years and older who were scheduled to undergo BT treatment for asthma. Subjects diagnosed with other medical conditions which, in the investigator’s opinion, made them inappropriate for BT treatment were excluded.

Primary and secondary outcome measures Baseline characteristics collected included demographics, Asthma Quality of Life Questionnaire (AQLQ), Asthma Control Test (ACT), medication usage, forced expiratory volume in one second and forced vital capacity, medical history, comorbidities and 12-month baseline recall data (severe exacerbations (SE) and healthcare utilisation). SE incidence and healthcare utilisation were summarised at 1 and 2 years post-BT.

Results Subjects’ baseline characteristics were representative of persons with severe asthma. A comparison of the proportion of subjects experiencing events during the 12 months prior to BT to the 2-year follow-up showed a reduction in SE (90.3% vs 56.1%, p<0.0001), emergency room visits (53.8% vs 25.5%, p<0.0001) and hospitalisations (42.9% vs 23.5%, p=0.0019). Reductions in asthma maintenance medication dosage were also observed. AQLQ and ACT scores improved from 3.26 and 11.18 at baseline to 4.39 and 15.54 at 2 years, respectively (p<0.0001 for both AQLQ and ACT).

Conclusions The BTGR demonstrates sustained improvement in clinical outcomes and reduction in asthma medication usage 2 years after BT in a real-world population. This is consistent with results from other BT randomised controlled trials and registries and further supports improvement in asthma control after BT.

Trial registration number NCT02104856.

Strengths and limitations of this study

The Bronchial Thermoplasty Global Registry (BTGR):

- Was designed to collect data on subjects undergoing bronchial thermoplasty treatment for asthma in a ‘real-world’ setting for 2 years at 18 clinical sites to investigate the effect of bronchial thermoplasty on severe asthma exacerbations, emergency department visits and hospitalisations.

- One limitation of this study was that it was registry-based and, thus, was a single-arm study with no comparator rather than a randomised controlled trial.

- Another limitation is that the level of investigator experience with the bronchial thermoplasty procedure varied between clinical sites and some sites were inexperienced with the conduct of clinical studies.

- The BTGR was also limited by a high attrition rate at 2 years post-treatment; approximately one-third of enrolled subjects dropped out of the study.

INTRODUCTION

Asthma is a chronic condition of the Airways characterised by airway inflammation, excess mucus production, airway hyperresponsiveness and airway remodelling. Ten per cent of patients have severe, poorly controlled asthma with frequent symptoms despite optimal therapy with inhaled corticosteroids (ICS) and long-acting bronchodilators (LABA), and this group accounts for more than 80% of the healthcare costs associated with the disease.1–3

Bronchial thermoplasty (BT) is the only U.S. Food and Drug Administration (FDA)-approved non-pharmacologic procedure approved for the treatment of asthma. It is indicated for patients 18 years and older with severe persistent asthma who is not well controlled with ICS and LABA. During the BT procedure, radiofrequency energy is used to heat the airway walls in a controlled manner. The mechanism of action may be, in
A lasting reduction in airway smooth muscle mass after the procedure and downstream mechanical and physiological actions resulting from this reduction. Reduction in airway smooth muscle has been shown to be associated with clinical improvement seen in patients undergoing BT. Other structural and immunohistological changes, including reduction in reticular basement membrane thickness, reduction in collagen type I deposition and changes in neuroendocrine cells and bronchial nerve endings, may also contribute to clinical improvement.

Several randomised controlled clinical trials of BT have been carried out in patients with moderate to severe asthma—including the AIR (Asthma Intervention Research), RISA (Research In Severe Asthma) and AIR2 (Asthma Intervention Research 2) studies. All of these randomised controlled trials (RCTs) have concluded that BT is a safe and effective procedure. Subjects enrolled in these studies experienced improvements in asthma control following BT, including decreased numbers of asthma exacerbations, emergency room (ER) visits for asthma and hospitalisations as well as improved quality of life as measured by Asthma Quality of Life Questionnaire (AQLQ) scores. Clinical improvements persisted to at least 5 years after the last BT treatment. Additionally, several recent studies have examined the effectiveness of BT outside the confines of an RCT, including the PAS2 study in the USA and Canada and a study in Australia in severe asthmatics. Data from both of these studies suggest that BT is safe and effective in populations of patients who may have more severe asthma than those included in the previous RCTs.

Nevertheless, additional data outside RCT studies can provide reassurance that these results can be duplicated in clinical practice. The Bronchial Thermoplasty Global Registry (BTGR) was designed to collect outcome data as well as clinical and demographic characteristics of patients undergoing BT treatment in the ‘real-world’ setting. In this manuscript, we describe the clinical outcomes for BTGR subjects over the 2 years following BT treatment.

**METHODOLOGY**

**Study design**

BTGR is a prospective, open-label, single-arm, observational registry (clinicaltrials.gov) designed to collect outcome data as well as clinical and demographic characteristics of patients undergoing BT treatment in the ‘real-world’ clinical setting. BTGR-enrolled subjects from 23 January 2014 to 28 December 2016 at 18 centres in Spain, Italy, Germany, the UK, the Netherlands, the Czech Republic, South Africa and Australia, and the last patient completed follow-up and exited the study on 26 June 2019.

**Study subjects**

Between 2014 and 2016, BTGR enrolled 157 subjects aged 18 years and older who were scheduled to undergo BT treatment with the Alair System (Boston Scientific Corporation, Marlborough, Massachusetts). Subjects diagnosed with other medical conditions which, in the investigator’s opinion, made them inappropriate for BT treatment were excluded. All medications were administered as part of the local standard of care asthma treatment and for BT procedures; there were no additional medication requirements mandated by this registry.

**Treatment**

All BTGR subjects were scheduled to undergo three bronchoscopy procedures performed approximately 3 weeks apart. BT treatments were administered using the Alair Bronchial Thermoplasty System (Boston Scientific, Marlborough, Massachusetts) per FDA labelling by the investigators and as previously described.

**Follow-up**

BTGR subjects were instructed to report any adverse events (AEs) occurring as a result of the BT procedure to clinic staff at any time. Subjects were evaluated at 6 weeks following the third BT procedure (the end of the treatment period) and at 6, 12, 18 and 24 months after completion of the treatment period. The 6-month and 18-month evaluations were performed either by phone or in the clinic office; the 12-month and 24-month evaluations were performed as office visits.

**Outcome measures**

The primary endpoint of the BTGR study was the proportion of subjects who experienced severe asthma exacerbations at 1 and 2 years following BT treatment, which were compared with the proportion of subjects who experienced severe exacerbations during the 12-month period prior to BT. Severe exacerbations were defined in a manner consistent with the National Asthma Education and Prevention Program (NAEPP) Guidelines for the Diagnosis and Management of Asthma as a worsening of asthma symptoms requiring the use of systemic corticosteroids (tablets, suspension or injection). For patients already taking maintenance systemic corticosteroids, a severe exacerbation was defined as a worsening of asthma symptoms requiring any increase in daily dose of systemic corticosteroids.

Other outcome measures analysed in BTGR included procedural data (including procedure time, anaesthesia type, number of activations of the BT catheter and length of hospital stay), the proportion and rate of emergency room (ER) visits during years 1 and 2 post-BT, the proportion and rate of hospitalisations for asthma during years 1 and 2 post-BT, the proportion and rate of unscheduled office visits during years 1 and 2 post-BT, respiratory AEs occurring during both the treatment period and the post-treatment period, pulmonary function test results (FEV₁), use of asthma maintenance medications, AQLQ scores, Asthma Control Test (ACT) scores and patient satisfaction survey scores.
AE monitoring
A respiratory AE was defined as any sign, symptom, illness, clinically significant abnormal laboratory value or other adverse medical event associated with the respiratory system that appeared or worsened, regardless of whether it was considered related to the BT procedure. An AE was considered serious if it required or prolonged hospitalisation, resulted in a permanent impairment of body structure or function, required medical or surgical intervention to prevent such permanent damage or was life threatening or fatal. AEs 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 post-treatment period.

Statistical analyses
Baseline demographics, clinical characteristics and outcomes were summarised 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 means between baseline and 2 years, the Fisher’s exact test, negative binomial test and t test were used, respectively. For the subgroup analyses, subgroups analysed were those based on gender, age (<40 and ≥40 years), baseline body mass index (BMI) (≥30 and >30 kg/m²) and smoking history as well as baseline AQLQ (≤4.0 and >4.0), baseline oral corticosteroid use, baseline postbronchodilator FEV₁ % predicted (≥70% and >70%) and number of complete catheter activations (≤140 and >140). A generalised linear mixed model with binomial error distribution was fit with factors of the subgroup, time and interaction of subgroup and time with subject as a random effect; if the interaction had a p value <0.10, contrasts of time within subgroup and subgroup within time were performed to explore differences. SAS V.9.4 (SAS Institute) was used for all analyses.

Patient and public involvement
Patients and the public were not involved in the design, conduct, reporting or dissemination of this research.

RESULTS
Baseline demographics and clinical characteristics of BTGR subjects
One hundred and fifty-seven adult subjects (mean age 49.8±12.7 years) underwent BT; 153 of these subjects had all three BT procedures. These subjects were 65.6% women with a BMI of 29.2±6.0 kg/m² and had been diagnosed with asthma for 20.7±14.6 years prior to BT treatment. Subjects had a mean AQLQ score of 3.26±1.10, a mean ACT score of 11.18±4.01 at baseline, and based on the ERS/ATS Guidelines for Severe Asthma, 95.5% of subjects were considered severe asthmatics. These data are summarised in table 1.

Severe asthma exacerbations
During the 12 months prior to BT treatment, 140/155 (90.3%) of BTGR subjects had a severe asthma exacerbation, requiring administration of systemic corticosteroids. Two years after BT, only 55/98 (56.1%) experienced exacerbations (p<0.0001 vs baseline; figure 1, top panel), which represents a 37.9% relative reduction in severe exacerbations by year 2 after BT. As shown in figure 1 (top panel), the data for severe exacerbations from BTGR recapitulate

| Variable | All patients (N=157) |
|----------|----------------------|
| Age (year) | 49.8±12.7 (157) |
| Gender | |
| Female | 65.6% (103/157) |
| Male | 34.4% (54/157) |
| Body mass index (kg/m²) | 29.2±6.0 (156) |
| Medication usage | |
| ICS dose (µg/day) | 1721±1239 (150) |
| LABA dose (µg/day) | 103.3±112.5 (125) |
| SABA used | 69.7% (106/152) |
| Puffs per day for asthma symptoms | 5.87±5.59 (106) |
| OCS (prednisone) used | 47.8% (75/157) |
| Mean dose (mg/day) | 21.0±19.0 (75) |
| Omalizumab used | 9.6% (15/157) |
| Years since diagnosis | 20.7±14.6 (155) |
| ERS/ATS guidelines on severe asthma | |
| (ICS ≥2000 µg/day and LABA/leukotriene modifiers) or ≥2 severe exacerbations in 12 month prior to first BT or ≥1 hospitalisation in 12 months prior to first BT or (post-BD FEV₁ <80% and FEV₁/FVC<0.7) | 95.5% (150/157) |
| Patient questionnaires | |
| AQLQ | 3.26±1.10 (148) |
| ACT | 11.18±4.01 (61) |
| Bronchoscopy information | |
| Number of complete activations | 168.06±54.09 (157) |
| Number of incomplete activations | 32.40±33.40 (151) |
| Number of total activations | 199.23±74.98 (157) |

*Beclomethasone equivalent. †Salmeterol equivalent.

ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; BD, bronchodilator; BT, bronchial thermoplasty; BTGR, Bronchial Thermoplasty Global Registry; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; OCS, oral corticosteroids; SABA, short-acting beta-agonist.
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Historical data from previous studies of BT, including the AIR, RISA, AIR2 and PAS2 studies (figure 1, middle and bottom panels).

Finally, there was a smaller reduction in unscheduled office visits, including those to urgent care facilities, after BT treatment in the BTGR population. During the year prior to BT, 92/156 (59.0%) of BTGR subjects had unscheduled office visits, but this was reduced to 48/98 (49.0%) during year two after BT treatment (p=0.12 vs baseline).

Lung function

Spirometry was performed at baseline and at each yearly follow-up visit for BTGR subjects (online supplemental table 1). As shown, both FEV1 and forced vital capacity remained stable over the 2-year study period, suggesting that BT did not adversely affect lung function in BTGR subjects.

Maintenance medication usage in BTGR subjects

Asthma maintenance medication usage at baseline and at 6 months, 1 year and 2 years after BT treatment is shown in table 2.

As shown, 2 years after BT treatment, reductions in several asthma maintenance medications compared with baseline were observed. Mean daily ICS dose had been reduced from 1721±1239 µg/day to 1217±912 µg/day (p=0.013), and, importantly, the proportion of subjects using maintenance oral corticosteroids (OCS) was significantly reduced from 47.8% to 24.8% by 2 years after BT (p=0.0002). The proportion of subjects using biologics was also reduced from 9.6% at baseline to 5.7% at 2 years after BT (p=0.045).

Quality of life measures and patient satisfaction questionnaires

Significant improvements were seen in both quality of life measures in BTGR subjects. As shown in figure 2, mean AQLQ scores rose from 3.26±1.10 at baseline to 4.39±1.50 2 years after BT (p<0.0001), and at 2 years after BT, 35/56 (62.5%) of BTGR subjects were classified as AQLQ-based responders to BT (defined as those subjects experiencing an increase in AQLQ score of ≥0.5 from baseline after treatment). Similarly, ACT scores rose from 11.18±4.01 at baseline to 15.54±6.21 2 years after BT (p=0.0001).

When asked at the 24-month visit if they would undergo BT again and if they would recommend BT to a friend or family member, 87.3% and 94.9% of subjects, respectively, replied yes.

Adverse events

The total number of procedure-related respiratory AEs occurring during the BTGR are summarised in table 3. During the treatment period, 71/157 (45.2%) subjects experienced procedure-related respiratory AEs related to the BT procedure and 44/157 (28.0%) of these were similar to the data for severe exacerbations, the data for both ER visits and hospitalisations from BTGR also recapitulates historical data for these endpoints from previous studies of BT, including the AIR, RISA, AIR2 and PAS2 studies (figure 1, middle and bottom panels).
considered serious. While 61/98 (62.2%) and 19/98 (19.4%) experienced respiratory AE and serious AE during year 2 after BT, none of these was related to the BT procedure. A listing of specific AEs considered related to BT is shown in table 4, and a listing of unrelated AEs is presented in (online supplemental table 1). Importantly, no deaths were reported during the course of this study.

**Responder and subgroup analysis**

Because of the small number of subjects enrolled in the BTGR, we were unable to perform a true responder analysis to identify likely responders to BT. However, we analysed several pairs of mutually exclusive subgroups of BT subjects to see whether BT treatment was effective in reducing the per cent of subjects with severe exacerbations, ER visits and hospitalisations. These subgroup analyses further confirmed that after BT, BTGR subjects experienced significant improvements in all three endpoints; however, we were unable to identify a specific subgroup of subjects for whom BT was most effective (online supplemental figures 1 and 2).

**DISCUSSION**

Previous clinical trials of BT (including the AIR, AIR2 and RISA trials) have shown that the procedure is safe and effective, but the subjects enrolled in these clinical trials may not be representative of the most severe asthma cases considered for BT treatment in a ‘real-world’ clinical practice. A few recent publications have reported on BT in more severe asthmatics who were older and had worse baseline lung function and quality of life.5-7,9,23,28,29 The data indicated a clinical improvement post-BT in these subjects as well as acceptable rates of AEs. The results presented here from the BTGR recapitulate the results from previously published studies and indicate that in the BTGR population, subjects undergoing treatment with BT experienced reductions in severe asthma exacerbations and other healthcare utilisation as well as reductions in asthma maintenance medication usage, particularly OCS. Additionally, clinically meaningful improvements in quality of life, measured by both ACT and AQLQ, were seen out to 2 years after BT treatment in the BTGR population, and these improvements in quality of life measures are similar to those reported in studies of current biologic treatments for asthma.30

**Figure 2** Asthma control test (ACT) values (top panel) and asthma quality of life questionnaire (AQLQ) (bottom panel) at baseline and at years 1 and 2 after bronchial thermoplasty (BT) treatment. *Significantly different than 12 months before BT (baseline).
The data from the BTGR add to the already-published body of evidence demonstrating the safety and durable effectiveness of BT in a study population that is more representative of those seen in clinical practice outside the setting of RCTs, in which more restrictive inclusion and exclusion criteria may not allow treatment of the most severe asthmatics. BTGR was an all-comers registry study, and, therefore, there were few inclusion and exclusion criteria for enrolment when compared with many previous studies of BT, including the AIR, RISA, AIR2 and PAS2 studies. The more restrictive eligibility criteria employed in these previous studies ensured that many potential subjects with very severe asthma who would normally be seen in the course of ‘real-world’ clinical practice were not included in those clinical trials of BT; however, these very ill subjects were not excluded from BTGR. Despite the enrolment of subjects with more severe asthma in BTGR, improvements in asthma control as indicated by reductions in severe exacerbations, ER visits and hospitalisations during BTGR, which were comparable to those observed in the previous studies (figure 1). This suggests that BT is still effective and safe for patients with very severe asthma.

However, this study had several important limitations that warrant discussion. Despite the lack of data defining patient populations that respond best to BT, several recent guidelines have recommended BT treatment for specific subsets of asthmatics. Most recently, an expert consensus panel that examined the fundamental guiding principles for severe asthma treatment-identified BT as the preferred treatment option for severe asthmatics suffering from non-allergic, non-eosinophilic (non-TH2) asthma with variable air flow obstruction as demonstrated by bronchodilator reversibility, who experience persistent symptoms despite treatment with triple therapy. These guidelines also state that BT should be considered an alternative treatment option for patients with severe eosinophilic or allergic asthma, particularly in patients who do not respond to treatment with anti-IgE and/or anti-IL5 therapies. A recent study by Langton et al indicated that, in fact, BT treatment was as effective as mepolizumab treatment in this patient population. However,

| Table 3 | Total procedure-related adverse events observed in BGTR subjects |
|---------|---------------------------------------------------------------|
| Adverse events | Treatment period* | 1 year† | 2 years‡ |
| Procedure-related events | | |
| Respiratory adverse events | 45.2% (71/157) | 2.4% (3/127) | 0.0% (0/98) |
| Respiratory serious adverse events | 28.0% (44/157) | 0.8% (1/127) | 0.0% (0/98) |

*Events between the date of the first BT procedure and 42 days after the last BT procedure.
†Events between 43 and 365+42 days after last BT procedure. Patients count in the denominator if they had any one of the events between 43 days and 365+42 days after the last BT procedure or had ≥335+42 days follow-up after the last BT procedure.
‡Events between 365+43 days and 730+42 days after last BT procedure. Patients count in the denominator if they had any one of the events between 365+43 days and 730+42 days after the last BT procedure or had ≥700+42 days follow-up after the last BT procedure.

| Table 4 | Reported asthma-related or bronchial thermoplasty-related adverse events in BTGR subjects |
|---------|--------------------------------------------------------------------------------------|
| Event | All (N) | Treatment period (N) | 1 year (N) | 2 years (N) |
| Asthma (wheezing/bronchospasm) | 293 | 100 | 115 | 71 |
| Lower respiratory infection (bronchitis, pneumonia) | 82 | 28 | 35 | 17 |
| Upper respiratory tract infection (influenza, viral, sinusitis) | 53 | 16 | 26 | 7 |
| Dyspnoea/breathlessness | 21 | 13 | 2 | 3 |
| Haemoptysis | 13 | 12 | 1 | 0 |
| Cough | 13 | 5 | 6 | 1 |
| Mucous production/plugging | 13 | 10 | 3 | 0 |
| Atelectasis | 11 | 11 | 0 | 0 |
| Laryngitis, laryngospasm, candidiasis | 11 | 7 | 1 | 3 |
| Chest pain/discomfort | 8 | 6 | 0 | 2 |
| Respiratory distress/respiratory failure | 5 | 2 | 3 | 0 |
| Pneumothorax | 2 | 2 | 0 | 0 |

*In addition, one patient was reported as having bronchomalacia in the treatment period. This was presumed to be a new bronchoscopic finding rather than a sequela of treatment.

BTGR, Bronchial Thermoplasty Global Registry.
additional data on asthma phenotypes that respond best to BT are required, and, unfortunately, baseline data on asthma phenotype were not routinely collected as a part of the BTGR. Thus, we are unable to address the critical question of whether BT is particularly effective for specific phenotypes in this study population. Another limitation of this registry was that the clinical study sites varied degrees of experience with the conduct of clinical studies, and this may have contributed to the high patient attrition rate seen in this study. Additionally, not all baseline measurements were required to be collected, and some sites did not routinely collect this information, leading to variability in the number of subjects that could be analyzed based on these measures. Finally, the manufacturer of the Alair BT system (Boston Scientific Corporation) sponsored this study, and one of the authors of this manuscript is a full-time employee of the study sponsor.

In conclusion, the data from the BTGR demonstrate sustained improvement in clinical outcomes and reduction in asthma medication usage 2 years after BT in a real-world population. This is consistent with the results from other BT RCTs and registries and further supports improvement in asthma control after BT, suggesting that BT is an effective and safe therapeutic option for severe asthmatics. Future randomized controlled studies designed to further investigate the responses to BT in participants with specific asthma phenotypes and/or studies designed to identify specific responders to BT would be beneficial. Additional clinical studies designed to investigate whether BT treatment can reduce the use of OCS in asthmatics and/or compare responses to BT to those seen with the newer biologic medications are also warranted.

Author affiliations
1Respiratory Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
2Thoraxklinik, University of Heidelberg, Heidelberg, Baden-Württemberg, Germany
3Respiratory Department, Hospital Josep Trueta, Girona, Catalunya, Spain
4Respiratory Department, Hospital General Universitario Gregorio Maranon—Facultad de Medicina Universidad Complutense, Madrid, Spain
5AUSL-IRCCS Reggio Emilia Pulmonology Unit, IRCCS Reggio Emilia Pulmonology Unit, Santa Maria Nuova, Italy
6Respiratory Department, Gartnavel General Hospital, Glasgow, UK
7Respiratory Department, Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Lombardia, Italy
8Respiratory Department, Università Politecnica delle Marche, Ancona, Marche, Italy
9Respiratory Department, University of Cape Town, Cape Town, South Africa
10Pulmonology Department, Hospital Universitari Germans Trias i Pujol—CIBERES, Badalona, Barcelona, Spain
11Respiratory Department, Klinika Tuberkulozy a Respiracínych Onemocnění, Prague, Czech Republic
12Respiratory Department, Frankston Hospital Peninsula Health, Frankston, Victoria, Australia
13Respiratory Department, Hospital Universitario Fundacion Jimenez Diaz—CIBERES IIS-FJD, Madrid, Spain
14Respiratory Department, Royal Brisbane and Women’s Hospital—Brisbane/AUS, Brisbane, Queensland, Australia
15Department of Respiratory Medicine, Amsterdam University Medical Centers, Amsterdam, The Netherlands
16Department of Cardiology and Pneumology, University of Bonn, Medizinische Klinik II, Bonn, Germany
17Respiratory Department, University Hospital Regensburg, Regensburg, Bayern, Germany
18Respiratory Department, Ruhrlandklinik—West German Lung Center, University Medicine Essen, Essen, Germany
19Boston Scientific Corp, Marlborough, Massachusetts, USA
20Respiratory Department, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

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Generalized asthma correlates with FEV1.