Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med 2007;356:1327-37.

Supplemental Appendix to Manuscript #06-4707:

Asthma Control during the Year after Bronchial Thermoplasty

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METHODS

Training

All investigators had experience performing bronchoscopy in patients with asthma. They received training in bronchial thermoplasty at an animal laboratory. They were observed and technical support was provided for at least their first human treatment procedure. All treatment procedures were videotaped; reviews and prompt feedback on technique were provided to the investigators. This review was performed by one reader at the study sponsor site who had provided device and procedure training to investigators at the start of the trial. In the few cases where this person was unavailable, a second reader (who also had been involved in investigator training) performed the reviews and discussed findings with the individual providing the

majority of the feedback, before conversations occurred with investigators. This helped to ensure consistency among sites. Of the 11 principal investigators, 5 received additional in-person training or assistance beyond their first procedure. All treating physicians became proficient with the technique after two procedures.

Outcomes

Data recorded in the Daily Diary included the best of 3 measurements of PEF made with a Mini-Wright™ Peak Flow Meter (Ferraris, Orchard Park, NY) in the morning (amPEF) and evening (pmPEF) before medication. The subject determined the timing of their morning and evening peak flow assessments, depending on their daily routine and sleep habits. Morning was taken at that time following their major sleep period. The Daily Diary instructed that "ideally, peak flow measurements should be done when a bronchodilator has not been used for 4 hours prior to the measurement. This may not be possible for every measurement: please do not hesitate to use a bronchodilator if you need to." The proportion of the days when bronchodilator was used within 4 hours of the PEF assessment was calculated for each subject and averaged by group. A t-test comparing the averages at each time point yielded no difference between groups.

Daily diary included symptoms of asthma during the nighttime and daytime (based on a 4 point scale, with 0 indicating no symptoms and 3 indicating severe or a lot of symptoms), nighttime awakenings due to asthma, nighttime and daytime use of rescue bronchodilators and whether usual asthma medications were taken. Specific symptom assessments were: for the morning assessment, Wheeze during night (0=none, 1=slept well, slightly wheezy, 2=sleep disturbed by wheeze, 3=severe – awake most of the night) and Cough during night (0=none, 1=slight, 2=moderate, 3=severe), and for the evening assessment, Wheeze during day (0=none, 1=slightly wheezy, 2=moderately bad, 3=severe), Cough during day (0=none, 1=slight, 2=moderate, 3=severe), Breathless during day (0=normal, 1=more breathless than normal on vigorous exertion, 2=breathless on moderate exertion, 3=breathless on mild exertion) and Sputum during day (0=none, 1=slight, 2=moderate, 3= a lot). Daily Diary parameters were averaged over the 6-12 week period for the assessment on all medications (ICS+LABA) and for 2-week periods during LABA abstinence at the 3-, 6- and 12-month follow-ups for comparisons between study groups over baseline.

Symptom score was obtained from the daily diary and was the total of the individual symptom scores (0 to 3), for wheeze and cough during nighttime and wheeze, cough, breathlessness and

sputum production during the daytime. The maximum score possible was 18. A Symptom-Free Day (SFD) was defined as a day with a symptom score of 0 (morning and evening assessments for each day combined to capture a 24-hour period) and no night awakenings.

Airway responsiveness was assessed by challenge with Provocholine® (Methapharm, Brantford, ON), delivered by a DeVilbiss 646 nebulizer (Sunrise Medical, Somerset, PA), and was assessed at the end of the 2-week attempt to abstain from LABA. Spirometry was performed in the clinic setting following a 48-hour withdrawal of LABA, and an 8 hour withdrawal of short acting β_2-agonist (if tolerated). If a subject could not tolerate this withdrawal, the interval they could tolerate was used for all subsequent assessments and the data were analyzed without modification.

The Asthma Control Questionnaire (ACQ) comprises 6 questions and measurement of FEV_1 by spirometry. All seven items have equal weighting and are scored from 0 to 6, with higher scores indicating worse control. The total score is averaged. While not thoroughly described, it is thought the minimal important difference is 0.5 (2). The Asthma Quality of Life Questionnaire comprises 32 items that report asthma-related symptoms and limitation over the preceding 2

weeks. The response scale is from 1 to 7, with higher scores indicating better clinical state. The AQLQ score is the average of the total score and the minimal important difference is believed to be 0.5 (3).

Treatment Period

All subjects in the bronchial thermoplasty (BT) group were given 50 mg prednisone or equivalent the day before and day of each procedure; all subjects in the Control group were given the same dose of prednisone the day before and day of their corresponding office visit. The prophylactic use of oral corticosteroids in the BT group was to reduce the potential for bronchoconstriction and risks of bronchoscopy.

Actual footage from a live case of bronchial thermoplasty with the Alair® system is available for viewing [see attached].

Follow-up Period

All subjects were first evaluated at 12 weeks post-BT or control treatment prior to the LABA withdrawal (i.e. on inhaled corticosteroid (ICS) + LABA), and then following the 2-week abstinence from LABA (if tolerated). For those subjects who could tolerate the continued

withdrawal of LABA, the 6-month and 12- month evaluations were performed on ICS alone. Those subjects who needed to resume their LABA prior to the 6-month and 12-month visits, were evaluated following another 2-week period (or as long as tolerated) of abstaining from LABA at those time points. At later time points, variation between groups in ability to abstain from LABA prevented further evaluation on ICS + LABA.

High Dose ICS Subset Analysis

In a post-hoc analysis the effectiveness and safety profile anticipated for bronchial thermoplasty in the cohort of patients with more severe asthma, was evaluated for subjects who were on higher maintenance doses of ICS (>1000μg beclomethasone or equivalent).

Adverse Event Monitoring

All subjects were carefully monitored to understand the tolerability of bronchial thermoplasty. Adverse events were designated as respiratory- or non-respiratory related, and were reported for baseline, treatment (day of first treatment session to 6 weeks after the last treatment session), and post-treatment (end of treatment period to last follow-up visit, at 12 Months). At each visit throughout the study, the investigator asked the subject an open-ended question of whether there

had been any adverse events since their last visit. Investigators reported the severity of adverse events using the following definitions:

Mild- Awareness of signs or symptoms, but easily tolerated; causing no loss of time from normal activities; symptoms would not require medication (other than short-acting bronchodilators) or a medical treatment; signs and symptoms are transient.

Moderate- Discomfort severe enough to cause interference with patient's usual activities. Symptomatic treatment is possible.

Severe- Incapacitating with inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical intervention and/or treatment. Hospitalization may be required or prolonged. Death.

Statistical analysis

Enrollment was planned for a total of 110 patients, calculated to provide for >90 percent power of detecting a difference in estimated rate of mild exacerbations of 8 exacerbations/patient/year between the two groups, using a t-test with an α of 0.05 (2-tailed). We estimated an average rate

of 8 mild exacerbations/patient/3 months for the control group and 6 exacerbations/patient/3 months for the treatment group, with a standard deviation of 3 exacerbations/patient/3months.

RESULTS

All Subjects

There was no significant difference between the BT and control groups with respect to ability to tolerate the absence of LABA (p=0.10, Log-Rank), Supplement Figure 1.

Secondary outcomes at 3 months, all subjects on usual care (ICS + LABA)

Significant improvements from baseline in amPEF were observed in the BT group (369.4±97.9 to 397.4±100.7 L/min) compared to Control (394.0±98.2 to 395.4±88.6 L/min) (Figure 3). The percent change in pre-bronchodilator FEV_1 (%predicted) from baseline was slightly but not significantly greater in the BT group (72.0±9.9 to 74.3±14.3) than in the Control group (75.8±9.0 to 75.7±10.1)(P=0.28). The post-bronchodilator FEV_1 was unchanged in both groups (%predicted: 83.7±12.4 to 83.3±14.1 in the BT group and 84.6±9.7 to 84.3±11.4 in the Control group, P=0.99). There was a trend toward decreased use of rescue medication over 7 days in the BT group but the difference was not statistically significant, P=0.07 (BT group decreased from

10.3±14.0 puffs/week to 6.6±11.7; Control group increased from 6.6±10.1 puff/week to 7.5 ±10.9). There was significantly greater improvement in %SFD in the BT group (from 36.9±35.3 to 59.5±39.8) compared to Control group (47.6±38.2 to 53.7±38.6) (P=0.03). This was paralleled by a significant reduction in the total symptom score (reflecting the number and/or severity of symptoms), from 2.49±2.31 to 1.31±1.86 in the BT group, compared with 1.97±2.67 to 1.64±1.87 in the Control group (P=0.05). AQLQ score significantly improved in the BT group from 5.58±1.05 to 6.06±1.02 but did not change in the Control group, 5.72±0.94 at baseline and 5.72±1.23 at 3 months (P=0.01). The ACQ score significantly improved in the BT group from 1.43±0.67 to 1.13±0.83 and again, there was no change in the Control group (1.39±0.81 to 1.38±0.93) (P=0.05) (Figure 3).

Secondary Outcomes at 3, 6 and 12 months (on ICS alone)

Measurements of Airflow

At 12 months after treatment, there was a significantly greater increase in amPEF in the BT group, from 349.3±90.6 at baseline to 388.6±105.0 L/min, when compared to the increase in the Control group, from 372.4±99.9 to 380.9±92.9 L/min (P=0.003, Figure 3A). This increase was evident at 3 and 6 months (Figure 3A). There was also a significantly greater increase in pmPEF

at 3, 6 and 12 months; at 12 months change in the BT group from 359.7 ± 88.4 L/min to 397.4±102.8 versus 379.1±98.7 to 389.0±93.9 in the Control group (P=0.006).

Change in FEV_1 was not different between groups at any time point. At 12 months, pre-bronchodilator, FEV_1 %predicted in the BT group was 75.2±13.9 compared with 70.4±12.1 at baseline while values for the Control group were 72.4±12.6 and 70.7±10.5 respectively (Figure 3B). Post-bronchodilator FEV_1 was unchanged in both groups (%predicted 83.5±12.0 at baseline to 83.7±13.4 at 12 months in the BT group; 81.2±11.0 to 81.6±11.4 in the Control group).

Airway Responsiveness

Airway responsiveness improved more in the BT group than the Control group. At 12 months the geometric mean (95%C.I.) PC_{20} increased from 0.24(0.15, 0.4) to 0.61(0.36, 1.03) mg/ml, or 1.31±2.39 doubling concentrations over baseline, in the BT group and from 0.32(0.20, 0.51) to 0.5(0.31, 0.80) mg/ml, or 0.66±2.69 doublings, in the Control group. The differences over baseline between groups did not reach statistical significance at any time point (P=0.06, 0.18 and 0.17 for 3, 6 and 12 months respectively) (Figure 3C).

Use of Rescue Medication

The BT group required significantly less short-acting bronchodilator than the Control group. At 12 months, the BT group required 10.9±15.0 puffs per week versus 19.8±17.2 at baseline; the Control group required 14.8±21.2 puffs per week at 12 months versus 16.0±18.8 at baseline (P=0.04). This improvement was evident at 3 months (Figure 3D).

Asthma Symptoms and Symptom-Free Days

At 12 months following the last treatment visit, the percent of days that subjects were free of symptoms increased over baseline in the BT group from 24.7±30.5 to 65.4±40.4. In the Control group SFD increased from 32.3±34.3 to 49.4±41.3 (P=0.005). This effect extrapolates to 148 additional symptom-free days per year in the BT group compared to 62 in the Control group. The significant difference between groups was present at 3 months (Figure 3E).

The change in the total symptom score was consistent with the improvement in percent SFD: the score was significantly reduced from baseline in the BT group (3.16±2.21 to 1.25±1.97) compared to the Control group (2.65±2.55 to 2.00±2.23) (P=0.01). This benefit was present at 3 and 6 months (Figure 3F).

Asthma Quality of Life and Asthma Control

At 12 months, AQLQ score in the BT group changed from baseline from 4.91±1.23 to 6.18±0.88 and in the Control group from 5.15±1.19 to 5.72±1.11 (P=0.003). This benefit was seen at 3- and 6- months also (Figure 3G).

Similarly, there was a significant improvement over baseline in the ACQ score in the BT group (from 2.50±0.92 to 1.32±0.85) at 12 months compared to the Control group (from 2.16±0.86 to 1.69±0.99) (P=0.001). The significant improvement was also noted at 3 and 6 months (Figure 3H).

High Dose ICS Subset Analysis

A post-hoc analysis was performed on thirty-two subjects (16 BT, 16 Control) who required >1000µg beclomethasone or equivalent at baseline. At 12 months post-bronchial thermoplasty, there were greater improvements with bronchial thermoplasty compared with control in measurements of airflow (amPEF from 378.2±69.8 at baseline to 441.8±103.9 L/min in the BT group and 321.9±65.9 to 346.2±66.4 L/min in the Control group, P=0.05), airway hyperresponsiveness [geometric mean (95%C.I.) PC_{20} from 0.33(0.11,0.97) to 1.71(0.65, 4.49)

mg/ml, or 2.39±2.78 doublings from baseline, compared with 0.45(0.19, 1.03) to 0.30(0.09, 1.01) mg/ml, or −0.57±3.04 doublings from baseline, in the Control group, P=0.03], AQLQ (4.45±1.48 to 6.17±0.89 for the BT group compared with 5.41±0.81 to 5.67±1.13 for the Control group, P=0.002) and ACQ (2.88±0.63 to 1.34±0.95 for the BT group compared with 2.20±0.67 to 1.99±1.02 for the Control group, P=0.004). The changes in FEV_1, use of rescue medication, SFD and total symptom score were not statistically significant at 12 months (Supplement Figure 2A-2H). The Kaplan-Meier plot in Supplement Figure 3 shows that subjects in the BT group were able to tolerate the absence of LABA significantly better than the Control subjects (p=0.003, Log-Rank). There were two hospitalizations for respiratory-related symptoms in one subject in the BT group and none in the Control group during the treatment period in this more severe cohort.

Adverse Event Monitoring

Non-respiratory events leading to hospitalization: In the treatment period there were no non-respiratory events in the BT group that led to a hospitalization. In the Control group, there were 3 non-respiratory events that led to hospitalization in this period; these included a hiatal hernia, gastric pain and vertebral fracture. In the post-treatment period, there were a total of 4

non-respiratory events leading to hospitalization. Two of these events occurred in 2 BT subjects: one for fever, sore throat and stomach pain and the other for severe headache. The other 2 non-respiratory events occurred in 2 Control subjects: one for atrial fibrillation and one for urinary tract lithiasis.

Post-study Follow-up

Following the completion of the AIR Trial at 1 year, subjects were asked to participate in the AIR Extension Trial, in which subjects would be followed annually out to 3 years. To date, 36 BT subjects have enrolled in this trial; follow-up time ranges from 22 to 37 months (mean of 28 months). 8 subjects have reported a total of 18 respiratory-related adverse events in this period (3 mild, 14 moderate and 1 severe); 4 subjects have reported 5 non-respiratory-related adverse events (2 mild and 3 moderate). The moderate respiratory-related adverse events included cough (3), colored mucus (2), URTI (2), asthma exacerbation (2), dyspnea (1), wheeze (1), nasal congestion (1), mucous production (1) and maxillary sinusitis (1). The moderate non-respiratory-related events were allergies (1), cutaneous lesions (1) and eczema (1). The single severe adverse event was a lung abscess thought to be secondary to an

infection that occurred 14 months after bronchial thermoplasty, as discussed in the main manuscript

FIGURE LEGENDS

Supplement Figure 1: Kaplan-Meier plot of the Time to Resumption of LABA for all Subjects. The time to resumption of LABA usage following the 12-week visit was computed. Subjects who were able to abstain from LABA following the first 12-week visit as specified by the protocol were included in the analysis. The time from their LABA withdrawal date at 12 weeks to the date of resumption of LABA usage or the end of the study for each subject was calculated. The log-rank P-value for the difference between the BT group and Control group is shown.

Supplement Figure 2: Measures of Asthma Control, for the cohort of Subjects on high doses of ICS (>1000 µg/day beclomethasone or equivalent). Mean values are shown for all subjects where data are available for the specific time point, on ICS alone. * indicates a statistically significant different ($P<0.05$) between groups for mean change from baseline.

A-amPEF; at 3 months, P = 0.007; 12 months, P = 0.05

B-% predicted FEV_1, pre-bronchodilator

C - Airway Responsiveness, (reported as methacholine PC_{20} mg/ml); for doublings from baseline to 3 months, P = 0.01; 6 months, P = 0.005; 12 months, P = 0.03

D - Rescue bronchodilator use (number of puffs per 7 days);

E – % Symptom-Free Days; 3 months, P = 0.05; 6 months, P = 0.04

F-Symptom score (the response scale is 0 to 18 with lower scores indicating fewer and/or less severe symptoms); 3 months, P = 0.008

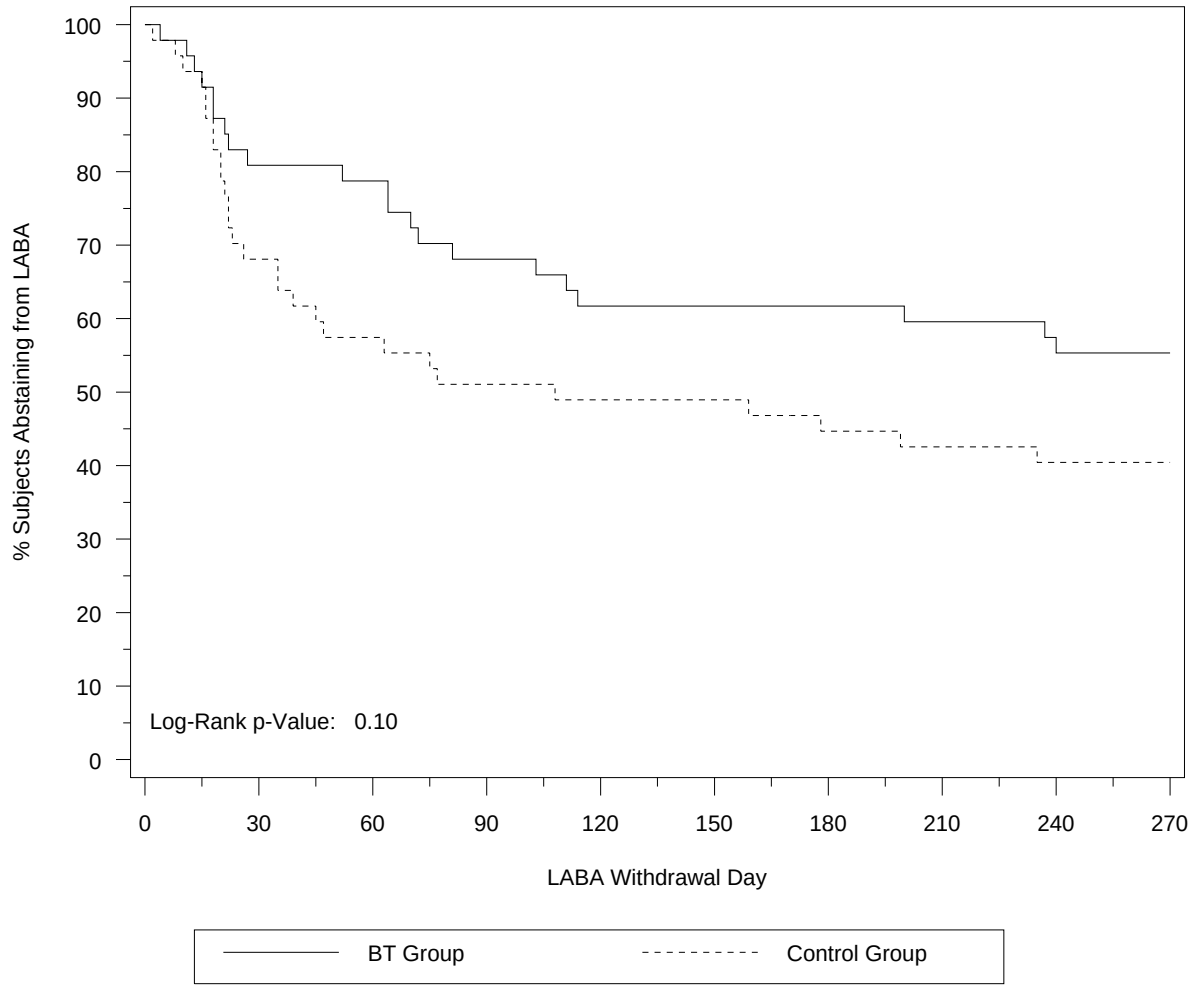
G-AQLQ score (The response scale is from 1 to 7, with higher scores indicating better clinical state*)*; 3 months, P = 0.001; 6 months, P < 0.001; 12 months, P = 0.002

H-ACQ score (the response scale is from 0 to 6 with lower scores indicating better clinical state); 3 months, P = 0.001; 6 months, P < 0.001; 12 months, P = 0.004

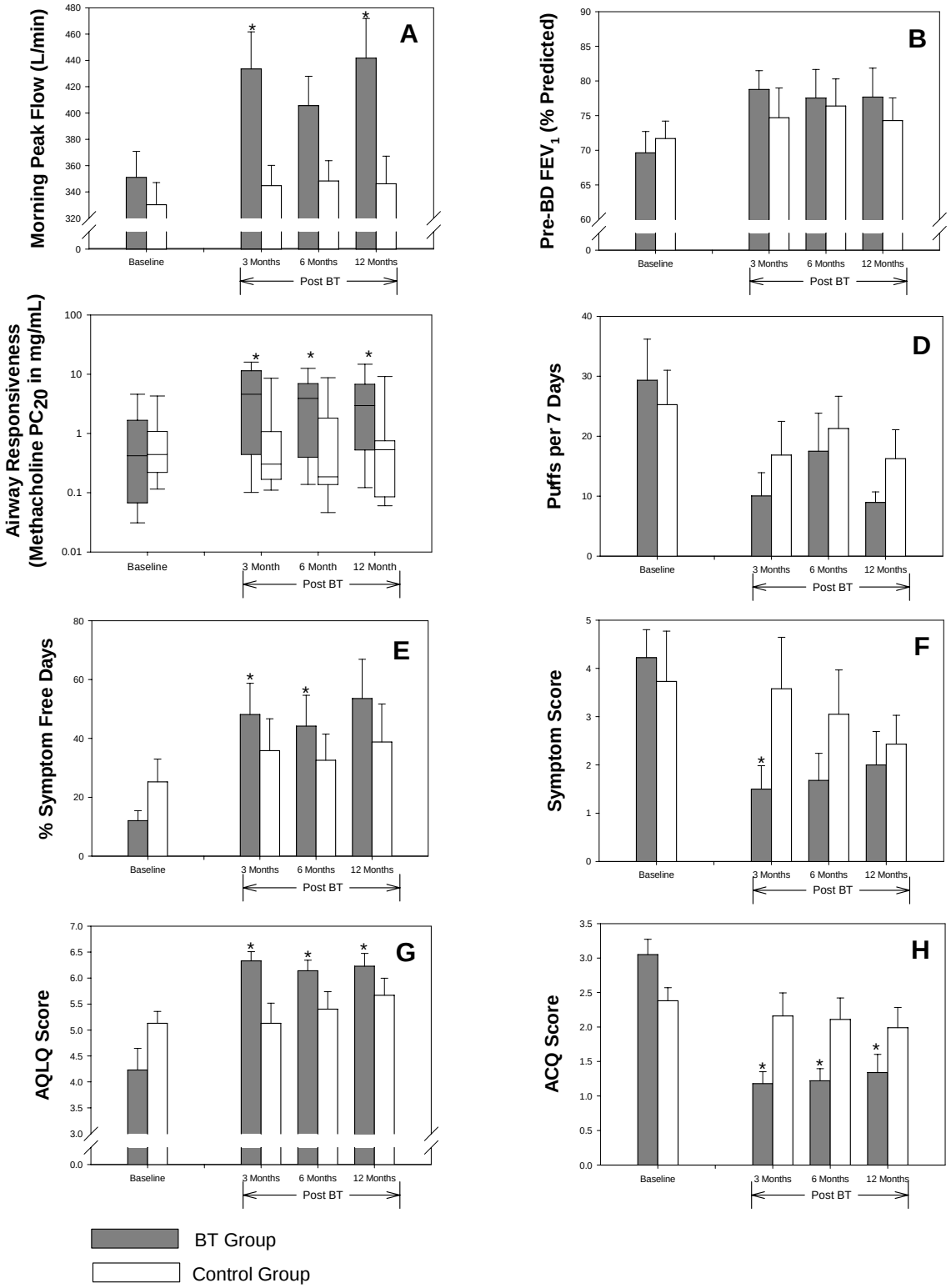
Supplement Figure 3: Kaplan-Meier plot of the Time to Resumption of LABA for High Dose ICS Subset (>1000µg/day beclomethasone or equivalent). The time to resumption of LABA usage following the 12-week visit was computed. Subjects who were able to abstain from LABA following the first 12-week visit as specified by the protocol were included in the

analysis. The time from their LABA withdrawal date at 12 weeks to the date of resumption of LABA usage or the end of the study for each subject was calculated. The log-rank P-value for the difference between the High Dose ICS Subset BT group and the High Dose ICS Subset Control group is shown.

Supplement Figure 1 - Time to Resumption of LABA for All Subjects



Supplement Figure 2: Measures of Asthma Control – High Dose ICS Subset



Supplement Figure 3: Time to Resumption of LABA for High Dose ICS Subset