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Effects of Early Intervention With Inhaled Budesonide on Lung Function in Newly Diagnosed Asthma*

Paul M. O’Byrne, MD, FCCP; Søren Pedersen, MD; William W. Busse, MD; Wan C. Tan, MD, FCCP; Yu-Zhi Chen, MD; Stefan V. Ohlsson, PhD; Anders Ullman, MD; Carl Johan Lamm, PhD; and Romain A. Pauwels, MD, FCCP†

Study objectives: Asthmatic patients lose lung function faster than normal subjects. The effectiveness of early intervention with inhaled corticosteroids on this decline in lung function is not established in recent-onset disease.

Design: The Inhaled Steroid Treatment as Regular Therapy in Early Asthma study was a randomized, double-blind study in 7,165 patients (5 to 66 years old), with persistent asthma for < 2 years to determine whether early intervention with low-dose inhaled budesonide prevents severe asthma-related events and the decline in lung function. Patients received budesonide (200 µg qd for children < 11 years old and 400 µg qd for others) or placebo for 3 years in addition to usual asthma medications.

Results: Treatment with budesonide significantly improved prebronchodilator and postbronchodilator FEV₁ percentage of predicted and reduced the mean declines from baseline for postbronchodilator FEV₁ at 1 year and 3 years: – 0.62% and – 1.79% for budesonide and – 2.11% and – 2.68% for placebo, respectively (p < 0.001). The decline was more marked for male patients, active smokers, and patients > 18 years old, and the smallest treatment effects were in adolescents.

Conclusions: Long-term, once-daily treatment with low-dose budesonide improved both prebronchodilator and postbronchodilator FEV₁ in patients with recent-onset, persistent asthma, and reduced the loss of lung function over time. (CHEST 2006; 129:1478–1485)

Key words: asthma; early intervention; inhaled corticosteroids; lung function

Abbreviations: CAMP = Childhood Asthma Management Program; START = Inhaled Steroid Treatment as Regular Therapy in Early Asthma

Asthma is identified by the presence of reversible airflow obstruction; however, irreversible airflow obstruction also develops in some asthmatic patients. Peat et al1 described a greater decline in lung function, as measured by height-adjusted FEV₁, in a cohort of asthmatic patients compared to normal subjects (50 mL/yr vs 35 mL/yr) followed up for 18 years. These observations have been confirmed by Lange et al,2 who reported on a Danish cohort followed up over 15 years, and by Sears et al3 in a New Zealand population-based birth cohort. The degree of loss in lung function has been shown to be related to asthma duration.4,5

The mechanisms of the loss in FEV₁ may result

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†Dr. Pauwels died in January 2005.

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from the development of airway remodeling; however, no prospective studies have been conducted to test this hypothesis. Nonetheless, one study⁶ suggested that the decline in FEV₁ may be related to the persistence of airway inflammation, albeit neutrophilic inflammation. Some studies have suggested that early treatment with inhaled corticosteroids may prevent the development of the accelerated decline in FEV₁. Agertoft and Pedersen⁷ and Haahtela et al⁸ reported that the early introduction of inhaled corticosteroids in newly diagnosed asthma in children or adults results in a greater improvement in lung function than when introduced as little as 2 years later. These results suggest that a delay in treating airway inflammation early in the course of the disease can result in airway abnormalities, which are less amenable to inhaled corticosteroid treatment later. The Childhood Asthma Management Program (CAMP) study⁹ prospectively evaluated the effects of inhaled corticosteroids (budesonide, 400 µg/d) on lung function in children with a mean duration of asthma of 5 years. No significant difference between budesonide and placebo was found in the degree of change in the postbronchodilator FEV₁ percentage of predicted; however, the mean postbronchodilator FEV₁ value at baseline was >100% of predicted normal in all treatment arms, and no significant decline over time was seen in the postbronchodilator FEV₁ percentage of predicted in the placebo group, making a treatment effect difficult to demonstrate. In addition, the children who received budesonide had a significantly smaller decline in the ratio of FEV₁ to FVC before the administration of a bronchodilator.

The effectiveness of early intervention of inhaled corticosteroids on asthma progression has yet to be established in recent-onset, persistent disease. Therefore, a large, worldwide, long-term, double-blind, placebo-controlled comparison of low doses of inhaled corticosteroids initiated within the first 2 years of a diagnosis of asthma, the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study,¹⁰ was undertaken to determine whether early intervention with low-dose inhaled budesonide in patients with persistent asthma would prevent severe asthma-related events and the accelerated decline in lung function. The main results of the START trial are reported elsewhere,¹¹ including the initial analysis of the postbronchodilator FEV₁. In this report, the first 3-year double-blind part of the study, examining the effects of early intervention on lung function, is described in more detail, with additional analysis.

**Materials and Methods**

The study design, methods, and inclusion and exclusion criteria of the START trial are described in detail elsewhere.¹⁰ The study enrolled 7,241 patients aged 5 to 66 years from 32 countries. Patients had asthma symptoms weekly, but not daily, during the 3 months prior to study. These symptoms had to be present for <2 years (ideally <1 year). Patients demonstrated airway obstruction by an increase in FEV₁ > 12% after a β₂-agonist, a fall in FEV₁ > 15% after exercise, or a variation >15% in peak expiratory flow rates over 14 days. The study was approved by all the Research Ethics Boards of participating institutions prior to initiation, and all subjects signed informed consent before being enrolled into the study.

The patients were randomly assigned to receive either once-daily budesonide or placebo delivered from a dry powder inhaler (Turbuhaler; AstraZeneca; Land, Sweden). The daily dose of budesonide was 200 µg in children aged <11 years at randomization and 400 µg in the others. The placebo was lactose. Changes in concurrent medication, including introducing inhaled or systemic corticosteroids, could be made during the study at the investigator’s discretion to achieve asthma control.

The outcomes measured were change from baseline in prebronchodilator and postbronchodilator FEV₁ percentage of predicted and in FVC percentage of predicted. The FVC values are only reported for adults because children often failed to complete the FVC maneuver correctly. Spirometry was performed (MicroLoop II; Micro Medical; Rochester, UK). The postbronchodilator FEV₁ was measured at randomization, after 6 and 12 weeks, and then quarterly 30 min after inhaling terbutaline at 0.5 mg from dry powder inhaler, or 1 mg via pressurized metered-dose inhaler (Breathaire; Novartis Pharmaceuticals Corporation; East Hanover, NJ). The prebronchodilator FEV₁ was measured at randomization and yearly thereafter.

Predicted normal values of FEV₁ and FVC were calculated based on gender, age, and height at each visit. For male patients ≤16.0 years old and for female patients ≤15.0 years old, the prediction formulas of Quanjer at al¹² were used, and race correction factors 1.00, 0.91, 0.87, and 0.88 were applied for white, Oriental, black, and other race, respectively. For male patients >18.0 years old and female patients >17.0 years old, predicted values were calculated from the official statement of the European Respiratory Society,¹³ and the race correction factors 1.00, 0.90, 0.87, and 0.85 were applied for white, Oriental, black, and other race, respectively. In the age range of 16.0 to 18.0 years for male and 15.0 to 17.0 years for female patients, predicted normal values were computed by linear (in age) interpolation between the two formulae.

For the purpose of analysis, the cohort was divided into subgroups determined by age, gender, and smoking history. Children were aged <11 years old (28% of patients), adolescents were aged 11 to 17 years (17% of patients), and adults were aged >18 years (55% of patients) at randomization. Cigarette smoking history was recorded as current (11.6%), previous (8.9%), non-smoker (50.5%), or passive smoker (29.0%).

**Statistical Methods**

Longitudinal analysis of change from baseline values in the spirometric variables was made using mixed models, the main model including the factors baseline, treatment, time (since baseline), time squared, treatment × time, treatment × time squared, region, and region × time. A covariance structure of the type compound symmetry was assumed. To study differences in response between demographic subgroups, extensions to the main model were used.
RESULTS

Of the 7,241 patients that entered the study, 7,165 were available for analysis, of whom 3,597 were randomized to budesonide and 3,568 to placebo. From this cohort, 2,010 patients did not complete the 3 years of double-blind treatment. The dropout rate (27.5% in the budesonide group and 28.6% in the placebo group) and the mean time in the study (2.47 years in the budesonide group and 2.44 years in the placebo group) were comparable for the two treatment arms. There were 3,419 patients in the budesonide group and 3,394 patients in the placebo group with assessments of postbronchodilator FEV\(_1\) at baseline and on at least one follow-up occasion. All these patients are used in the longitudinal analysis of postbronchodilator FEV\(_1\). The baseline characteristics were similar in the two treatment groups (Table 1).

The mean baseline prebronchodilator FEV\(_1\) percentage of predicted for the whole cohort was 86.5% (SD 13.9%), with the mean postbronchodilator FEV\(_1\) improving to 96.3% (SD 13.2%). The baseline FEV\(_1\) values were similar in both genders and across all age groups. The mean baseline prebronchodilator FEV\(_1\) of current or previous smokers was not different from nonsmokers; however, the postbronchodilator FEV\(_1\) values were slightly reduced to 95.7% when compared to the nonsmoker values of 96.9%.

Treatment with budesonide significantly improved both prebronchodilator and postbronchodilator FEV\(_1\) percentage of predicted (Fig 1). These differences were obvious by 6 weeks, when the changes from baseline in postbronchodilator FEV\(_1\) were + 0.27% in the budesonide group and – 1.65% in the placebo group (p < 0.001). Over 3 years, the postbronchodilator FEV\(_1\) declined significantly in both groups, but a significant treatment effect for budesonide persisted. After 3 years, the postbronchodilator FEV\(_1\) values were – 1.79% in the budesonide group and – 2.68% in the placebo group (p < 0.001). The mean difference in postbronchodilator FEV\(_1\) between budesonide and placebo was 0.88% (p < 0.001).

The mean baseline postbronchodilator FVC percentage of predicted in the adult patients was 97.2% (SD 13.6%), with the FEV\(_1\)/FVC ratio being 85.2% (SD 8.2%). Over 3 years, the FEV\(_1\)/FVC ratio declined significantly (p < 0.001) in both treatment groups by 1.74% in the placebo group and by 0.58% in the budesonide group. The magnitude of the change in the budesonide group was significantly less than that in the placebo group (p < 0.001).

The change in postbronchodilator FEV\(_1\) in the treatment groups demonstrated a Gaussian-like distribution (Fig 2), and the decline was more marked for males, current, or previous smokers, and patients > 18 years old. In the placebo group over years, the

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**Table 1—Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Budesonide (n = 3,597)</th>
<th>Placebo (n = 3,568)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–10</td>
<td>27.8</td>
<td>27.3</td>
</tr>
<tr>
<td>11–17</td>
<td>17.8</td>
<td>16.3</td>
</tr>
<tr>
<td>18–66</td>
<td>54.4</td>
<td>56.4</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>65.4</td>
<td>64.7</td>
</tr>
<tr>
<td>Black</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Oriental</td>
<td>27.7</td>
<td>27.9</td>
</tr>
<tr>
<td>Other</td>
<td>5.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45.8</td>
<td>46.0</td>
</tr>
<tr>
<td>Female</td>
<td>54.2</td>
<td>54.0</td>
</tr>
<tr>
<td>Duration of asthma prior to entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 mo</td>
<td>36.8</td>
<td>35.7</td>
</tr>
<tr>
<td>3 mo to &lt; 6 mo</td>
<td>14.4</td>
<td>13.3</td>
</tr>
<tr>
<td>6 mo to &lt; 1 yr</td>
<td>15.5</td>
<td>16.9</td>
</tr>
<tr>
<td>≥ 1 yr</td>
<td>33.3</td>
<td>34.1</td>
</tr>
<tr>
<td>Number of symptomatic days in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>past 2 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8.6</td>
<td>8.8</td>
</tr>
<tr>
<td>1–3 d</td>
<td>36.3</td>
<td>34.6</td>
</tr>
<tr>
<td>4–7 d</td>
<td>33.5</td>
<td>35.8</td>
</tr>
<tr>
<td>&gt; 7 d</td>
<td>21.6</td>
<td>20.8</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or previous smoker</td>
<td>20.5</td>
<td>20.3</td>
</tr>
<tr>
<td>Passive smoker</td>
<td>28.0</td>
<td>30.1</td>
</tr>
<tr>
<td>None</td>
<td>51.5</td>
<td>49.6</td>
</tr>
<tr>
<td>Prebronchodilator FEV(_1) % of predicted</td>
<td>86.3 (13.9)</td>
<td>86.6 (13.9)</td>
</tr>
<tr>
<td>Postbronchodilator FEV(_1) % of predicted</td>
<td>96.2 (13.1)</td>
<td>96.4 (13.3)</td>
</tr>
</tbody>
</table>

*Data are presented as % or mean (SD).
decline in male subjects was 3.6% and in female subjects was 1.95%; while in the budesonide group, the decline in male patients was 2.68% and in female patients was 1.13%. Similarly, in active smokers in the placebo group, the decline over 3 years was 4.36% and in nonsmokers was 2.45%, while in the budesonide group the decline in active smokers was 2.84% and in nonsmokers was 1.53%.

Interestingly, the smallest decline in postbronchodilator FEV1 over 3 years was seen in adolescents when compared to children or adults (Fig 3): change from baseline in the placebo group, −0.39%; change from baseline in the budesonide group, −0.91%. In addition, the smallest treatment effect of budesonide on postbronchodilator FEV1 was seen in adolescents.

The prebronchodilator FEV1 increased in both treatment groups but significantly more in the budesonide-treated group (p < 0.001 for all time points), especially after 1 year of treatment. The proportion of patients with a prebronchodilator FEV1 < 80% of predicted at baseline or having received a dose of corticosteroids during the preceding 6 weeks was 40%. For these patients, the 3-year change from baseline in postbronchodilator FEV1 percentage of predicted was −0.02% in the budesonide group and −1.43% in the placebo group (p = 0.003). The bronchodilator responses measured at baseline demonstrated a 9.9% improvement in FEV1 for the entire population. At 1 year, the improvement in FEV1 was 4.8% in the budesonide group and 5.8% in the placebo group (mean difference, −0.97%; p < 0.001). This difference was maintained at 2 years and 3 years: −0.81% and −1.04% respectively (each p < 0.001).

**Discussion**

This study is the first large, prospective evaluation of the effects of early intervention with inhaled corticosteroids on asthma progression, as determined by the development of severe asthma-related events and changes in lung function. In this study, average duration of time since asthma diagnosis was < 1 year. The study demonstrated that treatment with low doses of inhaled budesonide improved both prebronchodilator and postbronchodilator FEV1, and this effect persisted over the 3 years of the study. However, despite the benefits of inhaled budesonide, the postbronchodilator FEV1 declined in both treatment groups over the duration of the study. This article extends the description of the results previously described by focusing only on the effects of early intervention with inhaled corticosteroids on lung function, the distribution of the response, and the factors that may determine the response.

Almost all the patient population studied had symptoms more than weekly but less than daily, with a mean baseline prebronchodilator FEV1 value > 85% and postbronchodilator value > 95%, which would characterize this group as having mild persistent asthma according to the revised Global Initiative on Asthma guidelines. However, a proportion of...
the patients has a prebronchodilator (but not post-
bronchodilator) FEV₁ < 80% of predicted normal. The
effects of the intervention with inhaled budesonide were similar, in all respects, if these patients were
considered as a separate group, when compared to the whole population. Despite the fact that
asthma was new onset, the mean baseline postbronchodi-
lator FEV₁ was reduced by 3.7%, suggesting that
airway structural changes that result in a decline in FEV₁ begin early in asthma. This information is
consistent with a longitudinal birth cohort, initially studied at aged 9 years, which has demonstrated that
pulmonary function was consistently lower in individuals with persistent wheezing than in those with-
out persistent wheezing and that tracking of lung function occurred, with those with the lowest lung
function in adulthood having the lowest values in childhood, suggesting that the changes occur early in
the disease process.

Another explanation for the lower baseline FEV₁ may be imprecision in calculating the percentage of
predicted normal values. For this reason, the baseline values were recalculated using prediction equa-
tions produced by Knudson et al and Hankinson et
al for white subjects. For other races, the same race
correction factors as given above were used. Now the
baseline postbronchodilator FEV₁ values for the
population were 97.5% (SD 13.9%) and 95.5% (SD
14.9%), respectively. Thus, the baseline reduction in
postbronchodilator FEV₁ is unlikely to be explained
by predicted value equation.

The prebronchodilator FEV₁ value improved in
both the placebo- and budesonide-treated popula-
tions but significantly more so with budesonide treatment. The beneficial effect of budesonide is
consistent with many previous studies demonstrating an improvement in prebronchodilator FEV₁ over
time with inhaled corticosteroids. The improvement in the placebo-treated group is likely due to the
either the benefit that patients achieve from just being enrolled in clinical trials (the Hawthorne
effect), or the fact that patients were allowed to be treated with other antiasthma medications, including
inhaled or systemic corticosteroids, during the study, at the investigator’s discretion, to achieve asthma
control (indeed, by the end of year 1, 21.4% of placebo-treated patients had been administered a
nonstudy, inhaled or systemic corticosteroid treatment), or a combination of these two effects.

In the planning of this study, the effect of inhaled
budesonide on the postbronchodilator FEV₁ was
used as evidence that the inhaled corticosteroid
influenced processes leading to the decline in lung
function. The CAMP trial, in which asthmatic chil-
dren were enrolled with a mean duration of asthma
of 5.5 years and with approximately 300 patients in
each treatment group, did not demonstrate an effect
of treatment for 4 years with inhaled budesonide on
the postbronchodilator FEV₁ when compared to
placebo. As a result, the investigators concluded that
inhaled corticosteroids did not influence airway re-
modeling in asthma. In contrast, the present, much
larger study did demonstrate a statistically signifi-
cant, almost 1%, difference in the postbronchodila-
tor FEV₁ between the budesonide and placebo
treatment groups. This suggests that early introd-
tion of inhaled corticosteroids in newly diagnosed
asthma can partially prevent the airway remodeling
and its clinical consequence, loss in postbronchodi-
lator FEV₁. The finding that the treatment effect was
more marked in adults (> 18 years old), who re-
ceived 400 µg/d of budesonide (42% less decline),
than in children < 11 years old, who received 200
µg/d of budesonide (21% less decline), suggests that
the dose of inhaled budesonide may be important.
The difference between the budesonide and the
placebo treatment groups lessened over the 3 years
of the study. This is likely related to the fact that
> 25% of patients in the placebo arm of the study
had been started on additional inhaled corticoste-
roids by the end of the 3 years of the study.

A surprising result of this study was that no
significant effect was demonstrated in adolescents on
prebronchodilator or postbronchodilator FEV₁ over
the 3 years of the study. This result was similar to
that described in the CAMP trial, which contained
a large proportion of adolescent children. Features
of asthma are known to improve in many asthmatic
children during adolescence, which has coined the
phrase “growing out of asthma.” This improvement
may explain the lack of change in FEV₁ in these
patients. Alternatively, the prediction equation for
the FEV₁ was modeled from the predictions in
children and adults, which may have reduced the
precision to detect change over time. During pu-
berty, the relationship between height and lung
function is more complex that at other periods of life,
and assessment of FEV₁ percentage of predicted
may not be as precise a measure as at other ages. Also,
adherence with treatment is often worse as
children age, which may in part explain the lack of
effect of budesonide.

Despite the benefits of early intervention with
inhaled budesonide, postbronchodilator FEV₁ values
decline in both treatment groups. The differences
between the groups were most marked at the initial
postrandomization visit at 6 weeks. The reason for
the decline in postbronchodilator FEV₁ of almost 2%
in the placebo-treated patients over this short period,
which was not seen in the budesonide-treated pa-
tients, is not clear. However, part of the explanation may be the regression to the mean effect that is often seen in clinical trials, when efforts are being made to achieve enrolment criteria (in this study, postbronchodilator FEV1 values > 80% of predicted). Similar differences in FEV1 between placebo and inhaled corticosteroid treatments by the first study visit have been described in several long-term studies20–22 in COPD.

The magnitude of decline in postbronchodilator FEV1 was greater in male compared to female subjects, in adults compared to children, and in smokers compared to nonsmokers. The decline demonstrated a Gaussian-like distribution in both treatment groups but with fewer patients in the budesonide group in the tail with a greater loss in FEV1. Thus, 21.4% of patients in the placebo group had a decline in FEV1 ≥ 10% over the 3 years of the study, while 17.7% of patients in the budesonide group had a similar decline. In the placebo group, there was a 1.6% decline in FEV1 during the first 6 weeks; subsequently, there was on average, a decline by 0.4% per year up to the 3-year follow-up. In the budesonide group, there was a 0.3% increase in FEV1 during the first 6 weeks; subsequently, there was on average a decline of 0.7% per year up to the 3-year follow-up. These results suggest that there is an effect of the asthmatic process on airway remodeling that is either resistant to the effects of inhaled corticosteroids or may require a higher dose than was used in this study. Inhaled corticosteroids improve some of the airway structural changes that are found in patients with asthma, including the integrity of the airway epithelium,23 the extent of airway vascularity,24 and the extent of the extracellular matrix deposition below the basement membrane.25 Interestingly, these effects were seen with a higher dose of inhaled corticosteroid (an average dosage of inhaled fluticasone propionate of 1,000 µg/d or budesonide of 800 µg/d) than was used in the present study. Also, in the study of Sont et al.,25 both clinical outcomes and the reduction in airway extracellular matrix were seen with a higher dose rather than a lower dose of inhaled budesonide. Furthermore, no information exists on the effects of inhaled corticosteroids on some other components, such as the increases in airway smooth-muscle volume.

The FEV1/FVC ratio is a sensitive indicator of airflow obstruction and was improved by treatment with inhaled budesonide in childhood asthma in the CAMP trial.9 In the present study, reliable results for FVC were not obtained in children and adolescents because stringent efforts were not made in all centers to ensure a sufficiently long expiratory phase of the forced expiratory maneuver. Reliable information was, however, obtained in the adult patients. The results in the adults confirmed that treatment with budesonide significantly attenuated the decline in the FEV1/FVC ratio demonstrated in the placebo group.

The contribution of bias must be considered when interpreting the results of this study. Two potential sources of bias exist. These are as a result of the study design and in the calculation of the predicted normal values. The trial design has used the baseline FEV1 for many of the calculations described in this article. The baseline FEV1 was used as one of the entry criteria for the study and thereby may have given an erroneously high result as investigators and patients attempted to obtain the best possible value for FEV1 at the baseline visit. Also, the design allowed for concomitant treatment to be administered throughout the study; indeed, by the end of the 3 years of study, 45% of the placebo group had received inhaled oral or systemic corticosteroids. This could minimize any possible treatment differences, and the effect would increase as the study progressed. The second source of bias is in the calculation of predicted normal values, in which prediction equations used were > 30 years old and likely provide predicted normal values that are too low. Therefore, interpreting the absolute levels within the groups is likely not precise; however, the random allocation should allow accurate estimates of treatment differences between groups.

The bronchodilator response documented at the baseline visit was 9.9% improvement in FEV1, and the magnitude of the benefit is, in part, due to the baseline measurement bias described above. The subsequent measurements made at years 1, 2, and 3 show a consistent difference between the budesonide and placebo treatment groups, with the placebo group having approximately 1% greater bronchodilator response at each visit. This finding is in agreement with that in another study.26

In summary, this study has demonstrated that early intervention with inhaled budesonide within the first 2 years of asthma diagnosis in patients with persistent asthma improves both prebronchodilator and postbronchodilator FEV1. In addition, postbronchodilator FEV1 values declined in both the budesonide and placebo treatment groups. This suggests that there may be inhaled steroid-sensitive and inhaled steroid-insensitive components to airway structural changes associated with asthma, which cause the decline in percentage of predicted FEV1, or alternatively the complete inhibition of the decline in FEV1 requires a higher dose of inhaled corticosteroids than was used in this study.
Appendix: START Safety Committee and Investigators

Safety Committee

A. Sheffer (Boston, MA [Chairman]); A. Wooleck (Sydney, Australia); P. Díaz (Santiago, Chile); M. Silverman (Leicester, UK); B. Lindmark (Lund, Sweden [nonvoting member]).

START Investigators


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