Can Guideline-defined Asthma Control Be Achieved?
The Gaining Optimal Asthma ControL Study

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For most patients, asthma is not controlled as defined by guidelines; whether this is achievable has not been prospectively studied. A 1-year, randomized, stratified, double-blind, parallel-group study of 3,421 patients with uncontrolled asthma compared fluticasone propionate and salmeterol/fluticasone in achieving two rigorous, composite, guideline-based measures of control: totally and well-controlled asthma. Treatment was stepped-up until total control was achieved (or maximum 500 μg corticosteroid twice a day). Significantly more patients in each stratum (previously corticosteroid-free, low- and moderate-dose corticosteroid users) achieved control with salmeterol/fluticasone than fluticasone. Total control was achieved across all strata: 520 (31%) versus 326 (19%) patients after dose escalation (p < 0.001) and 690 (41%) versus 468 (28%) at 1 year for salmeterol/fluticasone and fluticasone, respectively. Asthma became well controlled in 1,071 (63%) versus 846 (50%) after dose escalation (p < 0.001) and 1,204 (71%) versus 988 (59%) at 1 year. Control was achieved more rapidly and at a lower corticosteroid dose with salmeterol/fluticasone versus fluticasone. Across all strata, 68% and 76% of the patients receiving salmeterol/fluticasone and fluticasone, respectively, were on the highest dose at the end of treatment. Exacerbation rates (0.07–0.27 per patient per year) and improvements in health status were significantly better with salmeterol/fluticasone than fluticasone. This study confirms that the goal of guideline-derived asthma control was achieved in a majority of the patients.

Keywords: antiasthmatic agents; fluticasone propionate; guidelines; quality of life; salmeterol

The goal of asthma management is to achieve and maintain control of the disease without side effects from the therapies used (1–3). Large, multinational, community-based surveys of asthma have shown, however, that the majority of patients have an alarmingly high rate of symptoms and disruption of life from their disease, indicating that this goal is not being achieved (4–6). As a result, some have suggested that asthma control, as defined in guidelines, is unrealistic for the “vast majority” of patients (7). If this conclusion is correct, it is necessary to consider whether this shortcoming is caused by the refractory nature of the disease, limitations of current treatments, or a problem of treatment strategies, coupled with low physician and patient expectations and treatment compliance (8). Surprisingly, most clinical studies assessing the efficacy of “controller” therapies in asthma do not address whether control was achieved but rather focus on improvements in individual end points obtained with fixed doses of treatment. Assessment of individual asthma end points alone, such as lung function, may overestimate the level of asthma control achieved (9). Furthermore, such limited end points may not reflect what is important to the patient, whose quality of life is more dependent on the overall impact of the disease rather than on a single measure (10). To date, no studies have assessed the benefits of aiming for complete, comprehensive, and sustained clinical control in a controlled study that allows for dose escalation, as necessary, to achieve this. As a result, the full efficacy potential of current treatments have not been formally evaluated. We therefore conducted a 1-year prospective trial, Gaining Optimal Asthma controL (GOAL), to compare the efficacy of two recommended controller therapies: an increasing dose of fluticasone propionate alone or in combination with the long-acting β2-agonist salmeterol to achieve asthma control as defined in the Global Initiative for Asthma/National Institutes of Health guidelines (3, 11). Some of the results of this study have been previously reported in abstract form (12–27).

METHODS

Study Design and Assessment of Asthma Control

GOAL was a 1-year, stratified, randomized, double-blind, parallel-group study comparing the efficacy and safety of individual, predefined, stepwise increases of salmeterol/fluticasone propionate (salmeterol/fluticasone; Seretide/Advair; GlaxoSmithKline, Middlesex, UK) with fluticasone propionate (fluticasone; Flixotide/Flovent; GlaxoSmithKline) alone in achieving two predefined composite measures of asthma control.

The definitions of control were derived from the treatment goals of the Global Initiative for Asthma/National Institutes of Health guidelines (3, 11): “totally controlled” or “well controlled” or uncontrolled (if neither definition was fulfilled). Both control definitions were composite measures that included the following asthma outcomes: PEF, rescue medication use, symptoms, night-time awakenings, exacerbations, emergency visits, and adverse events (Table 1). Equal weighting was given to each criterion. Totally controlled and well-controlled weeks were defined by achievement of all of the specified criteria for that week. Totally controlled asthma was achieved if the patient, during the 8 consecutive assessment weeks, recorded 7 totally controlled weeks and had no exacerbations, emergency room criteria, or medication-related adverse event criteria for each day of each week. Well-controlled asthma was achieved if the patient recorded 7 of 8 well-controlled weeks, and failure to achieve any one of these would result in failure to achieve control for that week. Failure of the exacerbation, emergency visit, or adverse event criteria resulted in the automatic failure of control status (totally and well-controlled definitions) for the entire 8-week period, irrespective of how well asthma was controlled at other time points during the 8 weeks. Well-controlled asthma was similarly assessed over 8 weeks but was allowed a low level of symptoms and rescue medication use, as outlined in Table 1.

During the run-in period, patients continued on their usual dose (if any) of inhaled corticosteroid treatment. Those who did not achieve at least two well-controlled weeks in the 4-week run-in period were randomized to one of three strata based on their inhaled corticosteroid...
TABLE 1. DEFINITIONS OF WELL CONTROLLED AND TOTALLY CONTROLLED ASTHMA BASED ON GLOBAL INITIATIVE FOR ASTHMA/NATIONAL INSTITUTES OF HEALTH GUIDELINE AIMS OF TREATMENT

<table>
<thead>
<tr>
<th>Goals of GINA/NIH</th>
<th>Totally Controlled Each Week All of</th>
<th>Well Controlled Each Week 2 or More of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>Minimal (ideally no)</td>
<td>None</td>
</tr>
<tr>
<td>Rescue β2-agonist use</td>
<td>Minimal (ideally no)</td>
<td>None</td>
</tr>
<tr>
<td>Morning PEF</td>
<td>Near normal</td>
<td>&gt; 80% predicted* every day</td>
</tr>
<tr>
<td>Night-time awakening</td>
<td>Minimal (ideally no)</td>
<td>None</td>
</tr>
<tr>
<td>Exacerbations*</td>
<td>Minimal (infrequent)</td>
<td>None</td>
</tr>
<tr>
<td>Emergency visits</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Treatment-related adverse events</td>
<td>Minimal</td>
<td>None enforcing change in asthma therapy</td>
</tr>
</tbody>
</table>

Definition of abbreviations: GINA = Global Initiative for Asthma; NIH = National Institutes of Health.

Totally and well-controlled asthma were defined by achievement of all of the specified criteria for that week. Totally controlled asthma was achieved if the patient during the 8 consecutive assessment weeks recorded 7 totally controlled weeks and had no exacerbations, emergency room criteria, or medication-related adverse events criteria. Well-controlled asthma was similarly assessed over the 8 weeks. These assessments were for an 8-week period during the double-blind treatment period. Baseline control and control during the open-label phase were assessed over a 4-week period.

* Exacerbations were defined as deterioration in asthma requiring treatment with an oral corticosteroid or an emergency department visit or hospitalization.

† Minimal or no exacerbations or asthma-related adverse events.

‡ Symptom score: 1 was defined as “symptoms for one short period during the day.” Overall scale: 0 (none)–5 (severe).

The results of this study indicate a clear advantage of the triple combination therapy in achieving better asthma control compared to the individual components. The data show a significant improvement in the proportion of patients achieving control in phase II, the dose of inhaled corticosteroid and time required to achieve the first well-controlled week, proportion of patients and dose to achieve totally controlled asthma; the time to achieve the first totally controlled week; asthma quality of life (using the Asthma Quality of Life Questionnaire [AQLQ]); the rate of exacerbations (requiring oral corticosteroids, hospitalizations or emergency visits); and morning predose FEV1. Adverse event information was collected at each clinic visit, and 24-hour urinary corticosterols were collected in all patients attending study centers in the United States and Canada. Information on study design and analysis of results is provided in the online supplement.

RESULTS

Subject Characteristics

A total of 5,068 patients from 326 centers in 44 countries were screened: 3,421 qualified for inclusion. Baseline characteristics of the intention-to-treat population (3,416) were comparable between treatment groups within each stratum (Table 2 and Table E1 of the online supplement). A total of 3,039 patients completed phase I, and 2,890 completed phase II. Reasons for withdrawal from each phase were adverse events (57 and 17 patients in phases I and II, respectively), consent withdrawn (81 and 30), lost to follow-up (74 and 37), asthma exacerbation (10 and 3), ineligible for the study, protocol violation, or un evaluable data (98 and 19), and other (57 and 43). Of the 1,659 patients who had not achieved totally controlled asthma in either phase I or phase II and were therefore eligible for the 4-week open-label phase, 157 were withdrawn before entry, and 22 were withdrawn during the 4 weeks. Reasons for withdrawal were adverse events (3 and 4 patients before or during the 4 weeks, respectively), consent withdrawn (6 and 2), lost to follow-up (3 and 8), protocol violation or un evaluable data (15 and 3), and other (130 and 5), which included a reluctance to take oral corticosteroids (see Figure E2 of the online supplement). Compliance (the proportion of patients who used ≥ 80% of study medication, as assessed using the dose counter on the Diskus/Accuhaler; GlaxoSmithKline) during the blinded phases was 89% for both treatment groups.

Effect of Treatment on Achievement of Guideline-defined Asthma Control

For all strata, the proportion of patients who achieved well-controlled and totally controlled asthma at the end of phase I...
of the study was significantly greater for salmeterol/fluticasone compared with fluticasone. Well-controlled asthma was achieved in 71% and 65% of patients for salmeterol/fluticasone and fluticasone, respectively, in stratum 1 (odds ratio [OR], 1.32; 95% confidence interval [CI], 1.01–1.73; p = 0.039), 69% and 52% in stratum 2 (OR, 2.13; 95% CI, 1.65–2.74; p < 0.001), and 51% and 33% in stratum 3 (OR, 2.25; 95% CI, 1.75–2.90; p < 0.001). Of those patients that achieved either well-controlled or totally controlled asthma (Figures 1A and 1B). The cumulative proportion of patients achieving both well-controlled and totally controlled asthma (Figure 1A).

In phase I, totally controlled asthma was achieved in 42% and 31% of patients for salmeterol/fluticasone and fluticasone, respectively, in stratum 1 (OR, 1.71; 95% CI, 1.30–2.24; p < 0.001), 32% and 20% in stratum 2 (OR, 2.07; 95% CI, 1.56–2.76; p < 0.001), and 19% and 8% in stratum 3 (OR, 2.90; 95% CI, 1.98–4.26; p < 0.001) (Figure 1B).

In each stratum, the proportion of patients achieving control at the same or a lower dose of inhaled corticosteroid was greater for those treated with salmeterol/fluticasone. A similar number of patients were able to achieve control with the lowest dose of salmeterol/fluticasone compared with up to 250 µg of fluticasone alone (Figures 1A and 1B). The odds of achieving well-controlled and totally controlled asthma at the same or lower dose of inhaled corticosteroid for salmeterol/fluticasone versus fluticasone in stratum 1 increased by at least 40% (well controlled: OR, 1.40; 95% CI, 1.12–1.76; p = 0.003; totally controlled: OR, 1.78; 95% CI, 1.38–2.30; p < 0.001) and was more than double in both stratum 2 (well controlled: OR, 2.20; 95% CI, 1.77–2.74; p < 0.001; and totally controlled: OR, 2.19; 95% CI, 1.66–2.89; p < 0.001) and stratum 3 (well controlled: OR, 2.32; 95% CI, 1.82–2.95; p < 0.001; and totally controlled: OR, 2.95; 95% CI, 2.01–4.33; p < 0.001). Of those patients that achieved either well-controlled or totally controlled asthma, most (well controlled: 60%, 45%, and 50%; and totally controlled: 40%, 40%, and 53% for strata 1, 2, and 3, respectively) did so at the lowest dose of combination treatment used for the stratum; however, because fewer than half of the entire study population achieved totally controlled asthma during phase I, most patients completed the trial on the highest dose of salmeterol/fluticasone or fluticasone (311 [57%] and 345 [63%] in stratum 1, 367 [63%] and 443 [77%] in stratum 2, and 492 [85%] and 510 [88%] in stratum 3 for salmeterol/fluticasone and fluticasone propionate, respectively).

Analysis of time to asthma control, defined as the time to the first well-controlled week or totally controlled week during Weeks 1–12, showed that control was achieved significantly faster with salmeterol/fluticasone compared with fluticasone alone (all strata p = 0.002). The week by which 50% of patients achieved their first well-controlled week was Week 3 versus Week 4 for salmeterol/fluticasone and fluticasone, respectively, in stratum 1, Week 2 versus Week 7 in stratum 2, and Week 5 versus Week 10 in stratum 3 (all p < 0.001). The week by which 50% of patients achieved their first totally controlled week over the 1-year study period was Week 16 versus Week 24 for salmeterol/fluticasone and fluticasone, respectively, in stratum 1, Week 21 versus Week 45 in stratum 2, and Week 38 for salmeterol/fluticasone in stratum 3. For fluticasone, this could not be calculated, as less than 50% of patients achieved a totally controlled week in stratum 3 on fluticasone alone.

Longitudinal Effect of Treatment on Achieving Guideline-defined Asthma Control

During the constant dose phase (phase II), additional patients achieved both well-controlled and totally controlled asthma (Figures 1A and 1B). The cumulative proportion of patients achieving well-controlled asthma at the end of phase II were as follows: stratum 1, 78% on salmeterol/fluticasone and 70% on fluticasone (p = 0.003); stratum 2, 75% and 60%, respectively (p < 0.001); and stratum 3, 62% and 47% (p < 0.001). The results for totally controlled asthma by the end of phase II were stratum 1, 50% on salmeterol/fluticasone and 40% on fluticasone; stratum 2, 44% and 28%, respectively; and stratum 3, 29% and 16% (all strata p < 0.001). Control was also sustained; the majority of patients who achieved control in phase I were also controlled at the end of phase II: 77–83% across strata of patients on salmeterol/fluticasone and 75–77% on fluticasone remained well controlled in phase II and 69–70% and 62–74%, respectively, maintained totally controlled asthma.

Figure 2 shows the proportion of patients (noncumulative) who achieved well-controlled asthma status for a single week.
Figure 1. Proportion of patients and dose at which (A) well-controlled and (B) totally controlled asthma was achieved by treatment with salmeterol/fluticasone (SFC) or fluticasone propionate (FP) across all strata (1–3), according to the use of inhaled corticosteroid (ICS) such as beclomethasone dipropionate (BDP) or equivalent in the previous 6 months. (A) Well-controlled asthma. For SFC versus FP: phase I: stratum 1, \( p < 0.039 \), strata 2 and 3, \( p < 0.001 \); cumulative phase I and phase II: stratum 1, \( p < 0.003 \), strata 2 and 3, \( p < 0.001 \). (B) Totally controlled asthma. phase I: all strata, \( p < 0.001 \); cumulative phase I and phase II: all strata \( p < 0.001 \). *Excludes patients with missing baseline FEV₁.

(a well-controlled week) in each week of the study. This increased progressively during the study and reached 1,142 (77%) for salmeterol/fluticasone and 966 (68%) for fluticasone across all strata.

Effect of Oral Corticosteroids and High-dose Combination Therapy in Patients not Totally Controlled at the End of the Study

An additional 40 (7%), 52 (9%), and 59 (10%) patients of those previously on fluticasone alone who had not achieved well-controlled asthma in phase I or phase II achieved it during the maximum treatment phase with oral corticosteroids plus salmeterol/fluticasone 50/500 (in strata 1–3, respectively). Similarly, an additional 35 (6%), 54 (9%), and 63 (11%) patients who had not achieved totally controlled asthma in phase I or phase II achieved it during the maximum treatment phase. Of those patients previously on salmeterol/fluticasone, an additional 25 (5%), 23 (4%), and 39 (7%) patients achieved well-controlled status, and 25 (5%), 37 (6%), and 31 (5%) achieved totally controlled asthma with the addition of oral corticosteroids in strata 1–3, respectively.

Effect of Treatments on Exacerbations

The mean annual rates of exacerbations requiring oral corticosteroids and/or hospitalization or emergency visits were low in both treatment groups but were significantly lower in the salmeterol/fluticasone group in each stratum (\( p < 0.009 \)) (Figure 3). In all strata, there was a consistent trend for a reduction in the annualized rate of exacerbations in phase II compared with the exacerbation rates in phase I (see online supplement Figure E3). This was seen even when allowing for patients who had withdrawn during the study. For patients achieving totally controlled and well-controlled asthma in phase I, the annualized exacerbation rates in phase II were 0.05 and 0.13, respectively; in contrast, the annualized exacerbation rate for those not achieving at least well-controlled asthma was 0.23 (all strata, both treatments combined).

Figure 3. Mean rate of exacerbations requiring either oral steroids or hospitalization/emergency visit per patient per year over Weeks 1–52 among patients treated with salmeterol/fluticasone or fluticasone propionate according to use of ICS in previous 6 months (S1–S3). \( p < 0.009 \) salmeterol/fluticasone versus fluticasone propionate, all strata.
**Effect of Treatments on Asthma Quality of Life**

Overall AQLQ scores improved in both groups throughout the study, with a statistically significant difference in favor of salmeterol/fluticasone in strata 2 and 3 (Table 3). The proportion of patients who achieved near-maximal mean overall AQLQ scores (≥6) increased from 6–10% at baseline to 62% versus 62% (salmeterol/fluticasone versus fluticasone) in stratum 1; 64% versus 53% in stratum 2; and 57% versus 45% in stratum 3 at Week 52. There was a trend for higher quality of life scores in patients who gained control. Achieving totally controlled and well-controlled asthma in phase I was associated with mean overall AQLQ scores of 6.4 and 6.1, respectively, in phase II; in contrast, the mean overall AQLQ score for those not achieving at least well-controlled asthma was 5.3 (all strata, both treatments combined).

**Effect of Treatments on FEV₁ Values**

The mean morning prebronchodilator FEV₁ increased in both groups, with significantly larger improvements in the salmeterol/fluticasone group (Table 3). For patients achieving totally controlled and well-controlled asthma in phase I, the percentage predicted FEV₁ was 82% (all strata, both treatments combined). The most common adverse events (not necessarily related to treatment) across all periods in 4% and 3% of patients in the salmeterol/fluticasone versus fluticasone (n = 840) treatment group and 14% in fluticasone group), upper respiratory tract infection (13% in both groups), headache (5% and 7%), sinusitis (5% and 4%), and influenza (5% and 4%). The overall incidence of drug-related adverse events was 10% in each group. The most common drug-related adverse events across all strata were oral candidal infections (3% in both groups), hoarseness (3% on salmeterol/fluticasone and 2% on fluticasone), and pharyngolaryngeal pain (<1% and 1%, respectively). In the subset of patients in which cortisol data were available at baseline and at Week 52 (n = 194), the geometric mean of the cortisol/creatinine ratio (nmol/mmol) at these time points was 3.74 versus 3.04 for salmeterol/fluticasone (n = 102) and 3.92 versus 2.85 for fluticasone (n = 92). No statistical differences between treatments at Week 52 were observed (p = 0.318; 95% CI, 0.92, 1.31). For patients who received the highest dose of corticosteroid (500 µg twice a day), the geometric means were 3.76 versus 2.90 for salmeterol/fluticasone (n = 82) and 3.82 versus 2.73 for fluticasone (n = 84). Despite these decreases (see Figure E4 in the online supplement), the majority of patients (92%) had normal or high values at Week 52. Seven of 102 patients on salmeterol/fluticasone and 8 of 92 on fluticasone had final values below the lower limit of the normal range, whereas 7 salmeterol/fluticasone and 5 fluticasone patients with initially low urinary 24-hour free cortisol values returned to normal.

**DISCUSSION**

Our results demonstrate that in the majority of patients with uncontrolled asthma across a wide range of severities, comprehensive

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**TABLE 3. MEAN MORNING PREDOSE FEV₁ AND ASTHMA QUALITY OF LIFE QUESTIONNAIRE SCORE IN PHASES I AND II**

<table>
<thead>
<tr>
<th>Strata</th>
<th>Phase I (SD)</th>
<th>Phase II (SD)</th>
<th>Phase II (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratum 1</td>
<td>Stratum 2</td>
<td>Stratum 3</td>
<td>Stratum 3</td>
</tr>
<tr>
<td>(Inhaled Corticosteroid Use in Previous 6 Months)</td>
<td>(≤ 500 µg BDP or Equivalent Daily)</td>
<td>(&gt; 500 to ≤ 1,000 µg BDP or Equivalent Daily)</td>
<td></td>
</tr>
<tr>
<td>(No Inhaled Corticosteroid)</td>
<td>SFC</td>
<td>FP</td>
<td>SFC</td>
</tr>
<tr>
<td>FEV₁</td>
<td>n</td>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Baseline, L (SD)</td>
<td>533 (0.85)</td>
<td>531 (0.85)</td>
<td>572 (0.83)</td>
</tr>
<tr>
<td>% predicted (SD)</td>
<td>76 (18.14)</td>
<td>79 (18.83)</td>
<td>78 (18.17)</td>
</tr>
<tr>
<td>SFC minus FP, (SE)</td>
<td>0.14 (0.03)</td>
<td>0.13 (0.02)</td>
<td>0.13 (0.02)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.09, 0.20</td>
<td></td>
<td>0.09, 0.18</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.001</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Phase I: adjusted mean change (SE)</td>
<td>0.52 (0.02)</td>
<td>0.34 (0.02)</td>
<td>0.37 (0.02)</td>
</tr>
<tr>
<td>SFC minus FP, (SE)</td>
<td>0.17 (0.03)</td>
<td>0.13 (0.02)</td>
<td>0.13 (0.02)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.12, 0.22</td>
<td></td>
<td>0.08, 0.18</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.001</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean overall AQLQ score</td>
<td>n</td>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td>282 (1.00)</td>
<td>275 (1.00)</td>
<td>339 (1.1)</td>
</tr>
<tr>
<td>Phase I (SD)</td>
<td>4.4 (1.0)</td>
<td>4.5 (1.0)</td>
<td>4.7 (1.1)</td>
</tr>
<tr>
<td>Phase I: adjusted mean change (SE)</td>
<td>5.9 (1.0)</td>
<td>5.8 (1.0)</td>
<td>5.9 (1.0)</td>
</tr>
<tr>
<td>SFC minus FP, (SE)</td>
<td>1.5 (0.1)</td>
<td>1.3 (0.1)</td>
<td>1.3 (0.1)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.5, 0.7</td>
<td></td>
<td>0.4, 0.9</td>
</tr>
<tr>
<td>p Value</td>
<td>0.053</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Phase II (SD)</td>
<td>6.0 (1.0)</td>
<td>5.9 (1.1)</td>
<td>6.0 (1.0)</td>
</tr>
<tr>
<td>Phase II: adjusted mean change (SE)</td>
<td>1.6 (0.1)</td>
<td>1.4 (0.1)</td>
<td>1.3 (0.1)</td>
</tr>
<tr>
<td>SFC minus FP, (SE)</td>
<td>0.1 (0.1)</td>
<td>0.2 (0.1)</td>
<td>0.2 (0.1)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.0, 0.3</td>
<td></td>
<td>0.1, 0.3</td>
</tr>
<tr>
<td>p Value</td>
<td>0.081</td>
<td></td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; CI = confidence interval; FP = fluticasone propionate; SFC = salmeterol/fluticasone combination.
guideline-defined control can be achieved and maintained. More patients achieved both totally controlled and well-controlled asthma with combination inhaled salmeterol/fluticasone more rapidly and at a lower dose of corticosteroid than with inhaled fluticasone alone. Patients that achieved control recorded very low rates of exacerbations and near-maximal health status scores. Furthermore, in stepping up treatment in an attempt to achieve guideline-defined total control, even those patients who did not attain our stringent definitions of control showed considerable improvements in health status and a reduction in exacerbation rates. The overall AQLQ score for all groups and strata approached or surpassed the value of 6, suggesting that asthma no longer had a significant impact on quality of life, and AQLQ scores were higher for salmeterol/fluticasone than for fluticasone (10, 28). A greater degree of improvement was also seen in lung function; morning FEV₁ improved to within a range considered normal. The absence of a reference group prevents a formal assessment of the improvement in these measures, but compared with rates and measures recorded before study entry, the improvements appear substantial, with a consistent trend for further improvement in the maintenance dose phase.

Because no widely accepted measures of asthma control were available, two composite measures from the Global Initiative for Asthma/National Institutes of Health guideline goals of treatment were developed and proposed as targets for control. As single measures are likely to overestimate control, a composite measure was selected to assess the total impact of this disease on patients (9). Totally controlled asthma was the complete absence of all features of asthma for at least 7 of 8 weeks. Well controlled was a pragmatic adaptation based on what is permitted by the guidelines as control, also sustained for at least 7 of 8 weeks. Such stringent and sustained measures of asthma control have never previously been assessed in a clinical trial. The results of our study suggest that total control should be the aim of treatment for all asthma patients. It is a realistic outcome for corticosteroid-naive patients, and although it may not be achieved by the majority of patients previously on moderate or high doses of inhaled corticosteroids, by stepping up treatment and aiming for total control of asthma, considerable benefits are achieved in almost all patients. This is particularly true for exacerbations, which were virtually eliminated in patients who achieved guideline-defined control (either total control or well controlled).

Because the focus of this study was to establish the proportion of patients with asthma that could achieve the target level of control, even if this took several months, the approach adopted was to continue treatment for the full duration of the trial and not step-down, as recommended in the guidelines. This also permitted evaluation of incremental benefit (in secondary outcomes), both in those that reached this level and those that did not. During sustained treatment, a further 8 to 12% achieved totally controlled asthma, and further improvements in FEV₁, exacerbation rates, and quality of life were observed, particularly in those that attained totally controlled asthma. This delayed realization of the full benefits of treatment may reflect a more gradual resolution of the airway inflammation with prolonged dosing (29, 30). This effect is suggested by the results of the open-label phase in which relatively few patients benefited from the additional “maximum” treatment with 10 days of high-dose oral corticosteroid and 4 weeks of salmeterol/fluticasone 50/500 μg twice a day. Those who showed a response in this phase were predominantly patients who had not previously received salmeterol/fluticasone. This finding suggests that the treatments and dosing approach had achieved as much as, or close to maximum benefit, at least as far as clinical total control is concerned. However, it must be recognized that some of the reasons for nonattainment of this level were technical (such as patients with missing data) and potentially diagnostic errors. In addition, the target threshold value for PEF of 80% of predicted used in the definition of control was a pragmatic interpretation of the Global Initiative for Asthma goal of achieving “normal or near-normal” lung function and for some patients might have been unduly strict. Even among those that failed to achieve the prescribed definitions of control, clinical benefit was considerable, as judged by the group mean data of individual end points, such as lung function and health status. Because for ethical reasons the study was not placebo controlled, the potential placebo effect of participation in a study on attainment of asthma control (resulting, e.g., from improved adherence to treatment) cannot be evaluated. This would not be expected to affect treatment comparisons. Further analysis of factors that might potentially be associated with no-attainment of asthma control, such as cigarette smoking history (31, 32), age, atopy, sex, and duration of asthma is required.

The greater benefit of the salmeterol/fluticasone combination over inhaled fluticasone alone is consistent with the results of many clinical trials (33, 34), but this is the first study to demonstrate its advantage in achieving comprehensive sustained asthma control. Differences between treatments were apparent for each end point: the number that achieved control, the dose of corticosteroid at which control was achieved, and the time to first control week. In addition, salmeterol/fluticasone was more effective than fluticasone in achieving improvement in all secondary end points, irrespective of whether patients achieved the predefined levels of control. The greater improvements noted with salmeterol/fluticasone over fluticasone alone were maintained over the duration of the trial with no evidence of the fluticasone alone group “catching up.” Such results further confirm the benefits of the addition of salmeterol to inhaled corticosteroids. These differences in treatment effect were consistently seen across all levels of baseline therapy, even those patients entering the study as corticosteroid-naive or corticosteroid-free. The greater efficacy of combination therapy in patients who were corticosteroid-naive contrasts with a previous report in which little additional benefit was found with the addition of the long-acting β₂-agonist formoterol to the inhaled corticosteroid budesonide in subjects who were corticosteroid-naive with mild disease (35). This difference may be accounted for by differences in patient selection (with OPTIMA recruiting patients with very mild asthma), treatment approach (as treatments were stepped up, if required, in GOAL as opposed to using fixed doses), and outcome selection (with GOAL using a rigorous composite measure).

Application of these findings to the management of patients with asthma in general is strengthened by the large size of this study, which involved subjects over a wide range of age, geographic location, ethnicity, and baseline treatment. The requirement for reversibility of at least 15% was to ensure that patients with asthma were selected, as is generally required in asthma treatment trials. It is recognized that this may limit the applicability of the results to patients who do not demonstrate this characteristic feature. The high median reversibility obtained likely reflects the fact that short-acting β₂-agonists were withheld for at least 6 hours before reversibility testing and patients were on no other bronchodilators. Furthermore, the aim of recruitment was to enroll patients who had failed to achieve guideline-defined control; evidence from recent surveys has shown that over 95% of patients with asthma failed to achieve this (6). A surprising feature was the similarity of baseline characteristics across the strata. This may be explained by the fact that only patients with uncontrolled asthma were recruited, and patients with different levels of severity might tolerate similar levels of symptoms and take just enough treatment to maintain themselves at that level (6, 8, 36).
Treatment guidelines recommend either a stepwise increase in treatment or starting with a high dose and then stepping down once control is achieved. A stepwise increase in treatment was used for all three strata. While the aim of this study was not to compare the stepwise approach to the high-dose approach, in each stratum, it was observed that between 40% and 53% of patients reached totally controlled asthma at the lowest dose of inhaled fluticasone when used in combination with salmeterol. Similarly, no attempt was made to step down treatment once control was achieved, as proposed in treatment guidelines. This aspect of treatment, although widely used, has not been well researched.

A study by Reddel and colleagues (30) has shown that reliever use, airway hyperresponsiveness, and overall asthma control (though less stringently defined than in GOAL) continued to improve during inhaled corticosteroid down titration. The results from our study suggest that additional benefit may be derived from sustaining regular treatment for up to 6 to 9 months (the duration of the trial) without stepping down; however, the absence of control arms employing step-down routines in GOAL prevents conclusions about whether this is an effect of prolonged treatment or of sustained dose. Further studies are required.

As the aim of treatment in this study was total control, it called for step up of treatment even though patients had become “well controlled.” For this reason, a majority ended the study on the highest dose of treatment (68% of patients on salmeterol/fluticasone and 76% of patients on fluticasone; all strata). Because the dose–response relationship for inhaled corticosteroids in asthma is relatively flat, the benefits of increasing the dose relative to risk diminish as the dose is increased. In relationship to benefit, the sustained treatment at higher doses enabled more patients to achieve the goal. However, there was also potential for additional adverse effects, particularly because the treatment was not stepped down once control was achieved. It is therefore significant that the overall frequency and nature of self-reported adverse events were similar to most other trials involving inhaled corticosteroids in asthma and predominantly affected the upper respiratory tract (33, 34, 37). In clinical practice, the decision on whether to aim for total control in patients who have reached a lesser level of control when this involves doubling the dose of controller treatment will need to be made on an individual basis in consultation with the patient.

One strategy for minimizing the risk of adverse effects is to step down treatment when the desired level of control is achieved. Although recommended in guidelines (1, 2), step down has not been extensively studied and is largely based on expert opinion. In this study, treatment was sustained at a constant dose throughout phase II to assess whether control could be maintained, and the study did not attempt to address the matter of step down. Sustained treatment carries the risk of other long-term effects that might take years to become significant. These include adrenocortical suppression and reduced bone mineral density. The doses of inhaled corticosteroids used in this study were those for which registration has been obtained and for which extensive safety data are available. For this reason, examination of these effects was restricted to a comparison of 24-hour urinary cortisol levels (a sensitive indicator of suppression) in a subset of patients. Interpretation of these results needs to consider a number of study design variables, including the corticosteroid dose on study entry and treatment duration at each dose. Consistent with other studies (38, 39) with fluticasone at similar doses, lowering of mean levels of 24-urinary cortisol was evident, but the values remained within or above the normal range in most patients (92%). There was also no difference between treatments, in spite of the larger number of patients in the salmeterol/fluticasone group that did not require the highest dose. Taken together, these results confirm an effect of inhaled corticosteroids on the hypothalamic–pituitary–adrenal axis, but in none was this associated with clinical evidence of adrenal suppression.

The recommendation that total control should be the aim of management for all patients with persistent asthma is based on the fact that, as demonstrated in this study, it is achievable in a considerable proportion of patients (41%; all strata) and that it is associated not only with the greatest improvement in usual asthma end points but also results in a majority of patients achieving health status that approaches complete freedom from the impact of asthma (asthmatic but without asthma). Additionally, asthma exacerbations are reduced to levels that are arguably as low as might be expected. As a treatment strategy, aiming at total control brings asthma management in line with approaches used in other chronic diseases, for example, sustained glycemic control in diabetes or ideal blood pressure in hypertension. This may serve to raise the expectations of patients and physicians and help to address the problem of the relatively poor level of care and of asthma control currently being experienced by patients with asthma worldwide (4–6).

In summary, this study has shown that guideline-defined control of asthma can be achieved in the majority of patients with uncontrolled asthma with combination salmeterol/fluticasone treatment. This approach should be the preferred treatment selection for patients whose asthma is uncontrolled, regardless of their previous inhaled corticosteroid regimen. Salmeterol/fluticasone achieves sustained control of asthma as defined by a composite of relevant clinical goals of treatment in more patients, more rapidly and at a lower dose of inhaled corticosteroids than fluticasone alone. In addition, the approach of aiming for total control and maintaining treatment resulted in the virtual elimination of exacerbations and near-normal quality of life in the majority of patients and brought substantial benefit even to those who failed to achieve this high level of control.

Conflict of Interest Statement: E.D.B. has received honoraria for speaking at scientific meetings and courses financed by AstraZeneca in 2003 and GlaxoSmithKline (GSK) in 2002 and 2003 and has served on Advisory Boards for AstraZeneca, Boehringer Ingelheim and GSK; H.A.B. has received the following payments from GSK ($1,399 in 2004 for speaking at an Advisory Board meeting and $7,000 in 2003 for chairing and lecturing in a Master Class and at a speakers summit, and as per University of California at San Francisco policy, consulting fees are paid to his department; J.B. has been reimbursed by GSK for attending several conferences as a speaker and received a total honorarium of €13,000 for the past 3 years and has been a member of the GSK Advisory Board and received a total honorarium of €13,000 for 2001 and 2002; W.W.B. has received consultancy fees for the past 3 years from the following companies with a total consultancy fee for these 3 years for Bristol-Myers Squibb ($2,000), Dynavax ($3,000), Hoffman La Roche ($2,000), InnoPharm ($3,000 for 1999–2000), Fujisawa ($2,000), and GSK for speaking or other educational activities in the past 3 years from Merck ($7,000 for 2003), GSK ($2,500 for 2003), and Aventis ($2,500 for 2003) and has received industry-sponsored support for research from GSK ($750,000 for 2002 and 2003) and for participation in multicenter trials for Fujisawa ($250,000 for 2002 and 2003), GSK ($500,000 for 2001–2003), Aventis ($200,000 for 2001–2003), Hoffman LaRoche ($120,000 for 2002), Pfizer ($100,000 for 2003), Genetech/Novartis ($100,000 for 2002 and 2003), and Merck ($100,000 for 2003); T.J.H.C. has received more than $10,000 per annum over the past 3 years to cover serving as a consultant to GSK as well as serving on advisory boards and giving lectures and has also participated as a speaker at scientific meetings organized and financed by AstraZeneca and Merck, Sharp, and Dohme; R.A.P. has received money from various pharmaceutical companies for serving as a consultant for Almirall Prodesfarma ($10,000 in 2003), Altana ($10,000 in 2002), AstraZeneca ($10,000 in 2002), Boehringer Ingelheim ($10,000 in 2002, 2003), GSK ($10,000 in 2002, 2003), Janssen-Cilag ($10,000 in 2001), Boehringer Ingelheim ($10,000 in 2003, $10,000 in 2002, $10,000 in 2001), GSK ($10,000 in 2003, $10,000 in 2002, $10,000 in 2001), Schering Plough ($10,000 in 2001); S.E.P. has received €13,000 in 2001 and €12,000 in 2002 for speaking at scientific meetings or courses organized and financed by AstraZeneca and GSK (€8,000 in 2001 and €10,000 in 2002 for speaking at scientific meetings or courses organized and financed by GSK. The Regents of the University of California has received payments from GlaxoSmithKline of $485,000 for research conducted under the terms of a Boushey’s direction between 1999 and 2001 and for course development and testing of two educational materials for research and training of $8,323 in 2002 and $4,500 in 2003 and $2,371 in 2004 and GSK also paid $7,390 to the Regents of the University of California for Homer Boushey’s service on the Scientific Advisory Board for this study. The
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References


Can guideline-defined asthma control be achieved?

The Gaining Optimal Asthma controL study

Eric D Bateman, Homer A Boushey, Jean Bousquet, William W Busse, Tim JH Clark, Romain A Pauwels, Søren E Pedersen on behalf of the GOAL Investigators Group

Online Data Supplement
Methods [Word count 996]

Study design

Phases of the study were: run-in (usual treatment); Phase I (treatment step-up); Phase II (treatment at a constant dose); and open-label phase (maximum treatment phase with salmeterol/fluticasone plus oral corticosteroid). During run-in, patients who did not achieve the criteria for Well-Controlled asthma on at least 2 of the 4 weeks were randomized to one of three strata based on the inhaled corticosteroid dose during the 6 months before screening — Stratum 1: no inhaled corticosteroid; Stratum 2: ≤ 500 µg beclomethasone dipropionate daily or equivalent; or Stratum 3: >500 – ≤1000 µg beclomethasone dipropionate daily or equivalent (Figure E1).

Randomization was done telephonically from a computer-generated allocation schedule balanced per stratum and per country. Baseline characteristics of patients are listed in Table E1.

During Phase I, treatment was stepped up every 12 weeks, salmeterol/fluticasone 50/100, 50/250, 50/500 µg bid or fluticasone 100, 250, 500 µg bid until Totally Controlled asthma was achieved (assessed over the last 8 weeks of each 12-week period) or the highest dose of study drug was reached (salmeterol/fluticasone 50/500 µg bid or fluticasone 500 µg bid).

Initial doses in Strata 1 and 2 were salmeterol/fluticasone 50/100 or fluticasone 100, whereas patients in Stratum 3 started on salmeterol/fluticasone 50/250 or fluticasone 250. After the Week 5–12 assessment, patients who had not achieved Totally Controlled asthma for at least 7 out of 8 consecutive weeks were stepped up to the next dose for 12 weeks, while individuals who
achieved Totally Controlled asthma entered Phase II immediately. All patients entered Phase II either after achieving Totally Controlled asthma or after 12 weeks on the maximum dose of study medication.

In Phase II, patients continued on their final dose of study medication in Phase I until the end of the 1-year double-blind treatment period. Those who had failed to achieve Totally Controlled asthma in Phase I were reassessed during the final 8 weeks of Phase II (Weeks 44–52). Patients who did not achieve Totally Controlled asthma in either Phase I or Phase II entered the 4-week, open-label phase. In this phase, regardless of initial randomization, all patients received a 10-day course of oral prednisolone (0.5 mg/kg, up to 60 mg/day) with salmeterol/fluticasone 50/500 µg bid for 4 weeks.

All salmeterol/fluticasone and fluticasone was administered via identical dry powder inhalers (Diskus®, Accuhaler®, GlaxoSmithKline, Middlesex, UK) to ensure both investigators and patients were blinded to treatment.

Other measures obtained at visits included morning pre-bronchodilator FEV₁ and adverse events, and, at selected sites, completed Asthma Quality of Life Questionnaires (AQLQ) and 24-hour urinary free cortisols.

**Exclusion criteria**

Patients who were assessed as having Well-Controlled asthma on ≥ 3 of the 4 weeks during run-in were not eligible for randomization. Patients were also excluded if any of the following
occurred during run-in: change in regular asthma medication; emergency visits due to asthma; treatment with systemic corticosteroids; respiratory tract infection; more than 3 days of morning PEF < 50% predicted; or non-compliance with the diary record card. The number of patients included in each phase of the study and reasons for withdrawal are listed in Figure E2.

Statistical analysis
The primary objective was to determine the proportion of patients who achieved Well-Controlled asthma with salmeterol/fluticasone compared with fluticasone alone during Phase I. The study was powered to show a 10% difference between treatment groups (significance level 5%, power 80%). To compensate for potentially unassessable patients, sample size was increased from 400 to 480 individuals per treatment group for each stratum. The study was analyzed on an intention-to-treat basis by individual strata. Control was assessed over an eight-week period. To allow for the possibility that some patients might have had missing data, a minimum of 4 weeks of evaluable data were required to make an assessment of control. An evaluable week was one with ≥ 5 days of complete diary record card data. For patients who recorded 7 or 8 evaluable weeks, criteria for Totally Controlled or Well-Controlled asthma were to be satisfied in all, or all but one, week. For patients who recorded 4–6 evaluable weeks, the criteria were to be satisfied in all of their evaluable weeks. If a patient experienced an exacerbation or required emergency treatment or failed the adverse event criteria, this was considered failure of control for the entire 8-week assessment period. All unassessable patients were classified as uncontrolled. Over the 4-week open-label phase, patients were assessed as Totally Controlled or Well Controlled if they met the required criteria on at least 3 out of the 4 weeks. No statistical analysis was performed on these results.
Secondary end points were dose of inhaled corticosteroid and time to achievement of Well-Controlled asthma. The proportion of patients who achieved Totally Controlled asthma (a more stringent definition than Well-Controlled asthma, with a complete absence of the clinical features of asthma) and the dose and time at which it was achieved was also assessed. By definition, if a patient achieved Totally Controlled asthma, they also achieved Well-Controlled asthma. Additional end points included asthma quality of life, exacerbation rates and morning pre-dose FEV₁.

The primary efficacy end point was assessed by use of maximum likelihood logistic regression. Dose of inhaled corticosteroid at which control was achieved was assessed using proportional odds logistic regression; both were adjusted for gender, country, age and baseline pre-bronchodilator FEV₁. Model and interaction tests were performed to confirm model validity. Odds ratios (OR), 95% confidence intervals (CI) and p-values were calculated. The time to achieve the first Well-Controlled Week was analyzed using the log-rank test, stratified by country. FEV₁, AQLQ and cortisol were analyzed using analysis of covariance adjusted as for the primary end point with baseline covariate matched to the end point of interest. Cortisol data was log transformed prior to analysis. Exacerbation rates were analyzed over the 1-year study period using Poisson regression. Again, this was adjusted as for the primary end point; this was not performed between Phases I and II, for single treatments or between the two treatment groups. Analyses were performed using SAS software (Version 8).
Reference

**Figure legends**

**Figure E1.** Study design for (A) Strata 1 and 2 and (B) Stratum 3.

*Definition of abbreviations:* FP = fluticasone propionate; SFC = salmeterol/fluticasone combination.

**Figure E2.** Patient flow and the intention-to-treat population for the two treatment arms: salmeterol/fluticasone combination (SFC) and fluticasone propionate (FP).

**Figure E3.** Comparison between salmeterol/fluticasone propionate (SFC) and fluticasone propionate (FP) of the mean rate of exacerbations per patient per year by phase of the study in (A) Stratum 1, (B) Stratum 2, and (C) Stratum 3. No statistical testing was performed. Exacerbations defined as episodes requiring oral steroids and/or hospitalization or emergency visit.

**Figure E4.** Summary of urinary cortisol/creatinine ratios assessed in a subset of patients over Weeks 1–52 (geometric mean with 95% confidence intervals [CI]). Statistical analysis (SFC vs FP) was performed at Week 12 (p=0.575; 95% CI 0.84, 1.10) and Week 52 (p=0.318; 95% CI 0.92, 1.31).
Table E1. Baseline characteristics of intention-to-treat population for each stratum

<table>
<thead>
<tr>
<th>Strata</th>
<th>Stratum 1</th>
<th>Stratum 2</th>
<th>Stratum 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Inhaled corticosteroid use in previous 6 months)</td>
<td>(no inhaled corticosteroid)</td>
<td>(≤ 500 µg BDP or equivalent daily)</td>
<td>(&gt; 500 – ≤ 1000 µg BDP or equivalent daily)</td>
</tr>
<tr>
<td>n</td>
<td>SFC 548 FP 550</td>
<td>SFC 585 FP 578</td>
<td>SFC 576 FP 579</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>36.1 (15.6)</td>
<td>40.4 (16.4)</td>
<td>44.1 (15.9)</td>
</tr>
<tr>
<td>Range</td>
<td>12–80</td>
<td>12–78</td>
<td>12–83</td>
</tr>
<tr>
<td>Sex , % female</td>
<td>57</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>Atopy, %</td>
<td>57</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>Mean pre-bronchodilator FEV₁, L (SD)</td>
<td>2.5 (0.87)</td>
<td>2.4 (0.83)</td>
<td>2.3 (0.82)</td>
</tr>
<tr>
<td>% predicted, (SD)</td>
<td>77 (18.7)</td>
<td>78 (18.2)</td>
<td>75 (18.6)</td>
</tr>
<tr>
<td>Mean morning PEF, L/min (SD)</td>
<td>344 (91.2)</td>
<td>349 (98.4)</td>
<td>345 (98.7)</td>
</tr>
<tr>
<td>% predicted, (SD)</td>
<td>76 (14.6)</td>
<td>78 (16.1)</td>
<td>78 (16.0)</td>
</tr>
<tr>
<td>Reversibility*</td>
<td>median %, (interquartile range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rescue medication</td>
<td>23 (15.8)</td>
<td>22 (12.2)</td>
<td>23 (12.8)</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>mean occasions/day, (SD)</strong></td>
<td>1.9 (1.7)</td>
<td>1.7 (1.4)</td>
<td>1.7 (1.5)</td>
</tr>
<tr>
<td><strong>Mean daily symptom score, † (SD)</strong></td>
<td>1.8 (0.8)</td>
<td>1.7 (0.9)</td>
<td>1.8 (0.9)</td>
</tr>
<tr>
<td><strong>Night-time awakenings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mean occasions/night, (SD)</strong></td>
<td>0.6 (0.7)</td>
<td>0.6 (0.6)</td>
<td>0.4 (0.6)</td>
</tr>
<tr>
<td><strong>Exacerbation rate, ‡ (SD)</strong></td>
<td>0.4 (1.4)</td>
<td>0.3 (0.8)</td>
<td>0.6 (1.3)</td>
</tr>
</tbody>
</table>

**Duration of asthma (% patients):**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
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</thead>
<tbody>
<tr>
<td>6 months – &lt; 1 year</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>≥ 1 – &lt; 10 years</td>
<td>39</td>
<td>43</td>
<td>41</td>
<td>39</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>54</td>
<td>50</td>
<td>58</td>
<td>60</td>
<td>64</td>
<td>64</td>
</tr>
</tbody>
</table>

**Smoking status (% patients):**

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>current smoker</td>
<td>9</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>former smoker</td>
<td>13</td>
<td>14</td>
<td>20</td>
<td>18</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: BDP = beclomethasone dipropionate; FEV₁ = forced expiratory volume in one second; FP = fluticasone propionate; PEF = peak expiratory flow; SD = standard deviation; SFC = salmeterol/fluticasone combination.

*Reversibility for those patients in whom it was measured during run-in; †Symptom score: 0 (none) – 5 (severe); ‡Documented episodes of hospitalization and/or course of oral steroids or antibiotics for the treatment of an exacerbation of asthma during the past 12 months.*
Figure E1

(A) Phase I

- Phase II

4-week assessment period

8-week assessment period

SFC 50/500 μg bid or FP 500 μg bid

SFC 50/250 μg bid or FP 250 μg bid

SFC 50/100 μg bid or FP 100 μg bid

Oral prednisolone* + SFC 50/500 μg bid

Week -4 0 4 12 24 36 52 56

(B)

SFC 50/500 μg bid or FP 500 μg bid

SFC 50/250 μg bid or FP 250 μg bid

Oral prednisolone* + SFC 50/500 μg bid

Week -4 0 4 12 24 36 52 56

*0.5 mg/kg up to 60 mg/day for 10 days
Figure E2

Screened
n=5068

Screen failures* (1652)
Did not fulfil entry criteria (797)
Well-Controlled for ≥3 weeks (412)
Lost to follow-up (159)
Consent withdrawn (89)
Adverse events (67)
Asthma exacerbation (57)
Other (54)
Protocol violation (47)
*Includes 5 patients randomised but not treated

ITT
FP=1707
SFC=1709

Withdrawals during Phase I FP/SFC (215/162)
Adverse events (28/26)
Consent withdrawn (47/34)
Lost to follow-up (39/35)
Protocol violation (39/23)
Asthma exacerbation (6/4)
Well-Controlled for ≤3 weeks (3/2)
Did not fulfil entry criteria (6/6)
Other (37/20)
UnEvaluable diary card data (10/9)

Completed Phase I
FP=1492
SFC=1547

Withdrawals during Phase II FP/SFC (74/76)
Adverse events (8/8)
Consent withdrawn (13/17)
Lost to follow-up (19/18)
Protocol violation (6/6)
Asthma exacerbation (1/2)
Other (22/21)
UnEvaluable diary card data (2/3)

Completed Phase II
FP=1418
SFC=1472

Withdrawals upon completion of Phase II FP/SFC (81/76)
Other (68/62)
Protocol violation (7/5)
Consent withdrawn (2/4)
Adverse events (1/2)
Lost to follow-up (2/1)
UnEvaluable diary card data (1/2)

Study completers not entered into open-label phase
FP=517
SFC=713

Withdrawals during the open-label phase
FP/SFC (11/11)
Lost to follow-up (3/5)
Other (3/2)
Adverse events (2/2)
Protocol violation (3/3)
Consent withdrawn (0/2)

Completed open-label phase
FP=809
SFC=672
Figure E3

(A)

(B)

(C)
For patients with both baseline and Week 52 data, geometric mean at these timepoints was 3.74 v 3.04 for SFC (n=102) and 3.92 v 2.85 for FP (n=92). For patients on the highest dose of corticosteroid (500 μg bid), this was 3.76 v 2.90 for SFC (n=82) and 3.82 v 2.73 for FP (n=84).