



## Department of Vermont Health Access

### Therapeutic Class Review

### Inhaled Corticosteroids

#### Overview/Summary

The inhaled corticosteroids (ICS) are Food and Drug Administration (FDA) approved for the maintenance treatment of asthma as prophylactic therapy. Some of the agents in this class also have the additional indication for use in asthma patients who require systemic corticosteroid therapy and the addition of an ICS could reduce or eliminate the need for the systemic corticosteroid. With the exception of the budesonide suspension for nebulization, none of the ICS agents are available as generic entities.<sup>1-10</sup>

Though not FDA-approved, these agents have been used in the treatment of chronic obstructive pulmonary disease (COPD). Beclomethasone and flunisolide have both been used to treat newborn bronchopulmonary dysplasia. Beclomethasone has additionally been used for the treatment of fentanyl induced cough, cystic fibrosis, and occupational asthma. Budesonide has been used to treat croup, cystic fibrosis, pulmonary sarcoidosis, and chronic respiratory disease in the perinatal period.<sup>1-11</sup>

These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils) and mediators (e.g., histamine, cytokines) which are involved in the asthmatic response. ICSs exert their anti-inflammatory effects by binding to the glucocorticoid receptors with a subsequent activation of genes involved in the anti-inflammatory processes as well as an inhibition of pro-inflammatory genes involved in the asthmatic response. Inflammation is also a component of COPD pathogenesis.<sup>5,12</sup>

Although ICS agents exert their effects through an identical mechanism of action, they differ in their characteristics such as potency, dosing schedules, and dosage form availability. Clinical trials comparing ICS of differing potencies have shown that those of higher potencies do not demonstrate greater clinical efficacy than those of lower potencies when administered at equipotent doses.<sup>13,14</sup> Clinical trials have additionally failed to demonstrate any major differences in clinical efficacy between any of the available ICS agents.<sup>14-60</sup>

Current treatment guidelines published by the National, Heart, Lung, Blood Institute (NHLBI) indicate that the ICS agents are the most potent and consistently effective long-term controller medications for asthma patients of all ages. As such, these agents are recommended as first-line therapy for long-term control of persistent asthma symptoms in all age groups. The guidelines further state that although ICS agents do reduce both impairment and risk of asthma exacerbations they do not appear to alter the progression or underlying severity of the disease. Of note, the NHLBI guidelines do not specifically recommend one ICS agent as possessing greater clinical efficacy or as a preferred agent over the other medications within the therapeutic class.<sup>61</sup>

The NHLBI guidelines also discuss the issue of growth velocity suppression in children treated with ICS agents. The guidelines indicate that the benefits of treatment with an ICS outweigh the concerns for growth, and that untreated or poorly controlled asthma can also cause a decrease in a child's growth. The adverse effect on growth rate associated with this therapeutic class does appear to be dose dependant; however it is not considered predictable. Furthermore, the effect on growth velocity appears to occur mainly in the first several months of treatment and is generally small and not progressive. However because of the possibility of growth suppression, ICS doses in children should be titrated to as low a dose as need to maintain good asthma control and children should be monitored for potential growth rate changes.<sup>61</sup> Clinical evidence regarding the effects of ICSs on growth velocity suggests that although there does appear to be a decrease in the growth velocity of children being treated with long-term ICS agents, these patients will ultimately reach their normal predicted height.<sup>15</sup>

The Global Initiative for Asthma (GINA) guidelines recommend that ICSs are the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. Additionally, the GINA guidelines indicate that although ICS agents differ in potency and bioavailability there have been few studies that have been able to demonstrate this difference as being of any clinical significance. The GINA guidelines also do not recommend a preferred ICS agent.<sup>62</sup>

The Global Initiative for Chronic Obstructive Lung Disease guidelines on COPD recommend that if an initial as needed short-acting bronchodilator is not effective for symptom relief, then the use of long-acting bronchodilator should be initiated, as these agents are central to COPD symptom management. ICSs are recommended as add-on therapy to whichever agent was selected for initial COPD maintenance therapy, in patients with severe stage-III COPD, who are patients with a forced expiratory volume in 1 second (FEV<sub>1</sub>) ≤50% predicted and repeated exacerbations. ICSs do not modify the long-term decline of FEV<sub>1</sub> but have been shown to reduce the frequency of exacerbations, causing an overall improvement in health status.<sup>63</sup>

The National Institute for Clinical Excellence COPD guidelines also recommend the use of ICSs as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV<sub>1</sub> ≤50% predicted and repeated exacerbations.<sup>64</sup>

As of as a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing, and sale of all meter dose inhalers containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008.<sup>65</sup> Currently the only CFC-propellant ICS agent available is flunisolide (Aerobid<sup>®</sup>, Aerobid-M<sup>®</sup>). Forest Laboratories has discontinued the manufacture and distribution of Aerobid<sup>®</sup> and Aerobid-M<sup>®</sup> in anticipation of an extended FDA deadline of June 30, 2011. Until that time, pharmacies still carrying Aerobid<sup>®</sup> or Aerobid-M<sup>®</sup> may dispense the product. An hydrofluoroalkanes formulation of flunisolide, Aerospan<sup>®</sup>, is under review by the FDA and an anticipated date of availability is unknown at this time. Triamcinolone (Azmacort<sup>®</sup>) was phased out in 2010 and no replacement product has been introduced at the time of this review.

## Medications

**Table 1. Medications Included Within Class Review**

Generic Name (Trade name)	Medication Class	Generic Availability
Beclomethasone (QVAR <sup>®</sup> )	Inhaled corticosteroid	-
Budesonide (Pulmicort Flexhaler <sup>®</sup> , Pulmicort Respules <sup>®*</sup> )	Inhaled corticosteroid	✓
Ciclesonide (Alvesco <sup>®</sup> )	Inhaled corticosteroid	-
Flunisolide (Aerobid <sup>®†</sup> , Aerobid-M <sup>®†</sup> , Aerospan <sup>®‡</sup> )	Inhaled corticosteroid	-
Fluticasone propionate (Flovent Diskus <sup>®</sup> , Flovent HFA <sup>®</sup> )	Inhaled corticosteroid	-
Mometasone (Asmanex Twisthaler <sup>®</sup> )	Inhaled corticosteroid	-

HFA=hydrofluoroalkane.

\*Generic available in at least one dosage form or strength.

†Aerobid<sup>®</sup> and Aerobid-M<sup>®</sup> have been discontinued by Forest Laboratories but may be dispensed until June 30, 2011.

‡Aerospan<sup>®</sup> is a chlorofluorocarbon-free flunisolide product which is not yet available. No release date has been established.

**Indications****Table 2. Food and Drug Administration Approved Indications<sup>1-10</sup>**

Generic Name	Maintenance Treatment of Asthma as Prophylactic Therapy	Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy, Where the Addition of an Inhaled Corticosteroid May Reduce or Eliminate the Need for the Systemic Corticosteroid
Beclomethasone	✓	✓
Budesonide	✓ (Pulmicort Flexhaler <sup>®</sup> , Pulmicort Respules <sup>®</sup> )	✓ (Pulmicort Flexhaler <sup>®</sup> )
Ciclesonide	✓	
Flunisolide	✓	✓
Fluticasone propionate	✓	✓
Mometasone	✓	

**Pharmacokinetics****Table 3. Pharmacokinetics<sup>1-11</sup>**

Generic Name	Onset (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Beclomethasone	0.5	<10	Yes	2.8
Budesonide	1 to 2	60	No	2 to 3
Ciclesonide	Not reported	≤20	Yes	6 to 7
Flunisolide	0.90 to 0.17	<1	Yes	1.8
Fluticasone propionate	Variable	<5	No	7.8*
Mometasone	1.0 to 2.5	8	No	5

\*Following intravenous administration.

**Clinical Trials**

Numerous placebo controlled trials have demonstrated the efficacy of inhaled corticosteroid agents in the treatment of asthma, and these agents are considered the most effective agents in the long-term management of the disease. Head-to-head studies examining these agents however have been inconclusive in showing efficacy “superiority” of one specific agent over any other, regardless of the potency or dosage form of the inhaled corticosteroid agent used.<sup>17-60,66-73</sup>

**Table 4. Clinical Trials**

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<b>Asthma</b>				
<p>Agertoft et al<sup>17</sup></p> <p>Budesonide vs control group</p> <p>Patients were enrolled in a 1 to 2 year run-in period where their asthma medication was adjusted according to Danish guidelines.</p> <p>Those patients considered acceptably controlled without continuous ICS use, were then asked to change treatment to budesonide.</p> <p>The mean duration of budesonide treatment and mean daily budesonide dose at the time of adult height attainment was 9.2 years and 412 µg respectively.</p>	<p>PRO</p> <p>Children with asthma</p>	<p>N=332</p> <p>10 years</p>	<p>Primary: Measured adult height in relation to the target adult height</p> <p>Secondary: Difference between measured height and target adult height in relation to (mean cumulative budesonide dose, duration of treatment, patient gender, age at beginning of budesonide treatment, age at which adult height was obtained, duration of asthma before budesonide start), growth rate of budesonide treatment compared to the run-in period</p>	<p>Primary: The measured and target adult height in the two groups was (173.2, 172.9 cm) and (173.9, 174.1 cm) for the budesonide and control group respectively. The mean differences between the measured and target adult heights were 0.3 cm (95% CI, -0.6 to 1.2) for the budesonide group, and -0.2 cm (95% CI, -2.4 to 2.1) for the control group.</p> <p>Secondary: Twenty children in the budesonide group did not achieve their adult height. Their mean cumulative dose of 1.25 g was not significantly different from that of children who had attained their adult height, which was 1.35 g (<math>P=0.72</math>).</p> <p>There was no significant correlation between the duration of treatment and the differences between the measured and target adult heights (<math>P=0.16</math>).</p> <p>The difference between measured and target adult heights was not significantly associated with the patient's gender (<math>P=0.30</math>), age at the beginning of budesonide treatment (<math>P=0.13</math>), age at which adult height was attained (<math>P=0.82</math>), or duration of asthma before the start of budesonide treatment (<math>P=0.37</math>).</p> <p>Budesonide was associated with a significant change in growth rate during the first years of treatment as compared with the run-in period. The mean growth rate was 6.1 cm/year (95% CI, 5.7 to 6.5) during the run-in period, 5.1 cm/year (95% CI, 4.7 to 5.5; <math>P&lt;0.001</math>) during the first year of treatment, 5.5 cm/year (95% CI, 5.1 to 5.9; <math>P=0.02</math>) during the second year of treatment, and 5.9 cm/year (95% CI, 5.5 to 6.3; <math>P=0.53</math>) during the third year of treatment. Changes in growth rate during this period were not correlated with the differences between measured and target adult heights (<math>P=0.44</math>). The initial growth retardation was significantly correlated with age, with a more pronounced reduction in younger children (<math>P=0.04</math>). Children with a low standard deviation score for height before budesonide treatment had a smaller adult height than expected (<math>P&lt;0.001</math>).</p>

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<p>Baker et al<sup>18</sup></p> <p>Budesonide 0.25 mg QAM and placebo QPM via nebulizer</p> <p>vs</p> <p>Budesonide 0.25 mg BID via nebulizer</p> <p>vs</p> <p>budesonide 0.5 mg BID via nebulizer</p> <p>vs</p> <p>budesonide 1 mg QAM and placebo QPM via nebulizer</p> <p>vs</p> <p>placebo BID</p>	<p>DB, MC, PC, PG, RCT</p> <p>Children, 6 months to 8 years of age, with a diagnosis of asthma as defined by accepted criteria</p>	<p>N=480</p> <p>12 weeks</p>	<p>Primary: Changes in asthma symptom improvement score from baseline, PEF, and improvements in FEV<sub>1</sub></p> <p>Secondary: Not reported</p>	<p>Primary: Symptom scores within two weeks after starting treatment showed separation between active treatment groups and placebo. When symptom scores for all active treatment groups were combined, a statistically significant difference between active treatment compared to placebo was seen as early as day two for nighttime asthma symptoms, and day five for daytime asthma symptoms (<math>P&lt;0.05</math>).</p> <p>There were statistically significant improvements in morning PEF in the 0.25 mg BID (10.9 L/minute), 0.5 mg BID (24.8 L/minute), and 1 mg QAM (17.1 L/minute) treatment groups compared to placebo (<math>P&lt;0.030</math>) and in evening PEF for each active treatment group (16.8 L/minute for 0.25 mg QAM; <math>P&lt;0.05</math>, 19.2 L/minute for 0.25 mg BID, <math>P&lt;0.05</math>; and 21.0 L/minute for 0.5 mg BID; <math>P&lt;0.010</math>) except 1 mg QAM (14.1 L/minute; <math>P</math> value not reported).</p> <p>All treatment groups showed numerical improvement in FEV<sub>1</sub> but the only improvement that was statistically significant for FEV<sub>1</sub> compared to placebo was for the 0.5 mg BID group (0.04 vs 0.17 L/minute; <math>P=0.031</math>).</p> <p>Secondary: Not reported</p>
<p>Rowe et al<sup>19</sup></p> <p>Budesonide 1,600 µg/day via DPI</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients 16 to 60 years of age presenting to the emergency department with acute asthma who were discharged with a nontapering course of oral</p>	<p>N=1,006</p> <p>21 days</p>	<p>Primary: Rates of relapse</p> <p>Secondary: Quality of life, rescue inhaler use, changes in pulmonary function, symptoms, global assessment, adverse effects, and compliance</p>	<p>Primary: The budesonide group experienced fewer relapses (12 patients [12.8%]; 95% CI, 7 to 21) than the placebo group (23 patients [24.5%]; 95% CI, 16 to 34) by 21 days (<math>P=0.049</math>). This represents a 48% relapse reduction and suggests as few as nine patients would require treatment with budesonide to prevent one relapse.</p> <p>Secondary: Quality of life scores were higher in the budesonide group than the placebo group (<math>P=0.001</math>).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	prednisone (50 mg/day) for 7 days			<p>The budesonide group was using fewer mean albuterol inhalations in 24 hours compared to the placebo group (2.4 vs 4.2; <math>P=0.01</math>) at 21 days. Mean and percent predicted peak flow and spirometry findings revealed no differences between the groups.</p> <p>At the conclusion of the study, the budesonide group had fewer symptoms of cough (<math>P=0.004</math>), breathlessness (<math>P=0.001</math>), wheezing (<math>P=0.001</math>), and nighttime awakenings (<math>P=0.001</math>) compared to placebo.</p> <p>Patients in the budesonide group assessed their asthma as more improved than those in the placebo group at the 21-day follow-up (6.2 vs 5.2; <math>P=0.001</math>).</p> <p>Adverse effects were greater in the placebo group for both hoarseness and sore throat (<math>P=0.02</math>). The overall incidence of adverse effects associated with ICS use (insomnia, fluid retention, acne) was equal between the two groups.</p> <p>Self-reported compliance with the use of oral prednisone was high within the first week of care in both groups (94% for budesonide vs 96% for placebo; <math>P=0.73</math>). Self-reported compliance with budesonide was similar between the groups at seven (100% for both groups) and 21 days (92% for budesonide vs 93% for placebo; <math>P=0.95</math>).</p>
<p>Sheffer et al<sup>20</sup></p> <p>Budesonide (200 µg in children &lt;11 years; 400 µg for those &gt;11 years) QD for 3 years via DPI</p> <p>vs</p> <p>placebo QD for 3 years in addition to their usual asthma therapy</p>	<p>DB, PC, RCT (first 3 years); OL (following 2 years)</p> <p>Patients 5 to 66 years of age with mild persistent asthma for fewer than 2 years and no previous regular corticosteroid treatment</p>	<p>N=7,241</p> <p>5 years</p>	<p>Primary: Time to the first severe asthma-related event; change in post-bronchodilator FEV<sub>1</sub> percent predicted from baseline to the end of the five-year study period</p> <p>Secondary: Number of asthma-related events during</p>	<p>Primary: Budesonide reduced the risk of a first severe asthma-related event in patients with mild persistent asthma by 44% (HR, 0.56; 95% CI, 0.45 to 0.71; <math>P&lt;0.001</math>).</p> <p>A significant improvement in both prebronchodilator and postbronchodilator FEV<sub>1</sub> percent values was observed after year one and year three of the study for the budesonide treatment group compared with the placebo arm. After one year the differences were 2.24% prebronchodilator and 1.48% postbronchodilator (<math>P&lt;0.0001</math> for both) and after three years was 1.71%, (<math>P&lt;0.0001</math>) and 0.88% (<math>P=0.0005</math>), respectively.</p>

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			<p>the double-blind period; time to first addition of a steroid treatment (systemic or inhaled) during the double-blind period; symptom-free days, data on healthcare utilization, days off work, and lost school days</p>	<p>Secondary: Of the 1,241 serious adverse events reported, 162 in the budesonide group and 276 in the placebo group were related to asthma. Significantly fewer patients in the budesonide group received additional corticosteroids over time compared with the placebo group (31 vs 45%, respectively; <math>P&lt;0.001</math>).</p> <p>An improvement in symptom-free days for both the budesonide and placebo groups from baseline was seen over time. However, patients receiving budesonide had significantly more symptom-free days over the three-year study period (<math>P&lt;0.001</math>).</p>
<p>Tinkelman et al<sup>21</sup></p> <p>Budesonide 100 to 800 µg via DPI depending upon asthma severity</p>	<p>OL for 52 weeks following 2 weeks to 5 months of treatment in one of four DB, PC studies</p> <p>Adults with persistent asthma not receiving corticosteroids (n=249), adults and children previously maintained on ICS (n=356), and adults previously maintained on oral corticosteroids (n=144)</p>	<p>N=1,133</p> <p>52 weeks</p>	<p>Primary: Percentage of predicted FEV<sub>1</sub> and oral corticosteroid use</p> <p>Secondary: Plasma cortisol levels and adverse events</p>	<p>Primary: FEV<sub>1</sub> values continued to improve in all patient populations through week six of OL treatment and were sustained for the remainder of the 52 week study. Patients who had not received prior ICS treatment demonstrated the greatest improvement in FEV<sub>1</sub> (67.1±18.0% to 81.2±14.8%).</p> <p>Of the 144 oral corticosteroid-dependent patients, 64 entered the OL study free of oral corticosteroids, and 58 (91%) of those patient remained free of long-term oral corticosteroid use throughout the course of the study.</p> <p>Secondary: There was no evidence of clinically significant suppression of basal or stimulated cortisol levels as a result of treatment with 100, 200, or 400 µg BID of budesonide.</p> <p>Basal and stimulated cortisol levels increased by 20.7±183.3 nmol/L and 34.8±283.7 nmol/L, respectively, from baseline to the last observation in patients treated with 800 µg BID of budesonide.</p> <p>Thirty-three patients discontinued treatment because of adverse events. Of these patients, the relationship between budesonide therapy and the adverse events was none in 18 patients, unlikely in four patients, possible in eight patients, probably in one patient, and highly probable in two patients. Ninety-two patients (8%) reported serious adverse events, of which the most commonly reported was asthma exacerbation (30</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Study #3031<sup>22</sup></p> <p>Ciclesonide 80 µg BID</p> <p>vs</p> <p>ciclesonide 160 µg QAM</p> <p>vs</p> <p>ciclesonide 80 µg BID for 4 weeks followed by ciclesonide 160 µg QAM for 8 weeks</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 12 years of age and older with a history of persistent asthma for ≥6 months prior to screening and an FEV<sub>1</sub> after 6 hours of SABA withholding of 60 to 85%; therapy was also limited to bronchodilators one month prior to screening</p>	<p>N=691</p> <p>16 weeks</p>	<p>Primary: Change in morning pre-dose FEV<sub>1</sub> from baseline to the average of weeks 12 and 16</p> <p>Secondary: Change from baseline to week 16 in morning PEF, change from baseline to week 16 in albuterol utilization, change in asthma symptom score, adverse events</p>	<p>patients). No substantial or unexpected changes in vital signs were observed.</p> <p>Primary: All three treatment arms showed a statistically significant improvement in FEV<sub>1</sub> scores from baseline to the average of weeks 12 and 16 (change for the 80 µg BID group, 0.24 L; <i>P</i>&lt;0.0001, change for the 160 µg QAM group, 0.12 L; <i>P</i>=0.0021, change for the 80 µg BID then 160 µg QAM group, 0.13 L; <i>P</i>=0.0016).</p> <p>Secondary: All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 16 in morning PEF (change for the 80 µg BID group, 36.16 L/minute; <i>P</i>&lt;0.0001, change for the 160 µg QAM, 23.32 L/minute; <i>P</i>=0.0006, change for the 80 µg BID then 160 µg QAM, 30.71 L/minute; <i>P</i>&lt;0.0001).</p> <p>All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 16 in albuterol utilization (puffs/day) (change for the 80 µg BID group, -0.73; <i>P</i>&lt;0.0001, change for the 160 µg QAM, -0.60; <i>P</i>=0.0002, change for the 80 µg BID then 160 µg QAM, -0.41; <i>P</i>=0.0116).</p> <p>For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for the 80 µg BID group (-0.57; <i>P</i>=0.0002) and the 80 µg BID then 160 µg QAM group (-0.32; <i>P</i>=0.0325).</p> <p>The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (BID, 55.5%; QAM, 52.8%; BID to QAM, 57.8%; placebo, 57.3%). The most common adverse events that occurred in at least 5% of patients for the treatment groups were: aggravated asthma, nasopharyngitis, and headache.</p>
<p>Berger et al<sup>23</sup> (abstract)</p> <p>Ciclesonide 80 µg BID</p>	<p>DB, MC, PC, PG RCT</p> <p>Patients 12 years of age and older</p>	<p>N=691</p> <p>16 weeks</p>	<p>Primary: Change in FEV<sub>1</sub> from baseline to the average of weeks 12 and 16</p>	<p>Primary: FEV<sub>1</sub> improved from baseline to the average of weeks 12 and 16 in all groups (<i>P</i>≤0.0251).</p> <p>The improvement in FEV<sub>1</sub> was greatest in the ciclesonide 80 µg BID group</p>

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vs ciclesonide 160 µg QAM vs ciclesonide 80 µg BID for 4 weeks followed by 160 µg QAM for 12 weeks vs placebo	with a history of persistent asthma for at least 6 months and not using an ICS for at least 30 days prior to study entry		Secondary: Morning PEF, rescue albuterol use, nighttime awakenings, asthma symptom scores, and safety	( $P<0.01$ ).  Secondary: At week 16, all ciclesonide groups significantly improved FEV <sub>1</sub> and morning PEF from baseline ( $P<0.0001$ ) and compared to placebo ( $P\leq 0.015$ ).  All treatments reduced albuterol use and nighttime awakenings and improved asthma symptom scores compared to baseline ( $P\leq 0.05$ ) and these improvements were greater for the ciclesonide 80 µg BID group compared to placebo ( $P<0.01$ ).  The incidence of adverse effects was similar among all groups.
Study #3030 <sup>24</sup> Ciclesonide 80 µg BID vs ciclesonide 160 µg QAM vs placebo	DB, MC, PC, PG, RCT  Patients 12 years of age and older with a history of persistent asthma for $\geq 6$ months prior to screening, a documented use of an ICS or an ICS/LABA for at least 1 month prior to screening, an FEV <sub>1</sub> 60 to 90% (ICS) or 70 to 95% (ICS/LABA) of predicted normal baseline	N=456  12 weeks	Primary: Change in morning pre-dose FEV <sub>1</sub> from baseline to week 12  Secondary: Change from baseline to week 12 in morning PEF, change from baseline to week 12 in albuterol utilization, change in asthma symptom score, and adverse events	Primary: Both treatment arms showed a statistically significant improvement in FEV <sub>1</sub> scores from baseline to week 12 (change for the 80 µg BID group, 0.19 L; $P<0.0001$ , change for the 160 µg QAM, 0.14 L; $P=0.0006$ ).  Secondary: Only the 80 µg BID treatment arm showed a statistically significant improvement compared to placebo in change from baseline to week 12 in morning PEF (change for the 80 µg BID group, 8.39 L/minute; $P=0.0349$ , change for the 160 µg QAM group, 7.05 L/minute; $P=0.0769$ ).  Both treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day) (change for the 80 µg BID group, -0.64; $P<0.0001$ , change for the 160 µg QAM group, -0.60; $P=0.0002$ ).  For the total asthma symptom score (zero to five scale) the treatment difference was statistically significant for the 80 µg BID group (-0.37; $P=0.0011$ ) and the 160 µg QAM group (-0.38; $P=0.0010$ ).  The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (BID, 52%; QAM, 57.9%; placebo, 55.3%). The most common adverse events that occurred in at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Meltzer et al<sup>25</sup> (abstract)</p> <p>Ciclesonide 80 µg BID vs ciclesonide 160 µg QD vs placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 12 years of age and older with stable mild to moderate persistent asthma being treated with an ICS or ICS/LABA</p>	<p>N=446</p> <p>12 weeks</p>	<p>Primary: Change in FEV<sub>1</sub></p> <p>Secondary: Morning PEF, rescue albuterol use, total asthma symptom score, nighttime awakenings, and safety</p>	<p>least 5% of patients for the treatment groups were: nasopharyngitis, upper respiratory infection, and pharyngolaryngeal pain.</p> <p>Primary: FEV<sub>1</sub> improved from baseline in the ciclesonide 80 µg BID group (<math>P=0.0232</math>) and was maintained in the 160 µg QD group (<math>P=0.6217</math>). FEV<sub>1</sub> declined from baseline in the placebo group (<math>P&lt;0.0001</math>).</p> <p>The difference between the ciclesonide groups and placebo was significant (<math>P&lt;0.001</math>).</p> <p>Secondary: At week 12, morning PEF maintained baseline values in the ciclesonide 80 µg BID group (<math>P=0.1272</math>), and decreased in the ciclesonide 160 µg QD and placebo groups (<math>P=0.0490</math> and <math>P&lt;0.0001</math> respectively). The difference between the ciclesonide 80 µg BID and placebo groups was significant (<math>P=0.035</math>).</p> <p>Baseline albuterol use, total daily asthma score, and nighttime awakenings were maintained after ciclesonide treatments but increased after placebo (<math>P\leq 0.002</math>). The difference between the ciclesonide 80 µg BID and placebo groups was significant (<math>P&lt;0.02</math>).</p> <p>The incidence of adverse events was similar among all groups.</p>
<p>Bateman et al<sup>26</sup></p> <p>Ciclesonide 320 µg BID vs ciclesonide 640 µg BID vs placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 12 years of age and older with a history of persistent asthma for <math>\geq 1</math> year prior to screening, were corticosteroid dependant with severe asthma and use of oral</p>	<p>N=141</p> <p>12 weeks</p>	<p>Primary: Percent change of oral prednisone dose from baseline to week 12 compared to placebo</p> <p>Secondary: Percentage of patients who were able to completely discontinue prednisone use, change from baseline to week 12 in morning pre-dose</p>	<p>Primary: The percentage reduction in oral prednisone dose was statistically significant in both treatment arms (change for the 320 µg BID group, -47.39; <math>P=0.0001</math>, change for the 640 µg BID group, -62.54; <math>P=0.0001</math>, change for the placebo group, 4.21).</p> <p>Secondary: The percentage of patients who were able to eliminate their prednisone usage was statistically significant in both treatment groups when compared to placebo (in the 320 µg BID group the percentage was 29.8; <math>P=0.0386</math>, in the 640 µg BID group the percentage was 31.3; <math>P=0.0233</math>, in the placebo group the percentage was 11.1).</p>

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	<p>prednisone at least every other day for 5 to 6 months prior to screening, a history of ICS during the 6 months prior to screening, use of a <math>\beta_2</math>-agonist for asthma control the 2 weeks prior to screening, an FEV<sub>1</sub> between 40 to 80% of predicted normal following a 6 hour <math>\beta_2</math>-agonist treatment withholding period</p>		<p>FEV<sub>1</sub>, change from baseline to week 12 in morning PEF, change from baseline in albuterol utilization, change in asthma symptom score, assessment of HPA-axis suppression, and adverse events</p>	<p>Both treatment arms showed a statistically significant improvement in FEV<sub>1</sub> scores when compared to placebo from baseline to week 12 (change for the 320 <math>\mu</math>g BID group, 0.17 L; <math>P=0.0237</math>, change for the 640 <math>\mu</math>g BID group, 0.17 L; <math>P=0.0277</math>).</p> <p>Neither treatment arm showed a statistically significant improvement in PEF scores when compared to placebo from baseline to week 12 (change for the 320 <math>\mu</math>g BID group, 5.02 L/minute; <math>P=0.5803</math>, change for the 640 <math>\mu</math>g BID group, 16.67 L/minute; <math>P=0.0736</math>).</p> <p>Neither treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day) (change for the 320 <math>\mu</math>g BID group, -0.39; <math>P=0.5854</math>, change for the 640 <math>\mu</math>g BID group, -0.40; <math>P=0.5806</math>).</p> <p>For total asthma symptom score (zero to five scale) the treatment difference was not statistically significant for either treatment group (change for the 320 <math>\mu</math>g BID group, 0.33; <math>P=0.2669</math>, change for the 640 <math>\mu</math>g BID group, -0.07; <math>P=0.8197</math>).</p> <p>At baseline the percentage of patients with suppressed HPA-axis was 66.0, 60.4, and 62.2% and at week 12 it was 46.8, 43.8, and 53.3% in the 320 <math>\mu</math>g BID group, 640 <math>\mu</math>g BID, and placebo groups respectively.</p> <p>The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (320 <math>\mu</math>g BID, 85.1%; 640 <math>\mu</math>g BID, 79.6%; placebo, 88.9%). The most common adverse event that occurred in at least 5% of patients for the treatment groups were: aggravated asthma, upper respiratory infection, headache, sinusitis, and nasopharyngitis.</p>
<p>Study #321<sup>27</sup> Ciclesonide 80 <math>\mu</math>g QAM vs</p>	<p>DB, MC, PC, RCT Patients 12 years of age and older with mild to moderate</p>	<p>N=526 12 weeks</p>	<p>Primary: Change from baseline to week 12 in morning pre-dose FEV<sub>1</sub> compared to placebo</p>	<p>Primary: Two of the three treatment arms showed a statistically significant improvement vs placebo in FEV<sub>1</sub> scores (change for the 80 <math>\mu</math>g group, 0.12 L; <math>P=0.0123</math>, change for the 160 <math>\mu</math>g group, 0.07 L; <math>P=0.1645</math>, change for the 320 <math>\mu</math>g group, 0.15 L; <math>P=0.0014</math>).</p>

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ciclesonide 160 µg QAM vs ciclesonide 320 µg QAM vs placebo	persistent asthma for 6 months prior, were nonsmokers for at least 1 year, and had an FEV <sub>1</sub> of 60 to 85% predicted normal with a reversibility of FEV <sub>1</sub> by ≥12% after 2 albuterol inhalations		Secondary: Change from baseline to week 12 in morning PEF, change from baseline to week 12 in albuterol utilization, change in asthma symptom score, change in AQLQ score, and adverse events	Secondary: All treatment arms showed a statistically significant improvement vs placebo in change from baseline to week 12 in morning PEF (change for the 80 µg group, 15.58 L/minute; <i>P</i> =0.0032, change for the 160 µg group, 18.93 L/minute; <i>P</i> =0.0004, change for the 320 µg group, 24.53 L/minute; <i>P</i> =0.0001).  All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day) (change for the 80 µg group, -1.52; <i>P</i> =0.0001, change for the 160 µg group, -1.60; <i>P</i> =0.0001, change for the 320 µg group, -1.88; <i>P</i> =0.0001).  For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for all three groups (change for the 80 µg group, -0.38; <i>P</i> =0.0146, change for the 160 µg group, -0.55; <i>P</i> =0.0006, change for the 320 µg group, -0.68; <i>P</i> =0.0001).  The overall score and two of the four domains in the AQLQ (symptoms and emotional function) were statistically significantly improved in all three treatment groups ( <i>P</i> value not reported).  The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (80 µg, 57.1%; 160 µg, 50.8%; 320 µg, 50.4%; placebo, 53.7%). The most common adverse event that occurred in at least 5% of patients for the treatment groups was nasopharyngitis and upper respiratory tract infection.
Study #322 <sup>28</sup> Ciclesonide 80 µg QAM vs ciclesonide 160 µg QAM vs	DB, MC, PC, RCT  Patients 12 years of age and older with mild to moderate persistent asthma for 6 months prior, were nonsmokers	N=489  12 weeks	Primary: Change from baseline to week 12 in morning pre-dose FEV <sub>1</sub> compared to placebo  Secondary: Change from baseline to week 12 in morning	Primary: All three treatment arms showed a statistically significant improvement vs placebo in FEV <sub>1</sub> scores from baseline to the week 12 (change for the 80 µg group, 0.12 L; <i>P</i> =0.0224, change for the 160 µg group, 0.19 L; <i>P</i> =0.0003, change for the 320 µg group, 0.12 L; <i>P</i> =0.0173).  Secondary: Two of the three treatment arms showed a statistically significant improvement vs placebo in change from baseline to week 12 in morning

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<p>ciclesonide 320 µg QAM</p> <p>vs</p> <p>placebo</p>	<p>for at least 1 year, and had an FEV<sub>1</sub> of 60 to 85% predicted normal with a reversibility of FEV<sub>1</sub> by ≥12% after 2 albuterol inhalations</p>		<p>PEF, change from baseline to week 12 in albuterol utilization, change in asthma symptom score, change in AQLQ score, and adverse events</p>	<p>PEF (change for the 80 µg group, 9.27 L/minute; <i>P</i>=0.0871, change for the 160 µg group, 26.8 L/minute; <i>P</i>=0.0001, change for the 320 µg group, 12.89 L/minute; <i>P</i>=0.0171).</p> <p>All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day) (change for the 80 µg group, -1.03; <i>P</i>=0.0002, change for the 160 µg group, -1.24; <i>P</i>=0.0001, change for the 320 µg group, -1.01; <i>P</i>=0.0002).</p> <p>For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for two of the three treatment groups (change for the 80 µg group, -0.46; <i>P</i>=0.0060, change for the 160 µg group, -0.52; <i>P</i>=0.0020, change for the 320 µg group, -0.25; <i>P</i>=0.1346).</p> <p>The overall score and three of the four domains in the AQLQ (symptoms, activity, limitation and emotional function) were statistically significantly improved in all three treatment groups (<i>P</i> value not reported).</p> <p>The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (80 µg, 62.1%; 160 µg, 65.9%; 320 µg, 65.3%; placebo, 66.9%). The most common adverse event that occurred in at least 5% of patients for the treatment groups was nasopharyngitis, headache and upper respiratory tract infection.</p>
<p>Busse et al<sup>29</sup></p> <p>Beclomethasone HFA MDI 100 µg/day</p> <p>vs</p> <p>beclomethasone HFA MDI 400 µg/day</p> <p>vs</p>	<p>DB, MC, PG, RCT</p> <p>Asthmatic subjects who had deteriorated in their asthma control after discontinuation of ICS</p>	<p>N=323</p> <p>6 weeks</p>	<p>Primary: Change from baseline in FEV<sub>1</sub> percent predicted at week six</p> <p>Secondary: Percent change from baseline in FEF<sub>25 to 75%</sub>, FVC, morning and evening PEF, asthma symptom scores, nighttime awakenings,</p>	<p>Primary: For each treatment group, FEV<sub>1</sub> percent predicted increased over the first four weeks of treatment and tended to reach a plateau by week six.</p> <p>Change from baseline at week six in FEV<sub>1</sub> percent predicted was greater with 800 µg/day HFA (-32.7%; <i>P</i>=0.049) than 400 µg/day HFA (-25.1%) and marginally, but not significantly greater (<i>P</i>=0.09) with 800 µg/day CFC (-31.3%) than 400 µg/day CFC (-22.6%).</p> <p>Secondary: ANOVA showed significant dose effects across both products for FEF<sub>25 to 75%</sub>, FVC, and morning PEF. Evening PEF, asthma symptom scores,</p>

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beclomethasone HFA MDI 800 µg/day  vs  beclomethasone CFC MDI 100 µg/day  vs  beclomethasone CFC MDI 400 µg/day  vs  beclomethasone CFC MDI 800 µg/day			and daily albuterol use	nighttime sleep disturbances, and daily albuterol use were similar in all treatment groups.
Brenner et al <sup>30</sup>  High-dose inhaled flunisolide  vs  placebo  At discharge, all patients were given prednisone 40 mg/day for 5 days and inhaled β <sub>2</sub> -agonists as needed.	PC, RCT  Patients 18 to 50 years of age with a diagnosis of asthma presenting to the emergency department with an acute asthma exacerbation	N=104  24 days	Primary: PEFR  Secondary: Overall symptoms and albuterol use	Primary: PEFR was similar between the two groups throughout the trial ( <i>P</i> =0.36 on day 24). There was a mean difference of four units, favoring flunisolide, between the groups.  Secondary: Both symptoms and albuterol use were similar in both groups for the duration of the trial. Seventy five percent of patients in the flunisolide group reported symptom improvement vs 70% in the placebo group (95% CI, -17 to 27).
Lee-Wong et al <sup>31</sup>  Flunisolide 2,000 µg BID via spacer (ICS Group)	DB, PC, RCT  Patients 18 to 55 years of age admitted to the	N=40  7 days	Primary: PEFR and FEV <sub>1</sub>  Secondary: Change in asthma	Primary: From day one to day seven, mean PEFR increased from 190 to 379 L/minute in the ICS group, and from 207 to 347 L/minute in the prednisone group ( <i>P</i> =0.95).

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vs placebo BID via spacer  Patients were also randomized to receive oral prednisone or placebo.	emergency department for an acute asthma exacerbation		symptom scores	Mean FEV <sub>1</sub> increased from 1.6 to 2.3 L in the ICS group and from 1.4 to 2.1 L in the prednisone group ( <i>P</i> =0.33).  Secondary: Mean symptom scores decreased from 1.4 to 0.7 in the ICS group and from 1.3 to 0.4 in the prednisone group ( <i>P</i> =0.39).
Nelson et al <sup>32</sup>  Fluticasone 500 µg BID  vs  fluticasone 1,000 µg BID  vs  placebo BID	DB, PC, PG, RCT  Male and female patients 12 years of age or older with chronic asthma diagnosed according to the American Thoracic Society criteria and receiving oral corticosteroid treatment over the preceding 6 months	N=111  16 weeks	Primary: Percentage of patients with a change in maintenance prednisone dose, and mean change from baseline in maintenance dose of prednisone  Secondary: Changes in FEV <sub>1</sub> , patient-measured morning and evening PEF, patient-rated asthma symptoms, and number of nighttime awakenings requiring albuterol	Primary: At study end point, oral prednisone use was eliminated by 75 and 89% of patients treated BID with 500 or 1,000 µg of fluticasone, respectively, compared to 9% of placebo treated patients.  Mean maintenance dose of oral prednisone decreased significantly in both fluticasone groups compared with placebo, with decreases of 12 mg and 13.0 mg in the 500 and 1,000 µg BID groups, respectively, compared with 5.2 mg in the placebo group ( <i>P</i> <0.001).  Secondary: Changes in FEV <sub>1</sub> were significantly greater in both the fluticasone 500 µg BID group (8.37±3.84) and the 1,000 µg BID group (24.21±5.67) vs placebo (0.56±5.56; <i>P</i> ≤0.05 for all).  Both morning and evening PEF improved in the fluticasone 500 µg BID group (23±10 morning, 3±7 evening) and 1,000 µg (67±12 morning, 48±10 evening) compared to placebo (-23±11 morning, -9±12 evening; <i>P</i> ≤0.05 for all).  Asthma symptom scores improved in both the fluticasone 500 µg BID (-0.26±0.08) and 1,000 µg BID groups (-0.47±0.13; <i>P</i> ≤0.05); symptom scores worsened in the placebo group (0.26±0.12; <i>P</i> ≤0.05).  Nighttime awakenings requiring albuterol decreased in both the fluticasone 500 µg BID (-0.19±0.11) and 1,000 µg BID groups (-0.42±0.13); nighttime awakenings increased in the placebo group (0.26±0.15; <i>P</i> ≤0.05 for all).

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Fish et al <sup>33</sup>  Mometasone 400 to 800 µg BID  vs  placebo	MC, PC, RCT  Patients with severe persistent, oral corticosteroid-dependent asthma	N=132  12 weeks, followed by 9 month OL phase	Primary: Percentage change in daily oral corticosteroid prednisone requirement  Secondary: Spirometric measurements (FEV <sub>1</sub> , FVC, forced expiratory flow, midexpiratory phase), morning and evening PEF, rescue albuterol use, asthma symptom scores, number of nocturnal awakenings caused by asthma that required albuterol use, and general and asthma-specific quality-of-life measures	Primary: Oral corticosteroid requirements were reduced by 46.0% for the mometasone 400 µg BID group and 23.9% for mometasone 800 µg BID group compared to the placebo group that had an increase in oral corticosteroid requirements by 164.4% ( <i>P</i> <0.01).  Oral corticosteroid requirements were eliminated in 40, 37, and 0% of the patients after 12 weeks and 71, 62, and 58% at the end of the nine month OL phase in the mometasone 400 and 800 µg BID and placebo groups, respectively.  Secondary: Nocturnal awakenings fell by 57 and 66% in the mometasone 400 and 800 µg BID groups, respectively and increased by 62% in the placebo group ( <i>P</i> <0.01).  Daily rescue medication use was significantly reduced in the mometasone 400 µg BID group ( <i>P</i> <0.01), but not in the mometasone 800 µg BID group when compared to placebo.  All other secondary endpoints did not exhibit any statistically differences between the active treatment groups.
Krouse et al <sup>34</sup> (abstract)  Mometasone 400 µg QPM  vs  placebo	DB, PC, RCT  Patients 18 to 60 years of age with mild to moderate asthma and a history of nocturnal asthma	N=20  14 days	Primary: Nocturnal decline in evening to morning FEV <sub>1</sub> values  Secondary: Nocturnal decline in evening to morning PEF values, polysomnographic indices of sleep, NRQLQ, SF-46, and AQLQ	Primary: No significant differences were observed between groups in the nocturnal decline in FEV <sub>1</sub> .  Secondary: No significant differences were observed between groups in polysomnographic indices of sleep, NRQLQ, SF-36, or AQLQ.  A trend toward improvement in the activity scale of the AQLQ was observed in the mometasone group.

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<p>Price et al<sup>35</sup></p> <p>Mometasone 400 µg QPM</p> <p>vs</p> <p>mometasone 200 µg BID</p>	<p>MC, OL</p> <p>Patients 12 years of age and older with mild to moderate persistent asthma and a diagnosis of asthma for at least 1 year</p>	<p>N=1,233</p> <p>12 weeks</p>	<p>Primary: Adherence as measured by automatic dose counter</p> <p>Secondary: Self-reported adherence, physician's assessment of therapeutic response, HRQOL, healthcare resource utilization, and days missed from work or school</p>	<p>Primary: Adherence as measured by the automatic dose counter was significantly higher in the QPM group compared to the BID group (<math>P&lt;0.001</math>).</p> <p>Secondary: Adherence as measured by self-report was significantly higher in the QPM group compared to the BID group (<math>P&lt;0.001</math>).</p> <p>No significant differences between groups were observed in physician's assessment of therapeutic response (<math>P</math> value not reported), HRQOL, healthcare resource utilization, or days missed from work or school (<math>P\geq 0.08</math>).</p>
<p>Aalderen et al<sup>36</sup></p> <p>Beclomethasone 200 µg/day via HFA MDI</p> <p>vs</p> <p>fluticasone 200 µg/day via CFC MDI</p> <p>During weeks 7 to 12 and 13 to 18 patients were stepped down to 100 and 50 µg/day respectively if they were achieving good control.</p> <p>Those with poor control discontinued the study, and those labeled as intermediate did not have a dose change.</p>	<p>DB, DD, PG, RCT</p> <p>Patients 5 to 12 years of age with an asthma diagnosis of at least 3 months, PEF <math>\geq 60\%</math> of predicted normal, and who are currently using a SABA on an as-required basis</p>	<p>N=139</p> <p>18 weeks</p>	<p>Primary: Morning PEF percent predicted</p> <p>Secondary: Evening PEF percent predicted, FEV<sub>1</sub> percent predicted, FVC percent predicted, symptom-free days, nights without sleep disturbances, use of a <math>\beta_2</math>-agonist, asthma control, quality of life, and adverse events</p>	<p>Primary: Mean change from baseline in morning PEF percent predicted was 5.7% in the beclomethasone group and 7.3% in the fluticasone group. The treatment difference was -1.9 (90% CI, -4.9 to 1.0; <math>P</math> value not reported).</p> <p>Secondary: Mean change from baseline in evening PEF percent predicted was 5.9% in the beclomethasone group and 7.3% in the fluticasone group. The treatment difference was -1.5 (90% CI, -4.6 to 1.6; <math>P=0.415</math>).</p> <p>Mean change from baseline in FEV<sub>1</sub> percent predicted was 3.0% in the beclomethasone group and 0.6% in the fluticasone group. The treatment difference was 1.6 (<math>P=0.335</math>).</p> <p>Mean change from baseline in FVC percent predicted was 5.3% in the beclomethasone group and 0.4% in the fluticasone group. The treatment difference was 4.6 (<math>P=0.084</math>).</p> <p>The percentage change from baseline of symptom-free days was 35.2% in both treatment groups (<math>P=0.897</math>).</p> <p>The percentage change in nights without sleep disturbances was 17.5%</p>

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				<p>and 20.8% in the beclomethasone and fluticasone groups respectively (<math>P=0.561</math>).</p> <p>The mean number of puffs of a <math>\beta_2</math>-agonist decreased from 1.59 to 0.73 puffs/day in the beclomethasone group, and from 1.40 to 0.69 puffs/day in the fluticasone group (<math>P=0.505</math>).</p> <p>At week six, 36% of patients in the beclomethasone group and 42% in the fluticasone group had good asthma control and were able to step down in their respective doses to 100 <math>\mu\text{g/day}</math>. At week-12 another step down therapy to 50 <math>\mu\text{g/day}</math> was possible in 66 and 61% of the patients in the beclomethasone and fluticasone groups respectively.</p> <p>The proportion of patients with a clinically significant improvement in asthma quality of life was similar in both groups (<math>P=0.369</math>).</p> <p>There were no statistically significant differences in the proportion of patients experiencing adverse events in the beclomethasone (47%) and fluticasone (49%) groups.</p>
<p>Raphael et al<sup>37</sup></p> <p>Beclomethasone 168 <math>\mu\text{g}</math> BID</p> <p>vs</p> <p>beclomethasone 336 <math>\mu\text{g}</math> BID</p> <p>vs</p> <p>fluticasone 88 <math>\mu\text{g}</math> BID</p> <p>vs</p> <p>fluticasone 220 <math>\mu\text{g}</math> BID</p>	<p>DB, PG, RCT</p> <p>Nonsmoking males and females 12 years of age or older with an established diagnosis of chronic asthma requiring daily ICS therapy for at least 6 months before the study</p>	<p>N=399</p> <p>14 weeks</p>	<p>Primary: Changes in morning pre-dose FEV<sub>1</sub></p> <p>Secondary: FEF<sub>25 to 75%</sub>, FVC, morning and evening PEF, probability of remaining in the study, albuterol use, nighttime awakenings, and asthma symptoms</p>	<p>Primary: The FEV<sub>1</sub> for all treatment groups improved with respect to baseline; however, a significant drug effect was observed in favor of fluticasone compared to beclomethasone in the mean change in FEV<sub>1</sub> from baseline to endpoint (0.31 to 0.36 L vs 0.18 to 0.21 L; <math>P=0.006</math>).</p> <p>At endpoint, mean FEV<sub>1</sub> values in the low-and medium-dose fluticasone treatment groups improved by 0.31 (14%) and 0.36 L (15%) respectively, compared with improvements of 0.18 (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone treatment groups, respectively.</p> <p>Secondary: FEF<sub>25 to 75%</sub> and FVC were improved from baseline in all treatment groups; fluticasone showed greater improvements than beclomethasone (<math>P\leq 0.034</math>).</p> <p>Fluticasone provided significantly greater improvement in morning PEF</p>

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				<p>when compared to beclomethasone at endpoint and in all of the other time points except week two (<math>P&lt;0.004</math>). The fluticasone group also experienced a significant improvement in morning PEF relative to baseline (15.8 to 22.8 L), but the beclomethasone groups did not (0.7 to 7.2 L). A similar trend was seen in evening PEF, but the improvement observed in response to fluticasone compared to beclomethasone did not achieve statistical significance.</p> <p>There were no significant differences noted in the analysis of the probability of remaining in the study.</p> <p>The percentage of days in which no albuterol was used was significantly higher with fluticasone than with beclomethasone (<math>P=0.01</math> at endpoint). Albuterol use declined by 0.9 (26%) and 0.5 (16%) puffs/day in the low and moderate fluticasone treatment groups, respectively, whereas it was unchanged in the beclomethasone low-dose group and decreased by 0.3 (9%) puffs/day in the moderate-dose group.</p> <p>There were no significant differences noted in the analysis of nighttime awakenings.</p> <p>Significant drug effects were observed at endpoint in favor of fluticasone for asthma symptom scores (<math>P=0.024</math>) and in the percentage of days in which no symptoms were recorded (<math>P=0.027</math>).</p>
<p>Sharek et al<sup>38</sup></p> <p>Beclomethasone 328 to 400 µg/day</p> <p>vs</p> <p>fluticasone 200 µg/day</p>	<p>MA</p> <p>1966 to 1998, DB, RCT studies that evaluated linear growth in children 6 to 16 years of age with asthma and concomitant ICS therapy</p>	<p>N=855</p> <p>(5 studies)</p>	<p>Primary: Linear growth velocity in cm/year</p> <p>Secondary: Not reported</p>	<p>Primary: Each of the four trials that evaluated beclomethasone revealed a decreased linear growth velocity, and the MA of these four trials concluded that there was a significant decrease in linear growth in children using beclomethasone for mild-moderate asthma. The WMD between 231 patients using beclomethasone compared to 209 patients using a non-steroid medication was -1.51 cm/year (95% CI, -1.15 to -1.87). For the fluticasone study the mean difference between 96 children treated with fluticasone and 87 patients treated with placebo was -0.43 cm/year (95% CI, -0.01 to -0.85; <math>P</math> value not reported).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Nathan et al<sup>39</sup></p> <p>Beclomethasone 168 µg BID</p> <p>vs</p> <p>mometasone 100 µg BID</p> <p>vs</p> <p>mometasone 200 µg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, MC, PC, RCT</p> <p>Patients with moderate persistent asthma previously maintained on an ICS</p>	<p>N=227</p> <p>12 weeks</p>	<p>Primary: Changes in FEV<sub>1</sub></p> <p>Secondary: PEFR, asthma symptoms, nocturnal awakenings, and albuterol use</p>	<p>Not reported</p> <p>Primary: FEV<sub>1</sub> significantly improved for all three active treatment groups compared to placebo (<math>P&lt;0.01</math>).</p> <p>There was no statistically significant difference in FEV<sub>1</sub> between mometasone 200 µg and beclomethasone (<math>P=0.07</math>) or mometasone 200 µg and mometasone 100 µg (<math>P=0.08</math>).</p> <p>Secondary: Improvement in FEV<sub>1</sub>, PEFR, asthma symptoms, nocturnal awakenings, and albuterol use were approximately twice as large for the mometasone 200 µg group as for the mometasone 100 µg and beclomethasone groups, but did not reach statistical significance.</p>
<p>Bernstein et al<sup>40</sup></p> <p>Beclomethasone 168 µg BID</p> <p>vs</p> <p>mometasone 100 µg BID</p> <p>vs</p> <p>mometasone 200 µg BID</p> <p>vs</p> <p>mometasone 400 µg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, MC, RCT</p> <p>Patients with asthma previously being treated with an ICS</p>	<p>N=365</p> <p>12 weeks</p>	<p>Primary: Mean change from baseline to endpoint for FEV<sub>1</sub></p> <p>Secondary: FVC, FEF<sub>25 to 75%</sub>, PEFR, patient evaluation of asthma symptoms, and physician evaluation of asthma symptoms</p>	<p>Primary: The difference in FEV<sub>1</sub>, FVC, FEF<sub>25 to 75%</sub>, and PEFR from baseline was significantly greater in all the active treatment groups compared to placebo (<math>P&lt;0.01</math>). The mometasone 200 µg BID group showed greater improvement than the mometasone 100 µg BID group, with the mometasone 400 µg BID group showing no additional benefit.</p> <p>Secondary: Changes in lung function from baseline for the mometasone 100 µg BID group and the beclomethasone group were similar.</p> <p>Asthma symptoms as evaluated subjectively by patients and physicians were similarly improved for the mometasone 200 (<math>P&lt;0.01</math>) and 400 (<math>P=0.05</math>) µg BID groups, which were slightly better than that of the mometasone 100 µg BID (<math>P=0.01</math>) and beclomethasone (<math>P=0.02</math>) groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Noonan et al <sup>41</sup> Mometasone 200 µg QD vs mometasone 100 µg BID vs beclomethasone 168 µg BID	MC, OL, PRO Patients 4 to 11 years of age with mild to moderate persistent asthma using an ICS within 30 days prior to the study and stable regimen at least 2 weeks before screening	N=233 52 weeks	Primary: Incidence of adverse effects Secondary: Laboratory tests including cortisol concentrations, vital signs, and physical examinations	Primary: The incidence of adverse effects was similar in all three treatment groups. Secondary: No significant differences between groups were observed in any secondary end points.
Bronsky et al <sup>42</sup> Beclomethasone 336 µg/day vs triamcinolone 800 µg/day vs placebo	DB, DD, MC, PC, PG, RCT Adults with mild to moderately severe asthma maintained on an ICS	N=328 56 days	Primary: Mean changes in FEV <sub>1</sub> from baseline Secondary: Asthma symptom scores, average use of albuterol, nighttime awakenings, mean change from baseline in FEF <sub>25 to 75%</sub> , and FVC	Primary: Throughout the study, mean change and percent mean change in FEV <sub>1</sub> for both active treatment groups were significantly greater than placebo (0.27 L for beclomethasone, 0.16 L for triamcinolone, and -0.10 L for placebo; $P \leq 0.01$ ). A pairwise comparison showed that mean percent change and mean change (SD) were consistently greater in the beclomethasone group throughout the study, with the difference statistically significant at day 28 ( $P=0.042$ and $P=0.036$ , respectively). Both active treatments were better than placebo ( $P \leq 0.003$ ). Secondary: At each visit and at study endpoint, mean reductions in total symptom severity scores were significantly greater in the beclomethasone group compared to the triamcinolone group ( $P=0.028$ ) and at endpoint in both active treatment groups compared to placebo (-1.37, -0.58, 0.83; $P < 0.001$ ). The mean average daily use of albuterol calculated weekly tended to be least in the beclomethasone group (2.86), greatest in the placebo group (4.43), and intermediate in the triamcinolone group (3.61).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Nighttime awakenings were not significantly different among the treatment groups.</p> <p>Mean change from baseline in FEF<sub>25 to 75%</sub>, and FVC showed both active treatment groups better than placebo, with beclomethasone being clinically better than triamcinolone throughout the study.</p>
<p>Berkowitz et al<sup>43</sup></p> <p>Beclomethasone 336 µg/day and triamcinolone placebo</p> <p>vs</p> <p>triamcinolone 800 µg/day and beclomethasone placebo</p> <p>vs</p> <p>triamcinolone and beclomethasone placebo</p>	<p>DB, DD, PC, RCT</p> <p>Patients aged 18 to 65 years of age with a documented history of bronchial asthma</p>	<p>N=339</p> <p>56 days</p>	<p>Primary: Change from baseline in FEV<sub>1</sub></p> <p>Secondary: FEF<sub>25 to 75%</sub>, PEFR, and FVC</p>	<p>Primary: For both active treatment groups, increases in baseline FEV<sub>1</sub> were evident at all time points; these results were statistically significant when compared to placebo (<i>P</i>&lt;0.05).</p> <p>At end point, FEV<sub>1</sub> had increased by 10.3% in the beclomethasone group and 11.2% in the triamcinolone group (<i>P</i>≤0.05 vs placebo).</p> <p>Secondary: Mean increases in FEF<sub>25 to 75%</sub> and PEFR were similar in both active treatment groups. The same trend was noticed for FVC. All results were numerically and statistically significant when compared to placebo (<i>P</i>&lt;0.05).</p>
<p>Newhouse et al<sup>44</sup></p> <p>Beclomethasone 750 µg, BID via AeroChamber<sup>®</sup> for a two week run-in period then randomized to:</p> <p>budesonide 600 µg BID via Turbuhaler<sup>®</sup></p> <p>vs</p>	<p>MC, PG, RCT</p> <p>Patients with moderate asthma (FEV<sub>1</sub> 40 to 85% of predicted)</p>	<p>N=176</p> <p>6 weeks</p>	<p>Primary: Change in prebronchodilator FEV<sub>1</sub> from week zero to week six, and change in mean albuterol usage during the weeks preceding week zero and week six</p> <p>Secondary: Changes in PEF, asthma scores, and nocturnal awakenings</p>	<p>Primary: There were no statistically significant differences between the two treatment groups in the changes in FEV<sub>1</sub> during the six week treatment period (difference of -0.031 L in percent predicted favoring flunisolide; <i>P</i>=0.544).</p> <p>There were also no significant changes in albuterol use between the two groups (difference of 0.261 puffs/day favoring budesonide; <i>P</i>=0.333).</p> <p>Secondary: There were no statistically significant differences between the two groups in the change in PEF, asthma symptoms scores, and nocturnal awakenings during the treatment period.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>flunisolide 750 µg BID via AeroChamber®</p> <p>Vermeulen et al<sup>45</sup></p> <p>Budesonide 800 µg QPM</p> <p>vs</p> <p>ciclesonide 320 µg QPM</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients 12 to 17 years of age with severe asthma for 6 months with an FEV<sub>1</sub> &gt;50 and &lt;80% who were not controlled with budesonide 400 µg/day for ≥4 weeks prior to study</p>	<p>N=403</p> <p>12 weeks</p>	<p>Primary: Change in evening pre-dose FEV<sub>1</sub> from baseline to week 12, and percentage of days without asthma symptoms and without use of rescue medication</p> <p>Secondary: Change in FEV<sub>1</sub> percent of predicted, change in FVC from baseline to week 12, percentage of patients experiencing an asthma exacerbation, change in morning PEF from baseline to week 12, change in asthma symptom score, change from baseline to week 12 in albuterol utilization, change in PAQLQS score, and adverse events</p>	<p>Primary: At week 12 significant increases in FEV<sub>1</sub> were seen in both treatment arms (ciclesonide, 0.505 L; <i>P</i>&lt;0.0001, budesonide, 0.536 L; <i>P</i>&lt;0.0001). There were no significant differences between treatment groups (<i>P</i>=0.076).</p> <p>Percentage of days without asthma symptoms and without use of rescue medication was 84% in the ciclesonide group and 85% in the budesonide group (<i>P</i> value not reported).</p> <p>Secondary: FEV<sub>1</sub> percent predicted increased in the ciclesonide group from 73.1 percent at baseline to 89.4% at the end of the study. In the budesonide group FEV<sub>1</sub> percent predicted was 73.0% at baseline and 90.7% at the end of the study. There was no significant difference between the two study groups (<i>P</i> value not reported).</p> <p>For FVC the change from baseline was significant in both treatment groups (0.433 L in the ciclesonide group and 0.472 L in the budesonide group). The difference between the two treatment groups was not significant (<i>P</i>=0.080).</p> <p>Asthma exacerbations were reported in 2.6% of the patients in the ciclesonide group and 1.5% in the budesonide group. There was no significant difference between the two treatment groups (<i>P</i> value not reported).</p> <p>Morning PEF increased from baseline to week 12 by 8.0 L/minute in the ciclesonide group (<i>P</i>=0.0424) and 4.9 L/minute in the budesonide group, which was not statistically significant (<i>P</i> value not reported).</p> <p>Asthma symptom scores (zero to five scale) were significantly reduced in both treatment groups (ciclesonide, -0.07; <i>P</i>&lt;0.0005, budesonide, -0.14; <i>P</i>&lt;0.0001). There were no significant differences between treatment groups (<i>P</i> value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>The median use of rescue medication at week 12 was reduced to zero puffs/day in both the ciclesonide (<math>P&lt;0.0001</math>) and budesonide groups (<math>P=0.0003</math>).</p> <p>Overall PAQLQS scores (one to seven scale) were improved in both treatment groups (ciclesonide, 0.19; <math>P=0.0001</math>, budesonide, 0.18; <math>P=0.0056</math>).</p> <p>The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (320 µg, 26.5%; 800 µg, 18.3%). The most common adverse event that occurred in at least 5% of patients for either treatment groups was pharyngitis (ciclesonide, 5.9%; budesonide, 3.8%).</p>
<p>Von Berg et al<sup>46</sup></p> <p>Budesonide 400 µg QPM</p> <p>vs</p> <p>ciclesonide 160 µg QPM</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients 6 to 11 years of age with persistent asthma for ≥6 months</p>	<p>N=621</p> <p>12 weeks</p>	<p>Primary: Change in FEV<sub>1</sub> from baseline to week 12</p> <p>Secondary: Change in morning PEF from baseline to week 12, change in asthma symptom score, change from baseline to week 12 in rescue medication utilization, percentage of days without asthma symptoms and without need for rescue medication, percentage of patients with asthma exacerbations, change in PAQLQS and PACQLQ score, adverse events, body height increase at week</p>	<p>Primary: At week 12 significant increases in FEV<sub>1</sub> compared to baseline were seen in both treatment arms (ciclesonide, 0.232 L; <math>P&lt;0.0001</math>, budesonide, 0.250 L; <math>P&lt;0.0001</math>). Ciclesonide proved to be non-inferior to budesonide with no significant differences between groups (<math>P=0.8158</math>).</p> <p>Secondary: Treatment with both groups achieved a statistically significant increase in morning PEF compared to baseline (ciclesonide, 22.5 L/minute; <math>P&lt;0.0001</math>, budesonide, 26.3 L/minute; <math>P&lt;0.0001</math>). There were no significant differences between treatment groups (<math>P=0.8531</math>).</p> <p>Both treatment groups achieved a statistically significant improvement in asthma symptom score (zero to five scale) after 12 weeks of treatment (ciclesonide, -1.21; <math>P&lt;0.0001</math>, budesonide, -1.21; <math>P&lt;0.0001</math>). There were no significant differences between treatment groups (<math>P=0.8379</math>).</p> <p>Both treatment group achieved a statistically significant improvement in the need for rescue medication after 12 weeks of treatment (ciclesonide, -1.58; <math>P&lt;0.0001</math>, budesonide, -1.64; <math>P&lt;0.0001</math>). There were no significant differences between treatment groups (<math>P=0.8593</math>).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			12, and change in 24-hour urinary cortisol	<p>The percentage of days without asthma symptoms and without need for rescue medication was 73% in the ciclesonide, and 70% in the budesonide group (<i>P</i> value not reported).</p> <p>The percentage of patients with asthma exacerbations was 2.6% in the ciclesonide group, and 1.0% in the budesonide group (<i>P</i> value not reported).</p> <p>Both treatment arms achieved a statistically significant improvement in overall PAQLQS (one to seven scale) and PACQLQ scores compared to baseline after 12 weeks of treatment (0.69, 0.88 and 0.70, 0.96 for the ciclesonide and budesonide groups respectively (<i>P</i>&lt;0.0001).</p> <p>The percentage of patients who experienced treatment emergent adverse events was 38% among both treatment groups. The most common adverse events that occurred in at least 5% of patients for either treatment groups were: pharyngitis: (5.9, 3.8%), nasopharyngitis: (4.1, 5.4%), and upper respiratory tract infection, (3.6, 6.3%) for the ciclesonide and budesonide groups respectively. The frequency of oropharyngeal adverse events was low in both treatment groups (0.2, 1.5%) for the ciclesonide and budesonide groups, respectively.</p> <p>At week 12 the body height increased by 1.18 cm in the ciclesonide group and by 0.70 cm in the budesonide group. Both of these values were significant when compared to baseline (<i>P</i>&lt;0.0001). The increase in height was significantly greater in the ciclesonide group than in the budesonide group (<i>P</i>=0.0025).</p> <p>Treatment with ciclesonide and budesonide resulted in significant decreases of urinary cortisol (nmol/mmol creatinine) (ciclesonide, -2.17; <i>P</i>&lt;0.0001, budesonide, -5.16; <i>P</i>&lt;0.0001). The difference between these two treatment groups was significant (<i>P</i>&lt;0.0001).</p>
Ferguson et al <sup>47</sup>  Budesonide 200 µg BID via DPI	DB, DD, MC, PG, RCT  Children 6 to 9	N=400  12 months	Primary: Growth velocity  Secondary:	Primary: Mean growth velocity from baseline to week 52 was 5.5 cm/year in the fluticasone group and 4.6 cm/year in the budesonide group. This difference of 0.9 cm/year was statistically significant ( <i>P</i> <0.001).The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs  fluticasone 100 µg BID via DPI	years of age with persistent asthmas ≥6 months, and an FEV <sub>1</sub> ≥60% predicted, with height between the 5 <sup>th</sup> and 95 <sup>th</sup> centiles for the patients' age and run-in growth velocity between the 20 <sup>th</sup> and 95 <sup>th</sup> percentiles		PEF <sub>R</sub> , FEV <sub>1</sub> , exacerbations, symptom-free days and nights, salbutamol-free nights, and adverse events	<p>difference in growth velocities increased over the 12 months. The majority of patients in the fluticasone group grew 5.0 to 7.0 cm/year whereas patients in the budesonide group grew 3.0 to 5.0 cm/year.</p> <p>Secondary:                      Change in morning PEF<sub>R</sub> was 29.7, and 26.2 L/minute for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (<i>P</i>=0.460).</p> <p>Change in FEV<sub>1</sub> was 0.19, and 0.25 L for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (<i>P</i>=0.154).</p> <p>Patients with no exacerbations were 75 and 68% for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (<i>P</i>=0.131).</p> <p>Patients with 100% symptom-free days were 49 and 48% for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (<i>P</i>=0.799).</p> <p>Patients with 100% symptom-free nights were 50 and 58% for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (<i>P</i>=0.232).</p> <p>Patients with 100% salbutamol-free nights were 57 and 52% for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (<i>P</i>=0.180).</p> <p>Adverse events were reported in 81 and 71% in the fluticasone and budesonide groups respectively. However only 3 and 2% of these events were considered to be treatment related. Serious adverse events were reported in &lt;1 and 3% in the fluticasone and budesonide groups respectively.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Ferguson et al<sup>48</sup></p> <p>Budesonide 400 µg BID via DPI</p> <p>vs</p> <p>fluticasone 200 µg BID via DPI</p>	<p>DB, DD, PG, RCT</p> <p>Children 4 to 12 years of age with a history of moderate to severe asthma who required moderate to high doses of an ICS to control symptoms for at least 1 month preceding the start of the run in period</p>	<p>N=442</p> <p>22 weeks</p>	<p>Primary: Mean morning PEF during the last seven treatment days, obtained from the daily record cards assessed by ANOVA</p> <p>Secondary: Adverse events</p>	<p>Primary: The adjusted mean morning PEF, measured over the last seven treatment days, were 271±82 and 259±75 L/minute, for the fluticasone and budesonide treatment groups, respectively. The difference in means was 12 L/minute (90% CI, 6 to 19; P=0.002).</p> <p>For the purpose of this study, the two treatment regimens were considered to be equivalent if the 90% CI for the difference in mean morning PEFs for the last seven days of the 20-week treatment period was within ±15 L/minute. The 90% upper and lower confidence limits for the treatment difference were 6 and 9 L/minute, respectively, indicating that the treatments were not equivalent, with fluticasone showing improved outcomes.</p> <p>Secondary: There was no significant difference in the number of children who experienced an adverse event in the two treatment groups.</p>
<p>Fitzgerald et al<sup>49</sup></p> <p>Budesonide 750 µg BID</p> <p>vs</p> <p>fluticasone 375 µg BID</p>	<p>DB, RCT, XO</p> <p>Children 5 to 16 years of age with persistent severe asthma requiring 1,000 to 2,000 µg/day of inhaled beclomethasone or budesonide continuously for symptom control over the previous 12 months</p>	<p>N=30</p> <p>12 weeks</p>	<p>Primary: The daily mean morning and evening PEF and day and night symptom scores</p> <p>Secondary: Physician/patient/parent assessment of efficacy, total number of exacerbations requiring systemic steroids, adrenal function, growth, and adverse events</p>	<p>Primary: Although the trend favored fluticasone, there was no statistically significant difference between the treatment groups in PEF and symptoms scores.</p> <p>Secondary: There was no difference in physician/patient/parent assessment of efficacy with 90% rating both fluticasone and budesonide effective or very effective.</p> <p>The total number of exacerbations (fluticasone, 33; budesonide, 35) and those exacerbations requiring systemic steroids (fluticasone, 9; budesonide, 11) suggested no difference between the treatment groups.</p> <p>There were no significant differences in adjusted means for urinary free cortisol levels at eight or 12 weeks, adrenocorticotropic hormone levels, or baseline and peak serum cortisol levels between the treatment phases.</p> <p>There was no significant treatment effect on growth which remained normal in either group.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Most of the adverse events were related to exacerbations of asthma or upper respiratory tract infections in both groups. There was no difference in either the total number of adverse events or the number of adverse events considered possibly related to ICSs between the treatment groups.</p>
<p>Bousquet et al<sup>50</sup>                      Budesonide 400 µg BID                      vs                      mometasone 100, 200, or 400 µg BID</p>	<p>DB, MC, RCT                      Patients with moderate persistent asthma previously maintained on a daily ICS</p>	<p>N=730                      12 weeks</p>	<p>Primary:                      Mean change from baseline to endpoint FEV<sub>1</sub>                      Secondary:                      Self-rated asthma symptom scores, nocturnal awakenings requiring albuterol use as rescue medication, daily albuterol use, and physician evaluation of response to therapy</p>	<p>Primary:                      FEV<sub>1</sub> was significantly improved in the mometasone 200 and 400 µg BID treatment groups compared to the budesonide treatment group (<i>P</i>&lt;0.05).                      Secondary:                      The morning wheezing scores were significantly improved in the mometasone 400 µg BID group compared to the budesonide group or mometasone 100 µg BID group (<i>P</i> value not reported).                      Patients treated with mometasone 200 and 400 µg BID required significantly less albuterol than did patients treated with budesonide.                      Physicians reported a significant improvement in asthma symptoms scores in the mometasone 400 and 200 µg BID groups compared to the budesonide group (63 and 65 vs 50%; <i>P</i> value not reported).</p>
<p>Corren et al<sup>51</sup>                      Budesonide 400 µg QD                      vs                      mometasone 440 µg QD                      vs                      placebo</p>	<p>DB, DD, MC, PC, RCT                      Patients with moderate persistent asthma previously using BID ICSs</p>	<p>N=262                      8 weeks</p>	<p>Primary:                      Percent change in FEV<sub>1</sub> from baseline to endpoint                      Secondary:                      Morning and evening PEFR, FVC, FEF<sub>25 to 75%</sub>, albuterol use, percentage of asthma symptom-free days, nocturnal awakenings due to asthma, physician-evaluated response to therapy, and asthma symptom</p>	<p>Primary:                      The percent change in FEV<sub>1</sub> was significantly greater in the mometasone group compared to the budesonide (<i>P</i>&lt;0.01) and placebo groups (<i>P</i>&lt;0.001).                      Secondary:                      Pulmonary function (FEF<sub>25 to 75%</sub>, FVC), evening asthma symptoms scores, albuterol use, percentage of asthma symptom-free days, and physician-evaluated response to therapy were significantly improved in the mometasone group compared to both the budesonide and placebo groups (<i>P</i>&lt;0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Weiss et al<sup>52</sup></p> <p>Budesonide 200 to 1,600 µg/day</p> <p>vs</p> <p>triamcinolone 1,200 to 1,600 µg/day</p>	<p>OL, RCT</p> <p>Adult patients (18 years of age and older) with persistent asthma enrolled in 25 United States health plans</p>	<p>N=945</p> <p>52 weeks</p>	<p>scores</p> <p>Primary: Mean change from baseline to the end of treatment in symptom-free days</p> <p>Secondary: Changes from baseline in number of episode-free days, episode-free days at 52 weeks, FEV<sub>1</sub>, FVC, asthma symptom scores, breakthrough bronchodilator use, and HRQOL</p>	<p>Primary: Increase in mean estimated symptom- and episode-free days from baseline observed in both treatment groups by month one and were maintained throughout the treatment period. These increases were consistently greater with budesonide than with triamcinolone (7.74 and 5.73 for the budesonide group compared to 3.78 and 2.12 for the triamcinolone group; <i>P</i>&lt;0.001).</p> <p>Secondary: The adjusted mean increase in symptom- and episode-free days from baseline to month 12 and the estimated mean number of symptom- and episode-free days over the 52-week treatment period were significantly greater in the budesonide group compared to the triamcinolone group (<i>P</i>&lt;0.001).</p> <p>FEV<sub>1</sub> and FVC improved from baseline to week 52 in both treatment groups. Patients receiving budesonide experienced a greater improvement in FEV<sub>1</sub> than patients receiving triamcinolone (0.35 vs 0.25 L; <i>P</i>=0.005). The difference between the two treatment groups in FVC was not statistically significant.</p> <p>Mean daytime and nighttime asthma symptom scores decreased from baseline in both groups. Decreases were significantly greater in patients receiving budesonide at month 12 (<i>P</i>=0.001 and <i>P</i>&lt;0.001, respectively).</p> <p>The mean amount of breakthrough bronchodilator use decreased from 4.42 to 2.58 puffs/week in the budesonide group (95% CI, -2.17 to -1.58) and from 4.56 to 3.68 puffs/week in the triamcinolone group (95% CI, -1.36 to -0.52; <i>P</i>&lt;0.001).</p> <p>Patients in both treatment groups reported significant improvements from baseline over the course of the study in overall quality of life and the individual domains of the HRQOL questionnaire. Compared to the triamcinolone group, the budesonide group reported significantly greater improvements in SF-36 general health scores at weeks 26 and 52 (<i>P</i>&lt;0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Study #323/324<sup>53</sup></p> <p>Ciclesonide 160 µg BID</p> <p>vs</p> <p>ciclesonide 320 µg BID</p> <p>vs</p> <p>fluticasone 440 µg BID</p> <p>vs</p> <p>placebo</p>	<p>AC, DB, MC, PC, PG, RCT</p> <p>Patients 12 years of age and older with a history of persistent asthma for ≥1 year prior to screening, a documented use of an ICS for the month prior to baseline, use of a β<sub>2</sub>-agonist for more than 2 times a week for the month prior to screening with an FEV<sub>1</sub> ≤80% of predicted normal following a 6 hour β<sub>2</sub>-agonist treatment withholding period at screening and an FEV<sub>1</sub> between 40 to 50% of predicted normal following a 6 hour β<sub>2</sub>-agonist treatment withholding period</p>	<p>N=531</p> <p>12 weeks</p>	<p>Primary: Change from baseline to week 12 in morning pre-dose FEV<sub>1</sub> compared to placebo</p> <p>Secondary: Change from baseline to week 12 in morning PEF, change from baseline to week 12 in albuterol utilization, change in asthma symptom score, change in AQLQ score, and adverse events</p>	<p>and <math>P=0.001</math>, respectively).</p> <p>Primary: All three treatment arms showed a statistically significant improvement in FEV<sub>1</sub> scores from baseline to week 12 (change for the 160 µg BID group, 0.11 L; <math>P=0.0374</math>, change for the 320 µg BID group, 0.18 L; <math>P=0.0008</math>, change for the fluticasone group, 0.24 L; <math>P=0.0001</math>).</p> <p>Secondary: All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in morning PEF (change for the 160 µg BID group, 27.8 L/minute; <math>P=0.0001</math>, change for the 320 µg BID group, 30.39 L/minute; <math>P=0.0001</math>, change for the fluticasone group, 41.42 L/minute; <math>P=0.0001</math>).</p> <p>All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day) (change for the 160 µg BID group, -1.69; <math>P=0.0001</math>, change for the 320 µg BID group, -1.57; <math>P=0.0001</math>, change for the fluticasone group, -2.19; <math>P=0.0001</math>).</p> <p>For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for all three treatment arms (change for the ciclesonide 160 µg BID group, -0.71; <math>P=0.0001</math>, change for the ciclesonide 320 µg BID group, -0.80; <math>P=0.0001</math>, change for the fluticasone group, -0.91; <math>P=0.0001</math>).</p> <p>All four domains (exposure to environmental stimuli, symptoms, activity limitation, and emotional function) in the AQLQ were statistically significantly improved in all three treatment arms (<math>P</math> value not reported).The percentage of patients who achieved the minimally important difference (an increase of at least 0.5) in the AQLQ overall score at week 12 were: 42.5% in the Ciclesonide 160 µg BID group, 43.1% in the ciclesonide 320 µg BID group, 58.8% in the fluticasone group, and 26.9% in the placebo group.</p> <p>The percentage of patients who experienced treatment emergent adverse</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>events was comparable among treatment groups (ciclesonide 160 µg BID, 61.4%; ciclesonide 320 µg BID, 54.6%; fluticasone, 60.1%; placebo, 61.8%). The most common adverse event that occurred in at least 5% of patients for the treatment groups was nasopharyngitis. The incidence of oropharyngeal adverse events was more common in the fluticasone treatment arm than in the Ciclesonide treatment arms. Oral candidiasis occurred in 1.6, 0, 11.6, and 2.2%, pharyngitis in 4.7, 3.1, 5.1, and 2.9% and dysphonia in 0, 1.5, 3.6, and 0.7% all in the ciclesonide 160 µg BID, ciclesonide 320 µg BID, fluticasone and placebo groups, respectively.</p>
<p>Sheikh et al<sup>54</sup></p> <p>Flunisolide 1,500 µg/day for a period of one year then XO to fluticasone 880 µg/day for one year</p>	<p>OL, XO</p> <p>Children with moderate to severe asthma with a mean age of 12.7 years</p>	<p>N=30</p> <p>2 years</p>	<p>Primary: Mean percent predicted values for FVC, FEV<sub>1</sub>, FEF<sub>25 to 75%</sub>, and PEFR</p> <p>Secondary: Not reported</p>	<p>Primary: Significant improvement in all clinical parameters was found while patients were receiving fluticasone compared to flunisolide.</p> <p>There was a significant improvement in FVC during the two to six and seven to 12-month time periods after the switch.</p> <p>Significant improvement was noted in FEV<sub>1</sub> and FEF<sub>25 to 75%</sub> at one month after the switch, and this improvement persisted during the two to six and seven to 12 month time periods.</p> <p>There was no significant difference in PEFR at any time period.</p> <p>Secondary: Not reported</p>
<p>Nakanishi et al<sup>55</sup></p> <p>Flunisolide with a valved holding chamber, four inhalations (1 mg) BID for 7 days and daily placebo tablets (ICS Group)</p> <p>vs</p> <p>oral prednisone 2 mg/kg (maximum of 60 mg/day)</p>	<p>PC, PG, RCT</p> <p>Children 6 to 16 years of age seeking emergent care for an acute exacerbation of asthma</p>	<p>N=58</p> <p>7 days</p>	<p>Primary: Percentage of predicted FEV<sub>1</sub></p> <p>Secondary: Symptom score, initial vital signs and oximetry, side effects, recurrence rate for acute asthma symptoms, and daily PEF</p>	<p>Primary: The FEV<sub>1</sub> percentage of predicted for the inhaled corticosteroids group was lower vs the oral corticosteroid group on day 3 (65 vs 78%; P=0.03) and day seven (77 vs 95%; P=0.002). Both groups continued to improve over the seven-day study period, with the most improvement in those patients receiving oral corticosteroids.</p> <p>Secondary: There was no significant difference in symptom severity between the two groups at any time during the study.</p> <p>There was no significant difference in initial vital signs or oximetry between</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for 7 days, and placebo pressurized MDI, four inhalations BID				<p>the two groups at any time during the study.</p> <p>One patient in the ICS group required additional corticosteroids after the seven-day study period to control symptoms. One patient in the oral corticosteroid group required hospital admission for asthma within 24 hours following enrollment.</p> <p>There was no significant difference in PEF between the two groups at any time during the study.</p>
<p>Harnest et al<sup>56</sup></p> <p>Fluticasone 500 µg BID</p> <p>vs</p> <p>mometasone 500 µg BID</p>	<p>AC, RCT</p> <p>Patients 18 years of age and older with moderate to severe persistent asthma who were previously using an ICS for daily maintenance therapy for ≥30 days</p>	<p>N=203</p> <p>12 weeks</p>	<p>Primary: Change from baseline in weekly average PEF</p> <p>Secondary: FEV<sub>1</sub>, asthma symptom scores, rescue medication use, response to therapy, and adverse events</p>	<p>Primary: The percent change from baseline in PEF was 7.8 for the mometasone group and 7.7 for the fluticasone group (<i>P</i>=0.815).</p> <p>Secondary: At week-12 the change from baseline in FEV<sub>1</sub> was 0.4 L in both the mometasone and fluticasone groups (<i>P</i>=0.988).</p> <p>Morning and evening asthma symptom scores were not significantly different between the mometasone (-.05,-0.6; <i>P</i>=0.251) and fluticasone (-0.6, -0.7; <i>P</i>=0.251) groups respectively.</p> <p>Rescue albuterol use decreased from baseline in both treatment groups with no significant differences between them (<i>P</i>=0.890).</p> <p>Treatment-emergent adverse events occurred in 51% of the patients in the mometasone group, and in 43% of the patients in the fluticasone group. The difference between the two groups was not significant (<i>P</i> value not reported).</p>
<p>O'Connor et al<sup>57</sup></p> <p>Fluticasone 250 µg BID</p> <p>vs</p> <p>mometasone 100, 200, or 400 µg BID</p>	<p>DB, MC, PG, RCT</p> <p>Patients with moderate persistent asthma previously treated with an ICS</p>	<p>N=733</p> <p>12 weeks</p>	<p>Primary: Change in FEV<sub>1</sub></p> <p>Secondary: Mean changes from baseline in PEFR, FEF<sub>25</sub> to 75%, FVC, asthma symptom scores,</p>	<p>Primary: At study endpoint, all treatment groups showed improvement in FEV<sub>1</sub>. No statistical difference was observed between the mometasone 200 µg BID, 400 µg BID, or fluticasone group.</p> <p>The mometasone 400 µg BID group showed significant improvement in FEV<sub>1</sub> compared with the mometasone 100 µg BID group (<i>P</i>=0.02).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			albuterol use, nocturnal awakenings due to asthma, and physician-evaluation of response to therapy	<p>Mometasone 200 µg BID and fluticasone groups showed similar improvements in FEV<sub>1</sub>.</p> <p>Secondary: FEF<sub>25 to 75%</sub> and PEFr were significantly improved in the mometasone 200 µg BID, 400 µg BID, and fluticasone groups compared with the mometasone 100 µg BID group. All other results showed no significant differences between the treatment groups.</p>
<p>Wardlaw et al<sup>58</sup></p> <p>Fluticasone 250 µg BID</p> <p>vs</p> <p>mometasone 400 µg QPM</p>	<p>OL, PG, RCT</p> <p>Patients with moderate persistent asthma previously using fluticasone</p>	<p>N=167</p> <p>8 weeks</p>	<p>Primary: Percent change in FEV<sub>1</sub> from baseline to endpoint</p> <p>Secondary: FVC, PEFr, asthma symptom scores, albuterol use, and device evaluation</p>	<p>Primary: No significant difference in the percent change in FEV<sub>1</sub> (<math>P \geq 0.14</math>) was observed between treatment groups at any point in the study (two, four, and eight weeks of treatment).</p> <p>Secondary: No significant difference in the percent change in FVC (<math>P \geq 0.24</math>), PEFr (<math>P = 0.60</math>), albuterol use or asthma symptom scores (<math>P \geq 0.06</math>) was observed between treatment groups at any point in the study (two, four, and eight weeks of treatment).</p> <p>There was a greater number of subjects that showed improvement in their asthma symptoms in the mometasone group compared to the fluticasone group (<math>P = 0.007</math>) as reported by physicians' evaluations of response to therapy.</p> <p>A significantly greater number of subjects reported having "liked the inhaler a lot" in the mometasone group vs the fluticasone group (<math>P = 0.01</math>).</p>
<p>Condemi et al<sup>59</sup></p> <p>Fluticasone 250 µg BID</p> <p>vs</p> <p>triamcinolone 200 µg QID</p> <p>vs</p>	<p>DB, DD, PC, PG, RCT</p> <p>Male and female patients 12 years of age and older with asthma (FEV<sub>1</sub> 50 to 80% of predicted value) who had</p>	<p>N=291</p> <p>24 weeks</p>	<p>Primary: Morning predose FEV<sub>1</sub>, probability of remaining in the study over time, patient-measured PEF, albuterol use, number of nighttime awakenings requiring albuterol, and asthma symptom scores</p>	<p>Primary: At end point, patients in both the fluticasone and triamcinolone groups experienced statistically significant improvements in FEV<sub>1</sub> compared with the placebo group (-0.18 L for placebo, 0.07 for triamcinolone, 0.27 for fluticasone; <math>P \leq 0.001</math>).</p> <p>Only 27% of patients in the placebo group remained in the study over time compared with 66% in the fluticasone group and 55% in the triamcinolone group. Survival analysis suggested that patients in both active treatment groups had a significantly greater probability of remaining in the study over</p>

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<p>placebo BID or QID</p>	<p>previously received maintenance therapy with beclomethasone or triamcinolone</p>		<p>Secondary: Adverse events, morning plasma cortisol levels</p>	<p>time than patients in the placebo group (<math>P&lt;0.001</math>). There was no significant difference seen between the two active treatment groups.</p> <p>Significant differences in mean change in PEF between the triamcinolone and fluticasone groups were observed by week one and maintained throughout the treatment period (<math>P&lt;0.05</math>). At end point, the mean increase over baseline values in patients who switched to fluticasone was 21 L/minute compared with mean decreases of 6 and 28 L/minute in the triamcinolone and placebo groups, respectively (<math>P&lt;0.001</math>).</p> <p>Patients treated with fluticasone had reduced albuterol use by 30% and those in the triamcinolone group by 6%. Patients in the placebo group increased their albuterol use by 50% (<math>P&lt;0.05</math>).</p> <p>At end point, the number of nighttime awakenings requiring albuterol significantly decreased (<math>P\leq 0.001</math> vs placebo) with either fluticasone (-0.03 SEM) or triamcinolone (-0.01 SEM). Nighttime awakenings increased after treatment with placebo (0.27 SEM; <math>P&lt;0.05</math>).</p> <p>There were no significant differences between the treatment groups with respect to symptom scores.</p> <p>Secondary: Thirteen percent of patients in the placebo group, 15% of patients in the fluticasone group, and 8% of patients in the triamcinolone group experienced at least one adverse event that was considered to be potentially related to treatment during the study (sore throat, oral candidiasis, hoarseness).</p> <p>One percent of patients in the placebo group, 3% of patient in the triamcinolone group, and 1% of patients in the fluticasone group had morning plasma cortisol concentrations <math>&lt;5 \mu\text{g/mL}</math>.</p>
<p>Berend et al<sup>60</sup>  Fluticasone at approximately half the</p>	<p>MC, OL, PG, RCT  Patients aged 18 years of age or</p>	<p>N=133  6 months</p>	<p>Primary: Changes in morning PEF and changes in FEV<sub>1</sub> at clinic visits</p>	<p>Primary: At week six, patients in the fluticasone group showed a significant improvement in morning PEF and this improvement was maintained until the end of the study (adjusted difference between two groups, <math>26\pm 32</math></p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>dose of their run-in ICS vs continuing the same dose of ICS used during the 4-week run-in period (beclomethasone or budesonide)</p>	<p>older, with a history of severe asthma who were currently receiving at least 1,750 µg /day of inhaled beclomethasone or budesonide</p>		<p>Secondary: Changes in relevant laboratory values, adverse events, asthma exacerbations, and quality of life</p>	<p>L/minute; 95% CI, 8 to 45; <i>P</i>=0.006).</p> <p>Changes in FEV<sub>1</sub> measured at clinic visits paralleled those values of the morning PEF (fluticasone, 1.87±0.70 L; beclomethasone/budesonide, 2.03±0.86 L; <i>P</i> value not reported).</p> <p>Secondary: Serum osteocalcin levels increased significantly only in the fluticasone group (adjusted mean [SD], 2.6 [4.0] µg/L; 95% CI, 0.2 to 4.9; <i>P</i>=0.03). There were no clinically significant changes during the study in plasma creatinine, plasma glucose, serum insulin, serum fasting lipids, or in any parameter associated with the calcium-parathyroid axis or the renal handling of calcium.</p> <p>There was no significant difference in the analysis of change in hoarseness between the two treatment groups.</p> <p>There was a low incidence of oropharyngeal candidiasis during the study in both treatment groups. By week 24, four patients (6%) in the fluticasone group and one patient (2%) in the beclomethasone/budesonide group had evidence of candidiasis. An analysis of change did not show any significant difference between the two groups.</p> <p>Thirty-four patients (51%) in the fluticasone group and 36 patients (55%) in the beclomethasone/budesonide group reported one or more exacerbations during the course of the trial. No significant difference was seen in the incidence of asthma between the groups.</p> <p>There was a significant increase in the overall asthma quality of life score in the fluticasone group (4.8±1.1 to 5.5±1.1 units; <i>P</i>&lt;0.001); no significant change was seen in the beclomethasone/budesonide group (4.9±1.1 to 5.0±1.2 units; <i>P</i>=0.13).</p>
<b>Chronic Obstructive Pulmonary Disease</b>				
<p>Weir et al<sup>66</sup> Beclomethasone 750 µg</p>	<p>DB, PC, PG, RCT Patients with</p>	<p>N=98 24 months</p>	<p>Primary: Change in FEV<sub>1</sub> and number of</p>	<p>Primary: Decline in FEV<sub>1</sub> was less in the beclomethasone treated group although the difference did not reach statistical significance (mean FEV<sub>1</sub> decline,</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID (<50 kg) or 1,000 µg BID (>50kg)  vs  placebo	COPD		exacerbations  Secondary: Change in histamine reactivity and respiratory symptoms	placebo 45.2 mL/year; budesonide 12.1 mL/year; 95% CI, -80 to 8 mL/year).  The active treatment had fewer exacerbations/year although the difference was not statistically significant (mean exacerbation rates/year: placebo, 0.57; budesonide, 0.36).  Secondary: Bronchial reactivity to inhaled histamine showed no significant change in either active treatment or placebo groups (placebo, -0.09; budesonide, -0.13).  There was no significant effect of active treatment on the Mahler dyspnea index over the study period (placebo, 5.4; beclomethasone, 6.7; <i>P</i> value not reported).
Bourbeau et al <sup>67</sup>  Budesonide 400 µg BID via DPI  vs  placebo	DB, PC, PG, RCT  Patients with COPD 40 years of age or older who did not respond to oral corticosteroids	N=79  6 months	Primary: Decline in FEV <sub>1</sub>  Secondary: Exercise capacity, dyspnea with exertion, quality of life, PEFR, and respiratory symptom scores	Primary: There was no difference in the change in FEV <sub>1</sub> from baseline between the two groups (-4 units difference; -95 to 87).  Secondary: None of the secondary endpoints differed significantly between the two groups (treatment difference, budesonide vs placebo; exercise capacity as measured by the six-minute walking test, -28 units difference; -45 to -10; dyspnea with exertion, 0.1 units difference; -1.0 to 1.1; quality of life, 1.3 units difference; -4.1 to 1.5).  Morning PEFR increased more from baseline in the budesonide group than in the placebo group, but this was observed after only four weeks of treatment and the difference was no longer apparent after one month of treatment.  Symptom scores with budesonide did not produce a significant improvement compared to placebo.
Pauwels et al <sup>68</sup>  Budesonide 400 µg BID	DB, MC, PC, PG, RCT	N=1,277  36 months	Primary: Change in FEV <sub>1</sub>	Primary: In the 912 patients who completed the study, the median decline in FEV <sub>1</sub> over the three-year period was 140 mL in the budesonide group and 180

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
via DPI vs placebo	Current smokers 30 to 65 years of age with COPD		Secondary: Adverse events	mL in the placebo group ( $P=0.05$ ), or 4.3 and 5.3% of their respective predicted values ( $P=0.04$ ).  Secondary: More subjects in the budesonide group had skin bruising (10%) than the placebo group (4%; $P<0.001$ ).  Serious adverse events were equally distributed between the groups. Seventy patients were withdrawn from the study in the budesonide group as compared with 62 patients in the placebo group ( $P=0.51$ ).
Vestbo et al <sup>69</sup>  Budesonide 800 µg QAM and 400 µg QPM for six months followed by 400 µg BID for 30 months administered via DPI  vs placebo for 36 months	DB, PC, PG, RCT  Patients with COPD	N=290  36 months	Primary: Rate of FEV <sub>1</sub> decline  Secondary: Decrease in symptoms	Primary: No significant effect of budesonide was found on the rate of FEV <sub>1</sub> decline. The crude rate of loss of lung function was 41.8 m/year in the placebo group and 45.1 mL/year in the budesonide group. The difference in estimated rates of decline (3.1 mL /year; 95% CI, -12.8 to 19.0) was not significant ( $P=0.70$ ).  Secondary: In both treatment groups, symptoms decreased substantially during the study period but no differences between the two groups was observed.
Burge et al <sup>70</sup>  Fluticasone 500 µg BID  vs placebo	DB, PC, RCT  Patients with COPD with a mean FEV <sub>1</sub> 50% of predicted normal	N=751  36 months	Primary: Rate of decline in FEV <sub>1</sub>  Secondary: Frequency of exacerbations, changes in health status, withdrawals due to respiratory disease, morning serum cortisol levels, and adverse events	Primary: The annual rate of decline in FEV <sub>1</sub> was 59 mL/year in the placebo group and 50 mL/year in the fluticasone group ( $P=0.16$ ). The predicted mean FEV <sub>1</sub> at three and 36 months in the fluticasone group was 76 and 100 mL higher, respectively, than in the placebo group ( $P<0.001$ ).  Secondary: The median yearly exacerbation rate was lower in the fluticasone group (0.99/year) compared to the placebo group (1.32/year), a reduction of 25% in those receiving fluticasone ( $P=0.026$ ).  The respiratory health questionnaire score increased (i.e., health status declined) after the first six months of treatment and this increase was linear ( $P<0.001$ ). The respiratory score worsened at a faster rate in the placebo group (3.2 units/year) than in the fluticasone group (2.0

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>units/year) (<math>P=0.004</math>).</p> <p>More patients in the placebo group than in the fluticasone group withdrew because of respiratory disease (25 vs 19%, respectively; <math>P=0.034</math>).</p> <p>There was a small decrease in mean cortisol concentrations with fluticasone compared with placebo (<math>P\leq 0.032</math>). No decreases were associated with any signs or symptoms of hypoadrenalism or other clinical effects.</p> <p>Reported events were similar between treatments overall, with the exception of side effects secondary to ICSs: hoarseness (35 vs 16), throat irritation (43 vs 27), and candidiasis of the mouth and throat (41 vs 24) were more common in the fluticasone group than in the placebo group.</p>
<p>Paggiaro et al<sup>71</sup></p> <p>Fluticasone 500 µg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients with COPD aged 50 and 75 years of age</p>	<p>N=281</p> <p>6 months</p>	<p>Primary: Number of patients who had at least one exacerbation at the end of the study period</p> <p>Secondary: Mean change from baseline in PEFR, daily symptom scores, and frequency of adverse events</p>	<p>Primary: More patients in the placebo group (37%) experienced at least one exacerbation than in the fluticasone group (32%; <math>P&lt;0.001</math>).</p> <p>Secondary: The adjusted mean change from baseline daily PEFR in the placebo group was -2 L/minute compared to 15 L/minute in the fluticasone group (9 to 26; <math>P&lt;0.001</math>).</p> <p>Symptom scores showed a distribution of significantly lower median daily cough scores in the fluticasone group compared to the placebo group (<math>P=0.004</math>).</p> <p>The overall frequency of adverse events during treatment was similar in the two treatment groups, occurring in 68% of patients receiving placebo and 64% of patients receiving fluticasone.</p>
<p>Lung Health Study Research Group<sup>72</sup></p> <p>Triamcinolone 600 µg BID</p>	<p>PC, RCT</p> <p>Patients with COPD with an FEV<sub>1</sub> 30 to 90% of predicted value</p>	<p>N=1,116</p> <p>48 months</p>	<p>Primary: Rate of decline in FEV<sub>1</sub></p> <p>Secondary: Respiratory symptoms, use of health care</p>	<p>Primary: There were no significant effects of treatment assignment on the decline in FEV<sub>1</sub>. The mean decline in FEV<sub>1</sub> in the triamcinolone group was 44.2±2.9 mL/year, as compared with 47.0±3.0 mL/year in the placebo group (95% CI, -11.0 to 5.4 for the difference).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			services, and airway reactivity	<p>Secondary: The incidence of respiratory symptoms did not differ significantly between the treatment groups, with the exception of dyspnea, which was more frequent in the placebo group (<math>P=0.02</math>).</p> <p>Unscheduled physicians' visits and hospitalizations for respiratory conditions were less frequent in the triamcinolone group (<math>P&lt;0.07</math>).</p> <p>At nine and 33 months, the triamcinolone group had less reactivity in response to methacholine than the placebo group (<math>P=0.02</math>).</p>
Lee et al <sup>73</sup>  Exposure to ICSs, ipratropium, LABAs, theophylline, and SABAs	Nested case-control  Patients treated in the United States Veterans Health Administration health care system	N=145,020  Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	<p>Primary: All-cause mortality, respiratory mortality, and cardiovascular mortality</p> <p>Secondary: Subgroup analyses of primary outcomes</p>	<p>Primary: After adjusted for differences in covariates, ICSs and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICSs and 0.92 (95% CI, 0.88 to 0.96) for LABAs was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15).</p> <p>Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared with the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABAs (OR, 1.12; 95% CI, 0.97 to 1.30), however the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICSs (OR, 0.88; 95% CI, 0.79 to 1.00), however this also did not reach statistical significance.</p> <p>Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABAs (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths.</p> <p>Secondary: In a sensitivity analysis based on the dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICSs, 1.08 for ipratropium, and 0.90 for LABAs.</p> <p>Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICSs with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; <math>P &lt; 0.001</math>).</p> <p>In the all-cause mortality group, ICSs were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.</p>

Drug regimen abbreviations: BID=twice daily, QAM=every morning, QD=once daily, QID=four times daily, QPM=every evening

Study abbreviations: AC=active control, ANOVA=analysis of variance, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SD=standard deviation, SEM=standard error of the mean, XO=cross over

Miscellaneous abbreviations: AQLQ=asthma quality of life questionnaire, CFC=chlorofluorocarbon, COPD=chronic obstructive pulmonary disease, DPI=dry-powder inhaler, FEV<sub>25 to 75%</sub>=forced expiratory flow at 25 to 75% of FVC, FEV<sub>1</sub>=forced expiratory volume in 1 second, FVC=forced vital capacity HFA=hydrofluoroalkane, HPA=hypothalamic-pituitary-adrenal, HRQOL=health-related quality of life, ICS=inhaled corticosteroid, LABA=long acting  $\beta_2$ -agonist, MDI=metered-dose inhaler, NRQLQ=Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire, PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire, PAQLQS=Pediatric Asthma Quality of Life Questionnaire, PEF=peak expiratory flow, PEFr=peak expiratory flow rate, SABA=short acting  $\beta_2$ -agonist, SF-36=Short-Form-36, WMD=weighted mean difference

**Special Populations****Table 5. Special Populations<sup>1-10</sup>**

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Beclomethasone	Dosage adjustment not required in the elderly population.  Approved for use in children five years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes
Budesonide	Dosage adjustment not required in the elderly population.  Approved for use in children 12 months to eight years of age (suspension for nebulization) and six years of age and older (Pulmicort Flexhaler®).	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Yes (0.3 to 1%)
Ciclesonide	Dosage adjustment not required in the elderly population.  Approved for use in children 12 years of age and older.	Not studied in renal dysfunction.	Dosage adjustment not required.	C	Unknown
Flunisolide	Dosage adjustment not required in the elderly population.  Approved for use in children six years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Fluticasone propionate	Dosage adjustment not required in the elderly population.  Approved for use in children four years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Mometasone	Dosage adjustment not required in the elderly population.  Approved for use in children four years of age and older.	Not studied in renal dysfunction.	No dosage adjustment required.	C	Unknown

**Adverse Drug Events**

**Table 6. Adverse Drug Events (%)<sup>1-10</sup>**

Adverse Event(s)	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Propionate	Mometasone
<b>Cardiovascular</b>							
Chest pain	-	-	1 to <3	≥3	3 to 9	-	-
Palpitations	-	-	-	-	3 to 9	-	-
<b>Central Nervous System</b>							
Aggression	-	✓	1 to <3	-	-	✓	-
Agitation	-	-	-	-	-	✓	-
Anxiety	-	✓	1 to <3	-	-	-	-
Depression	-	✓	1 to <3	-	-	✓	11
Dizziness	-	-	-	-	3 to 9	-	-
Emotional lability	-	-	1 to <3	-	-	-	-
Fatigue	-	-	1 to <3	-	≥3	>3	1 to 13
Headache	8 to 25	≥3	≥3	5 to 11	25	2 to 14	17 to 22
Hyperactivity	-	-	-	-	-	✓	-
Hyperkinesia	-	-	1 to <3	-	-	-	-
Hypertonia	-	1 to 3	-	-	-	-	-
Insomnia	-	1 to 3	-	-	-	-	-
Irritability	-	✓	1 to <3	-	-	✓	-
Migraines	-	1 to 3	-	-	-	✓	-
Nervousness	-	✓	1 to <3	-	3 to 9	-	-
Psychosis	-	✓	1 to <3	-	-	-	-
Restlessness	-	✓	1 to <3	-	-	✓	-
Syncope	-	1 to 3	-	-	-	-	-
<b>Dermatological</b>							
Contact dermatitis	-	✓	1 to <3	-	-	-	-
Ecchymoses	-	1 to 3	1 to <3	-	-	✓	-
Eczema	-	-	1 to <3	-	3 to 9	-	-
Pruritis	-	-	1 to <3	-	3 to 9	✓	✓
Rash	✓	✓	≤4	-	3 to 9	✓	✓
Urticaria	✓	✓	1 to <3	≥3	-	✓	-
Viral skin infection	-	-	-	-	-	✓	-
<b>Endocrine and Metabolic</b>							
Edema	-	-	-	-	3 to 9	✓	-

Adverse Event(s)	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Propionate	Mometasone
<b>Gastrointestinal</b>							
Abdominal pain	-	1 to 3	2 to 3	-	-	-	2 to 6
Anorexia	-	-	1 to <3	-	3 to 9	-	1 to <3
Diarrhea	-	-	2 to 4	-	10	✓	-
Dyspepsia	-	1-4	-	-	10	✓	3 to 5
Gastroenteritis	-	1.8	5	≥3	-	-	1 to <3
Gastrointestinal pain	-	1-3	-	-	3 to 9	2 to 4	-
Nausea	≤2	1.8	-	<1	25	1 to 8	1 to 3
Oral candidiasis	-	1.3	-	≥3	3 to 9	≤9	4 to 22
Taste alteration	-	1-3	-	-	10	-	-
Viral gastrointestinal infection	-	-	-	-	-	3 to 5	-
Vomiting	-	1 to 3	2 to 4	-	25	1 to 8	1 to 3
<b>Respiratory</b>							
Angioedema	✓	✓	1 to <3	-	-	✓	✓
Bronchitis	-	-	≥3	-	1 to 3	≤8	-
Bronchospasm	✓	✓	≥3	-	-	✓	✓
Cold symptoms	-	-	-	-	15	-	-
Coughing	1 to 3	✓	5 to 9	<1	3 to 9	1 to 6	✓
Dry mouth	-	1 to 3	-	<1	-	-	-
Dyspnea	-	-	-	-	-	-	✓
Epistaxis	-	-	2 to 4	-	-	-	1 to <3
Hoarseness	-	-	-	≥3	3 to 9	2 to 6	-
Increased asthma symptoms	≤4	-	-	-	-	✓	-
Laryngitis	-	-	-	-	-	✓	-
Nasal congestion	-	2.7	-	1.8 to 5.5	15	-	9
Nasal disorders	-	-	-	-	-	✓	-
Nasal irritation	-	-	-	-	-	-	1 to <3
Nasopharyngitis	-	9.3	-	-	-	-	-
Oropharyngeal edema	-	-	-	-	-	✓	-
Pharyngolaryngeal pain	-	-	-	2.4 to 4.7	-	-	-
Pharyngitis	5 to 27	2.7	≥3	7.0 to 10.5	1 to 3	-	8 to 13
Respiratory disorder	-	-	-	-	-	-	1 to <3
Rhinitis	3 to 8	2.2	7 to 12	3.1 to 5.5	3 to 9	1 to 4	4 to 20
Sinusitis	≤3	≥3	≥3	≥3	-	4 to 10	5 to 22
Stridor	-	-	1 to <3	-	-	-	-

Adverse Event(s)	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Propionate	Mometasone
Upper respiratory tract infection	7 to 11	≥3	34 to 38	4.1 to 8.7	25	14 to 21	8 to 15
Viral respiratory infection	-	-	-	-	-	1 to 5	-
Wheezing	-	✓	-	-	-	✓	✓
<b>Other</b>							
Adrenal suppression	✓	✓	✓	✓	✓	✓	✓
Aphonia	-	-	-	-	-	✓	-
Arthralgia	-	-	-	0.9 to 3.5	-	>3	13
Articular rheumatism	-	-	-	-	-	>3	-
Avascular necrosis of the femoral head	-	-	<1	-	-	-	-
Back pain	1 to 5	≥3	-	0.6 to 3.1	-	-	3 to 6
Bruising	-	-	-	-	-	-	2
Cataracts	✓	✓	✓	✓	✓	✓	✓
Cervical lymphadenopathy	-	-	1 to <3	-	-	-	-
Conjunctivitis	-	-	≤4	≥3	-	-	-
Cushingoid features	-	-	-	-	-	✓	-
Dental caries	-	-	-	-	-	✓	-
Dysmenorrhea	1 to 3	-	-	-	3 to 9	-	4 to 9
Dysphonia	1 to 4	1-6	1 to <3	<1	-	2 to 6	1 to <3
Earache	-	-	1 to <3	-	-	-	1 to <3
Ear infection	-	-	1 to <3	-	3 to 9	-	-
Eye infection	-	-	1 to <3	-	-	-	-
Facial edema	-	-	-	≥3	-	✓	-
Fever	-	≥3	≥3	-	3 to 9	1 to 7	7
Flu syndrome	-	6-14	1 to <3	≥3	10	-	1 to <3
Fracture	-	1 to 3	1 to <3	-	-	-	-
Glaucoma	✓	✓	✓	✓	✓	✓	✓
Growth effects	✓	✓	✓	✓	✓	✓	✓
Herpes simplex	-	-	1 to <3	-	-	-	-
Hyperglycemia	-	-	-	-	-	✓	-
Hyposalivation	-	-	-	-	-	✓	-
Immunosuppression	✓	✓	✓	✓	✓	✓	✓
Infection	-	1 to 3	-	-	-	-	1 to <3
Injury	-	-	-	-	-	≤5	-
Malaise	-	-	-	-	-	>3	-

Adverse Event(s)	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Propionate	Mometasone
Muscle injuries	-	-	-	-	-	✓	-
Musculoskeletal pain	-	-	-	≥3	-	2 to 5	4 to 22
Myalgia	-	1 to 3	1 to <3	-	-	✓	2 to 3
Neck pain	-	1 to 3	-	-	-	-	-
Osteoporosis	-	-	<1	-	-	✓	-
Otitis media	-	1.3	4 to 12	-	-	-	-
Pain	1 to 5	≥3	≥3	0.3 to 3.1	-	✓	1 to <3
Pneumonia	-	-	-	≥3	-	✓	-
Purpura	-	-	1 to <3	-	-	-	-
Soft tissue injuries	-	-	-	-	-	✓	-
Sore Throat	-	✓	-	-	20	3 to 13	1 to <3
Taste perversion	-	1 to 3	-	-	-	-	-
Tooth discoloration	-	-	-	-	-	✓	-
Urinary tract infection	-	-	-	-	-	✓	2
Vasculitis consistent with Churg-Strauss syndrome	-	-	-	-	-	✓	-
Viral infection	-	-	3 to 5	-	-	≤2	-
Voice alteration	-	1 to 3	-	-	-	-	-
Weight gain	-	1 to 3	-	-	-	✓	-

✓ Percent not specified.

- Event not reported.

**Contraindications/Precautions**

All inhaled corticosteroids (ICSs) are contraindicated for the primary treatment of status asthmaticus or in any other acute asthma episodes where intensive measures might be required. These agents are additionally contraindicated in patients with a hypersensitivity to any of the ingredients that are included in the products.<sup>1-10</sup>

Systemic absorption of ICSs can potentially lead to suppression of the hypothalamic-pituitary-adrenal axis. Monitoring for adrenal suppression is recommended. If adrenal suppression should occur, the patient's ICS dose should be decreased in accordance with acceptable procedures. Additionally, when transferring patients from oral systemic corticosteroids to any ICS, particular care is required as deaths due to adrenal insufficiency have occurred, as have the exacerbation of conditions previously controlled by systemic therapy, such as arthritis, rhinitis, eczema, etc.<sup>1-10</sup>

Patients being treated with these agents have also, in rare cases, presented with systemic eosinophilia. Clinical features of the eosinophilia, such as vasculitis, can be consistent with Churg-Strauss syndrome. Health care providers should be alert to the presentation of eosinophilia, vasculitic rash, worsening of pulmonary symptoms, cardiac complications, and neuropathy in patients.<sup>1-10</sup>

Bronchospasms or an immediate increase in wheezing may occur after dosing with any ICS. If bronchospasms do occur they should be treated with a fast-acting inhaled bronchodilator.<sup>1-10</sup>

Patients who are being treated with ICSs for prolonged periods have an increased risk of secondary infections due to immunosuppression. Viral infections such as chickenpox or measles can have a much more serious course in the susceptible adult or pediatric population. Particular care should be taken to avoid exposure in patients who have not had either of these diseases or have not been properly immunized. Furthermore these agents should be used with caution in patients with active or quiescent tuberculosis infection, untreated systemic fungal infections, bacterial, viral, or parasitic infections, or ocular herpes simplex.<sup>1-10</sup>

In the pediatric population, ICSs can cause a decrease in growth velocity. Monitoring of growth in pediatric patients who are receiving ICS routinely is recommended.<sup>1-10</sup>

The use of long-term ICSs also leads to the development of oropharyngeal fungal infections.<sup>1-10</sup> Patients should be advised to rinse their mouth after inhalation of either agent. A decrease in bone mineral density has also been observed with long term ICS treatment.<sup>1-10</sup> Patients with major risk factors for decreased mineral content should be monitored and treated with the established standards of care. Close monitoring of patients with glaucoma and cataracts who are being treated with ICSs is also recommended as increased intraocular pressure has been observed. Routine ocular examination should be considered in this patient population.<sup>1-10</sup>

**Drug Interactions**

**Table 7. Drug Interactions**<sup>1-10</sup>

Generic Name	Interacting Medication or Disease	Potential Result
Budesonide, fluticasone propionate, mometasone	Strong CYP 3A4 inhibitors	CYP3A4 inhibitors such as the azole antifungals (ketoconazole, fluconazole) may inhibit the metabolism of corticosteroids resulting in enhanced corticosteroid effects and toxicity. Doses of inhaled corticosteroids may need to be adjusted.

**Dosage and Administration****Table 8. Dosing and Administration**<sup>1-10</sup>

<b>Generic Name</b>	<b>Adult Dose</b>	<b>Pediatric Dose</b>	<b>Availability</b>
Beclomethasone	<p><u>Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy, where the addition of an inhaled corticosteroid may reduce or eliminate the need for the systemic corticosteroid:</u></p> <p>Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators: initial, 40 to 80 µg BID; maximum, 320 µg BID; patients treated previously with an inhaled corticosteroid; initial, 40 to 160 µg BID; maximum, 320 µg BID</p>	<p><u>Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy, where the addition of an inhaled corticosteroid may reduce or eliminate the need for the systemic corticosteroid:</u></p> <p>Meter dose aerosol inhaler (HFA): children 5 to 11 years of age: initial, 40 µg BID; maximum, 80 µg BID</p>	<p>Meter dose aerosol inhaler (HFA) (100 or 120 inhalations): 40 µg 80 µg</p>
Budesonide	<p><u>Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy, where the addition of an inhaled corticosteroid may reduce or eliminate the need for the systemic corticosteroid:</u></p> <p>Dry powder inhaler: initial, 360 µg BID (selected patients can be initiated at 180 µg BID); maximum, 720 µg BID</p>	<p><u>Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy, where the addition of an inhaled corticosteroid may reduce or eliminate the need for the systemic corticosteroid:</u></p> <p>Dry powder inhaler: children 6 to 17 years of age; initial, 180 µg BID (selected patients can be initiated at 360 µg BID); maximum, 360 µg BID</p> <p>Suspension for nebulization: children 12 months to 8 years of age treated previously with only bronchodilators; initial, 0.5 mg total daily dose administered either QD or in divided doses; maximum, 0.5 mg total daily dose; children 12 months to 8 years of age treated previously with an inhaled corticosteroid;</p>	<p>Dry powder inhaler (60 or 120 inhalations): 90 µg 180 µg</p> <p>Suspension for nebulization: 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL (30 units/carton)</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
		initial, 0.5 mg total daily dose administered either QD or BID in divided doses; maximum, 1 mg total daily dose; children 12 months to 8 years of age treated previously with an oral corticosteroid; initial, 1 mg total daily dose administered either as 0.5 mg BID or 1 mg QD; maximum, 1 mg total daily dose	
Ciclesonide	<u>Maintenance treatment of asthma as prophylactic therapy:</u> Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators; initial, 80 µg BID; maximum, 160 µg BID; patients treated previously with an inhaled corticosteroid; initial, 80 µg BID; maximum, 320 µg BID; patients treated previously with oral corticosteroids; initial, 320 µg BID; maximum, 320 µg BID	Not indicated for children <12 years of age.	Meter dose aerosol inhaler (HFA) (60 inhalations): 80 µg 160 µg
Flunisolide	<u>Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy, where the addition of an inhaled corticosteroid may reduce or eliminate the need for the systemic corticosteroid:</u> Meter dose aerosol inhaler (HFA and CFC): initial, 2 inhalations BID; maximum, 4 inhalations BID	<u>Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy, where the addition of an inhaled corticosteroid may reduce or eliminate the need for the systemic corticosteroid:</u> Meter dose aerosol inhaler (HFA): children 6 to 11 years of age; initial, 1 inhalation BID; maximum, 2 inhalations BID  Meter dose aerosol inhaler (CFC): children 6 to 15 years of age; 2 inhalations BID; maximum 2 inhalations BID	Meter dose aerosol inhaler (HFA) (60 and 120 inhalations): 80 µg  Meter dose aerosol inhaler (CFC) (100 inhalations): 250 µg
Fluticasone propionate	<u>Maintenance treatment of asthma as prophylactic therapy and treatment of</u>	<u>Maintenance treatment of asthma as prophylactic therapy and treatment of</u>	Dry powder inhaler (Diskus®) (60 inhalations):

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p><u>asthma patients requiring systemic corticosteroid therapy, where the addition of an inhaled corticosteroid may reduce or eliminate the need for the systemic corticosteroid:</u></p> <p>Dry powder inhaler: patients treated previously with only bronchodilators; initial, 100 µg BID; maximum, 500 µg BID; patients treated previously with an inhaled corticosteroid; initial, 100 to 250 µg BID; maximum, 500 µg BID; patients treated previously with oral corticosteroids; initial, 500 to 1,000 µg BID; maximum, 1,000 µg BID</p> <p>Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators; initial, 88 µg BID; maximum, 440 µg BID; patients treated previously with an inhaled corticosteroid; initial, 88 to 220 µg BID; maximum, 440 µg BID; patients treated previously with oral corticosteroids; initial, 440 µg BID; maximum, 880 µg BID</p>	<p><u>asthma patients requiring systemic corticosteroid therapy, where the addition of an inhaled corticosteroid may reduce or eliminate the need for the systemic corticosteroid:</u></p> <p>Dry powder inhaler: children 4 to 11 years of age treated previously with only bronchodilators or with inhaled corticosteroids; initial, 50 µg BID; maximum, 100 µg BID</p> <p>Meter dose aerosol inhaler (HFA): children 4 to 11 years of age; initial 88 µg BID; maximum, 88 µg BID</p>	<p>50 µg 100 µg 250 µg</p> <p>Meter dose aerosol inhaler (HFA) (120 inhalations): 44 µg 110 µg 220 µg</p>
Mometasone	<p><u>Maintenance treatment of asthma as prophylactic therapy:</u></p> <p>Dry powder inhaler: patients treated previously with only bronchodilators or inhaled corticosteroids; initial, 220 µg QD in the evening; maximum, 440 µg administered as QD in the evening or as 220 µg BID; patients treated previously with oral corticosteroids; initial, 440 µg BID; maximum, 880 µg daily</p>	<p><u>Maintenance treatment of asthma as prophylactic therapy:</u></p> <p>Dry powder inhaler: children 4 to 11 years of age; initial, 110 µg QD in the evening; maximum, 110 µg QD in the evening</p>	<p>Dry powder inhaler (Twisthaler®): 110 µg (7 and 30 inhalations) 220 µg (14, 30, 60 and 120 inhalations)</p>

BID=twice daily, CFC=chlorofluorocarbons, HFA=hydrofluoroalkane, MDI=meter dose inhaler, QD=once daily

## Clinical Guidelines

**Table 9. Clinical Guidelines**

Clinical Guidelines	Recommendations
<p>The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: <b>Guidelines for the Diagnosis and Management of Asthma (2007)</b><sup>61</sup></p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> <li>• To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded.</li> <li>• The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses.</li> <li>• A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night.</li> <li>• Spirometry is needed to establish a diagnosis of asthma.</li> <li>• Additional studies such as additional pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses.</li> </ul> <p><u>Treatment</u></p> <ul style="list-style-type: none"> <li>• Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction.</li> <li>• The initial treatment of asthma should correspond to the appropriate asthma severity category.</li> <li>• Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma.</li> <li>• Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing.</li> <li>• Quick relief medications include short-acting <math>\beta_2</math>-adrenergic agonists (SABAs), anticholinergics and systemic corticosteroids.</li> </ul> <p><u>Long-term control medications</u></p> <ul style="list-style-type: none"> <li>• ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages.</li> <li>• Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma.</li> <li>• When patients <math>\geq 12</math> years of age require more than low-dose ICSs, the addition of a long-acting <math>\beta_2</math>-adrenergic agonists (LABAs) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton.</li> <li>• Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens.</li> <li>• Omalizumab, an immunomodulator, is used as adjunctive therapy in</li> </ul>

Clinical Guidelines	Recommendations																		
	<p>patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy.</p> <ul style="list-style-type: none"> <li>Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma.</li> <li>LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma.</li> <li>LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA.</li> <li>Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.</li> <li>Tiotropium bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease and has not been studied in the long-term management of asthma.</li> </ul> <p><u>Quick-relief medications</u></p> <ul style="list-style-type: none"> <li>SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise induced bronchospasm.</li> <li>There is inconsistent data regarding the efficacy of levalbuterol compared to albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol.</li> <li>Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations.</li> <li>Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations.</li> <li>The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma.</li> </ul> <p><u>Assessment, treatment and monitoring</u></p> <ul style="list-style-type: none"> <li>A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.</li> <li>Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.</li> <li>The stepwise approach for managing asthma is outlined below:</li> </ul> <table border="1" data-bbox="500 1465 1421 1852"> <thead> <tr> <th data-bbox="500 1465 630 1549">Intermittent Asthma</th> <th colspan="5" data-bbox="630 1465 1421 1549">Persistent Asthma: Daily Medication</th> </tr> <tr> <th data-bbox="500 1549 630 1581">Step 1</th> <th data-bbox="630 1549 784 1581">Step 2</th> <th data-bbox="784 1549 954 1581">Step 3</th> <th data-bbox="954 1549 1125 1581">Step 4</th> <th data-bbox="1125 1549 1263 1581">Step 5</th> <th data-bbox="1263 1549 1421 1581">Step 6</th> </tr> </thead> <tbody> <tr> <td data-bbox="500 1581 630 1852">Preferred SABA as needed</td> <td data-bbox="630 1581 784 1852">Preferred Low-dose ICS  Alternative Cromolyn, leukotriene receptor antagonists, nedocromil,</td> <td data-bbox="784 1581 954 1852">Preferred Low-dose ICS+LABA or medium-dose ICS  Alternative Low-dose ICS+either a leukotriene</td> <td data-bbox="954 1581 1125 1852">Preferred Medium-dose ICS+LABA  Alternative Medium-dose ICS+either a leukotriene</td> <td data-bbox="1125 1581 1263 1852">Preferred High-dose ICS+LABA and consider omalizumab for patients who have</td> <td data-bbox="1263 1581 1421 1852">Preferred High-dose ICS+LABA + oral steroid and consider omalizumab for patients who have</td> </tr> </tbody> </table>	Intermittent Asthma	Persistent Asthma: Daily Medication					Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Preferred SABA as needed	Preferred Low-dose ICS  Alternative Cromolyn, leukotriene receptor antagonists, nedocromil,	Preferred Low-dose ICS+LABA or medium-dose ICS  Alternative Low-dose ICS+either a leukotriene	Preferred Medium-dose ICS+LABA  Alternative Medium-dose ICS+either a leukotriene	Preferred High-dose ICS+LABA and consider omalizumab for patients who have	Preferred High-dose ICS+LABA + oral steroid and consider omalizumab for patients who have
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Clinical Guidelines	Recommendations					
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<p>Global Initiative for Asthma: <b>Global Strategy for Asthma Management and Prevention (2009)</b><sup>62</sup></p>	<p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> <li>Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.</li> </ul> <p><u>Special populations</u></p> <ul style="list-style-type: none"> <li>For exercise induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs. The addition of cromolyn to a SABA is helpful in some individuals who have exercise induced bronchospasm.</li> <li>Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.</li> <li>Albuterol is the preferred SABA in pregnant women because of an excellent safety profile.</li> <li>ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.</li> </ul> <p><u>Diagnosis</u></p> <ul style="list-style-type: none"> <li>A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough and chest tightness.</li> <li>Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity, reversibility and variability of airflow limitation and provide confirmation of the diagnosis of asthma.</li> </ul> <p><u>Treatment</u></p> <ul style="list-style-type: none"> <li>Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages.</li> <li>Measures to prevent the development of asthma, asthma symptoms and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible.</li> <li>Controller medications are administered daily on a long-term basis and include inhaled and systemic glucocorticosteroids, leukotriene receptor antagonists, LABAs in combination with ICS, sustained-released theophylline, cromones and anti-immunoglobulin E (IgE).</li> <li>Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include SABAs, inhaled anticholinergics and short-acting theophylline.</li> </ul> <p><u>Controller medications</u></p> <ul style="list-style-type: none"> <li>ICSs are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages.</li> <li>ICSs differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences.</li> </ul>					

Clinical Guidelines	Recommendations
	<ul style="list-style-type: none"> <li>• To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of ICS.</li> <li>• Leukotriene receptor antagonists are generally less effective than ICSs and therefore may be used as an alternative treatment in patients with mild persistent asthma.</li> <li>• Some patients with aspirin-sensitive asthma respond well to leukotriene receptor antagonists.</li> <li>• Leukotriene receptor antagonists used as add-on therapy may reduce the dose of ICS required by patients with moderate to severe asthma and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of ICS.</li> <li>• Several studies have demonstrated that leukotriene receptor antagonists are less effective than LABAs as add-on therapy.</li> <li>• LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation.</li> <li>• When a medium-dose ICS fails to achieve control, the addition of a LABA is the preferred treatment.</li> <li>• Controlled studies have shown that delivering a LABA and an ICS in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance and ensure that the LABA is always accompanied by an ICS.</li> <li>• Although the guideline indicates that combination inhalers containing budesonide and formoterol may be used for rescue and maintenance therapy, this use is not approved by the Food and Drug Administration (FDA).</li> <li>• Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on ICS alone.</li> <li>• Cromolyn and nedocromil are less effective than a low dose of an ICS.</li> <li>• Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed.</li> <li>• Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE.</li> <li>• Long-term oral corticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects.</li> <li>• Other anti-allergic compounds have limited effect in the management of asthma.</li> </ul> <p><u>Reliever medications</u></p> <ul style="list-style-type: none"> <li>• SABAs are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise induced bronchospasm in patients of all ages.</li> <li>• SABAs should be used only on an as-needed basis at the lowest dose and frequency required.</li> <li>• Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with ICS, the use of this agent as a rescue inhaler is not approved by the FDA.</li> <li>• Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than SABAs.</li> <li>• Short-acting theophylline may be considered for relief of asthma</li> </ul>

Clinical Guidelines	Recommendations																																				
	<p>symptoms.</p> <ul style="list-style-type: none"> <li>Short-acting oral <math>\beta_2</math>-adrenergic agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication; however, they are associated with a higher prevalence of adverse effects.</li> <li>Systemic corticosteroids are important in the treatment of severe acute exacerbations.</li> </ul> <p><u>Assessment, treatment, and monitoring</u></p> <ul style="list-style-type: none"> <li>The goal of asthma treatment is to achieve and maintain clinical control.</li> <li>To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled or uncontrolled.</li> <li>Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained, treatment can be stepped down to the lowest step and dose of treatment that maintains control.</li> <li>Asthma control is defined as: no (twice or less/week) daytime symptoms; no limitations of daily activities, including exercise; no nocturnal symptoms or awakening because of asthma; no (twice or less/week) need for reliever treatment; normal or near-normal lung function results and no exacerbations.</li> <li>Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.</li> <li>The management approach based on control is outlined below:</li> </ul>																																				
<table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:15%;">Step 1</th> <th style="width:15%;">Step 2</th> <th style="width:15%;">Step 3</th> <th style="width:15%;">Step 4</th> <th style="width:15%;">Step 5</th> </tr> </thead> <tbody> <tr> <td colspan="5" style="text-align:center;"><i>Asthma Education and Environmental Control</i></td> </tr> <tr> <td style="text-align:center;"><i>As Needed SABAs</i></td> <td colspan="4" style="text-align:center;"><i>As Needed SABAs</i></td> </tr> <tr> <td rowspan="4" style="text-align:center; vertical-align:middle;"><b>Controller Options*</b></td> <td style="text-align:center;">Select One</td> <td style="text-align:center;">Select One</td> <td style="text-align:center;">To Step 3 Treatment, Select One or More</td> <td style="text-align:center;">To Step 4 Treatment, Add Either</td> </tr> <tr> <td style="text-align:center;"><u>Low-dose ICS</u></td> <td style="text-align:center;"><u>Low-dose ICS+LABA</u></td> <td style="text-align:center;"><u>Medium- or high-dose ICS+LABA</u></td> <td style="text-align:center;">Oral corticosteroid</td> </tr> <tr> <td style="text-align:center;">Leukotriene receptor antagonists</td> <td style="text-align:center;">Medium- or high-dose ICS Low-dose ICS + leukotriene receptor antagonists</td> <td style="text-align:center;">Leukotriene receptor antagonists Sustained release theophylline</td> <td style="text-align:center;">Anti-IgE treatment</td> </tr> <tr> <td style="text-align:center;">-</td> <td style="text-align:center;">Low-dose ICS + sustained-release theophylline</td> <td style="text-align:center;">-</td> <td style="text-align:center;">-</td> </tr> </tbody> </table>	Step 1	Step 2	Step 3	Step 4	Step 5	<i>Asthma Education and Environmental Control</i>					<i>As Needed SABAs</i>	<i>As Needed SABAs</i>				<b>Controller Options*</b>	Select One	Select One	To Step 3 Treatment, Select One or More	To Step 4 Treatment, Add Either	<u>Low-dose ICS</u>	<u>Low-dose ICS+LABA</u>	<u>Medium- or high-dose ICS+LABA</u>	Oral corticosteroid	Leukotriene receptor antagonists	Medium- or high-dose ICS Low-dose ICS + leukotriene receptor antagonists	Leukotriene receptor antagonists Sustained release theophylline	Anti-IgE treatment	-	Low-dose ICS + sustained-release theophylline	-	-	<p>*Preferred controller options are underlined.</p>				
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	<ul style="list-style-type: none"> <li>Patients who do not reach an acceptable level of control at Step 4 can be considered to have difficult-to-treat asthma. In these patients, a compromise may need to be reached focusing on achieving the best level of control feasible, with as little disruption of activities and as few daily symptoms as possible, while minimizing the potential for adverse effects. Consideration of utilizing an asthma specialist should occur.</li> </ul>																																				

Clinical Guidelines	Recommendations
	<p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> <li>• Repeated administration of SABAs is the best method of achieving relief for mild to moderate exacerbations.</li> <li>• Systemic corticosteroids should be considered if the patient does not immediately respond to SABAs or if the episode is severe.</li> </ul> <p><u>Special populations</u></p> <ul style="list-style-type: none"> <li>• LABAs may also be used to prevent exercise induced bronchospasm and because of a more rapid onset of action, formoterol is more suitable for symptom relief as well as symptom prevention over salmeterol.</li> <li>• Appropriately monitored use of theophylline, ICS, <math>\beta_2</math>-adrenergic agonists and leukotriene receptor antagonists, specifically montelukast, are not associated with an increased incidence of fetal abnormalities.</li> <li>• ICS has been shown to prevent exacerbations of asthma during pregnancy.</li> <li>• Acute exacerbations during pregnancy should be treated with nebulized SABAs and oxygen. Systemic corticosteroids should be instituted when necessary.</li> </ul>
<p>Global Initiative for Chronic Obstructive Lung Disease: <b>Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2010)</b><sup>63</sup></p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> <li>• A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease.</li> <li>• A diagnosis of COPD should be confirmed by spirometry.</li> <li>• The presence of a post-bronchodilator forced expiratory volume in one second (FEV<sub>1</sub>)/forced vital capacity (FVC) &lt;0.70 confirms the presence of airflow limitation that is not fully reversible.</li> <li>• Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications.</li> <li>• A detailed medical history should be obtained for all patients suspected of developing COPD.</li> <li>• Severity of COPD is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications such as respiratory failure, right heart failure, weight loss and arterial hypoxemia.</li> <li>• Chest radiograph may be useful to rule out other diagnoses and to establish the presence of significant comorbidities such as cardiac failure.</li> <li>• Arterial blood gas tension measurements should be considered for all patients with FEV<sub>1</sub> &lt;50% predicted or clinical signs suggestive of respiratory failure or right heart failure.</li> <li>• COPD is typically a progressive disease; therefore, lung function can be expected to worsen over time, even with the best available care.</li> <li>• Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy. In addition, symptom monitoring is used to determine when to modify therapy and to identify any complications that may develop.</li> <li>• Comorbidities are common in COPD and should be actively identified. Comorbidities often complicate the management of COPD, and vice versa.</li> <li>• Screening for <math>\alpha_1</math>-antitrypsin deficiency may be valuable in patients of Caucasian descent who develop COPD at a young age (&lt;45 years of age)</li> </ul>

Clinical Guidelines	Recommendations
	<p>or who have a strong family history of the disease.</p> <ul style="list-style-type: none"> <li>In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques and it is assumed that asthma and COPD coexist in these patients. In these instances, current management is similar to that of asthma. Other potential diagnoses (e.g., congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis, and diffuse panbronchiolitis) are usually easier to distinguish from COPD.</li> </ul> <p><u>Treatment</u></p> <ul style="list-style-type: none"> <li>The management of COPD should be individualized to address symptoms and improve the patient's quality of life.</li> <li>None of the medications for COPD have been shown to modify the long term decline in lung function that is hallmark of this disease. Treatment should be focused on reducing symptoms and complications.</li> <li>Choice of agent within each medication class depends on the availability of medication and the patient's response.</li> <li>Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms.</li> <li>Inhaled therapy is preferred.</li> <li>When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. COPD patients may have more problems in effective coordination with a metered dose inhaler compared to healthy patients; alternative breath-activated or spacer devices are available for most formulations. Dry powder inhalers may be more convenient and possibly provide improved drug deposition, although this has not been established in COPD.</li> <li>Principle bronchodilators include <math>\beta_2</math>-agonists, anticholinergics and methylxanthines used as monotherapy or in combination.</li> <li>Regular treatment with long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.</li> <li>The choice between <math>\beta_2</math>-agonists, anticholinergics, theophylline or combination therapy depends on availability and individual response in terms of symptom relief and side effects.</li> <li>The order in which the bronchodilator medications are normally introduced into patient care (based on the level of disease severity and clinical symptoms) is: <math>\beta</math>-agonists, anticholinergics and methylxanthines.</li> <li>Regular use of LABAs or short- or long-acting anticholinergics improves health status.</li> <li>Long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation.</li> <li>Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. All theophylline studies were performed with slow-release preparations.</li> <li>Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.</li> <li>For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators.</li> <li>The addition of regular treatment with ICSs to bronchodilator treatment is</li> </ul>

Clinical Guidelines	Recommendations
	<p>appropriate for symptomatic COPD patients with an FEV<sub>1</sub> &lt;50% predicted and repeated exacerbations.</p> <ul style="list-style-type: none"> <li>• Regular treatment with ICSs has been shown to reduce the frequency of exacerbations and thus improve health status for symptomatic patients with an FEV<sub>1</sub> &lt;50% of the predicted value and repeated exacerbations.</li> <li>• Treatment with ICSs increases the likelihood of pneumonia and does not reduce overall mortality.</li> <li>• An ICS combined with a LABA is more effective than the individual components in reducing exacerbations and improving lung function and health status.</li> <li>• Combination ICS/LABA therapy increases the likelihood of pneumonia.</li> <li>• Addition of an ICS/LABA to an anticholinergic appears to provide additional benefits.</li> <li>• There is insufficient evidence to recommend a therapeutic trial with systemic corticosteroids in patients with Stage II, Stage III or Stage IV COPD and poor response to an inhaled bronchodilator.</li> <li>• Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio.</li> <li>• In COPD patients influenza vaccines can reduce serious illness.</li> <li>• The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients &lt;65 years old with an FEV<sub>1</sub> &lt;40% of the predicted value.</li> <li>• Long-term administration of oxygen (&gt;15 hours/day) increases survival in patients with chronic respiratory failure.</li> </ul> <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> <li>• The most common causes of an exacerbation are tracheobronchial tree infections and air pollution.</li> <li>• Inhaled β<sub>2</sub>-agonists (particularly inhaled β<sub>2</sub>-agonists with or without anticholinergics) and systemic corticosteroids are effective treatments for exacerbations of COPD.</li> <li>• Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.</li> </ul>
<p>National Institute for Health and Clinical Excellence:  <b>Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)</b><sup>64</sup></p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> <li>• Diagnosis should be considered in patients &gt;35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze.</li> <li>• The primary risk factor is smoking.</li> <li>• Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV<sub>1</sub> &lt;80% predicted and FEV<sub>1</sub>/FVC &lt;70%.</li> </ul> <p><u>Treatment</u></p> <ul style="list-style-type: none"> <li>• Smoking cessation should be encouraged for all patients with COPD.</li> <li>• Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation.</li> <li>• Long-acting bronchodilators (beta<sub>2</sub> agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators.</li> <li>• Once-daily long-acting muscarinic antagonists are preferred compared to four-times-daily short-acting muscarinic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use</li> </ul>

Clinical Guidelines	Recommendations
	<p>of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with a muscarinic antagonist.</p> <ul style="list-style-type: none"> <li>○ FEV<sub>1</sub> ≥50% predicted: long-acting β<sub>2</sub>-agonist or long-acting muscarinic antagonist.</li> <li>○ FEV<sub>1</sub> &lt; 50% predicted: either long-acting β<sub>2</sub>-agonist with an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist.</li> </ul> <ul style="list-style-type: none"> <li>• In patients with stable COPD and FEV<sub>1</sub> ≥50% who remain breathless or have exacerbations despite maintenance therapy with a long-acting β<sub>2</sub>-agonist, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist when inhaled corticosteroids are not tolerated or declined.</li> <li>• Consider a long-acting muscarinic antagonist in patients remaining breathless or having exacerbations despite therapy with long-acting β<sub>2</sub>-agonist and inhaled corticosteroids and vice versa.</li> <li>• Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs.</li> <li>• In most cases, inhaled bronchodilator therapy is preferred.</li> <li>• Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation.</li> <li>• Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β<sub>2</sub>-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy.</li> <li>• Pulmonary rehabilitation should be made available to patients.</li> <li>• Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure.</li> </ul> <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> <li>• Patients with exacerbations should be evaluated for hospital admission.</li> <li>• Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial.</li> <li>• Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days.</li> <li>• Oxygen should be given to maintain oxygen saturation above 90%.</li> <li>• Patients should receive invasive and noninvasive ventilation as necessary.</li> <li>• Respiratory physiotherapy may be used to help remove sputum.</li> <li>• Before discharge, patients should be evaluated by spirometry.</li> <li>• Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.</li> </ul>

**Conclusions**

Inhaled corticosteroids (ICS) have evolved into the cornerstone of drug therapy for long-term asthma control. The single entity inhaled corticosteroids are Food and Drug Administration (FDA) approved for the maintenance treatment of asthma as prophylactic therapy. They are also approved for asthmatic patients requiring oral corticosteroid therapy.<sup>1-10</sup> Current clinical evidence does not demonstrate that one ICS is safer or more efficacious than another.<sup>17-60,66-73</sup>

Asthma guidelines stress the role of ICSs as long-term controller medications. Both the National, Heart, Lung, Blood Institute and the Global Initiative for Asthma guidelines state that ICSs are the preferred treatment for initiating therapy in children and adults of all ages with persistent asthma. It is important to note, that the current consensus guidelines do not give preference to one ICS over another.<sup>61,62</sup>

ICS agents are frequently prescribed in patients with chronic obstructive pulmonary disease (COPD). Both the Global Initiative for Chronic Obstructive Lung Disease guidelines, as well as the National Institute for Clinical Excellence COPD guidelines recommend ICSs as add-on therapy to long-acting bronchodilators in patients with an forced expiratory volume in 1 second  $\leq$  50% predicted and repeated exacerbations.<sup>63,64</sup>

**Appendix I: Utilization Within This Drug Class for DVHA: July 1, 2010 to December 31, 2010**

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Flovent HFA	2,783	3,719	77.33%	\$723,515.92	\$194.55
Pulmicort	413	545	11.35%	\$190,416.66	\$349.39
Pulmicort Flexhaler	155	187	3.89%	\$30,177.60	\$161.38
Asmanex 30 metered doses	82	94	1.95%	\$17,783.87	\$189.19
QVAR	60	86	1.79%	\$11,044.29	\$128.42
Budesonide	31	63	1.31%	\$27,303.16	\$433.38
Asmanex 60 metered doses	43	57	1.18%	\$11,341.41	\$198.97
Flovent Diskus	36	41	0.85%	\$5,265.37	\$128.42
Asmanex 120 metered doses	9	9	0.19%	\$4,483.01	\$498.11
Alvesco	3	6	0.12%	\$1,334.61	\$222.44
Aerobid-M	1	2	0.04%	\$171.72	\$85.86
<b>Class Total:</b>	<b>NA</b>	<b>4,809</b>	<b>100%</b>	<b>\$1,022,837.62</b>	<b>\$212.69</b>

**Recommendations**

In recognition of the well-established role of the inhaled corticosteroids for the treatment of asthma, as well as chronic obstructive pulmonary disease, their equivalent efficacy and safety in the management of both disease states, and the limited availability of these agents as generic entities, it is recommended that no changes be made to the current Department of Vermont Health Access (DVHA) approval criteria (see below).

Metered-dose inhalers (single agent):

- The patient has been started and stabilized on the medication.
- OR
- The patient has had a documented side effect, allergy, or treatment failure to at least two preferred agents.

Budesonide Inh Suspension (all ages):

- The patient requires a nebulizer formulation.
- AND
- The patient has a documented intolerance to the brand product.

Pulmicort Respules<sup>®</sup> (age > 12 years):

- The patient requires a nebulizer formulation.

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