Therapeutic Class Overview
Inhaled Corticosteroids

Therapeutic Class

- **Overview/Summary:** The inhaled corticosteroids (ICSs) are Food and Drug Administration (FDA)-approved for the maintenance treatment of asthma as prophylactic therapy. Beclomethasone (QVAR®) and fluticasone propionate (Flovent Diskus®, Flovent HFA®) are also indicated for use in asthma patients who require systemic corticosteroid therapy when the addition of an ICS could reduce or eliminate the need for systemic corticosteroids.[1-7] Though not FDA-approved, these single-entity ICS have been used in the treatment of chronic obstructive pulmonary disease (COPD). The ICSs are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response. These agents exert their anti-inflammatory effects by binding to 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.[1-8] Inflammation is also a component of COPD pathogenesis. Although the ICSs exert their therapeutic effects through identical mechanisms of action, they differ in their potency, dosing schedules, and dosage form availability. Currently, a generic formulation of Pulmicort Respules® is available.[9] 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. As a result, hydrofluoroalkane replaced CFCs as the propellant in currently available inhaler products.[10]

Table 1. Current Medications Available in Therapeutic Class[1-8]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Beclomethasone (QVAR®)	Maintenance treatment of asthma as prophylactic therapy in patients five years of age and older**,** 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	Meter dose aerosol inhaler (HFA) (100 or 120 inhalations): 40 µg 80 µg	-
Budesonide (Pulmicort Flexhaler®, Pulmicort Respules®*****)	Maintenance treatment of asthma as prophylactic therapy in patients six years of age and older (Pulmicort Flexhaler®) and in patients 12 months to eight years of age (Pulmicort Respules®)	Dry powder inhaler (60 or 120 inhalations): 90 µg 180 µg Suspension for nebulization: 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL (30 units/carton)	✔
Ciclesonide (Alvesco®)	Maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older	Meter dose aerosol inhaler (HFA) (60 inhalations): 80 µg 160 µg	-
Fluticasone propionate (Flovent Diskus®, Flovent HFA®)	Maintenance treatment of asthma as prophylactic therapy in patients four years of age and older, treatment of	Dry powder inhaler (Diskus®) (60 inhalations): 50 µg 100 µg	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	asthma patients requiring systemic corticosteroid therapy, where the addition of an inhaled corticosteroid may reduce or eliminate the need for the systemic corticosteroid in patients four years of age and older	250 µg Meter dose aerosol inhaler (HFA) (120 inhalations): 44 µg 110 µg 220 µg	
Mometasone (Asmanex Twisthaler®)	Maintenance treatment of asthma as prophylactic therapy in patients four years of age and older	Dry powder inhaler (Twisthaler®): 110 µg (seven and 30 inhalations) 220 µg (14, 30, 60 and 120 inhalations)	-

HFA=hydrofluoroalkane.
*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- 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. The results of head-to-head trials directly comparing the inhaled corticosteroids products have not demonstrated one agent to be significantly more effective than another, regardless of the potency or dosage form of the inhaled corticosteroid agent used.[11-52]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Inhaled corticosteroids (ICSs) are the preferred treatment for initiating therapy in children and adults of all ages with persistent asthma.[53,54]
  - ICSs are recommended as first-line therapy for long-term control of persistent asthma symptoms in all age groups.[53,54]
  - ICS agents reduce both impairment and risk of asthma exacerbations.[53,54]
  - In patients with an forced expiratory volume in one second (FEV_1) <60% of the predicted value, regular treatment with ICS improves symptoms, lung function and quality of life as well as reduces exacerbations. However, long term therapy ICS as monotherapy is not recommended.[55]
  - ICSs are recommended as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤50% predicted and repeated exacerbations.[56]
- Other Key Facts:
  - The role of the inhaled corticosteroids in treatment of asthma has been well established.
  - The ICSs have been shown to be safe and effective in the treatment of asthma and are recommended as first-line treatment for long-term control in all age groups; however, study results have not consistently demonstrated a significant difference between products.
  - Currently, budesonide suspension for nebulization is the only generic product available within the therapeutic class.[9]

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Therapeutic Class Review
Inhaled Corticosteroids

Overview/Summary

The inhaled corticosteroids (ICSs) are Food and Drug Administration (FDA)-approved for the maintenance treatment of asthma as prophylactic therapy. Beclomethasone (QVAR®) and fluticasone propionate (Flovent Diskus®, Flovent HFA®) are also indicated for use in asthma patients who require systemic corticosteroid therapy when the addition of an ICS could reduce or eliminate the need for systemic corticosteroids.[1-7] 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 and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response. The ICSs exert their anti-inflammatory effects by binding to 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 chronic obstructive pulmonary disease (COPD) pathogenesis; however, no single-entity ICS has been FDA-approved for use in COPD.[1-9]

Although ICSs exert their therapeutic effects through identical mechanisms of action, they differ in their potency, dosing schedules, and dosage form availability. Clinical trials comparing ICSs of varying potencies have shown that those of higher potencies do not demonstrate greater clinical efficacy than those of lower potencies when administered at equipotent doses.[10-12] Clinical trials have not demonstrated any major differences in clinical efficacy between the available ICSs.[13-54] Currently, budesonide suspension for nebulization is available generically.[55]

Treatment guidelines published by the National Heart, Lung and Blood Institute (NHLBI) state that the ICSs are the most potent and consistently effective long-term controller medications for asthma patients of all ages. These agents are recommended as first-line therapy for long-term control of persistent asthma symptoms in all age groups. Although ICSs 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 as possessing greater clinical efficacy or as a preferred agent over the other medications within the therapeutic class.[56] The NHLBI guidelines also discuss the issue of growth velocity suppression in children treated with ICSs. The benefits of treatment with an ICS outweigh the concerns for growth, and that untreated or poorly controlled asthma may also cause a decrease in a child's growth. The adverse effect on growth rate associated with these agents does appear to be dose dependant; however, it is not considered predictable. The effect on growth velocity appears to occur mainly in the first several months of treatment and is generally small and not progressive. Due to the possibility of growth suppression, ICS doses in children should be titrated to as low of a dose as need to maintain good asthma control and children should be monitored for potential growth rate changes.[56] 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 ICSs, these patients will ultimately reach their normal predicted height.[12,57,58] 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. In addition, the GINA guidelines indicate that although ICSs 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 do not recommend one ICS over another.[59]

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. Principle bronchodilators include β_2-agonists and anticholinergics and the use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator. In patients with an FEV_1 <60% of the predicted value, regular treatment with ICS improves symptoms, lung function and quality of life as well as reduces exacerbations. However, long term therapy ICS as monotherapy is not recommended.[60] 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_1 ≤50% predicted and repeated exacerbations.[61] 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. As a result, hydrofluoroalkane replaced CFCs as the propellant in currently available inhaler products.[62]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Beclomethasone (QVAR®)	Inhaled corticosteroid	-
Budesonide (Pulmicort Flexhaler®, Pulmicort Respules®*)	Inhaled corticosteroid	✔
Ciclesonide (Alvesco®)	Inhaled corticosteroid	-
Fluticasone propionate (Flovent Diskus®, Flovent HFA®)	Inhaled corticosteroid	-
Mometasone (Asmanex Twisthaler®)	Inhaled corticosteroid	-

HFA=hydrofluoroalkane.
*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-10]

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®†, Pulmicort Respules®‡)	
Ciclesonide	✔ §	
Fluticasone propionate	✔ ‖	✔ ‖
Mometasone	✔ ‖	

*In patients five years of age and older.
† In patients six years of age and older.
‡ In patients 12 months to eight years of age.
§ In patients 12 years of age and older.
‖ In patients four years of age and older.

In addition to their Food and Drug Administration-approved indications, the inhaled corticosteroids have been used off-label in the treatment of graft vs host disease, inflammatory bowel disease, eosinophilic esophagitis and chronic obstructive pulmonary disease.

Pharmacokinetics

Table 3. Pharmacokinetics[1-11]

Generic Name	Onset (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Beclomethasone	0.5	<10	Beclomethasone-17-monopropionate	2.8
Budesonide	1 to 2	60	No	2 to 3*
Ciclesonide	Not reported	≤20	Des-ciclesonide	6 to 7
Fluticasone propionate	Variable	<5	No	7.8†
Mometasone	1.0 to 2.5	8	No	5

*Budesonide Respules in asthmatic children four to six years of age.
†Following intravenous administration.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the inhaled corticosteroids in their respective Food and Drug Administration-approved indication are described in Table 4.[13-54]

Numerous placebo controlled trials have demonstrated the efficacy of inhaled corticosteroids in the treatment of asthma, and these agents are considered the most effective agents in the long-term management of the disease. The results of head-to-head trials directly comparing the inhaled corticosteroids have not demonstrated one agent to be significantly more effective than another, regardless of the potency or dosage form of the inhaled corticosteroid agent used.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Busse et al[13] Beclomethasone HFA MDI 100 µg/day vs beclomethasone HFA MDI 400 µg/day vs 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	DB, MC, PG, RCT Asthmatic patients who had deteriorated in their asthma control following discontinuation of ICS	N=323 6 weeks	Primary: Change from baseline in FEV_1 percent predicted Secondary: Percent change from baseline in $FEF_{25\ to\ 75\%}$, FVC, morning and evening PEF, asthma symptom scores, nighttime awakenings and daily albuterol use	Primary: For each treatment group, the FEV_1 percent predicted increased over the first four weeks of treatment and plateaued by week six. The change from baseline in FEV_1 percent predicted was greater with beclomethasone 800 µg/day HFA (-32.7%; *P*=0.049) compared to beclomethasone 400 µg/day HFA (-25.1%) and numerically, but not significantly greater (*P*=0.09) with beclomethasone CFC 800 µg/day (-31.3%) compared to beclomethasone CFC 400 µg/day (-22.6%). Secondary: ANOVA showed significant dose effects across both products for $FEF_{25\ to\ 75\%}$, FVC and morning PEF. Evening PEF, asthma symptom scores, nighttime sleep disturbances, and daily albuterol use were similar among all treatment groups.
Bronsky et al[14] Beclomethasone 336 µg/day	AC, DB, DD, MC, PC, PG, RCT Adults with mild to moderately severe	N=328 56 days	Primary: Mean changes from baseline in FEV_1 Secondary:	Primary: The mean change from baseline in FEV_1 for both active treatments was significantly greater compared to placebo (0.27 and 0.16 vs -0.10 L for beclomethasone and triamcinolone compared to placebo; $P \leq 0.01$ for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs triamcinolone 800 µg/day vs placebo	asthma maintained on an ICS		Asthma symptom scores, average use of albuterol, nighttime awakenings, mean change from baseline in $FEF_{25\ to\ 75\%,}$ and FVC	Secondary: At each visit, the mean improvements 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 the placebo group (-1.37, -0.58 and 0.83; *P*<0.001 for all). The mean average daily use of albuterol calculated weekly was lowest in the beclomethasone group (2.86) followed by the triamcinolone group (3.61) and the placebo group (4.43; *P* values not reported). Nighttime awakenings were not significantly different among the treatment groups. The mean change from baseline in $FEF_{25\ to\ 75\%,}$ and FVC demonstrated both active treatment groups to be more effective compared to the placebo group, and beclomethasone being more effective than triamcinolone throughout the study.
Nathan et al[15] Beclomethasone 168 µg BID vs mometasone 100 µg BID vs mometasone 200 µg BID vs placebo	AC, DB, DD, MC, PC, RCT Patients with moderate persistent asthma previously maintained on an ICS	N=227 12 weeks	Primary: Changes in FEV_1 Secondary: PEFR, asthma symptoms, nocturnal awakenings and albuterol use	Primary: The FEV_1 was significantly improved in all three active treatment groups compared to the placebo group (*P*<0.01). There was no statistically significant difference in FEV_1 between the mometasone 200 µg and beclomethasone groups (*P*=0.07) or the mometasone 200 µg and mometasone 100 µg groups (*P*=0.08). Secondary: The improvements in FEV_1, 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; however, the difference was not significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bernstein et al[16] Beclomethasone 168 µg BID vs mometasone 100 µg BID vs mometasone 200 µg BID vs mometasone 400 µg BID vs placebo	AC, DB, DD, MC, RCT Patients with asthma previously treated with an ICS	N=365 12 weeks	Primary: Mean change from baseline in FEV_1 Secondary: FVC, $FEF_{25\ to\ 75\%}$, PEFR, patient evaluation of asthma symptoms and physician evaluation of asthma symptoms	Primary: The changes from baseline in FEV_1, FVC, $FEF_{25\ to\ 75\%}$, and PEFR were significantly greater in all the active treatment groups compared to the placebo group (*P*<0.01 for all). The mometasone 200 µg BID group demonstrated a greater improvement compared to the mometasone 100 µg BID group, with the mometasone 400 µg BID group showing no additional benefit. Secondary: Changes in lung function were similar between the mometasone 100 µg BID group and the beclomethasone group. Improvements in asthma symptoms as evaluated subjectively by patients and physicians were similar for the mometasone 200 (*P*<0.01) and 400 (*P*=0.05) µg BID groups, which were also significantly better than the mometasone 100 µg BID (*P*=0.01) and beclomethasone (*P*=0.02) treatment groups.
van Aalderen et al[17] Beclomethasone 200 µg/day via HFA MDI vs fluticasone 200 µg/day via CFC MDI During weeks seven to 12 and 13 to 18 patients were stepped down to 100 and 50 µg/day respectively if they were achieving good control.	AC, DB, DD, PG, RCT Patients five to 12 years of age with asthma for at least three months, a PEF ≥60% of predicted normal, and currently using a SABA on an as-needed basis	N=139 18 weeks	Primary: Morning PEF percent predicted Secondary: Evening PEF percent predicted, FEV_1 percent predicted, FVC percent predicted, symptom-free days, nights without sleep disturbances, use of a β_2-agonist, asthma control, quality of life and adverse events	Primary: The 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; *P* value not reported). Secondary: The 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; *P*=0.415). The mean change from baseline in FEV_1 percent predicted was 3.0% in the beclomethasone group and 0.6% in the fluticasone group. The treatment difference was 1.6 (*P*=0.335). The mean change from baseline in FVC percent predicted was 5.3% in the beclomethasone group and 0.4% in the fluticasone group. The treatment

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Those with poor control discontinued the study, and those labeled as intermediate did not have a dose change.				difference was 4.6 (*P*=0.084). The percent change from baseline in symptom-free days was 35.2% in both treatment groups (*P*=0.897). The percent change in nights without sleep disturbances was 17.5 and 20.8% in the beclomethasone and fluticasone groups, respectively (*P*=0.561*).* The mean use of a β_2-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 (*P*=0.505). At six weeks, 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 µg/day. At 12 weeks, another step down therapy to 50 µg/day was possible in 66 and 61% of the patients in the beclomethasone and fluticasone groups, respectively. The proportion of patients with a clinically significant improvement in asthma quality of life was similar in both groups (*P*=0.369). There were no statistically significant differences in the proportion of patients experiencing adverse events in the beclomethasone (47%) and fluticasone (49%) groups.
Sharek et al[18] Beclomethasone 328 to 400 µg/day vs fluticasone 200 µg/day	MA 1966 to 1998, DB, RCT studies that evaluated linear growth in children six to 16 years of age with asthma and concomitant ICS therapy	N=855 (5 studies)	Primary: Linear growth velocity in cm/year Secondary: Not reported	Primary: There was a significant decrease in linear growth in children using beclomethasone for mild-to-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; *P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Berkowitz et al[19] Beclomethasone 336 µg/day and triamcinolone placebo vs triamcinolone 800 µg/day and beclomethasone placebo vs triamcinolone and beclomethasone placebo	AC, DB, DD, PC, RCT Patients 18 to 65 years of age with a documented history of bronchial asthma	N=339 56 days	Primary: Change from baseline in FEV_1 Secondary: $FEF_{25\ to\ 75\%}$, PEFR and FVC	Primary: For both active treatment groups, patients experienced statistically significant increases from baseline in FEV_1 compared to the placebo group at all time points ($P<0.05$ for all). Over the course of the study, the FEV_1 was significantly increased by 10.3% in the beclomethasone group and by 11.2% in the triamcinolone group compared to the placebo group ($P\leq0.05$ for both). Secondary: The mean increases in $FEF_{25\ to\ 75\%}$ FVC and PEFR were among the beclomethasone and triamcinolone treatment groups. All results were numerically and statistically significant compared to the placebo group ($P<0.05$).
Raphael et al[20] Beclomethasone 168 µg BID vs beclomethasone 336 µg BID vs fluticasone 88 µg BID vs fluticasone 220 µg BID	AC, DB, PG, RCT Nonsmoking patients 12 years of age or older with a diagnosis of chronic asthma requiring daily ICS therapy for at least six months prior to the study	N=399 14 weeks	Primary: Changes in morning predose FEV_1 Secondary: $FEF_{25\ to\ 75\%}$, FVC, morning and evening PEF, probability of remaining in the study, albuterol use, nighttime awakenings and asthma symptoms	Primary: The FEV_1 was significantly improved from baseline in both treatment groups; however, greater improvements occurred with fluticasone compared to beclomethasone (0.05 vs 0.03 L; $P=0.006$). At endpoint, mean FEV_1 values in the low-and medium-dose fluticasone treatment groups improved by 0.31 (14%) and 0.36 L (15%) respectively, compared to improvements of 0.18 (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone treatment groups, respectively. Secondary: The $FEF_{25\ to\ 75\%}$ and FVC were significantly improved from baseline in all treatment groups; however, patients receiving fluticasone experienced greater improvements compared to patients receiving beclomethasone ($P\leq0.034$ for all). Fluticasone treatment provided a significantly greater improvement in morning PEF compared to beclomethasone treatment at all time points except week two ($P<0.004$ for all). There was a significant improvement in morning PEF relative to baseline in the fluticasone group (15.8 to 22.8 L),

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				but not in the beclomethasone groups (0.7 to 7.2 L; *P* values not reported). A similar trend was seen in evening PEF, but the differences between treatments was not statistically significant. There were no significant differences noted in the analysis of the probability of remaining in the study. The percentage of albuterol-free days was significantly higher in the fluticasone group compared to the beclomethasone group (*P*=0.01 at 14 weeks). 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. There were no significant differences noted in the analysis of nighttime awakenings. Significant improvements in asthma symptom scores (*P*=0.024) and in the percentage of days in which no symptoms were recorded (*P*=0.027) occurred with fluticasone treatment compared to beclomethasone treatment.
Tinkelman et al[21] Budesonide 100 to 800 µg via DPI depending upon asthma severity	OL for 52 weeks following two weeks to five months of treatment in one of four DB, PC studies Adults with persistent asthma not receiving corticosteroids, adults and children previously maintained on	N=1,133 52 weeks	Primary: FEV_1 and oral corticosteroid use Secondary: Plasma cortisol levels and adverse events	Primary: The mean FEV_1 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_1 (67.1±18.0 to 81.2±14.8%). 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. 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 of budesonide BID.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	ICS, and adults previously maintained on oral corticosteroids			Basal and stimulated cortisol levels increased by 20.7±183.3 and 34.8±283.7 nmol/L, respectively, from baseline to the last observation in patients treated with 800 µg of budesonide BID. Thirty-three patients discontinued treatment due to 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, likely in one patient, and highly likely in two patients. Ninety-two patients (8%) reported serious adverse events, of which the most commonly reported was asthma exacerbation (30 patients). No substantial or unexpected changes in vital signs were observed.
Agertoft et al[22] Budesonide vs control group Patients were enrolled in a one to two year run-in period where their asthma medication was adjusted according to Danish guidelines. Patients considered controlled without continuous ICS use, were then asked to change treatment to budesonide.	PRO Children with asthma	N=332 10 years	Primary: Measured adult height in relation to the target adult height 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	Primary: The measured and target adult height was 173.2 and 172.9 cm, respectively, in the budesonide group and 173.9 and 174.1 cm, respectively, in the control group. 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. 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 (*P*=0.72). There was no significant correlation between the duration of treatment and the differences between the measured and target adult heights (*P*=0.16). The difference between measured and target adult heights was not associated with gender (*P*=0.30), age at the beginning of budesonide treatment (*P*=0.13), age at which adult height was attained (*P*=0.82) or duration of asthma before the start of budesonide treatment (*P*=0.37). Budesonide was associated with a significant change in growth rate during the first years of treatment compared to the run-in period. The mean

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				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; *P*<0.001) during the first year of treatment, 5.5 cm/year (95% CI, 5.1 to 5.9; *P*=0.02) during the second year of treatment and 5.9 cm/year (95% CI, 5.5 to 6.3; *P*=0.53) 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 (*P*=0.44). The initial growth retardation was correlated with age, with a more pronounce reduction in younger children (*P*=0.04). Children with a low standard deviation score for height before budesonide treatment had a smaller adult height than expected (*P*<0.001).
Rowe et al[23] Budesonide 1,600 µg/day via DPI vs placebo	DB, PC, RCT Patients 16 to 60 years of age presenting to the emergency department with acute asthma who were discharged with a course of oral prednisone (50 mg/day) for seven days	N=1,006 21 days	Primary: Rates of relapse Secondary: Quality of life, rescue inhaler use, changes in pulmonary function, symptoms, global assessment, adverse effects and compliance	Primary: The budesonide group experienced fewer relapses (12 patients [12.8%]; 95% CI, 7 to 21) compared to the placebo group (23 patients [24.5%]; 95% CI, 16 to 34) by 21 days (*P*=0.049). This represents a 48% relapse reduction and suggests as few as nine patients would require treatment with budesonide to prevent one relapse. Secondary: Quality of life scores were higher in the budesonide group compared to the placebo group (*P*=0.001). The budesonide group used fewer mean albuterol inhalations/day compared to the placebo group (2.4 vs 4.2; *P*=0.01). The mean and percent predicted peak flow and spirometry findings revealed no differences between the groups. At the conclusion of the study, patients in the budesonide group had fewer symptoms of cough (*P*=0.004), breathlessness (*P*=0.001), wheezing (*P*=0.001), and nighttime awakenings (*P*=0.001) compared to patients receiving placebo. 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; *P*=0.001). Adverse events were more frequent in the placebo group for both

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				hoarseness and sore throat (*P*=0.02). The overall incidence of adverse events associated with ICS use (insomnia, fluid retention, acne) was equal between the two groups. 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; *P*=0.73). 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; *P*=0.95).
Sheffer et al[24] Budesonide (200 µg in children <11 years of age and 400 µg for those >11 years of age) QD via DPI vs placebo QD in addition to usual asthma therapy	DB, PC, RCT (first three years); OL (following two years) Patients five to 66 years of age with mild persistent asthma for less than two years and with no previous regular corticosteroid treatment	N=7,241 5 years	Primary: Time to the first severe asthma-related event, change in post-bronchodilator FEV_1 percent predicted Secondary: Number of asthma-related events during the DB period, time to first addition of a steroid treatment (systemic or inhaled) during the DB period, symptom-free days, data on healthcare utilization, days off work, and lost school days	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; *P*<0.001). A significant improvement in both prebronchodilator and postbronchodilator FEV_1 percent values was observed after years one and three of the study for the budesonide treatment group compared to the placebo group. After one year, the differences were 2.24% prebronchodilator and 1.48% postbronchodilator (*P*<0.0001 for both) and after three years were 1.71%, (*P*<0.0001) and 0.88% (*P*=0.0005), respectively. 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 to the placebo group (31 vs 45%, respectively; *P*<0.001). An improvement from baseline in symptom-free days occurred for both the budesonide and placebo groups over time. Patients receiving budesonide had significantly more symptom-free days over the three-year study period compared to patients receiving placebo (*P*<0.001).
Baker et al[25] Budesonide 0.25 mg	DB, MC, PC, PG, RCT	N=480 12 weeks	Primary: Changes in asthma symptom improvement	Primary: When symptom scores for all active treatment groups were combined, a statistically significant difference between budesonide and placebo was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QAM and placebo QPM via nebulizer vs budesonide 0.25 mg BID via nebulizer vs budesonide 0.5 mg BID via nebulizer vs budesonide 1 mg QAM and placebo QPM via nebulizer vs placebo BID	Children, six months to eight years of age, with a diagnosis of asthma		score from baseline, PEF and improvements in FEV_1 Secondary: Not reported	seen as early as day two for nighttime asthma symptoms, and day five for daytime asthma symptoms (*P*<0.05). There were statistically significant improvements in morning PEF in the budesonide 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 (*P*<0.030 for all) and in evening PEF for each active treatment group (16.8 L/minute for 0.25 mg QAM; *P*<0.05, 19.2 L/minute for 0.25 mg BID, *P*<0.05; and 21.0 L/minute for 0.5 mg BID; *P*<0.010) except 1 mg QAM (14.1 L/minute; *P* value not reported). All treatment groups experienced a numerical improvement in FEV_1; however, only the improvement with budesonide 0.5 mg BID dose was statistically significant compared to placebo (*P*=0.031). Secondary: Not reported
Corren et al[26] Budesonide 400 µg QD vs mometasone 440 µg QD vs placebo	AC, DB, DD, MC, PC, RCT Patients with moderate persistent asthma previously using ICSs	N=262 8 weeks	Primary: Percent change from baseline in FEV_1 Secondary: Morning and evening PEFR, FVC, $FEF_{25\ to\ 75\%}$, albuterol use, percentage of asthma symptom-free days, nocturnal awakenings due to asthma, physician-evaluated response to therapy and	Primary: The percent change in FEV_1 was significantly greater in the mometasone group compared to the budesonide (*P*<0.01) and placebo groups (*P*<0.001). Secondary: Pulmonary function ($FEF_{25\ to\ 75\%}$, 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 (*P*<0.05 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			asthma symptom scores	
Vermeulen et al[27] Ciclesonide 320 µg QPM vs budesonide 800 µg QPM	AC, DB, DD, MC, PG, RCT Patients 12 to 17 years of age with severe asthma for six months with an FEV_1 50 to <80% who were not controlled with budesonide 400 µg/day for at least four weeks prior to study	N=403 12 weeks	Primary: Change from baseline in evening pre-dose FEV_1, percentage of days without asthma symptoms and without use of rescue medication Secondary: Change from baseline in FEV_1, percentage of patients experiencing an asthma exacerbation, morning PEF, asthma symptom score, albuterol utilization, PAQLQS score and adverse events	Primary: At 12 weeks, significant increases from baseline in FEV_1 were reported in both the ciclesonide (0.505 L; *P*<0.0001) and budesonide (0.536 L; *P*<0.0001) treatment groups. There were no significant differences between treatment groups (*P*=0.076). The percentage of days without asthma symptoms and without use of rescue medication was 84% in the ciclesonide group and 85% in the budesonide group (*P* value not reported). Secondary: FEV_1 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_1 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 (*P* value not reported). The change from baseline in FVC was significant in both the ciclesonide and budesonide treatment groups (0.433 and 0.472 L, respectively). The difference between the treatment groups was not significant (*P*=0.080). Asthma exacerbations were reported in 2.6% of patients in the ciclesonide group and 1.5% of patients in the budesonide group. There was no significant difference between the two treatment groups (*P* value not reported). Morning PEF increased from baseline by 8.0 L/minute in the ciclesonide group (*P*=0.0424) and 4.9 L/minute in the budesonide group, which was not statistically significant (*P* value not reported). Asthma symptom scores (zero to five scale) were significantly improved from baseline in both the ciclesonide and budesonide treatment groups (-0.07 and -0.14, respectively; *P*<0.05 for both). There were no significant differences between treatment groups (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The median use of rescue medication was reduced to zero puffs/day in both the ciclesonide (*P*<0.0001) and budesonide groups (*P*=0.0003). Overall PAQLQS scores (one to seven scale) were improved in both treatment groups (ciclesonide, 0.19; *P*=0.0001 and budesonide, 0.18; *P*=0.0056). The percentage of patients who experienced treatment emergent adverse events was comparable among the ciclesonide and budesonide treatment groups (26.5 vs 18.3%, respectively). The most common adverse event that occurred in at least 5% of patients for either treatment groups was pharyngitis (5.9 vs 3.8%, respectively).
Von Berg et al[28] Ciclesonide 160 µg QPM vs budesonide 400 µg QPM	AC, DB, DD, MC, PG, RCT Patients six to 11 years of age with persistent asthma for at least six months	N=621 12 weeks	Primary: Change from baseline in FEV_1 Secondary: Change in morning PEF, asthma symptom score, rescue medication utilization, percentage of days without asthma symptoms and without need for rescue medication, percentage of patients with asthma exacerbations, PAQLQS and PACQLQ score, adverse events, body height increase at week 12, and change in 24-hour urinary cortisol	Primary: Significant increases from baseline in FEV_1 occurred in both the ciclesonide (0.232 L; *P*<0.0001) and budesonide (0.250 L; *P*<0.0001) treatment groups. Ciclesonide proved to be non-inferior to budesonide with no significant differences between treatment groups (*P*=0.8158). Secondary: Both treatment groups experienced a statistically significant increase in morning PEF compared to baseline (ciclesonide, 22.5 L/minute; *P*<0.0001, budesonide, 26.3 L/minute; *P*<0.0001).There were no significant differences between treatment groups (*P*=0.8531). Both treatment groups experienced a statistically significant improvement in asthma symptom score (zero to five scale) after 12 weeks of treatment (ciclesonide, -1.21; *P*<0.0001, budesonide, -1.21; *P*<0.0001). There were no significant differences between treatment groups (*P*=0.8379). Both treatment groups experienced a statistically significant reduction in the need for rescue medication (puffs/day) after 12 weeks of treatment compared to baseline (ciclesonide, -1.58; *P*<0.0001, budesonide, -1.64; *P*<0.0001). There were no significant differences between treatment groups (*P*=0.8593). The percentage of days without asthma symptoms and without need for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				rescue medication was 73% in the ciclesonide treatment group, and 70% in the budesonide treatment group (*P* value not reported). The percentage of patients with asthma exacerbations was 2.6% in the ciclesonide treatment group and 1.0% in the budesonide treatment group (*P* value not reported). Both treatment groups experienced a statistically significant improvement in overall PAQLQS (one to seven scale) and PACQLQ scores compared to baseline (0.69, 0.88 and 0.70, 0.96 for the ciclesonide and budesonide treatment groups respectively (*P*<0.0001 for all). 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 in the ciclesonide and budesonide treatment groups, respectively, were pharyngitis (5.9 vs 3.8%), nasopharyngitis (4.1 vs 5.4%), upper respiratory tract infection (3.6 vs 6.3%) and oropharyngeal infection (0.2 vs 1.5%). At week 12 the body height increased by 1.18 cm in the ciclesonide treatment group and by 0.70 cm in the budesonide treatment group (*P*<0.0001 for both). The increase in height was significantly greater in the ciclesonide treatment group than in the budesonide treatment group (*P*=0.0025). Treatment with ciclesonide and budesonide resulted in significant decreases of urinary cortisol (nmol/mmol creatinine) (ciclesonide, -2.17; *P*<0.0001, budesonide, -5.16; *P*<0.0001). The difference between treatment groups was significant (*P*<0.0001).
Newhouse et al[29] Beclomethasone 750 µg, BID via AeroChamber® for a two week run-in period then randomized to:	AC, MC, PG, RCT Patients with moderate asthma (FEV_1 40 to 85% of predicted)	N=176 6 weeks	Primary: Change from baseline in prebronchodilator FEV_1 and albuterol usage Secondary: Changes in PEF,	Primary: There were no statistically significant differences between the two groups in the changes in FEV_1 during the six week treatment period (difference of -0.031 L in percent predicted favoring flunisolide; *P*=0.544). There were no significant changes in albuterol use between the two groups (difference of 0.261 puffs/day favoring budesonide; *P*=0.333).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
budesonide 600 µg BID via Turbuhaler® vs flunisolide 750 µg BID via AeroChamber®			asthma scores and nocturnal awakenings	Secondary: There were no statistically significant differences between the two groups in the changes in PEF, asthma symptoms scores or nocturnal awakenings during the treatment period.
Ferguson et al[30] Budesonide 200 µg BID via DPI vs fluticasone 100 µg BID via DPI	AC, DB, DD, MC, PG, RCT Children six to nine years of age with persistent asthma for at least six months, and an FEV ≥60% predicted, height between the 5th and 95th percentiles for the patients' age and run-in growth velocity between the 20th and 95th percentiles	N=400 12 months	Primary: Growth velocity Secondary: PEFR, FEV_1, exacerbations, symptoms-free days and nights, salbutamol-free nights and adverse events	Primary: Mean growth velocity from baseline 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 (*P*<0.001).The 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. Secondary: Change in morning PEFR was 29.7 and 26.2 L/minute for the fluticasone and budesonide groups, respectively (*P*=0.460). Change in FEV_1 was 0.19 and 0.25 L for the fluticasone and budesonide groups, respectively (*P*=0.154). The proportions of patients with no exacerbations were 75 and 68% in the fluticasone and budesonide groups, respectively (*P*=0.131). The proportion of patients who were 100% symptom-free was 49 and 48% in the fluticasone and budesonide groups respectively (*P*=0.799). The proportion of patients who had 100% symptom-free nights was 50 and 58% in the fluticasone and budesonide groups respectively (*P*=0.232). The proportion of patients who had 100% salbutamol-free nights was 57 and 52% in the fluticasone and budesonide groups respectively (*P*=0.180). Adverse events were reported in 81 and 71% of the fluticasone and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				budesonide groups, respectively. Less than 3% of these events were considered to be treatment-related.
Ferguson et al[31] Budesonide 400 µg BID via DPI vs fluticasone 200 µg BID via DPI	AC, DB, DD, PG, RCT Children four 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 one month preceding the study	N=442 22 weeks	Primary: Mean morning PEF during the last seven treatment days Secondary: Adverse events	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). 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 were 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 demonstrating improved outcomes. Secondary: There was no significant difference in the number of children who experienced an adverse event in the two treatment groups.
Fitzgerald et al[32] Budesonide 750 µg BID vs fluticasone 375 µg BID	AC, DB, RCT, XO Children five 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	N=30 12 weeks	Primary: The daily mean morning and evening PEF and day and night symptom scores Secondary: Physician/patient/parent assessment of efficacy, total number of exacerbations requiring systemic steroids, adrenal function, growth and adverse events	Primary: There was no statistically significant difference between the treatment groups in PEF or symptoms scores. Secondary: There was no difference in physician/patient/parent assessment of efficacy with 90% rating both fluticasone and budesonide effective or very effective. The total number of exacerbations (33 in the fluticasone group and 35 in the budesonide group) and those exacerbations requiring systemic steroids (nine in the fluticasone group and 11 in the budesonide group) suggested no difference between the treatment groups. There were no significant differences in adjusted means for urinary free cortisol levels, adrenocorticotropic hormone levels, or baseline and peak serum cortisol levels between the treatment phases.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no significant treatment effect on growth which remained normal in either group. Most adverse events were related to exacerbations of asthma or upper respiratory tract infections. 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.
Bousquet et al[33] Budesonide 400 µg BID vs mometasone 100 µg BID vs mometasone 200 µg BID vs mometasone 400 µg BID	AC, DB, MC, RCT Patients with moderate persistent asthma previously maintained on a daily ICS	N=730 12 weeks	Primary: Mean change from baseline in FEV_1 Secondary: Self-rated asthma symptom scores, nocturnal awakenings requiring albuterol use as rescue medication, daily albuterol use and physician evaluation of response to therapy	Primary: The FEV_1 was significantly improved from baseline in the mometasone 200 and 400 µg BID treatment groups compared to the budesonide treatment group (*P*<0.05 for both). Secondary: Morning wheezing scores were significantly improved in the mometasone 400 µg BID group compared to the budesonide group and mometasone 100 µg BID group (*P* value not reported). Patients treated with mometasone 200 or 400 µg BID required significantly less albuterol compared to patients treated with budesonide. Physicians reported a significant improvement in asthma symptom scores in the mometasone 200 and 400 µg BID groups compared to the budesonide group (65 and 63 vs 50%; *P* value not reported).
Weiss et al[34] Budesonide 200 to 1,600 µg/day vs triamcinolone 1,200 to 1,600 µg/day	AC, OL, RCT Adult patients with persistent asthma enrolled in 25 United States health plans	N=945 52 weeks	Primary: Mean change from baseline in symptom-free days Secondary: Changes from baseline in number episode-free days, FEV_1, FVC, asthma symptom scores, breakthrough bronchodilator use and	Primary: Increases from baseline in mean estimated symptom- and episode-free days occurred in both 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; *P*<0.001 for both). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			HRQOL	greater in the budesonide group compared to the triamcinolone group (*P*<0.001). The mean FEV_1 and FVC improved from baseline in both groups. Patients receiving budesonide experienced a greater improvement in FEV_1 compared to patients receiving triamcinolone (0.35 vs 0.25 L; *P*=0.005). The difference between the two groups in FVC was not statistically significant. The mean daytime and nighttime asthma symptom scores improved from baseline in both groups. Improvements were significantly greater in patients receiving budesonide at month 12 compared to patients receiving triamcinolone (*P*=0.001 and *P*<0.001, respectively). 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; *P*<0.001). 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 (*P*<0.05 and *P*=0.001, respectively).
Vogelmeier et al[35] Ciclesonide 160 µg QD All treatment decisions were left to the discretion of the investigator (dose and concomitant rescue medication).	3 MC, OL, OS, PRO Patients 12 years of age and older with persistent, mild to moderate asthma who newly started or switched to treatment with	N=24,037 3 months	Primary: Change from baseline in FEV_1 and symptomatic improvements Secondary: Adverse events and changes in rescue medication use	Primary: The mean FEV_1 was increased from 2.66 L (95% CI, 2.65 to 2.67) at baseline to 3.00 L (95% CI, 2.99 to 3.01) following three months treatment with ciclesonide. This represents an increased from 80.7% (95% CI, 80.5 to 80.9) to 90.1% (96% CI, 89.9 to 90.2) of predicted values. Ciclesonide treatment was associated with a significant increase in PEF of 14% from baseline (from 338 L/min [95% CI, 335 to 340] to 392 L/min [95% CI, 390 to 395]). The concentration of NO significantly decreased from 53.6 PPB (95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	ciclesonide			51.8 to 55.4) to 26.2 PPB (95% CI, 25.2 to 27.1), representing a 51% reduction with ciclesonide treatment. The proportion of patients with daily daytime symptoms was reduced from 24.3 to 1.9% after three months of ciclesonide treatment. The proportion of patients with symptoms that occurred >1 day per week was reduced from 59.4 to 24.4% with ciclesonide treatment (*P* values not reported). The proportion of patients reporting less frequent symptoms (<1 day per week) increased from 14.1 to 68.9% with ciclesonide treatment. A similar improvement was observed for night-time symptoms. The number of nights of the preceding month with nocturnal symptoms decreased from 5.4±5.1 days at baseline to 2.5±2.8 days with ciclesonide treatment. The proportion of patients with impaired sleep quality was reduced from 39.8% at baseline to 8.2% after three months of ciclesonide treatment. Secondary: Adverse events were reported in 0.2% of patients receiving ciclesonide treatment. Most adverse events were mild or moderate in severity. The most commonly reported adverse events were dysphonia (n=11) and cough (n=10). The proportion of patients with daily use of β_2-agonists decreased from 26.9% at baseline to 8.8% after three months of ciclesonide treatment.
Study #3030[36] Ciclesonide 80 µg BID vs ciclesonide 160 µg QAM vs	DB, MC, PC, PG, RCT Patients 12 years of age and older with persistent asthma with use of an ICS or an ICS/LABA for at	N=456 12 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol utilization, asthma symptom score and	Primary: Both groups experienced a statistically significant improvement in FEV_1 from baseline (change for the 80 µg BID group, 0.19 L; *P*<0.0001 and change for the 160 µg QAM, 0.14 L; *P*=0.0006). Secondary: Only the 80 µg BID group experienced a statistically significant improvement in morning PEF compared to the placebo group (change for the 80 µg BID group, 8.39 L/minute; *P*=0.0349, change for the 160 µg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	least one month prior to screening, an FEV_1 60 to 90% (ICS) or 70 to 95% (ICS/LABA) of predicted value		adverse events	QAM group, 7.05 L/minute; *P*=0.0769). Both groups experienced statistically significant improvements in albuterol utilization (puffs/day) compared to the placebo group (change for the 80 µg BID group, -0.64; *P*<0.0001, change for the 160 µg QAM group, -0.60; *P*=0.0002). The total asthma symptom score (zero to five scale) was significantly improved in the 80 µg BID group (-0.37; *P*=0.0011) and the 160 µg QAM group (-0.38; *P*=0.0010) compared to the placebo group. The proportion of patients who experienced treatment-emergent adverse events was comparable among groups. The most common adverse events that occurred in at least 5% of patients for the groups were nasopharyngitis, upper respiratory infection and pharyngolaryngeal pain.
Meltzer et al[37] (abstract) Ciclesonide 80 µg BID vs ciclesonide 160 µg QD vs placebo	DB, MC, PC, PG, RCT Patients 12 years of age and older with mild to moderate persistent asthma being treated with an ICS or ICS/LABA	N=446 12 weeks	Primary: Change in FEV_1 Secondary: Morning PEF, rescue albuterol use, total asthma symptom score, nighttime awakenings and safety	Primary: The mean change from baseline in FEV_1 was significant in the ciclesonide 80 µg BID group (*P*=0.0232) and was maintained in the 160 µg QD group (*P*=0.6217). The FEV_1 declined significantly from baseline in the placebo group (*P*<0.0001). The difference between the ciclesonide groups and the placebo group was significant (*P*<0.001). Secondary: At 12 weeks, the morning PEF value in the ciclesonide 80 µg BID group was not significantly different from baseline (*P*=0.1272), while the PEF decreased in the ciclesonide 160 µg QD and placebo groups (*P*=0.0490 and *P*<0.0001 respectively). The difference between the ciclesonide 80 µg BID and placebo group was significant (*P*=0.035). Baseline albuterol use, total daily asthma score and nighttime awakenings were maintained after ciclesonide treatments but increased after placebo treatment (*P*≤0.002). The difference between the ciclesonide 80 µg BID and placebo groups was significant (*P*<0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The incidence of adverse events was similar among all groups.
Bateman et al[38] Ciclesonide 320 µg BID vs ciclesonide 640 µg BID vs placebo	DB, MC, PC, PG, RCT Patients 12 years of age and older with a history of persistent asthma for at least one year prior to screening, were corticosteroid dependant with severe asthma and use of oral prednisone at least every other day for five to six months prior to screening, a history of ICS during the six months prior to screening, use of a β_2-agonist for asthma control the two weeks prior to screening, an FEV_1 between 40 to 80% of predicted normal following a six-hour β_2-agonist treatment withholding period	N=141 12 weeks	Primary: Percent change from baseline in oral prednisone dose Secondary: Percentage of patients who were able to completely discontinue prednisone, change in morning pre-dose FEV_1, change in morning PEF, change in albuterol utilization, change in asthma symptom score, assessment of HPA-axis suppression and adverse events	Primary: The percent reduction in oral prednisone dose was statistically significant in both treatment groups (-47.39% for the 320 µg BID group; *P*=0.0001, -62.54% for the 640 µg BID group; *P*=0.0001 and 4.21% for the placebo group). Secondary: The percent of patients who were able to eliminate their prednisone usage was statistically significant in both treatment groups when compared to the placebo group (29.8% in the 320 µg BID group; *P*=0.0386, 31.3% in the 640 µg BID group; *P*=0.0233 and 11.1% in the placebo group). Both treatment groups demonstrated statistically significant improvements in FEV_1 compared to the placebo group (0.17 L for the 320 µg BID group; *P*=0.0237, 0.17 L for the 640 µg BID group; *P*=0.0277). Neither treatment group experienced a statistically significant improvement in PEF compared to the placebo group (5.02 L/min for the 320 µg BID group; *P*=0.5803, 16.67 L/min for the 640 µg BID group; *P*=0.0736). Neither treatment group experienced a statistically significant improvement in albuterol utilization (puffs/day) compared to the placebo group (*P*>0.05 for both). The total asthma symptom score (zero to five scale) was not statistically significant compared to the placebo group for either treatment group (change for the 320 µg BID group, 0.33; *P*=0.2669, change for the 640 µg BID group, -0.07; *P*=0.8197). 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 µg BID group, 640 µg BID and placebo groups, respectively. The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups (320 µg BID, 85.1%; 640

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				µg 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.
Study #3031[39] Ciclesonide 80 µg BID vs ciclesonide 160 µg QAM vs ciclesonide 80 µg BID for four weeks followed by ciclesonide 160 µg QAM for eight weeks vs placebo	DB, MC, PC, PG, RCT Patients 12 years of age and older with a history of persistent asthma for ≥6 months prior to screening and an FEV_1 after six hours of SABA withholding of 60 to 85%; therapy was also limited to bronchodilators one month prior to screening	N=691 16 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol utilization, asthma symptom score and adverse events	Primary: All three treatment groups experienced a statistically significant improvement in FEV_1 from baseline (0.24 L for the 80 µg BID group; *P*<0.0001, 0.12 L for the 160 µg QAM group; *P*=0.0021 and 0.13 L for the 80 µg BID then 160 µg QAM group; *P*=0.0016). Secondary: All treatment groups experienced a statistically significant improvement compared to the placebo group in morning PEF (36.16 L/minute for 80 µg BID; *P*<0.0001, 23.32 L/minute for the 160 µg QAM; *P*=0.0006 and 30.71 L/minute for the 80 µg BID then 160 µg QAM; *P*<0.0001). All treatment groups experienced a statistically significant improvement from baseline compared to the placebo group in albuterol utilization (puffs/day) (-0.73 for the 80 µg BID group; *P*<0.0001, -0.60 for the 160 µg QAM group; *P*=0.0002 and -0.41 for the 80 µg BID then 160 µg QAM group; *P*=0.0116). For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for the 80 µg BID group (-0.57; *P*=0.0002) and the 80 µg BID then 160 µg QAM group (-0.32; *P*=0.0325). The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups. The most common adverse events that occurred in at least 5% of patients for the treatment groups were aggravated asthma, nasopharyngitis and headache.
Berger et al[40] (abstract) Ciclesonide 80 µg BID vs	DB, MC, PC, PG RCT Patients 12 years of age and older with a history of	N=691 16 weeks	Primary: Change from baseline in FEV_1 Secondary: Morning PEF, rescue	Primary: The mean FEV_1 improved from baseline in all treatment groups (*P*≤0.0251 for all). The improvement in FEV_1 was greatest in the ciclesonide 80 µg BID group (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ciclesonide 160 µg QAM vs ciclesonide 80 µg BID for four weeks followed by 160 µg QAM for 12 weeks vs placebo	persistent asthma for at least six months and not using an ICS for at least 30 days prior to study entry		albuterol use, nighttime awakenings, asthma symptom scores and safety	Secondary: All ciclesonide groups experienced significant improvements in FEV_1 and morning PEF from baseline ($P<0.0001$ for all) and compared to the placebo group ($P\leq0.015$ for all). All treatments reduced albuterol use, nighttime awakenings and improved asthma symptom scores compared to baseline ($P\leq0.05$ for all). These improvements were greater for the ciclesonide 80 µg BID group compared to the placebo group ($P<0.01$). The incidence of adverse effects was similar among all groups.
Study #321[41] Ciclesonide 80 µg QAM vs ciclesonide 160 µg QAM vs ciclesonide 320 µg QAM vs placebo	DB, MC, PC, RCT Patients 12 years of age and older with mild to moderate persistent asthma for six months prior, nonsmokers for at least one year, an FEV_1 60 to 85% of predicted normal with a reversibility of FEV_1 by ≥12% after two albuterol inhalations	N=526 12 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol utilization, asthma symptom score, AQLQ score and adverse events	Primary: Two of the three treatment groups experienced a statistically significant improvement in FEV_1 compared to the placebo group (0.12 L for the 80 µg group; $P=0.0123$, 0.07 L for the 160 µg group; $P=0.1645$ and 0.15 L for the 320 µg group; $P=0.0014$). Secondary: All treatment groups experienced a statistically significant improvement in morning PEF compared to the placebo group (15.58 L/minute for the 80 µg group; $P=0.0032$, 18.93 L/minute for the 160 µg group; $P=0.0004$ and 24.53 L/minute for the 320 µg group; $P=0.0001$). All treatment groups experienced a statistically significant improvement in albuterol utilization (puffs/day) compared to the placebo group ($P=0.0001$ for all). For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for all three treatment groups (-0.38 for the 80 µg group; $P=0.0146$, -0.55 for the 160 µg group; $P=0.0006$ and -0.68 for the 320 µg group; $P=0.0001$). The overall score and two of the four domains in the AQLQ (symptoms and emotional function) were significantly improved in all three treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups (*P* 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[42] Ciclesonide 80 µg QAM vs ciclesonide 160 µg QAM vs ciclesonide 320 µg QAM vs placebo	DB, MC, PC, RCT Patients 12 years of age and older with mild to moderate persistent asthma for six months prior and nonsmokers for at least one year, an FEV_1 60 to 85% of predicted normal with a reversibility of FEV_1 by ≥12% after two albuterol inhalations	N=489 12 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol utilization, asthma symptom score, AQLQ score and adverse events	Primary: All three treatment groups experienced a statistically significant improvement in FEV_1 compared to the placebo group (0.12 L in the 80 µg group; *P*=0.0224, 0.19 L in the 160 µg group; *P*=0.0003 and 0.12 L in the 320 µg group; *P*=0.0173). Secondary: Two of the three treatment groups experienced a statistically significant improvement in morning PEF compared to the placebo group (9.27 L/minute in the 80 µg group; *P*=0.0871, 26.8 L/minute in the 60 µg group; *P*=0.0001 and 12.89 L/minute in the 320 µg group; *P*=0.0171). All treatment groups experienced a statistically significant improvement in albuterol utilization (puffs/day) compared to the placebo group (-1.03 in the 80 µg group; *P*=0.0002, -1.24 in the 160 µg group; *P*=0.0001 and -1.01 in the 320 µg group; *P*=0.0002). 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; *P*=0.0060, change for the 160 µg group, -0.52; *P*=0.0020 and change for the 320 µg group, -0.25; *P*=0.1346). The overall score and three of the four domains in the AQLQ (symptoms, activity, limitation and emotional function) were significantly improved in all three treatment groups (*P* value not reported). The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups (80 µg, 62.1%; 160 µg,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				65.9%; 320 µg, 65.3%; placebo, 66.9%).The most common adverse events that occurred in at least 5% of patients for the treatment groups were nasopharyngitis, headache and upper respiratory tract infection.
Study #323/324[43] Ciclesonide 160 µg BID vs ciclesonide 320 µg BID vs fluticasone 440 µg BID vs placebo	AC, DB, MC, PC, PG, RCT Patients 12 years of age and older with a history of persistent asthma for at least one year prior to screening, use of an ICS for the month prior to baseline, use of a β_2-agonist more than two times a week for the month prior to screening with an FEV_1 ≤80% of predicted normal following a six-hour β_2-agonist treatment withholding period at screening and an FEV_1 40 to 50% of predicted normal following a six-hour β_2-agonist treatment withholding period	N=531 12 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol utilization, asthma symptom score, AQLQ score and adverse events	Primary: All three treatment groups experienced a statistically significant improvement in FEV_1 from baseline compared to the placebo group (0.11 L in the 60 µg BID group; *P*=0.0374, 0.18 L 320 µg BID group; *P*=0.0008 and 0.24 L in the fluticasone group; *P*=0.0001). Secondary: All treatment groups experienced a statistically significant improvement from baseline in morning PEF (27.8 L/minute for the 160 µg BID group; *P*=0.0001, 30.39 L/minute for the 320 µg BID group; *P*=0.0001 and 41.42 L/minute for the fluticasone group; *P*=0.0001). All treatment groups experienced a statistically significant improvement in albuterol utilization (puffs/day) compared to the placebo group (-1.69 for the 160 µg BID group; *P*=0.0001, -1.57 for the 320 µg BID group; *P*=0.0001 and -2.19 for the fluticasone group; *P*=0.0001). For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for all three treatment groups compared to the placebo group (*P*=0.0001 for all). All four domains (exposure to environmental stimuli, symptoms, activity limitation and emotional function) in the AQLQ were significantly improved in all three treatment groups (*P* 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 was 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. The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups The most common adverse event that occurred in at least 5% of patients for the treatment groups was nasopharyngitis. The incidence of oropharyngeal adverse

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				events was more common in the fluticasone treatment group than in the ciclesonide treatment groups.
Nelson et al[44] Fluticasone 500 µg BID vs fluticasone 1,000 µg BID vs placebo BID	DB, PC, PG, RCT Patients 12 years of age or older with chronic asthma diagnosed according to the American Thoracic Society criteria who were receiving oral corticosteroid treatment over the preceding six 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_1, patient-measured morning and evening PEF, patient-rated asthma symptoms and number of nighttime awakenings requiring albuterol	Primary: At 16 weeks, oral prednisone use was discontinued in 75 and 89% of patients treated with fluticasone 500 or 1,000 µg BID, respectively, compared to 9% of placebo-treated patients. The mean maintenance dose of oral prednisone decreased significantly in both fluticasone groups compared to the placebo group ($P<0.001$). Secondary: Changes in FEV_1 were significantly greater in both the fluticasone 500 µg BID group (8.37±3.84) and 1,000 µg BID group (24.21±5.67) compared to the placebo group (0.56±5.56; $P\leq0.05$ for all). Both morning and evening PEF improved in the fluticasone 500 µg BID group (23+10 morning and 3±7 evening) and 1,000 µg group (67±12 morning and 48±10 evening) compared to the placebo group (-23±11 morning and -9±12 evening; $P\leq0.05$ 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; $P\leq0.05$), while symptom scores worsened in the placebo group (0.26±0.12; $P\leq0.05$). 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), while nighttime awakenings increased in the placebo group (0.26±0.15; $P\leq0.05$ for all).
Condemi et al[45] Fluticasone 250 µg BID vs triamcinolone 200 µg QID	AC, DB, DD, PC, PG, RCT Patients 12 years of age and older with asthma (FEV_1 50 to 80% of predicted value)	N=291 24 weeks	Primary: Morning predose FEV_1, probability of remaining in the study over time, patient-measured PEF, albuterol use, number of nighttime awakenings requiring albuterol and	Primary: Patients in both the fluticasone and triamcinolone groups experienced statistically significant improvements in FEV_1 compared to the placebo group (0.27 and 0.07 vs -0.18 L for fluticasone and triamcinolone compared to placebo, respectively; $P\leq0.001$ for both). Only 27% of patients in the placebo group remained in the study over time compared to 66% of patients in the fluticasone group and 55% of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo BID or QID	who had previously received maintenance therapy with beclomethasone or triamcinolone		asthma symptom scores Secondary: Adverse events and morning plasma cortisol levels	in the triamcinolone group. Patients in either active treatment group had a significantly greater probability of remaining in the study over time compared to patients in the placebo group (P<0.001). There was no significant difference between the two active treatment groups. The mean PEF was significantly improved in patients who received fluticasone (21 L/minute) compared to mean decreases of six and 28 L/minute in the triamcinolone and placebo groups, respectively (P<0.001). Albuterol use was reduced by 30% in the fluticasone group and by 6% in the triamcinolone group. Patients in the placebo group increased their albuterol use by 50% (P<0.05). The number of nighttime awakenings requiring albuterol was significantly decreased with either fluticasone or triamcinolone compared to placebo ($P\leq$0.001 for both). The frequency of nighttime awakenings significantly increased after treatment with placebo (P<0.05). There were no significant differences between the treatment groups with respect to symptom scores. 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 treatment-related. 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 <5 µg/mL.
Berend et al[46] Fluticasone at approximately half the dose of their run-in ICS	MC, OL, PG, RCT Patients 18 years of age or older with a history of severe asthma,	N=133 6 months	Primary: Changes from baseline in morning PEF and FEV_1 Secondary:	Primary: Patients in the fluticasone group experienced a significant improvement in morning PEF compared to patients continuing the same dose of their ICS (adjusted difference between two groups, 26±32 L/minute; 95% CI, 8 to 45; P=0.006).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs continuing the same dose of ICS used during the four-week run-in period (beclomethasone or budesonide)	currently receiving at least 1,750 µg/day of inhaled beclomethasone or budesonide		Changes in relevant laboratory values, adverse events, asthma exacerbations and quality of life	The changes from baseline in FEV_1 measured at clinic visits paralleled those values of the morning PEF (1.87±0.70 L with fluticasone and 2.03±0.86 L with beclomethasone/budesonide; *P* values not reported). Secondary: Serum osteocalcin levels increased significantly in the fluticasone group (adjusted mean [SD], 2.6 [4.0] µg/L; 95% CI, 0.2 to 4.9; *P*=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. There was no significant difference in the analysis of change in hoarseness between the two groups. There was a low incidence of oropharyngeal candidiasis during the study in both groups. Four patients (6%) in the fluticasone group and one patient (2%) in the beclomethasone or budesonide group had evidence of candidiasis. There was no significant difference between the two groups. 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. There was a significant increase in the overall asthma quality of life score in the fluticasone group (*P*<0.001); however, there was no significant difference in the beclomethasone or budesonide group (*P*=0.13).
Sheikh et al[47] Flunisolide 1,500 µg/day vs fluticasone 880 µg/day	AC, OL, XO Children with moderate to severe asthma with a mean age of 12.7 years	N=30 2 years	Primary: Mean percent predicted values for FVC, FEV_1, $FEF_{25\ to\ 75\%}$ and PEFR Secondary: Not reported	Primary: There were significant improvements in all clinical parameters in patients treated with fluticasone compared to patients treated with flunisolide. There was a significant improvement in FVC during the two to six and seven to 12-month periods after switching to fluticasone. Significant improvements were noted in FEV_1 and $FEF_{25\ to\ 75\%}$ at all time points evaluated after switching to fluticasone.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no significant difference in PEFR between groups at any time period. Secondary: Not reported
Harnest et al[48] Fluticasone 500 µg BID vs mometasone 500 µg BID	AC, RCT 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	N=203 12 weeks	Primary: Change from baseline in weekly average PEF Secondary: FEV_1, asthma symptom scores, rescue medication use, response to therapy and adverse events	Primary: The change from baseline in PEF was 7.8% in the mometasone group and 7.7% in the fluticasone group (*P*=0.815). Secondary: At week 12, the change from baseline in FEV_1 was 0.4 L in both the mometasone and fluticasone groups (*P*=0.988). The morning and evening asthma symptom scores were not significantly different between the mometasone and fluticasone groups (*P*=0.251). Rescue albuterol use decreased from baseline in patients receiving either treatment; however, there was no significant difference between the groups (*P*=0.890). Treatment-emergent adverse events occurred in 51% of the patients in the mometasone group and 43% of the patients in the fluticasone group. The difference between the two groups was not significant (*P* value not reported).
O'Connor et al[49] Fluticasone 250 µg BID vs mometasone 100 µg BID vs mometasone 200 µg BID	AC, DB, MC, PG, RCT Patients with moderate, persistent asthma previously treated with an ICS	N=733 12 weeks	Primary: Change from baseline in FEV_1 Secondary: Mean changes from baseline in PEFR, $FEF_{25 \text{ to } 75\%}$, FVC, asthma symptom scores, albuterol use, nocturnal awakenings due to	Primary: Patients in either group experienced an improvement from baseline in FEV_1. There was no statistically significant difference between the groups. Patients in the mometasone 400 µg BID group experienced a significant improvement in FEV_1 compared to patients in the mometasone 100 µg BID group (*P*=0.02). Patients in the mometasone 200 µg BID and fluticasone groups experienced similar improvements in FEV_1.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mometasone 400 µg BID			asthma and physician-evaluation of response to therapy	Secondary: The $FEF_{25 \text{ to } 75\%}$ and PEFR were significantly improved in the mometasone 200 µg BID, 400 µg BID and fluticasone groups compared to the mometasone 100 µg BID group. There were no statistically significant differences in the other outcomes between groups.
Wardlaw et al[50] Fluticasone 250 µg BID vs mometasone 400 µg QPM	AC, OL, PG, RCT Patients with moderate, persistent asthma previously using fluticasone	N=167 8 weeks	Primary: Percent change from baseline in FEV_1 Secondary: FVC, PEFR, asthma symptom scores, albuterol use and device evaluation	Primary: There were no significant differences in the percent change in FEV_1 between the groups at any point in the study (*P*≥0.14 for all). Secondary: There were no significant differences in the percent change in FVC (*P*≥0.24), PEFR (*P*=0.60), albuterol use or asthma symptom scores (*P*≥0.06) between the groups at any point in the study. A greater proportion of patients in the mometasone group experienced an improvement in asthma symptoms compared to the fluticasone group (*P*=0.007) as reported by physicians' evaluations of response to therapy. A significantly greater proportion of patients reported having "liked the inhaler a lot" in the mometasone group compared to the fluticasone group (*P*=0.01).
Fish et al[51] 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_1, FVC, FEF, midexpiratory phase), morning and evening PEF, rescue albuterol use, asthma symptom scores, number of nocturnal awakenings	Primary: Oral corticosteroid requirements were reduced by 46.0% in the mometasone 400 µg BID group and by 23.9% in the mometasone 800 µg BID group compared to the placebo group (+164.4%; *P*<0.01). Oral corticosteroids were discontinued in 40, 37 and 0% of patients after 12 weeks and 71, 62 and 58% of patients at the end of the nine month OL phase in the mometasone 400 and 800 µg BID and placebo groups, respectively. Secondary: Nocturnal awakenings were reduced by 57 and 66% in the mometasone 400 and 800 µg BID groups, respectively, and increased by 62% in the placebo group (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			caused by asthma that required albuterol use and general and asthma-specific quality-of-life measures	Daily rescue medication use was significantly reduced in the mometasone 400 µg BID group (P<0.01), but not in the mometasone 800 µg BID group compared to the placebo group. There were no statistically significant differences between the treatment groups with regard to all other secondary endpoints.
Krouse et al (abstract)[52] 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_1 values Secondary: Nocturnal decline in evening to morning PEFR values, polysomnographic indices of sleep, NRQLQ, SF-36 and AQLQ	Primary: No significant differences were observed between groups with regard to nocturnal decline in FEV_1. Secondary: No significant differences were observed between groups with regard to 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.
Price et al[53] Mometasone 400 µg QPM vs mometasone 200 µg BID	MC, OL Patients 12 years of age and older with mild to moderate persistent asthma for at least one year	N=1,233 12 weeks	Primary: Adherence, measured by automatic dose counter Secondary: Self-reported adherence, physician's assessment of therapeutic response, HRQOL, healthcare resource utilization and days missed from work or school	Primary: Adherence, as measured by the automatic dose counter was significantly higher in the QPM group compared to the BID group (P<0.001). Secondary: Adherence, as measured by self-report was significantly higher in the QPM group compared to the BID group (P<0.001). No significant differences between groups were observed in physician's assessment of therapeutic response, HRQOL, healthcare resource utilization, or days missed from work or school ($P\geq$0.08 for all).
Noonan et al[54] Mometasone 200 µg QD	AC, MC, OL, PRO Patients four to 11	N=233 52 weeks	Primary: Incidence of adverse events	Primary: The incidence of adverse events was similar in all three groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mometasone 100 µg BID vs beclomethasone 168 µg BID	years of age with mild to moderate persistent asthma using an ICS within 30 days prior to the study and on a stable regimen at least two weeks before screening		Secondary: Laboratory tests including cortisol concentrations, vital signs and physical examinations	Secondary: No significant differences between groups were observed in any secondary end points.

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, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SD=standard deviation, XO=cross over
Miscellaneous abbreviations: AQLQ=asthma quality of life questionnaire, CFC=chlorofluorocarbon, DPI=dry-powder inhaler, $FEF_{25\ to\ 75\%}$=forced expiratory flow at 25 to 75% of FVC, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, HFA=hydrofluoroalkane, HPA=hypothalamic-pituitary-adrenal, HRQOL=health-related quality of life, ICS=inhaled corticosteroid, LABA=long-acting β_2-agonist, MDI=metered-dose inhaler, NO=nitrous oxide, 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, PPB=parts per billion, SABA=short acting β_2-agonist, SF-36=Short-Form-36, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[1-8]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Beclomethasone	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children five years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes
Budesonide	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. 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 1.0%).
Ciclesonide	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children 12 years of age and older.	Not studied in renal dysfunction.	Dosage adjustment not required.	C	Unknown
Fluticasone propionate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children four years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Mometasone	No evidence of overall differences in safety or efficacy	Not studied in renal dysfunction.	No dosage adjustment required.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	observed between elderly and younger adult patients. Approved for use in children four years of age and older.				

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-8]

Adverse Event(s)	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Fluticasone Propionate	Mometasone
Cardiovascular						
Chest pain	-	-	1 to <3	≥3	-	-
Palpitations	-	-	-	-	-	-
Central Nervous System						
Aggression	-	✔	1 to <3	-	✔	-
Agitation	-	-	-	-	✔	-
Anxiety	-	✔	1 to <3	-	-	-
Depression	-	✔	1 to <3	-	✔	11
Dizziness	-	-	-	-	-	-
Emotional lability	-	-	1 to <3	-	-	-
Fatigue	-	-	1 to <3	-	>3	1 to13
Headache	8 to 25	≥3	≥3	5 to11	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	-	-	-
Psychosis	-	✔	1 to <3	-	-	-
Restlessness	-	✔	1 to <3	-	✔	-
Syncope	-	1 to 3	-	-	-	-
Dermatological						
Contact dermatitis	-	✔	1 to <3	-	-	-
Ecchymoses	-	1 to 3	1 to <3	-	✔	-
Eczema	-	-	1 to <3	-	-	-
Pruritus	-	-	1 to <3	-	✔	✔
Rash	✔	✔	≤4	-	✔	✔
Urticaria	✔	✔	1 to <3	≥3	✔	-
Viral skin infection	-	-	-	-	✔	-
Endocrine and Metabolic						
Edema	-	-	-	-	✔	-

Adverse Event(s)	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Fluticasone Propionate	Mometasone
Gastrointestinal						
Abdominal pain	-	1 to 3	2 to 3	-	-	2 to 6
Anorexia	-	-	1 to <3	-	-	1 to <3
Diarrhea	-	-	2 to 4	-	✔	-
Dyspepsia	-	1 to 4	-	-	✔	3 to 5
Gastroenteritis	-	1.8	5	≥3	-	1 to <3
Gastrointestinal pain	-	1 to 3	-	-	2 to 4	-
Nausea	≤2	1.8	-	<1	1 to 8	1 to 3
Oral candidiasis	-	1.3	-	≥3	≤9	4 to 22
Taste alteration	-	1 to 3	-	-	-	-
Viral gastrointestinal infection	-	-	-	-	3 to 5	-
Vomiting	-	1 to 3	2 to 4	-	1 to 8	1 to 3
Respiratory						
Angioedema	✔	✔	1 to <3	-	✔	✔
Bronchitis	-	-	≥3	-	≤8	-
Bronchospasm	✔	✔	≥3	-	✔	✔
Cold symptoms	-	-	-	-	-	-
Coughing	1 to 3	✔	5 to 9	<1	1 to 6	✔
Dry mouth	-	1 to 3	-	<1	-	-
Dyspnea	-	-	-	-	-	✔
Epistaxis	-	-	2 to 4	-	-	1 to <3
Hoarseness	-	-	-	≥3	2 to 6	-
Increased asthma symptoms	≤4	-	-	-	✔	-
Laryngitis	-	-	-	-	✔	-
Nasal congestion	-	2.7	-	1.8 to 5.5	-	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	-	8 to 13
Respiratory disorder	-	-	-	-	-	1 to <3
Rhinitis	3 to 8	2.2	7 to 12	3.1 to 5.5	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	Fluticasone Propionate	Mometasone
Upper respiratory tract infection	7 to 11	≥3	34 to 38	4.1 to 8.7	14 to 21	8 to 15
Viral respiratory infection	-	-	-	-	1 to 5	-
Wheezing	-	✔	-	-	✔	✔
Other						
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	-	-	-	-	4 to 9
Dysphonia	1 to 4	1 to 6	1 to <3	<1	2 to 6	1 to <3
Earache	-	-	1 to <3	-	-	1 to <3
Ear infection	-	-	1 to <3	-	-	-
Eye infection	-	-	1 to <3	-	-	-
Facial edema	-	-	-	≥3	✔	-
Fever	-	≥3	≥3	-	1 to 7	7
Flu syndrome	-	6 to 14	1 to <3	≥3	-	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	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	-	✔	-	-	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

Table 7. Contraindications[1-8]

Contraindication	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Fluticasone Propionate	Mometasone
Acute episodes of asthma where intensive measures are required	✔	✔	✔	✔	✔	✔
Hypersensitivity to any components of the product	-	✔	✔	✔	✔	✔
Hypersensitivity to milk proteins	-	✔	-	-	-	✔
Primary treatment of status asthmaticus	✔	✔	✔	✔	✔	✔

Warnings/Precautions

Table 8. Warnings and Precautions[1-8]

Warning/Precaution	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Fluticasone Propionate	Mometasone
Candida albicans; infections occur in the mouth and pharynx of some patients	✔	✔	✔	✔	✔	✔
Eosinophilic conditions and Churg-Strauss Syndrome	-	✔	✔	-	✔	-
Glaucoma, increased intraocular pressure, and cataracts	✔	✔	✔	✔	✔	✔
Hypercorticism and adrenal suppression; may appear at particularly at higher doses	✔	✔	✔	✔	✔	✔
Hypersensitivity reactions following transition from systemic corticosteroids	✔	✔	✔	✔	✔	✔
Inhaled corticosteroids do not provide the mineralocorticoid necessary during times of trauma, surgery or infections	✔	✔	✔	✔	✔	✔
Infections; persons on immunosuppressive medications are more susceptible to infections than healthy individuals	✔	✔	✔	✔	✔	✔
Not indicated for relief of acute bronchospasm	✔	✔	✔	✔	✔	✔
Oral corticosteroid withdrawal; some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function	✔	✔	✔	✔	✔	✔
Paradoxical bronchospasm following administration	✔	✔	✔	✔	✔	✔
Patients transferred from systemically active steroids to inhaled corticosteroids due to adrenal insufficiency	✔	✔	✔	✔	✔	✔
Reduction in bone mineral density with long-term use	-	✔	✔	✔	✔	✔
Reduction in growth velocity in pediatric patients	-	✔	✔	✔	✔	✔
Systemic absorption at recommended doses	✔	✔	✔	✔	✔	✔

Drug Interactions

Table 8. Drug Interactions[1-8]

Generic Name	Interacting Medication or Disease	Potential Result
Budesonide, fluticasone propionate, mometasone	Strong cytochrome (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 9. Dosing and Administration[1-8]

Generic Name	Adult Dose	Pediatric Dose	Availability
Beclomethasone	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: 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	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: Meter dose aerosol inhaler (HFA): children five to 11 years of age: initial, 40 µg BID; maximum, 80 µg BID	Meter dose aerosol inhaler (HFA) (100 or 120 inhalations): 40 µg 80 µg
Budesonide	Maintenance treatment of asthma as prophylactic therapy: Dry powder inhaler: initial, 360 µg BID (selected patients can be initiated at 180 µg BID); maximum, 720 µg BID	Maintenance treatment of asthma as prophylactic therapy: Dry powder inhaler: children six to 17 years of age; initial, 180 µg BID (selected patients can be initiated at 360 µg BID); maximum, 360 µg BID Suspension for nebulization: children 12 months to eight 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 eight years of age treated previously with	Dry powder inhaler (60 or 120 inhalations): 90 µg 180 µg Suspension for nebulization: 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL (30 units/carton)

Generic Name	Adult Dose	Pediatric Dose	Availability
		an inhaled corticosteroid; 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 eight 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	Maintenance treatment of asthma as prophylactic therapy: 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
Fluticasone propionate	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: 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 Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators; initial, 88 µg	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: Dry powder inhaler: children four to 11 years of age treated previously with only bronchodilators or with inhaled corticosteroids; initial, 50 µg BID; maximum, 100 µg BID Meter dose aerosol inhaler (HFA): children four to 11 years of age; initial 88 µg BID; maximum, 88 µg BID	Dry powder inhaler (Diskus®) (60 inhalations): 50 µg 100 µg 250 µg Meter dose aerosol inhaler (HFA) (120 inhalations): 44 µg 110 µg 220 µg

Generic Name	Adult Dose	Pediatric Dose	Availability
	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		
Mometasone	Maintenance treatment of asthma as prophylactic therapy: 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	Maintenance treatment of asthma as prophylactic therapy: Dry powder inhaler: children four to 11 years of age; initial, 110 µg QD in the evening; maximum, 110 µg QD in the evening	Dry powder inhaler (Twisthaler®): 110 µg (seven and 30 inhalations) 220 µg (14, 30, 60 and 120 inhalations)

BID=twice daily, HFA=hydrofluoroalkane, QD=once daily

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guidelines	Recommendations
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[55]	Diagnosis • 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. • 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. • 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. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. Treatment • 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. • The initial treatment of asthma should correspond to the appropriate asthma severity category. • Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline

Clinical Guidelines	Recommendations
	and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. • Quick relief medications include short-acting β_2-adrenergic agonists (SABAs), anticholinergics and systemic corticosteroids. Long-term control medications • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • 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. • When patients ≥12 years of age require more than a low-dose ICS, the addition of a long-acting β_2-adrenergic agonist (LABA) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. • 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. • Omalizumab, an immunomodulator, is used as adjunctive therapy in 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. • Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma. • LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma. • 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. • Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma. • Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease (COPD) and has not been studied in the long-term management of asthma. Quick-relief medications • SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm. • 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. • 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. • Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>exacerbations.
• The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma.

<u>Assessment, treatment and monitoring</u>
• A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
• 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.
• The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td><u>Preferred</u>
SABA as needed</td><td><u>Preferred</u>
Low-dose ICS

<u>Alternative</u>
Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline</td><td><u>Preferred</u>
Low-dose ICS+LABA or medium-dose ICS

<u>Alternative</u>
Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td><u>Preferred</u>
Medium-dose ICS+LABA

<u>Alternative</u>
Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td><u>Preferred</u>
High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies</td><td><u>Preferred</u>
High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies</td></tr>
</table>
<u>Management of exacerbations</u>
• Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

<u>Special populations</u>
• 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.
• Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.
• Albuterol is the preferred SABA in pregnant women because of an excellent safety profile.
• 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.</td></tr>
<tr><td>Global Initiative for Asthma:
Global Strategy for Asthma Management</td><td><u>Treatment</u>
• Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages.</td></tr>
</table>

Clinical Guidelines	Recommendations
and Prevention (2012)[59]	• 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. • Controller medications are administered daily on a long-term basis and include inhaled and systemic corticosteroids, leukotriene modifiers, LABAs in combination with ICSs, sustained-released theophylline, chromones, and anti-immunoglobulin E (IgE). • Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline and SABAs. Controller medications • ICSs are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. • ICSs differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences. • Most clinical benefit from an ICS in adults is achieved at relatively low doses, equivalent to 400 µg of budesonide daily. Higher doses provide little further benefit but increase the risk of adverse events. • To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of the ICS. • Leukotriene modifiers are generally less effective than low doses of ICSs therefore may be used as an alternative treatment in patients with mild persistent asthma. • Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. • Leukotriene modifiers used as add-on therapy may reduce the dose of the 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 ICSs. • Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. • LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. • When a medium dose of the ICS fails to achieve control, the addition of a LABA is the preferred treatment. • 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. • Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, this use is not approved by the Food and Drug Administration (FDA). • Tiotropium has been evaluated in adults with uncontrolled asthma compared to double-dose ICSs and salmeterol. Study results are conflicting and no effect on asthma exacerbations has been demonstrated. • Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on ICSs alone.

<table>
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<tr><td></td><td>
Furthermore, withdrawal of sustained-release theophylline has been associated with worsening asthma control.
• Cromolyn and nedocromil are less effective than a low dose of ICSs.
• Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed.
• Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE.
• Long-term oral corticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects.
• Other anti-allergic compounds have limited effect in the management of asthma.

<u>Reliever medications</u>
• Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages.
• Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required.
• Although the guidelines state that formoterol, a LABA, is approved for symptom relief due to its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with ICSs, the use of this agent as a rescue inhaler is not approved by the FDA.
• Ipratropium, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists.
• Short-acting theophylline may be considered for relief of asthma symptoms.
• Short-acting oral β_2-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.
• Systemic corticosteroids are important in the treatment of severe acute exacerbations.

<u>Assessment, treatment, and monitoring</u>
• The goal of asthma treatment is to achieve and maintain clinical control.
• To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.
• 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 for at least three months, treatment can be stepped down.
• Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.
• The management approach based on control is outlined below:
<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma education and environmental control</td></tr>
<tr><td colspan="5">As needed rapid-acting β_2-agonist</td></tr>
<tr><td rowspan="2">Controller options</td><td>Select one</td><td colspan="2">Select one</td><td>Add one or more</td><td>Add one or both</td></tr>
<tr><td>Low-dose ICS</td><td colspan="2">Low-dose ICSs + LABA</td><td>Medium- or high-dose ICS +</td><td>Oral corticoster</td></tr>
</table>
</td></tr>
</table>

Clinical Guidelines	Recommendations
	<table><tr><td></td><td></td><td></td><td>LABA</td><td>oid</td></tr><tr><td></td><td>Leukotriene modifier</td><td>Medium- or high-dose ICS</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr><tr><td></td><td>-</td><td>Low-dose ICS +leukotriene modifier</td><td>-</td><td>-</td></tr><tr><td></td><td>-</td><td>Low-dose ICS +sustained-release theophylline</td><td>-</td><td>-</td></tr></table> Management of exacerbations • Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mile to moderate exacerbations. Systemic corticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is severe.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2014)**[60]	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking. • A diagnosis of COPD should be confirmed by spirometry. • COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. • The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and COPD. • A detailed medical history should be obtained for all patients suspected of developing COPD. • Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. • Chest radiograph may be useful to rule out other diagnoses. • Arterial blood gas measurements should be performed in advanced COPD. • Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. • Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. Treatment • Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. • The management of COPD should be individualized to address symptoms and improve the patient's quality of life. • None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. • Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. • The use of long-acting bronchodilators is more effective and convenient

Clinical Guidelines	Recommendations
	than short-acting bronchodilators. • For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. • Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator. • In patients with an FEV_1 <60% of the predicted value, regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function and quality of life as well as reduces exacerbations. • Long term therapy ICS as monotherapy is not recommended. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • COPD patients should receive an annual influenza vaccine. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value. • Exercise training programs should be implemented for all COPD patients. • Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. Management of exacerbations • The most common causes of an exacerbation are respiratory tract infections. • Inhaled short-acting β_2-agonists, with or without short-acting anticholinergics are the preferred bronchodilators for treatment for exacerbations of COPD. • Roflumilast may also be used to reduce exacerbations for patients with chronic bronchitis, severe to very severe airflow limitation and frequent exacerbations not adequately controlled by long-acting bronchodilators. • Antibiotics are recommended in patients with increased dyspnea, increased sputum volume or increased sputum purulence; or increase sputum purulence and increased dyspnea or increased sputum volume, or patients that require mechanical ventilation.
National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)**[61]	Diagnosis • Diagnosis should be considered in patients >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. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%. Treatment • Smoking cessation should be encouraged for all patients with COPD. • SABAs, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. • Long-acting bronchodilators (beta$_2$ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. • Once-daily, long-acting anticholinergics are preferred compared to four-times-daily short-acting anticholinergics in patients with stable COPD who

Clinical Guidelines	Recommendations
	remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic. o FEV_1 ≥50% predicted: LABA or long-acting anticholinergic. o FEV_1 <50% predicted: either LABA with an ICS in a combination inhaler or a long-acting anticholinergic. • In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an ICS in a combination inhaler or a long-acting anticholinergic when ICSs are not tolerated or declined. • Consider a long-acting anticholinergic in patients remaining breathless or having exacerbations despite therapy with LABAs and ICSs and vice versa. • Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, adverse events and costs. • In most cases, inhaled bronchodilator therapy is preferred. • 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. • Theophylline should only be used after a trial of LABA and SABA or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of exacerbations • Patients with exacerbations should be evaluated for hospital admission. • 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. • 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. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • 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.

Conclusions

Inhaled corticosteroids (ICSs) have evolved into the cornerstone of drug therapy for long-term asthma control. The single-entity ICSs are Food and Drug Administration (FDA)-approved for the maintenance treatment of asthma as prophylactic therapy. Both beclomethasone (QVAR®) and fluticasone propionate (Flovent Diskus®, Flovent HFA®) are also approved for asthmatic patients requiring oral corticosteroid therapy.[1-8] To date, the results of head-to-head trials with the various single-entity ICSs have not

demonstrated one agent to be significantly more effective than another in the management of asthma.[13-54] Currently, budesonide suspension for nebulization is available generically.[55]

Consensus guidelines address 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.[56,59] The 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 a forced expiratory volume in one second <60% predicted as it improves symptoms, lung function and quality of life as well as reduce exacerbations.[60,61]

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