Therapeutic Class Overview
Inhaled Corticosteroids

Overview/Summary:
The inhaled corticosteroids (ICSs) are Food and Drug Administration (FDA)-approved for the maintenance treatment of asthma as prophylactic therapy with beclomethasone (QVAR®), flunisolide (Aerospan®) and fluticasone propionate (Flovent Diskus®, Flovent HFA®) also being indicated for use in asthma patients who require systemic corticosteroid therapy. [1-11] 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. [1-10]

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 and have not demonstrated any major differences in clinical efficacy between the available ICSs. [12-67] Currently, only budesonide nebulizer suspension is available generically.

Table 1. Current Medications Available in Therapeutic Class [1-10]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Beclomethasone (QVAR®)	Maintenance Treatment of Asthma as Prophylactic Therapy¶; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy¶	Inhalation aerosol (HFA inhaler, metered dose): 40 µg 80 µg	-
Budesonide (Pulmicort Flexhaler®, Pulmicort Respules®*)	Maintenance Treatment of Asthma as Prophylactic Therapy†,‡	Dry powder for inhalation (inhaler, breath activated, metered dose): 90 µg 180 µg Suspension for inhalation (nebulizer): 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL	a
Ciclesonide (Alvesco®)	Maintenance Treatment of Asthma as Prophylactic Therapy§	Inhalation aerosol (HFA inhaler, metered dose): 80 µg 160 µg	-
Flunisolide (Aerospan®)	Maintenance Treatment of Asthma as Prophylactic Therapy#; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy#	Inhalation aerosol (HFA inhaler, metered dose): 80 µg	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Fluticasone furoate (Arnuity Ellipta®)	Maintenance Treatment of Asthma as Prophylactic Therapy§	Aerosol powder (breath activated inhaler): 100 µg 200 µg	-
Fluticasone propionate (Flovent Diskus®, Flovent HFA®)	Maintenance Treatment of Asthma as Prophylactic Therapy‖; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy‖	Dry powder for inhalation (inhaler with blister pack; Flovent Diskus®): 50 µg 100 µg 250 µg Inhalation aerosol (HFA inhaler, metered dose; Flovent HFA®): 44 µg 110 µg 220 µg	-
Mometasone furoate (Asmanex HFA®, Asmanex Twisthaler®)	Maintenance Treatment of Asthma as Prophylactic Therapy‖	Dry powder for inhalation (inhaler, metered dose; Asmanex Twisthaler®): 110 µg 220 µg Inhalation powder (HFA inhaler, metered dose, breath activated; Asmanex HFA®):	-

* Generic available in at least one dosage form or strength.
¶ In patients five years of age and older.
† Pulmicort Flexhaler®: In patients six years of age and older.
‡ Pulmicort Respules®: 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 patients six years of age and older.

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.[12-67]
- FDA-approval for fluticasone furoate was based on the results of three dose-ranging trials and four confirmatory trials which included a total of 3,611 patients aged ≥12 years with various asthma severities, FEV_1 of 40 to 90% predicted and varied (or no) previous ICS use.[13-15,19-22] Pre-dose, pre-bronchodilator FEV_1 (primary endpoint) was significantly improved upon treatment with the FDA-approved doses of fluticasone furoate when compared to placebo in each of the seven clinical trials.
  - Fluticasone furoate also significantly improved percentage of rescue-free 24-hour periods and although statistical significance could not be determined in some cases, fluticasone furoate also improved symptom-free 24-hour periods over the course of the studies.[13-15,19-22]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - 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. No ICS is recommended over another.[68,71]
    - § 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.[68]
  - o For COPD: 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.[72]
  - o ICSs should be used as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤50% predicted and repeated exacerbations.[73]
- Other Key Facts:
  - o None of the inhaled corticosteroid products are indicated for the relief of acute bronchospasm[1-10]
  - o Currently, budesonide suspension for nebulization is the only generic product available within the therapeutic class.

References

1. QVAR® [package insert]. Horsham (PA): Teva Respiratory LLC.; 2014 Jul.
2. Pulmicort Flexhaler® [package insert]. Wilmington (DE): Astra-Zeneca; 2010 Jul.
3. Pulmicort Respules® [package insert]. Wilmington (DE): Astra-Zeneca; 2010 Jul.
4. Alvesco® [package insert]. Marlborough (MA): Sepracor Inc.; 2013 Jan.
5. Aerospan® [package insert]. Marlborough (MA): Acton Pharmaceuticals Inc.; 2014 Sep.
6. Arnuity Ellipta® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2014 Nov.
7. Flovent Diskus® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2014 May.
8. Flovent HFA® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2014 May.
9. Asmanex Twisthaler® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2014 Apr.
10. Asmanex HFA® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2014 Sep.
11. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Truven Health Analytics; Updated periodically [cited 2015 Jan 13]. Available from: http://www.thomsonhc.com/.
12. van den Berge M, Luijk B, Bareille P, Dallow N, Postma DS, Lammers JW. Prolonged protection of the new inhaled corticosteroid fluticasone furoate against AMP hyperresponsiveness in patients with asthma. Allergy. 2010 Dec;65(12):1531-5. doi: 10.1111/j.1398-9995.2010.02414.x.
13. Bleecker ER, Bateman ED, Busse WW, Woodcock A, Frith L, House KW, et al. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. Thorax. 2012 Jan;67(1):35-41. doi: 10.1136/thoraxjnl-2011-200308. Epub 2011 Aug 9.
14. Busse WW, Bleecker ER, Bateman ED, Lötvall J, Forth R, Davis AM, et al. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. Thorax. 2012 Jan;67(1):35-41. doi: 10.1136/thoraxjnl-2011-200308. Epub 2011 Aug 9.
15. Bateman ED, Bleecker ER, Lötvall J, Woodcock A, Forth R, Medley H et al. Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial. Respir Med. 2012 May;106(5):642-50. doi: 10.1016/j.rmed.2012.01.004. Epub 2012 Feb 18.
16. Woodcock A, Bateman ED, Busse WW, Lötvall J, Snowise NG, Forth R, et al. Efficacy in asthma of once-daily treatment with fluticasone furoate: a randomized, placebo-controlled trial. Respir Res. 2011 Oct 6;12:132. doi: 10.1186/1465-9921-12-132.
17. Woodcock A, Bleecker ER, Busse WW, Lötvall J, Snowise NG, Frith L, et al. Fluticasone furoate: once-daily evening treatment versus twice-daily treatment in moderate asthma. Respir Res. 2011 Dec 21;12:160. doi: 10.1186/1465-9921-12-160.
18. Medley H1, Orozco S, Allen A. Efficacy and safety profile of fluticasone furoate administered once daily in the morning or evening: a randomized, double-blind, double-dummy, placebo-controlled trial in adult and adolescent patients with persistent bronchial asthma. Clin Ther. 2012 Aug;34(8):1683-95. doi: 10.1016/j.clinthera.2012.06.024. Epub 2012 Jul 13.
19. Lötvall J, Bleecker ER, Busse WW, O'Byrne PM, Woodcock A, Kerwin EM, et al. Efficacy and safety of fluticasone furoate 100 µg once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial. Respir Med. 2014 Jan;108(1):41-9. doi: 10.1016/j.rmed.2013.11.009. Epub 2013 Nov 19.
20. Bleecker ER, Lötvall J, O'Byrne PM, Woodcock A, Busse WW, Kerwin EM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014 Sep-Oct;2(5):553-61. doi: 10.1016/j.jaip.2014.02.010. Epub 2014 Apr 24.
21. Woodcock A1, Lötvall J, Busse WW, Bateman ED, Stone S, Ellsworth A, et al. Efficacy and safety of fluticasone furoate 100 µg and 200 µg once daily in the treatment of moderate-severe asthma in adults and adolescents: a 24-week randomised study. BMC Pulm Med. 2014 Jul 9;14:113. doi: 10.1186/1471-2466-14-113.
22. O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J. 2014 Mar;43(3):773-82. doi: 10.1183/09031936.00064513. Epub 2013 Oct 17.

23. O'Byrne PM1, Woodcock A, Bleecker ER, Bateman ED, Lötvall J, Forth R, et al. Efficacy and safety of once-daily fluticasone furoate 50 mcg in adults with persistent asthma: a 12-week randomized trial. Respir Res. 2014 Aug 11;15:88. doi: 10.1186/s12931-014-0088-z.
24. Busse WW, Bateman ED, O'Byrne PM, Lötvall J, Woodcock A, Medley H, et al. Once-daily fluticasone furoate 50 mcg in mild-to-moderate asthma: a 24-week placebo-controlled randomized trial. Allergy. 2014 Nov;69(11):1522-30. doi: 10.1111/all.12480. Epub 2014 Aug 22.
25. Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. J Allergy Clin Immunol. 1999;104(6):1215-22.
26. Bronsky E, Korenblat P, Harris AG, Chen R. Comparative clinical study of inhaled beclomethasone dipropionate and triamcinolone acetonide in persistent asthma. Ann Allergy Asthma Immunol. 1998;90:295-302.
27. Nathan RA, Nayak AS, Graft DF, Lawrence M, Picone FJ, Ahmed T, et al. Mometasone furoate: efficacy and safety in moderate asthma compared to beclomethasone dipropionate. Ann Allergy Asthma Immunol. 2001;86:203-10.
28. Bernstein DI, Berkowitz RB, Chervinsky P, Dvorin DJ, Finn AF, Gross GN, et al. Dose-ranging study of a new steroid for asthma: mometasone furoate dry powder inhaler. Respir Med. 1999;93:603-12.
29. van Aalderen WM, Price D, De Baets FM, Price J. Beclomethasone dipropionate extra fine aerosol vs fluticasone propionate in children with asthma. Respiratory Medicine. 2007;101:1585-93.
30. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Pediatrics. 2000;106(1):1-7.
31. Berkowitz R, Rachelefsky G, Harris AG, Chen R. A comparison of triamcinolone MDI with a built-in tube extended and beclomethasone dipropionate MDI in adult asthmatics. Chest. 1998;114:757-65.
32. Raphael GD, Lanier RQ, Baker J, Edwards L, Rickard K, Lincourt WR. A comparison of multiple doses of fluticasone propionate and beclomethasone dipropionate in subjects with persistent asthma. J Allergy Clin Immunol. 1999;103(5):796-803.
33. Tinkelman DG, Bronsky EA, Gross G, Schoenwetter WF, Spector SL. Efficacy and safety of budesonide inhalation powder (Pulmicort Turbuhaler®) during 52 weeks of treatment in adults and children with persistent asthma. J of Asthma. 2003;40(3):225-36.
34. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. NEJM. 2000;343:1064-9.
35. Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jacono J. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department. JAMA. 1999;281(22):2119-26.
36. Sheffer AL, Silverman M, Woolcock AJ, et al. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the inhaled steroid treatment as regular therapy in early asthma (START) study. Ann Allergy Asthma Immunol. 2005;94(1):48-54.
37. Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. Pediatrics. 1999 Feb;103(2):414-21.
38. Corren J, Berkowitz R, Murray JJ, Prenner B. Comparison of once-daily mometasone furoate vs once-daily budesonide in patients with moderate persistent asthma. Int J Clin Pract. 2003;57(7):567-72.
39. Vermeulen JH, Gyurkovits K, Rauer H, Engelstatter R. Randomized comparison of the efficacy and safety of ciclesonide and budesonide in adolescents with severe asthma. Respir Med. 2007;101:2182-91.
40. von Berg A, Engelstätter R, Minic P, Sréckovic M, Garcia ML, Latoś T, et al. Comparison of the efficacy and safety of ciclesonide 160 µg once daily vs budesonide 400 µg once daily in children with asthma. Pediatr Allergy Immunol. 2007;18:391-400.
41. Newhouse M, Knight A, Wang S, Newman K. Comparison of efficacy and safety between flunisolide/AeroChamber® and budesonide/Turbuhaler® in patients with moderate asthma. Ann Allergy Asthma Immunol. 2000;84:313-9.
42. Ferguson AC, Van Bever HP, Teper AM, Lasytsya O, Goldfrad CH, Whitehead PJ. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. Respiratory Medicine. 2007;101:118-29.
43. Ferguson AC, Spier S, Manjra A, Versteegh FG, Mark S, Zhang P. Efficacy and safety of high-dose inhaled steroids in children with asthma: A comparison of fluticasone propionate with budesonide. J Pediatr. 1999;134(4):422-7.
44. Fitzgerald D, Van Asperen P, Mellis C, Honner M, Smith L, Ambler G. Fluticasone propionate 750 µg/day vs beclomethasone dipropionate 1500 µg/day: comparison of efficacy and adrenal function in pediatric asthma. Thorax. 1998;53(8):656-61.
45. Bousquet J, D'Urzo A, Hebert J, Barraza CH, Boulet LP, Suárez-Chacón R, et al. Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler®. Eur Respir J. 2000;16:808-16.
46. Weiss KB, Liljas B, Schoenwetter W, Schatz M, Luce BR. Effectiveness of budesonide administered via dry-powder inhaler vs triamcinolone acetonide administered via pressurized metered-dose inhaler for adults with persistent asthma in managed care settings. Clinical Therapeutics. 2004;26(1):102-14.
47. Vogelmeier CF, Hering T, Lewin T, Sander P, Bethke TD. Efficacy and safety of ciclesonide in the treatment of 24,037 asthmatic patients in routine medical care. Respir Med. 2011 Feb;105(2):186-94.
48. Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma treated previously with inhaled steroids. Clinical Study Report 3030; Marlborough Mass: Sepracor Inc.
49. Meltzer E, Korenblat P, Weinstein S, Noonan M, Karafilidis J. Efficacy and safety evaluation of ciclesonide in mild to moderate persistent asthma previously treated with inhaled corticosteroids [abstract]. Allergy & Asthma Proceedings. 2009;30(3):293-303.
50. Bateman E, Karpel J, Casale T, Wenzel S, Banerji D. Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma. CHEST. 2006;129:1176-87.
51. Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma not treated with steroids. Clinical Study Report 3031; Marlborough Mass: Sepracor Inc.

52. Berger W, Kerwin E, Bernstein D, Pedinoff A, Bensch G, Karafilidis J. Efficacy and safety evaluation of ciclesonide in subjects with mild to moderate asthma not currently using inhaled corticosteroids [abstract]. Allergy & Asthma Proceedings. 2009;30(3):304-14.
53. Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma administered once-daily. Data on File. Clinical Study Report 321; Marlborough, Mass: Sepracor Inc.
54. Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma administered once-daily. Data on File. Clinical Study Report 322; Marlborough, Mass: Sepracor Inc.
55. Efficacy and safety of ciclesonide metered-dose inhaler MDI and fluticasone MDI in adults and adolescents with moderate to severe persistent asthma treated previously with inhaled steroids. Clinical Study Report 323/324; Marlborough Mass: Sepracor Inc.
56. Nelson HS, Busse WW, deBoisblanc BP, Berger WE, Noonan MJ, Webb DR, et al. Fluticasone propionate powder: Oral corticosteroid-sparing effect and improved lung function and quality of life in patients with severe chronic asthma. J Allergy Clin Immunol. 1999;103(2 pt 1):267-75.
57. Condemi JJ, Chervinsky P, Goldstein MF, Ford LB, Berger WE, Ayars GH, et al. Fluticasone propionate powder administered through Diskhaler vs triamcinolone acetonide aerosol administered through metered-dose inhaler in patients with persistent asthma. J Allergy Clin Immunol. 1997;100(4):467-74.
58. Berend N, Kellett B, Kent N, Sly PD; Collaborative Study Group of the Australian Lung Foundation. Improved safety with equivalent asthma control in adults with chronic severe asthma on high-dose fluticasone propionate. Respirology. 2001;6(3):237-46.
59. Sheikh S, Goldsmith LJ, Howell L. Comparison of the efficacy of inhaled fluticasone propionate, 880 µg/day, with flunisolide, 1,500 µg/day, in moderate-to-severe persistent asthma. Ann Allergy Asthma Immunol. 1999;83:300-4.
60. Harnest U, Price D, Howes T, Sussman G. Comparison of mometasone furoate dry powder inhaler and fluticasone propionate dry powder inhaler in patients with moderate to severe persistent asthma requiring high-dose inhaled corticosteroid therapy: findings from a non inferiority trial. Journal of Asthma. 2008;45:215-20.
61. O'Connor B, Bonnaud G, Haahtela T, Luna JM, Querfurt H, Wegener T, et al. Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator. Ann Allergy Asthma Immunol. 2001;86:397-404.
62. Wardlaw A, Larivee P, Eller J, Cockcroft DW, Ghaly L, Harris AG, et al. Efficacy and safety of mometasone furoate dry powder inhaler vs fluticasone propionate metered-dose inhaler in asthma subjects previously using fluticasone propionate. Ann Allergy Asthma Immunol. 2004;93:49-55.
63. Fish JE, Karpel JP, Craig TJ, Bensch GW, Noonan M, Webb DR, et al. Inhaled mometasone furoate reduces oral prednisone requirements while improving respiratory function and health-related quality of life in patients with severe persistent asthma. J Allergy Clin Immunol. 2000;106:852-60.
64. Krouse J, Krouse H, Janisse J. Effects of mometasone furoate administered via dry powder inhaler once daily in the evening on nocturnal lung function and sleep parameters in patients with moderate persistent asthma: a randomized, double-blind, placebo-controlled pilot study [abstract]. Clinical Drug Investigation. 2009;29(1):51-8.
65. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily vs twice-daily dosing of mometasone furoate administered via dry powder inhaler: a randomized open-label study. BMC Pulmonary Medicine. 2010;10(1).
66. Noonan M, Leflein J, Corren J, Staudinger H. Long-term safety of mometasone furoate administered via a dry powder inhaler in children: results of an open-label study comparing mometasone furoate with beclomethasone dipropionate in children with persistent asthma. BMC Pediatrics. 2009;9:43.
67. Kramer S, Rottier BL, Scholten RJ, Boluyt N. Ciclesonide versus other inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev. 2013 Feb 28;2:CD010352. doi: 10.1002/14651858.CD010352.
68. National Heart, Lung, and Blood Institute and National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma full report 2007. [guideline on the internet]. 2007. [cited 2015 Jan 13]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
69. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, et al. Effect of inhaled glucocorticoids in childhood on adult height. N Engl J Med. 2012 Sep 6;367(10):904-12.
70. Roizen J, Alter C, Bamba V. Recent research on inhaled corticosteroids and growth. Curr Opin Endocrinol Diabetes Obes. 2012 Feb;19(1):53-6.
71. Fitzgerald M, Bateman ED, Bousquet J, Cruz A, Haahtela T, O'Byrne P, et al. Global Initiative for Asthma. Global strategy for asthma management and prevention 2012 [guideline on the internet]. 2012. [cited 2015 Jan 13]. Available from: http://www.ginasthma.com.
72. Global Initiative for Chronic Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [guideline on the internet]. Global Initiative for Chronic Lung Disease World Health Organization; 2014 [cited 2015 Jan 13]. Available from: http://www.goldcopd.org/.
73. National Institute for Health and Clinical Excellence. Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). [guideline on the internet]. 2010 [cited 2015 Jan 13]. Available from: www.nice.org.uk/guidance/CG101.

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 with certain agents also having the indication for use in asthma patients who require systemic corticosteroid therapy.[1-11] These agents are summarized in Table 1 and include beclomethasone (QVAR®), budesonide (Pulmicort Flexhaler®, Pulmicort Respules®), ciclesonide (Alvesco®), flunisolide (Aerospan®), fluticasone propionate (Flovent Diskus®, Flovent HFA®), mometasone furoate (Asmanex HFA®, Asmanex Twisthaler®) and the newest agent recently approved by the FDA, fluticasone furoate (Arnuity Ellipta®). 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.[1-11]

Although ICSs exert their therapeutic effects through identical mechanisms of action, they differ in their potency, dosing schedules, and dosage form availability.[1-10] 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 and have not demonstrated any major differences in clinical efficacy between the available ICSs.[12-67] Currently, only budesonide nebulizer suspension is available generically.

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.[68] 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.[68] 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.[69,70] 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.[71]

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 a 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.[72] 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.[73]

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.[74]

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	a
Ciclesonide (Alvesco®)	Inhaled corticosteroid	-
Flunisolide (Aerospan®)	Inhaled corticosteroid	-
Fluticasone furoate (Arnuity Ellipta®)	Inhaled corticosteroid	-
Fluticasone propionate (Flovent Diskus®, Flovent HFA®)	Inhaled corticosteroid	-
Mometasone furoate (Asmanex HFA®, Asmanex Twisthaler®)	Inhaled corticosteroid	-

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

Indications

None of the inhaled corticosteroid products are indicated for the relief of acute bronchospasm[1-10]

Table 2. Food and Drug Administration-Approved Indications[1-11]

Generic Name	Maintenance Treatment of Asthma as Prophylactic Therapy	Treatment of Asthma In Patients Requiring Systemic Corticosteroid Therapy
Beclomethasone	a *	a *
Budesonide	a †,‡	
Ciclesonide	a §	
Flunisolide	a ‖	a ‖
Fluticasone furoate	a §	
Fluticasone propionate	a ¶	a ¶
Mometasone furoate	a ¶	

*In patients five years of age and older.
† Pulmicort Flexhaler®: In patients six years of age and older.
‡ Pulmicort Respules®: In patients 12 months to eight years of age.
§ In patients 12 years of age and older.
‖ In patients six 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 versus host disease, inflammatory bowel disease, eosinophilic esophagitis and chronic obstructive pulmonary disease.[11]

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
Flunisolide	Variable	<1	6ß-OH flunisolide	1.3 to 1.7
Fluticasone furoate	Variable	1 to 2	No	24
Fluticasone propionate	Variable	<5	No	7.8†
Mometasone furoate	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.[12-67]

The safety and efficacy of fluticasone furoate dry powder inhaler has been evaluated in several clinical trials in patients with asthma.[12-24] FDA-approval for this agent was based on the results of three dose-ranging trials (phase II/IIb) and four confirmatory trials (phase III) which included 3,611 patients with asthma, an FEV_1 of 40% to 90% predicted and varied use of previous ICSs.[13-15,19-22] Each of these trials were double-blind and if appropriate double-dummy. Different doses of fluticasone propionate, including once every evening, was compared to either placebo or an active control (fluticasone propionate twice daily or fluticasone furoate/vilanterol once daily) or both. The primary endpoint for these studies was pre-bronchodilator, pre-dose (trough) FEV_1 at the end of the study (week eight, week 12 or week 24). Pre-dose FEV_1 was significantly improved upon treatment with the FDA-approved doses of fluticasone furoate when compared to placebo in each of the seven clinical trials.[13-15,19-22] Fluticasone furoate also significantly improved percentage of rescue-free 24-hour periods and although statistical significance could not be determined in some cases, fluticasone furoate also improved symptom-free 24-hour periods over the course of the studies.[13-15,19-22] Generally, results from clinical trials suggest that fluticasone propionate and fluticasone furoate have similar effects when compared to placebo; however, statistical analyses were rarely performed that directly compared each formulation to one another.[12-15,17,20,22] Two studies included the active control of combination fluticasone furoate/vilanterol. In these studies, fluticasone furoate provided significant improvements when compared to placebo but when compared directly to fluticasone furoate/vilanterol, data is varied. Treatment differences in the primary end-point (pre-dose FEV_1) in one trial suggested superiority of combination fluticasone furoate/vilanterol over fluticasone furoate alone, while the other trial suggested non-inferiority.[20,22] The percentage of rescue-free and symptom-free 24-hour periods were significantly improved with fluticasone furoate/vilanterol when compared to fluticasone furoate alone ($P<0.001$ and $P=0.010$, respectively).[22]

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
van den Berge et al[12] Fluticasone furoate 1,000 µg inhaled 2, 14, or 26 hours prior to measure of eNO and PC_{20} AMP vs fluticasone propionate 1,000 µg inhaled 14 or 26 hours prior to measure of eNO and PC_{20} AMP vs placebo Each treatment period was separated by at least five days and a maximum of 10 days.	MC, DB, PC, PG, RCT, XO (six-way) Patients 18 to 55 years of age diagnosed with asthma, FEV_1 >70% predicted, PC_{20} AMP< 50 mg/mL, presence of atopy	N=24 8 weeks	Primary: PC_{20} AMP, eNO Secondary: Adverse reactions	Primary: Fluticasone furoate significantly improved the PC_{20} AMP at all time points compared to placebo. The mean difference in doubling concentrations being 2.18 (95% CI, 1.13 to 3.23), 1.54 (95% CI, 0.48 to 2.59), and 1.30 (95% CI, 0.26 to 2.34) at two, 14, and 26 hours, respectively (P<0.05 for all time points). Fluticasone propionate significantly improved the PC_{20} AMP at 14 hours but not at 26 hours compared to placebo. The difference in doubling concentrations being 1.72 (95% CI, 0.70 to 2.75; P<0.05) and 0.33 (95% CI, −0.69 to 1.34; no P value reported) at 14 and 26 hours respectively. No significant changes in the concentration of eNO were observed after treatment with fluticasone furoate or propionate at any time point. Secondary: The most frequently occurring adverse event was bronchospasm (33%), followed by dyspnea, dizziness, headache, nausea, palpitations and fatigue. None of the adverse events occurred more frequently during treatment with fluticasone furoate when compared to fluticasone propionate or placebo.
Bleecker et al[13] Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 300	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with moderate persistent symptomatic asthma while receiving low-dose ICS therapy (for at least eight weeks); reversibility to	N=622 8 weeks	Primary: Pre-dose FEV_1 Secondary: Morning and evening pre-dose PEF averaged, percentage symptom-free and rescue-free 24-hour periods, withdrawals due to lack of efficacy, safety	Primary: At week eight, all active treatment groups demonstrated significant placebo-adjusted improvements from baseline in predose FEV_1 (P<0.001) and achieved the predefined 200 mL difference from placebo. Improvements with fluticasone furoate were similar to or greater than those reported for twice-daily fluticasone propionate. The treatment interaction with each of the covariates modeled was not statistically significant. Similar results were obtained for the per-protocol population. Secondary: Morning and evening predose PEF values over weeks one through eight were also significantly different from placebo, indicating greater improvement with therapy (morning PEF, P<0.001 for all doses; evening

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg inhaled QPM vs fluticasone furoate 400 µg inhaled QPM vs fluticasone propionate 250 µg inhaled BID vs placebo	albuterol, pre-bronchodilator FEV_1 of 40% to 90% predicted			PEF, P=0.18 for fluticasone furoate and P<0.001 for all other active treatments). Mean symptom- and rescue-free 24-hour periods increased over eight weeks in all groups. Significant improvements in symptoms were observed with fluticasone furoate 400 µg once daily and fluticasone propionate 250 µg twice daily, and for rescue use with all treatments except fluticasone furoate 200 µg once daily (P values not reported). Withdrawals attributable to lack of efficacy were significantly greater with placebo (33%) compared with all fluticasone furoate treatment groups (10%, 11%, 8%, and 7% for 100, 200, 300, and 400 µg, respectively; P<0.001) and twice-daily fluticasone propionate 250 µg (14%; P=0.002). On-treatment adverse events were reported in 33 to 41% of patients across the fluticasone furoate groups, 42% with fluticasone propionate and 30% with placebo. The most commonly reported on-treatment adverse events were headache (6 to 9% across treatment groups) and nasopharyngitis (4 to 9%). No dose-related increases in the frequency of the most common adverse events were observed. The incidence of oral/oropharyngeal candidiasis across the fluticasone furoate groups was less than 1 to 4%, 4% with fluticasone propionate 250 µg, and 0% with placebo.
Busse et al[14] Fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 400 µg inhaled QPM vs fluticasone furoate 600	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with persistent asthma not controlled using medium-dose ICS, FEV1 of 40 to 90% predicted; reversibility of	N=627 8 weeks	Primary: Pre-dose FEV_1 Secondary: Asthma symptom scores, rescue salbutamol use, morning and evening pre-dose PEF averaged, percentage symptom-free and rescue-free 24-hour periods, withdrawals due to	Primary: Pre-dose FEV_1 was significantly improved in all active treatment groups when compared with placebo at week eight (P<0.001). The predefined 200 mL difference relative to placebo was achieved in all fluticasone furoate groups. Secondary: All active treatments provided significant improvement from baseline in evening PEF over the eight-week treatment period (P<0.001). Similar improvements for all active treatments were also observed in morning PEF and were significantly improved when compared with placebo (P<0.001). Based on patient-reported data, the proportion of symptom-free 24-hour

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg inhaled QPM vs fluticasone furoate 800 µg inhaled QPM vs fluticasone propionate 500 µg inhaled BID vs placebo	asthma with inhaled salbutamol		worsening asthma	periods during weeks one to eight increased relative to baseline in all study groups and was greater with all active treatments than placebo (P<0.001, P<0.001, P=0.022 and P=0.002 for fluticasone furoate 200 µg, 400 µg, 600 µg and 800 µg, respectively; P=0.017 for fluticasone propionate). Similar significant improvements were observed for rescue-free 24-hour periods in the treatment groups compared to placebo (P<0.001 for all). The proportion of patients with symptom-free and rescue-free days were also significantly greater in the all treatment groups than in the placebo group (comparisons with placebo P<0.001, except for P=0.006 with fluticasone furoate 600 µg for symptom-free days). Withdrawal rates due to lack of efficacy were significantly lower in all active treatment groups compared with the placebo group (6 to 12% compared with 33%; P<0.001 for all comparisons). The fewest withdrawals due to lack of efficacy occurred in the fluticasone furoate 400 µg and fluticasone propionate groups (6% and 7%, respectively). Overall, fluticasone furoate was well tolerated; 31% to 35% of patients in the fluticasone furoate groups and 22% in the placebo group experienced one or more adverse event during treatment. The most frequently reported adverse events were oral candidiasis (<1 to 12%), headache (3 to 11%), nasopharyngitis (2 to 7%) and dysphonia (<1 to 5%). The incidence of drug-related adverse events was 2% in the placebo group and 11%, 11%, 3%, 17% and 9% of patients in the fluticasone furoate 200, 400, 600 and 800 µg groups and fluticasone propionate group, respectively; the most frequent of these were oropharyngeal candidiasis, oral candidiasis and dysphonia. The frequency of these events was similar in all active treatment groups, with the exception of oral candidiasis, which occurred most frequently in the fluticasone furoate 800 µg group. The incidence of asthma exacerbations was lower in the active treatment groups (<1 to 6%) than in the placebo group (16%). Most exacerbations in the placebo group were attributed to lack of efficacy. Eight percent of patients in the placebo arm required oral corticosteroids compared with 0 to 2% in the fluticasone furoate groups and 3% in the fluticasone propionate group. Three patients were hospitalized due to asthma

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				exacerbation, one each in the placebo, fluticasone furoate 200 µg once daily and fluticasone propionate 500 µg twice daily arms.
Bateman et al[15] Fluticasone furoate 25 µg inhaled QPM vs fluticasone furoate 50 µg inhaled QPM vs fluticasone furoate 100 µg inhaled QPM fluticasone furoate 200 µg inhaled QPM vs fluticasone propionate 25 µg inhaled BID vs placebo	AC, DB, DD, MC PC, PG, RCT Patients ≥12 years of age with a diagnosis of persistent asthma, FEV_1 40 to 90% predicted, and not adequately controlled on SABAs (or other non-steroidal controllers) that they had been using for ≥3 months	N=598 8 weeks	Primary: Pre-dose evening FEV_1 Secondary: PEF average, percentage of symptom-free 24-hour periods, rescue-free 24-hour periods and number of withdrawals due to lack of efficacy, safety	Primary: A significant dose–response relationship for change in pre-dose evening FEV_1 (baseline to week eight) was achieved across once-daily fluticasone furoate (25 to 200 µg) both when placebo was included (P<0.001) and when placebo was not included (P=0.03). At week eight, all active treatment groups showed a >200 mL improvement in pre-dose FEV_1 from baseline; the fluticasone furoate 100 µg and 200 µg once daily doses achieved a >200 mL difference compared with placebo (P<0.001). Fluticasone furoate 50 µg once daily, although failing to reach the pre-defined 200 mL difference, was also significantly better than placebo (P<0.05). Fluticasone furoate 25 µg and fluticasone propionate failed to show superiority compared with placebo (P value not reported). Secondary: Evening PEF improvements from baseline were largest in the fluticasone furoate 50 µg and 200 µg once-daily groups (mean difference 20.7 and 21.7 L/min, respectively, compared with placebo; P<0.001). Significant but smaller differences were also achieved with fluticasone furoate 25 µg once daily (14.0 L/min, P=0.019) and 100 µg once daily (16.1 L/min, P=0.005) and were of a similar magnitude to the fluticasone propionate 100 µg twice daily group (14.9 L/min; P=0.011). Similarly, all active treatment groups improved morning PEF relative to baseline and these changes were significantly greater than with placebo (P values not reported). Fluticasone furoate 200 µg once daily exhibited the greatest difference in morning PEF (22.0 L/min; P<0.001). For symptom-free periods, fluticasone furoate 100 µg once daily demonstrated the greatest increase from baseline relative to placebo (20.2%). Fluticasone furoate 50 µg and 200 µg once daily showed numerically lower increases, similar in magnitude to the fluticasone propionate 100 µg twice-daily group. For all except the fluticasone furoate 25 µg once-daily group, the effect was significantly better than for placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(P values not reported). A similar pattern was evident for rescue-free periods (P values not reported). Withdrawal rates due to lack of efficacy were highest in the placebo and fluticasone propionate twice-daily groups (15% and 11%, respectively). Rates for fluticasone furoate once-daily ranged from 3 to 9%. The differences in the fluticasone furoate 50 µg (3%) and 100 µg (5%) once-daily groups were significantly lower than for placebo (P=0.004 and P=0.032, respectively). Overall, 26%, 34%, and 20% to 32% of patients in the placebo, fluticasone propionate twice-daily and fluticasone furoate once-daily groups, respectively, reported at least one on-treatment adverse events. Drug-related adverse events were low in all groups (0 to 6%), with no apparent dose-dependent events.
Woodcock et al[16] Fluticasone furoate 200 µg inhaled QAM vs fluticasone furoate 400 µg inhaled QAM vs fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 400 µg inhaled QPM vs	DB, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma, FEV_1 50 to 80% predicted, and reversibility with inhaled salbutamol	N=545 8 weeks	Primary: Pre-dose FEV_1 Secondary: Safety	Primary: Pre-dose FEV_1 was significantly improved for each of the fluticasone furoate treatment arms compared to placebo at week eight (P=0.033 for 200 µg once-daily arms, P<0.001 for 400 µg once daily and 200 µg twice daily arms). Fluticasone furoate 400 µg once daily in the evening resulted in similar placebo-adjusted improvements in evening pre-dose FEV_1 at week eight compared with 200 µg twice daily (240 mL compared with 235 mL). Fluticasone furoate 200 µg twice daily resulted in greater improvements in placebo-adjusted morning pre-dose FEV_1 than 400 µg once daily in the morning at week eight (315 mL compared with 202 mL). A ≥200 mL increase in placebo-adjusted pre-dose FEV_1 was observed for the 400 µg once daily in the morning or evening groups and for 200 µg twice daily group but not for either of the 200 µg once daily groups. However, the increase from baseline was ≥200 mL with both 200 µg once daily groups. Results for the per protocol population were consistent with those of the intention to treat population; although, the relative treatment effect of all

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone furoate 200 µg inhaled BID vs placebo				active treatment groups was generally lower. The effect of fluticasone furoate 200 µg once daily in the evening FEV_1 was not significantly different from placebo (P=0.264). Secondary: The proportion of patients who reported any adverse event during the treatment period was 28% in the placebo group and 31 to 39% in the active treatment groups. The most frequently reported adverse events during treatment were headache (6 to 9%), nasopharyngitis (3 to 8%), bronchitis (0 to 4%), pharyngolaryngeal pain (<1 to 3%), and upper respiratory tract infection (<1 to 3%). The incidence and type of adverse events were generally similar to placebo and the frequency of adverse events did not appear to be related to the dose of fluticasone furoate. A total of four serious adverse events were reported, with angioedema the only one considered to be possibly related to the study drug. A total of 11 patients reported 13 adverse events that resulted in study withdrawal: three patients in the 200 µg once-daily morning group, one in the 200 µg once-daily evening group, three in the 400 µg once-daily morning group, three in the 400 µg once-daily evening group and one in the 200 µg twice-daily group. There was no safety concerns related to vital signs, or laboratory safety tests. No treatment-related changes were apparent. The incidence of oral candidiasis was low in the active treatment groups (0%to 4% compared with <1% for placebo) as was the incidence of asthma exacerbations (<1 to 4% compared with 14% for placebo).
Woodcock et al[17] Fluticasone furoate 200 µg QD for 28 days and	AC, DB, MC, PC, RCT, XO Patients ≥12 years of age with moderate persistent asthma, FEV_1 40 to 80%	N=190 28 days (per period)	Primary: Pre-dose FEV_1 at day 28 of each treatment period Secondary: Safety	Primary: Pre-dose FEV_1 increased in all groups, but the mean increases in the four active treatment groups were approximately twice those in the placebo group. The differences compared to placebo were statistically significant in all four active treatment groups, as assessed in the ITT population (P<0.001 for fluticasone furoate 200 µg once daily, fluticasone furoate 100 µg twice daily and fluticasone propionate 100 µg twice daily; P=0.02 for the fluticasone propionate 200 µg once daily).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone propionate 100 µg BID for 28 days and placebo vs Fluticasone furoate 200 µg QD for 28 days and fluticasone furoate 100 µg BID for 28 days and placebo Twelve sequences comprising three 28-day treatment periods. Patients received either a fluticasone furoate plus placebo regimen or a fluticasone propionate plus placebo regimen. The order of receiving different periods is varied by sequence.	predicted and reversibility to inhaled salbutamol			In the ITT population, the lower 95% CI for the mean difference between fluticasone furoate 200 µg once daily and 100 µg twice daily in pre-dose FEV_1 on day 28 was -35 mL (LS mean difference of 11 mL). This difference was within the pre-defined limit of -110 mL, thus demonstrating non-inferiority of the fluticasone furoate 200 µg once-daily regimen. Similar results were obtained from the non-inferiority analysis in the PP population. Data from patients treated with fluticasone propionate indicated numerically reduced improvement in pre-dose FEV_1 with the 200 µg once-daily dose in comparison with 100 µg twice daily, although no statistical comparison of these groups was performed. Secondary: No serious adverse events were reported and no adverse events led to permanent discontinuation of drug or to patient withdrawal. The frequency of on-treatment adverse events was higher in the fluticasone furoate 200 µg once-daily, fluticasone furoate 100 µg twice-daily and dry powder inhaler placebo groups (16%, 18%, and 14%, respectively) than in the fluticasone propionate 200 µg once-daily, fluticasone propionate 100 µg twice-daily and diskus placebo groups (5%, 7% and 12% respectively). Upper respiratory tract infections were the most commonly reported adverse event, occurring in 5% of patients in each of the fluticasone furoate groups and 1% in the placebo group; no other AEs were reported by more than 1% of patients in either of the fluticasone furoate groups or the placebo group during the treatment period. However, only three of the adverse events reported, headache, dry throat, and tachycardia, were considered to be potentially drug-related. One patient reported dysphonia in the fluticasone propionate 200 µg once daily group. There were no cases of oral candidiasis. Asthma exacerbations occurred in five (3%) patients on placebo, and one (<1%) patient on fluticasone furoate 200 µg once daily. None of the exacerbations were severe enough to require hospitalization.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Medley et al[18] Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 100 µg inhaled QAM vs fluticasone furoate 200 µg inhaled QPM vs placebo BID (QAM and QPM)	DB, DD, MC, PC, PG, RCT Patients 16 to 55 years of age with a diagnosis of persistent asthma and PEF 50 to 90% predicted; reversibility with inhaled salbutamol	N=578 28 days	Primary: Change from baseline in pre-treatment daily trough PEF between morning and evening doses Secondary: FEV1, PEF, percentage of symptom-free 24-hour periods, symptom-free days and nights, nights with no awakenings, rescue medication-free 24-hour periods, and withdrawals due to lack of efficacy, adverse events	Primary: The mean difference in trough PEF between fluticasone furoate 100 µg once daily in the morning compared with 100 µg once daily in the evening was 13.4 L/min (95% CI, 2.3 to 24.4). However, the placebo response was greater in the morning than in the evening (18.8 L/min compared with 8.8 L/min. All fluticasone furoate groups were associated with a statistically significant improvement in trough PEF compared to placebo (P<0.001 for 100 µg QAM and 250 µg QPM, P=0.005 for 100 µg QPM). There was an indication that the 250 µg once daily in the evening produced greater increases in PEF than 100 µg once daily in the evening (by 6.7 L/min), but the difference was not statistically significant. Secondary: Analyses of change from baseline in pre-dose FEV_1 found substantial improvements from baseline in FEV_1 that were greater with fluticasone furoate (203 mL to 317 mL) than with placebo (99 mL). However, statistical superiority of any dose was not demonstrated. When compared to placebo, fluticasone propionate was associated with a significant reduction in symptoms, rescue medication taken, and night-time awakenings (all P<0.001; except: P=0.001 for percent symptom-free days with 100 µg evening; P=0.006 for percent symptom-free nights with 100 µg in the morning, and P=0.002 for percent rescue medication-free days with 100 µg in the evening). Analysis of the effect of fluticasone furoate 250 µg once daily in the evening compared to 100 µg once daily in the evening indicated a greater improvement with 250 µg once daily in the evening in 24-hour symptom-free periods, rescue medication-free 24-hour periods, and night-time awakenings, but the differences were not significant. Three patients withdrew from the study due to lack of efficacy (other than exacerbations); two on placebo and one on fluticasone furoate 100 µg once daily in the morning. The number of withdrawals with fluticasone furoate was not statistically significant compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The proportion of patients reporting an adverse event during the treatment period was 26% in the placebo group and 23 to 26% with fluticasone furoate. Rates of occurrence of the most frequent adverse events (≥3% of patients in any treatment group) and treatment-related adverse events were low and similar across the treatment groups. The most frequently reported AEs during treatment were headache (4% to 9%) and nasopharyngitis (3% to 4%). None of the three serious adverse events were considered related to study treatment and all were resolved within three weeks after withdrawal. No clinically significant abnormalities or shifts from baseline were observed in any treatment group for hematological, clinical chemistry, vital signs, or ECG parameters. The incidence of oropharyngeal candidiasis was low (≤3% of patients in any treatment group), with slightly higher incidence (3% [4 patients]) in the 250 µg group than in any of the other three groups.
Lötvall et al[19] Fluticasone furoate 100 µg inhaled QPM vs fluticasone propionate 250 µg inhaled BID vs placebo QPM or BID	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12 weeks with a stable ICS dose for ≥ 4 weeks, FEV_1 40 to 90% predicted; reversible on inhalation of albuterol or salbutamol	N=343 24 weeks	Primary: Pre-dose FEV_1 at 24 weeks Secondary: Mean change in percentage of rescue-free 24-hour periods, PEF and percentage of symptom-free 24-hour periods over the 24 weeks, change in AQLQ score at weeks 12 and 24, Asthma Control Test score at weeks 12 and 24 and withdrawal due to lack of efficacy	Primary: Pre-dose evening FEV_1 was significantly improved at week 24 with fluticasone µg QPM and fluticasone propionate 250 µg BID when compared to placebo (P=0.009 and P=0.011, respectively); both active treatments resulted in similar effects compared with placebo. Secondary: The percentage of rescue-free 24-hour periods was significantly increased compared with placebo for both fluticasone furoate µg QPM and fluticasone propionate 250 µg BID (P<0.001). Initial analysis of evening PEF found no significant difference between placebo and active therapy. Because of the step-down closed testing procedure employed, significance could not be inferred for all subsequent efficacy comparisons regardless of P value. Morning PEF, percentage of symptom-free 24-h periods over the course of the study and AQLQ at weeks 12 and 24 were numerically improved by both active treatments compared with placebo (P value not reported).
Bleecker et al[20] (abstract)	DB, PC, PG, RCT Patients ≥12 years	N=609 12 weeks	Primary: Pre-dose (trough) FEV_1, and serial (0 to 24	Primary: When compared with placebo, trough FEV_1 was significantly improved in both the fluticasone furoate and fluticasone furoate/vilanterol groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate/vilanterol 100/25 µg inhaled QPM vs placebo QPM	of age with a diagnosis of persistent asthma		hours) wmFEV$_1$ Secondary: Rescue-free 24-hour periods, safety	(placebo, 196 mL; fluticasone furoate, 136 mL; P=0.002; fluticasone furoate/vilanterol, 172 mL;P<0.001). There was also a significant difference in serial (0 to 24 hours) wmFEV$_1$ for both treatment groups when compared to placebo. The serial (0 to 24 hour) wmFEV$_1$ for the placebo group was 212 mL as compared to 186 mL in the fluticasone furoate group (P=0.003) and 302 mL in the fluticasone furoate/vilanterol (P=<0.001). When fluticasone furoate/vilanterol was compared to fluticasone furoate, treatment differences approached significance for serial wmFEV1 (116 mL; P=0.060), but not for trough FEV1 (36 mL; P=0.405). Secondary: The percentage of rescue-free 24-hour periods with fluticasone furoate/vilanterol was 10.6% greater than fluticasone furoate and 19.3% greater than placebo. Urinary cortisol suppression was observed with fluticasone furoate/vilanterol (ratio, 0.82) relative to placebo (P=0.032), but not with fluticasone furoate (no P value reported). Adverse event and safety profiles were similar across treatment groups.
Wooodcock et al[21] Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 200 µg inhaled QPM	DB, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and stable use of any ICS dose for ≥12 weeks or for ≥ 4 weeks for mid-high dose, FEV$_1$ 40 to 90% predicted and	N=238 24 weeks	Primary: Pre-dose (trough) FEV$_1$ at week 24 Secondary: Percentage of rescue-free and symptom-free 24-hour periods, change in PEF average, ACT scores	Primary: Both strengths of fluticasone furoate were associated with improvements in trough FEV$_1$ of >200 mL from baseline at week 24. A numerically greater increase was observed in with the fluticasone furoate 200 µg dose than with 100 µg dose (treatment difference, 77 mL;95% CI, -39 to 192). Repeated-measures analysis of change from baseline in trough FEV$_1$ over 24 weeks of treatment showed that improvement in trough FEV$_1$ was apparent within two weeks of randomization and was maintained throughout the treatment period. Secondary: Improvements over 24 weeks in percentage of rescue-free and symptom-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	reversibility with albuterol			free 24-hour periods and PEF, as well as in ACT score at week 24, were observed in both treatment groups. No treatment differences were observed in incidence of severe asthma exacerbations or healthcare resource utilization. There were no asthma-related inpatient hospitalizations.
O'Byrne et al[22] Fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate/vilanterol 200/25 µg inhaled QPM vs fluticasone propionate 500 µg inhaled BID	AC, DB, DD, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12 weeks with a stable ICS dose for ≥ 4 weeks, FEV_1 40% to 90% predicted; reversible on inhalation of albuterol or salbutamol	N=586 24 weeks	Primary: Pre-dose FEV_1 and $wmFEV_1$ (0 to 24 hours post-dose) Secondary: Mean change in percentage of rescue-free 24-hour periods, percentage of symptom-free 24-hour periods and total AQLQ score after 12 and 24 weeks	Primary: Trough FEV_1 at week 24 was improved from baseline with all active therapies. The differences between fluticasone furoate/vilanterol and fluticasone furoate, and fluticasone furoate/vilanterol and fluticasone propionate were both significant (P<0.001 for both), while fluticasone furoate was noninferior to fluticasone propionate. Change from baseline in trough FEV_1 by treatment showed sustained benefit with fluticasone furoate/vilanterol over fluticasone furoate and fluticasone propionate at all study time-points. The $wmFEV_1$ from 0 to 24 hours post-dose at week 24 compared with baseline was improved in all treatment arms. When compared to the single entity fluticasone furoate and fluticasone propionate, fluticasone furoate/vilanterol significantly improved $wmFEV_1$ 0 to 24 hours post-dose (P=0.048 and P=0.003, respectively). Secondary: The percentage of rescue-free 24-hour periods increased over the study with all therapies. The difference in improvement was significant for the comparison of fluticasone furoate/vilanterol with fluticasone furoate, but not for fluticasone furoate/vilanterol compared with fluticasone propionate (P<0.001 and P=0.067, respectively). The percentage of symptom-free 24-hour periods increased over the course of the study. Fluticasone furoate/vilanterol provided a significant improvement when compared to fluticasone furoate but not fluticasone propionate (P=0.010 and P=0.137, respectively). Improvements from baseline in the AQLQ score were seen in all treatment groups at week 24. The improvements were similar in each arm and were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				not statistically significant. Over the 24-week treatment period, fewer patients withdrew due to lack of efficacy in the fluticasone furoate/vilanterol group (3%) compared with the fluticasone furoate (11%) or fluticasone propionate (9%) groups.
O'Byrne et al[23] Fluticasone furoate 50 µg inhaled QPM vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and treatment with non-ICS, FEV_1 ≥60% predicted, and reversibility with albuterol or salbutamol	N=248 12 weeks	Primary: Pre-dose (trough) FEV_1 Secondary: Percentage of rescue-free 24-hour periods, daily morning and evening PEF averaged, percentage of symptom-free 24-hour periods, number of withdrawals due to lack of efficacy, ACT test score, percentage of patients controlled, AQLQ total score, ease of use of the ELLIPTA® dry powder inhaler	Primary: Pre-dose FEV_1 at week 12 for the fluticasone furoate group was 157 mL as compared to 38 mL in the placebo group, resulting in a treatment difference of 120 mL (P=0.012). The per protocol population was similar, with a treatment difference in favor of fluticasone furoate 50 mcg of 131 mL; 95% CI, 38 to 224; P=0.006). Secondary: There was a significant improvement in the percentage of rescue-free 24-hour periods in patients treated with fluticasone furoate (28.7%) compared to placebo (17.1%), resulting in a treatment difference of 11.6% (P=0.004). This equated to an additional 0.8 rescue-free 24-hour periods per week with fluticasone 50 µg treatment. Change from baseline in evening PEF over the 12-week treatment period was increased with treatment with fluticasone furoate 50 µg (22.8 L/min) and placebo (19.5 L/min), but the treatment difference (3.3 L/min) was not statistically significant (P=0.536). Due to this, significance could not be inferred for the remaining endpoints. Morning PEF was numerically increased and greater for fluticasone furoate 50 µg (34.5 L/min) compared with placebo treatment (22.9 L/min; treatment difference of 11.6 L/min). Increase from baseline in the percentage of symptom-free 24-hour periods was also numerically greater for fluticasone furoate 50 µg (22.6%) compared with placebo treatment (14.0%; treatment difference of 8.6%), which equates to an additional 0.6 symptom-free 24-hour periods per week with fluticasone furoate treatment. A numerically greater proportion of patients in the placebo group withdrew

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				due to lack of efficacy (14%) compared with patients in the fluticasone furoate 50 µg group (6%) Numerically greater increases in ACT scores, proportion of patients with an ACT score ≥20 and change from baseline in total AQLQ scores were observed for fluticasone furoate 50 µg compared with placebo. At baseline, most patients were able to use the ELLIPTA® inhaler correctly after being instructed once (98% fluticasone furoate; 96% placebo). At week four, most patients rated the ELLIPTA® inhaler as 'easy/very easy' to use (97%) and 'easy/very easy' to see how many doses of medication were left in the inhaler (95%).
Busse et al[24] Fluticasone furoate 50 µg inhaled QPM vs fluticasone propionate 100 µg inhaled BID vs placebo	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma for ≥12 weeks, treatment with non-ICS controllers or short-acting beta agonists, FEV_1 ≥60% predicted, and reversibility with salbutamol	N=222 24 weeks	Primary: Pre-dose (trough) FEV_1 Secondary: Percentage of rescue-free 24-hour periods, daily AM and PM PEF averaged, percentage of symptom-free 24-hour periods, number of withdrawals due to lack of efficacy, ACT test score, percentage of patients with ACT score ≥20, change in total AQAQ score, and unscheduled asthma-related healthcare resource utilization	Primary: Improvement in change from baseline of FEV_1 at week 24 for fluticasone furoate was not statistically significant when compared to placebo (37 mL, P=0.430). When fluticasone propionate was compared to placebo, there was a significant improvement in favor of the active treatment (102 mL, P=0.030). Because of the the lack of statistical significance on the primary endpoint, all subsequent endpoints were interpreted as descriptive only for the fluticasone furoate group when compared to placebo treatment. Secondary: The percentage of rescue-free 24-hour periods increased from baseline over weeks 0 to 24 in all treatment groups; mean improvements compared to placebo, were not statistically significant for fluticasone furoate (7.8%; 95% CI, −1.0 to 16.7), but were significant for fluticasone propionate (10.6%; 95% CI, 1.7 to 19.6). The number of additional rescue-free days per week compared to placebo was similar for fluticasone furoate (0.5) and fluticasone propionate (0.7). Mean change from baseline in evening PEF over the 24-week study for fluticasone furoate compared to placebo was 17.2 L/min (95% CI, 5.9 to 28.6) and 4.3 L/min (95% CI, −7.0 to 15.7) for fluticasone propionate compared to placebo. Change in morning PEF compared to placebo was 19.2 L/min (95% CI, 8.5 to 29.9) for and 10.6 L/min (95% CI, −0.2 to 21.3) for fluticasone propionate.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Changes from baseline in percentage of symptom-free 24-hour periods for fluticasone furoate and fluticasone propionate when compared to placebo were 8.3 (95% CI, 0.3 to 16.3) and 7.5 (95% CI, −0.5 to 15.5), respectively. The equivalent number of additional symptom-free days per week compared to placebo was similar for fluticasone furoate (0.6) and fluticasone propionate (0.5). There were more withdrawals due to lack of efficacy with placebo (20%) than with fluticasone furoate (12%) or fluticasone propionate (8%).
Busse et al[25] 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	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
beclomethasone CFC MDI 800 µg/day				
Bronsky et al[26] Beclomethasone 336 µg/day vs triamcinolone 800 µg/day vs placebo	AC, DB, DD, MC, PC, PG, RCT Adults with mild to moderately severe asthma maintained on an ICS	N=328 56 days	Primary: Mean changes from baseline in FEV_1 Secondary: Asthma symptom scores, average use of albuterol, nighttime awakenings, mean change from baseline in $FEF_{25\ to\ 75\%,}$ and FVC	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). 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[27] Beclomethasone 168 µg BID vs mometasone 100 µg BID	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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mometasone 200 µg BID vs placebo				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.
Bernstein et al[28] 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[29] Beclomethasone 200 µg/day via HFA MDI vs fluticasone propionate	AC, DB, DD, PG, RCT Patients five to 12 years of age with asthma for at least three months, a PEF ≥60% of	N=139 18 weeks	Primary: Morning PEF percent predicted Secondary: Evening PEF percent predicted, FEV_1 percent predicted, FVC percent	Primary: The mean change from baseline in morning PEF percent predicted was 5.7% in the beclomethasone group and 7.3% in the fluticasone propionate 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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. Those with poor control discontinued the study, and those labeled as intermediate did not have a dose change.	predicted normal, and currently using a SABA on an as-needed basis		predicted, symptom-free days, nights without sleep disturbances, use of a β_2-agonist, asthma control, quality of life and adverse events	5.9% in the beclomethasone group and 7.3% in the fluticasone propionate 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 propionate 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 propionate group. The treatment 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 propionate 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 propionate group (*P*=0.505). At six weeks, 36% of patients in the beclomethasone group and 42% in the fluticasone propionate 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 propionate 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 propionate (49%) groups.
Sharek et al[30]	MA	N=855	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Beclomethasone 328 to 400 µg/day vs fluticasone propionate 200 µg/day	1966 to 1998, DB, RCT studies that evaluated linear growth in children six to 16 years of age with asthma and concomitant ICS therapy	(5 studies)	Linear growth velocity in cm/year Secondary: Not reported	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 propionate study the mean difference between 96 children treated with fluticasone propionate 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
Berkowitz et al[31] 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[32] Beclomethasone 168 µg BID vs beclomethasone 336 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	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	Primary: The FEV_1 was significantly improved from baseline in both treatment groups; however, greater improvements occurred with fluticasone propionate 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 propionate 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone propionate 88 µg BID vs fluticasone propionate 220 µg BID	the study		awakenings and asthma symptoms	Secondary: The $FEF_{25\ to\ 75\%}$ and FVC were significantly improved from baseline in all treatment groups; however, patients receiving fluticasone propionate experienced greater improvements compared to patients receiving beclomethasone ($P \leq 0.034$ for all). Fluticasone propionate 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 propionate group (15.8 to 22.8 L), 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 propionate 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 propionate 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 propionate treatment compared to beclomethasone treatment.
Tinkelman et al[33]	OL for 52 weeks following two	N=1,133	Primary: FEV_1 and oral	Primary: The mean FEV_1 values continued to improve in all patient populations

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Budesonide 100 to 800 µg via DPI depending upon asthma severity	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 ICS, and adults previously maintained on oral corticosteroids	52 weeks	corticosteroid use Secondary: Plasma cortisol levels and adverse events	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. 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[34] Budesonide vs control group Patients were enrolled in a one to two year run-in period where their	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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
asthma medication was adjusted according to Danish guidelines. Patients considered controlled without continuous ICS use, were then asked to change treatment to 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	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 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[35] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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[36] 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	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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			period, symptom-free days, data on healthcare utilization, days off work, and lost school days	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[37] Budesonide 0.25 mg 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	DB, MC, PC, PG, RCT Children, six months to eight years of age, with a diagnosis of asthma	N=480 12 weeks	Primary: Changes in asthma symptom improvement score from baseline, PEF and improvements in FEV_1 Secondary: Not reported	Primary: When symptom scores for all active treatment groups were combined, a statistically significant difference between budesonide and placebo was 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[38]	AC, DB, DD, MC,	N=262	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Budesonide 400 µg QD vs mometasone 440 µg QD vs placebo	PC, RCT Patients with moderate persistent asthma previously using ICSs	8 weeks	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 asthma symptom scores	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).
Vermeulen et al[39] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). 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[40] 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	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			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	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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*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[41] Beclomethasone 750 µg, BID via AeroChamber® for a two week run-in period then randomized to: budesonide 600 µg BID via Turbuhaler® vs flunisolide 750 µg BID via AeroChamber®	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, asthma scores and nocturnal awakenings	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). 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[42] Budesonide 200 µg BID via DPI vs fluticasone propionate 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	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 propionate 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 propionate 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 propionate and budesonide groups, respectively (*P*=0.460). Change in FEV_1 was 0.19 and 0.25 L for the fluticasone propionate and budesonide groups, respectively (*P*=0.154). The proportions of patients with no exacerbations were 75 and 68% in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	the 20th and 95th percentiles			fluticasone propionate and budesonide groups, respectively (*P*=0.131). The proportion of patients who were 100% symptom-free was 49 and 48% in the fluticasone propionate and budesonide groups respectively (*P*=0.799). The proportion of patients who had 100% symptom-free nights was 50 and 58% in the fluticasone propionate and budesonide groups respectively (*P*=0.232). The proportion of patients who had 100% salbutamol-free nights was 57 and 52% in the fluticasone propionate and budesonide groups respectively (*P*=0.180). Adverse events were reported in 81 and 71% of the fluticasone propionate and budesonide groups, respectively. Less than 3% of these events were considered to be treatment-related.
Ferguson et al[43] Budesonide 400 µg BID via DPI vs fluticasone propionate 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 propionate 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 propionate 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[44]	AC, DB, RCT, XO	N=30	Primary: The daily mean morning	Primary: There was no statistically significant difference between the treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Budesonide 750 µg BID vs fluticasone propionate 375 µg BID	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	12 weeks	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	groups in PEF or symptoms scores. Secondary: There was no difference in physician/patient/parent assessment of efficacy with 90% rating both fluticasone propionate and budesonide effective or very effective. The total number of exacerbations (33 in the fluticasone propionate group and 35 in the budesonide group) and those exacerbations requiring systemic steroids (nine in the fluticasone propionate 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. 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[45] Budesonide 400 µg BID vs mometasone 100 µg BID vs mometasone 200 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	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mometasone 400 µg BID			response to therapy	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[46] 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 HRQOL	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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[47] 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 ciclesonide	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, 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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[48] Ciclesonide 80 µg BID vs ciclesonide 160 µg QAM vs placebo	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 least one month prior to screening, an FEV_1 60 to 90% (ICS) or 70 to 95% (ICS/LABA) of predicted value	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 adverse events	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 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[49] (abstract) Ciclesonide 80 µg BID	DB, MC, PC, PG, RCT Patients 12 years of age and older	N=446 12 weeks	Primary: Change in FEV_1 Secondary: Morning PEF, rescue	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ciclesonide 160 µg QD vs placebo	with mild to moderate persistent asthma being treated with an ICS or ICS/LABA		albuterol use, total asthma symptom score, nighttime awakenings and safety	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). The incidence of adverse events was similar among all groups.
Bateman et al[50] 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	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	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			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 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[51] 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	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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	screening			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[52] (abstract) Ciclesonide 80 µg BID vs ciclesonide 160 µg QAM vs ciclesonide 80 µg BID for four weeks followed by 160 µg QAM for 12 weeks vs placebo	DB, MC, PC, PG RCT Patients 12 years of age and older with a history of persistent asthma for at least six months and not using an ICS for at least 30 days prior to study entry	N=691 16 weeks	Primary: Change from baseline in FEV_1 Secondary: Morning PEF, rescue albuterol use, nighttime awakenings, asthma symptom scores and safety	Primary: The mean FEV_1 improved from baseline in all treatment groups ($P \leq 0.0251$ for all). The improvement in FEV_1 was greatest in the ciclesonide 80 µg BID group ($P<0.01$). 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 ($P \leq 0.015$ for all). All treatments reduced albuterol use, nighttime awakenings and improved asthma symptom scores compared to baseline ($P \leq 0.05$ 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[53] Ciclesonide 80 µg QAM vs ciclesonide 160 µg QAM	DB, MC, PC, RCT Patients 12 years of age and older with mild to moderate persistent asthma	N=526 12 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol	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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ciclesonide 320 µg QAM vs placebo	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		utilization, asthma symptom score, AQLQ score and adverse events	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 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[54] Ciclesonide 80 µg QAM vs ciclesonide 160 µg QAM vs ciclesonide 320 µg QAM vs	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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	with a reversibility of FEV_1 by ≥12% after two albuterol inhalations			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, 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[55] Ciclesonide 160 µg BID vs ciclesonide 320 µg BID vs fluticasone propionate 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	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 propionate 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 propionate 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 propionate group; *P*=0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	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			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 propionate 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 events was more common in the fluticasone propionate treatment group than in the ciclesonide treatment groups.
Nelson et al[56] Fluticasone propionate 500 µg BID vs fluticasone propionate 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	Primary: At 16 weeks, oral prednisone use was discontinued in 75 and 89% of patients treated with fluticasone propionate 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 propionate groups compared to the placebo group (*P*<0.001). Secondary: Changes in FEV_1 were significantly greater in both the fluticasone propionate 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*≤0.05 for all). Both morning and evening PEF improved in the fluticasone propionate 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 (-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			albuterol	23±11 morning and -9±12 evening; $P \leq 0.05$ for all). Asthma symptom scores improved in both the fluticasone propionate 500 µg BID (-0.26±0.08) and 1,000 µg BID groups (-0.47±0.13; $P \leq 0.05$), while symptom scores worsened in the placebo group (0.26±0.12; $P \leq 0.05$). Nighttime awakenings requiring albuterol decreased in both the fluticasone propionate 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; $P \leq 0.05$ for all).
Condemi et al[57] Fluticasone propionate 250 µg BID vs triamcinolone 200 µg QID vs placebo BID or QID	AC, DB, DD, PC, PG, RCT Patients 12 years of age and older with asthma (FEV_1 50 to 80% of predicted value) who had previously received maintenance therapy with beclomethasone or triamcinolone	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 asthma symptom scores Secondary: Adverse events and morning plasma cortisol levels	Primary: Patients in both the fluticasone propionate 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 propionate and triamcinolone compared to placebo, respectively; $P \leq 0.001$ for both). Only 27% of patients in the placebo group remained in the study over time compared to 66% of patients in the fluticasone propionate group and 55% of patients 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 propionate (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 propionate 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 propionate or triamcinolone compared to placebo ($P \leq 0.001$ for both). The frequency of nighttime awakenings significantly increased after treatment with placebo ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 propionate 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 propionate group had morning plasma cortisol concentrations <5 µg/mL.
Berend et al[58] Fluticasone propionate at approximately half the dose of their run-in ICS vs continuing the same dose of ICS used during the four-week run-in period (beclomethasone or budesonide)	MC, OL, PG, RCT Patients 18 years of age or older with a history of severe asthma, currently receiving at least 1,750 µg/day of inhaled beclomethasone or budesonide	N=133 6 months	Primary: Changes from baseline in morning PEF and FEV_1 Secondary: Changes in relevant laboratory values, adverse events, asthma exacerbations and quality of life	Primary: Patients in the fluticasone propionate 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). 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 propionate and 2.03±0.86 L with beclomethasone/budesonide; *P* values not reported). Secondary: Serum osteocalcin levels increased significantly in the fluticasone propionate 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				in both groups. Four patients (6%) in the fluticasone propionate 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 propionate 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 propionate group (*P*<0.001); however, there was no significant difference in the beclomethasone or budesonide group (*P*=0.13).
Sheikh et al[59] Flunisolide 1,500 µg/day vs fluticasone propionate 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 propionate 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 propionate. Significant improvements were noted in FEV_1 and $FEF_{25\ to\ 75\%}$ at all time points evaluated after switching to fluticasone propionate. There was no significant difference in PEFR between groups at any time period. Secondary: Not reported
Harnest et al[60] Fluticasone propionate 500 µg BID vs	AC, RCT Patients 18 years of age and older with moderate to severe persistent asthma who were	N=203 12 weeks	Primary: Change from baseline in weekly average PEF Secondary: FEV_1, asthma symptom scores, rescue	Primary: The change from baseline in PEF was 7.8% in the mometasone group and 7.7% in the fluticasone propionate 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 propionate groups (*P*=0.988).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mometasone 500 µg BID	previously using an ICS for daily maintenance therapy for ≥30 days		medication use, response to therapy and adverse events	The morning and evening asthma symptom scores were not significantly different between the mometasone and fluticasone propionate 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 propionate group. The difference between the two groups was not significant (*P* value not reported).
O'Connor et al[61] Fluticasone propionate 250 µg BID vs mometasone 100 µg BID vs mometasone 200 µg BID vs mometasone 400 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 asthma and physician-evaluation of response to therapy	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 propionate groups experienced similar improvements in FEV_1. Secondary: The $FEF_{25 \text{ to } 75\%}$ and PEFR were significantly improved in the mometasone 200 µg BID, 400 µg BID and fluticasone propionate groups compared to the mometasone 100 µg BID group. There were no statistically significant differences in the other outcomes between groups.
Wardlaw et al[62] Fluticasone propionate 250 µg BID vs	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,	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mometasone 400 µg QPM	propionate		albuterol use and device evaluation	(*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 propionate 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 propionate group (*P*=0.01).
Fish et al[63] 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 caused by asthma that required albuterol use and general and asthma-specific quality-of-life measures	Primary: Oral corticosteroid requirements were reduced by 46.0% 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). 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)[64] Mometasone 400 µg QPM	DB, PC, RCT Patients 18 to 60 years of age with mild to moderate	N=20 14 days	Primary: Nocturnal decline in evening to morning FEV_1 values	Primary: No significant differences were observed between groups with regard to nocturnal decline in FEV_1. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	asthma and a history of nocturnal asthma		Secondary: Nocturnal decline in evening to morning PEFR values, polysomnographic indices of sleep, NRQLQ, SF-36 and AQLQ	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[65] 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 ($P\geq0.08$ for all).
Noonan et al[66] Mometasone 200 µg QD vs mometasone 100 µg BID vs beclomethasone 168 µg BID	AC, MC, OL, PRO Patients four to 11 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	N=233 52 weeks	Primary: Incidence of adverse events Secondary: Laboratory tests including cortisol concentrations, vital signs and physical examinations	Primary: The incidence of adverse events was similar in all three groups. Secondary: No significant differences between groups were observed in any secondary end points.
Kramer et al[67]	MA of 6 RCTs	N=3,256	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ciclesonide inhalation vs other inhaled corticosteroids Certain asthma drugs were permitted (beta-2-agonists, theophyllines, long-acting beta-2-agonits and inhaled anticholinergic) as long as the type of drug remained stable and were the same in both groups. Certain asthma drugs were not permitted (anti-leukotrienes, combination inhalers, or anti-inflammatory agents [chromones]).	with a parallel group design and cross-over trials with a wash-out period of two weeks or more (Cochrane Review 2014) Children <18 years of age with chronic asthma (trials including adults were included, provided data for children were reported separately)	At least four weeks	Asthma symptoms (asthma symptom scores, number of days without symptoms, number of days without use of a rescue inhaler), severe asthma exacerbations, and adverse effects Secondary: Quality of life, compliance, change in lung function (FEV1, mid expiratory flow 25 to 75%), and airway inflammation	Ciclesonide compared to Budesonide: Two studies on 1,024 children found no significant differences between the groups regarding the outcome asthma symptoms (symptom scores, asthma symptom and rescue medication-free days). Pooled data for exacerbations (as defined in the original studies) showed no significant difference between ciclesonide compared to budesonide (RR, 2.20; 95% CI, 0.75 to 6.43; two studies; N=1,024) The occurrence of adverse effects was similar in both treatment groups in both studies. The second study provided specific details between ciclesonide and budesonide (RR, 1.44; 95% CI, 0.96 to 2.18; N=403). One study reported that the increase in height was significantly bigger in the ciclesonide compared to the budesonide group (1.18 cm compared to 0.70 cm, respectively; P value not reported). Both studies (N=1,024) reported that 24-hour urine cortisol adjusted for creatinine levels showed a significant decrease in the budesonide group compared to the ciclesonide group, but no numerical data were reported. Ciclesonide compared to fluticasone propionate (dose ratio 1:1): For asthma symptom scores, the results could not be pooled since data were reported as medians and this indicates skewed data. The other two studies on 932 children did not provide information on how asthma symptoms were measured No significant differences were found in asthma symptoms and rescue medication-free days (four studies; N=1,934). Non-inferiority of ciclesonide was confirmed (limit was set at 0.3) for asthma symptom scores in one study on 492 children. Pooled data comparing ciclesonide 160 µg compared to fluticasone propionate 88 µg twice daily showed no significant difference in number of patients with exacerbations (RR, 1.37; 95% CI, 0.58 to 3.21; two studies;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				N=1,003). Another study on 420 children reported that the number of patients with exacerbations was similar in both the ciclesonide and fluticasone propionate groups (2.3% and 2.2%, respectively). One study on 492 children reported that five (2.1%) children treated with ciclesonide 160 µg and two (0.8%) children treated with fluticasone propionate 88 µg twice daily discontinued the study prematurely due to asthma exacerbation. No significant difference in number of patients with adverse events were found between ciclesonide 160 µg and fluticasone propionate 88 µg twice daily (RR, 0.88; 95% CI, 0.72 to 1.07; one study; N=492). The other two studies on 1,023 children reported that adverse effects were similar in both groups. One study did not assess adverse effects. The outcome 24-hour urine cortisol adjusted for creatinine levels was reported in one study. No significant differences were found for ciclesonide compared to fluticasone propionate (mean difference 0.54 nmol/mmol; 95% CI, -5.92 to 7.00; one study; N=492). Ciclesonide compared to fluticasone propionate (dose ratio 1:2): In one study on 502 children, no significant differences were found in asthma symptoms and rescue medication-free days. For asthma symptom sum scores non-inferiority (limit was set at 0.3) was confirmed The number of exacerbations was significantly higher in the ciclesonide 80 µg once-daily group compared to the fluticasone propionate 88 µg twice-daily group (RR, 3.57; 95% CI, 1.35 to 9.47; one study; N=502). Thirteen (5.2%) participants treated with ciclesonide 80 µg and two (0.8%) treated with fluticasone propionate 88 µg discontinued the study prematurely due to asthma exacerbation. No significant differences in number of patients with adverse effects were found between ciclesonide 80 µg once daily and fluticasone propionate 88 µg twice daily (RR, 0.98; 95% CI, 0.81 to 1.1; one study; N=502).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant difference was found for 24-hour urine cortisol adjusted for creatinine levels in ciclesonide 80 µg once daily compared to fluticasone propionate 88 µg twice daily (mean difference 1.15 nmol/mmol; 95% CI, 0.07 to 2.23; one study; N=502). Secondary: Ciclesonide compared with Budesonide: Pooled results for quality of life assessment showed no significant differences between the groups (RR, -0.00; 95% CI, -0.09 to 0.09; two studies; N=1,010). Pooled result of FEV_1 showed no significant mean difference between groups (RR, -0.02; 95% CI, -0.10 to 0.05; two studies; N=1,021). Compliance and airway inflammation were not formally assessed in either of the studies comparing ciclesonide to budesonide. Ciclesonide compared to fluticasone propionate (dose ratio 1:2): Non-inferiority was confirmed for both quality of life measurements (PAQLQ and PACQLQ) for ciclesonide compared to fluticasone propionate (P<0.0001, one-sided; N=492). The other studies did not formally assess quality of life. Pooled data of two studies showed no significant difference in FEV_1 between ciclesonide 160 µg and fluticasone propionate 88 µg (-0.01 L; 95% CI, -0.04 to 0.02; two studies; N=1,000) None of the studies formally assessed outcomes on compliance or airway inflammation. Ciclesonide compared to fluticasone propionate (dose ratio 1:2): Non-inferiority of ciclesonide compared to fluticasone propionate was confirmed for both quality of life measurements, PAQLQ and PACQLQ (P<0.0001, one-sided).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Results were similar in both groups and non-significant for FEV_1 and non-inferiority was confirmed (mean difference -0.05 L; 95% CI, -0.11 to 0.01; one study; N=499). The compliance or airway inflammation outcomes were not formally assessed.

Drug regimen abbreviations: BID=twice daily, QAM=every morning, QD=once daily, QID=four times daily, QPM=every evening
Study abbreviations: AC=active control, ACT=asthma control test, 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, RR=relative risk, SD=standard deviation, XO=cross over
Miscellaneous abbreviations: AMP PC_{20}=provocation dose of AMP to decrease forced vital capacity by 20%, AQLQ=asthma quality of life questionnaire, CFC=chlorofluorocarbon, DPI=dry-powder inhaler, ECG=electrocardiogram, eNO=exhaled nitric oxide, $FEF_{25\ to\ 75\%}$=forced expiratory flow at 25 to 75% of FVC, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, ITT=intention to treat, HFA=hydrofluoroalkane, HPA=hypothalamic-pituitary-adrenal, HRQOL=health-related quality of life, ICS=inhaled corticosteroid, LABA=long-acting β_2-agonist, LS=least square, 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, PP=per protocol, SABA=short acting β_2-agonist, SF-36=Short-Form-36, WMD=weighted mean difference, wmFEV= weighted mean FEV_1

Special Populations

Table 5. Special Populations[1-10]

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 (Pulmicort Respules®) 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, use with caution
Flunisolide	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children six years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown, use with caution
Fluticasone furoate	No evidence of overall differences in safety or efficacy	No dosage adjustment required.	Use with caution in patient with	C	Unknown, use with caution

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 12 years of age and older.		moderate or severe hepatic impairment. Systemic exposure increased by up to 3-fold.		
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, use with caution
Mometasone furoate	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.	No dosage adjustment required.	C	Unknown, use with caution

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-10]

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Cardiovascular								
Chest pain	-	-	1 to <3	≥3	1 to 3	-	-	-
Palpitations	-	-	-	-	-	-	-	-
Central Nervous System								
Aggression	-	a	1 to <3	-	-	-	a	-
Agitation	-	-	-	-	-	-	a	-
Anxiety	-	a	1 to <3	-	-	-	-	-
Depression	-	a	1 to <3	-	-	-	a	11
Dizziness	-	-	-	-	1 to 3	-	-	-
Emotional lability	-	-	1 to <3	-	-	-	-	-
Fatigue	-	-	1 to <3	-	-	-	>3	1 to13
Headache	8 to 25	≥3	≥3	5 to11	8.8 to 9.0	6 to 13	2 to 14	17 to 22
Hyperactivity	-	-	-	-	-	-	a	-
Hyperkinesia	-	-	1 to <3	-	-	-	-	-
Hypertonia	-	1 to 3	-	-	-	-	-	-
Insomnia	-	1 to 3	-	-	-	-	-	-
Irritability	-	a	1 to <3	-	-	-	a	-
Migraines	-	1 to 3	-	-	1 to 3	-	a	-
Nervousness	-	a	1 to <3	-	-	-	-	-
Psychosis	-	a	1 to <3	-	-	-	-	-
Restlessness	-	a	1 to <3	-	-	-	a	-
Syncope	-	1 to 3	-	-	-	-	-	-
Dermatological								
Contact dermatitis	-	a	1 to <3	-	-	-	-	-
Ecchymoses	-	1 to 3	1 to <3	-	-	-	a	-
Eczema	-	-	1 to <3	-	-	-	-	-
Pruritus	-	-	1 to <3	-	-	-	a	a
Rash	a	a	≤4	-	-	-	a	a

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Urticaria	a	a	1 to <3	≥3	-	-	a	-
Viral skin infection	-	-	-	-	-	-	a	-
Endocrine and Metabolic								
Edema	-	-	-	-	1 to 3	-	a	-
Gastrointestinal								
Abdominal pain	-	1 to 3	2 to 3	-	1 to 3	3	-	2 to 6
Anorexia	-	-	1 to <3	-	-	-	-	1 to <3
Diarrhea	-	-	2 to 4	-	1 to 3	-	a	-
Dyspepsia	-	1 to 4	-	-	-	-	a	3 to 5
Gastroenteritis	-	1.8	5	≥3	1 to 3	3	-	1 to <3
Gastrointestinal pain	-	1 to 3	-	-	-	-	2 to 4	-
Nausea	≤2	1.8	-	<1	1 to 3	-	1 to 8	1 to 3
Oral candidiasis	-	1.3	-	≥3	-	3	≤9	4 to 22
Taste alteration	-	1 to 3	-	-	-	-	-	-
Viral gastrointestinal infection	-	-	-	-	-	-	3 to 5	-
Vomiting	-	1 to 3	2 to 4	-	4.2 to 4.6	-	1 to 8	1 to 3
Respiratory								
Angioedema	a	a	1 to <3	-	-	-	a	a
Bronchitis	-	-	≥3	-	1 to 3	7	≤8	-
Bronchospasm	a	a	≥3	-	-	-	a	a
Cold symptoms	-	-	-	-	-	-	-	-
Coughing	1 to 3	a	5 to 9	<1	1.8 to 8.5	3	1 to 6	a
Dry mouth	-	1 to 3	-	<1	-	-	-	-
Dyspnea	-	-	-	-	-	-	-	a
Epistaxis	-	-	2 to 4	-	0.9 to 3.2	-	-	1 to <3
Hoarseness	-	-	-	≥3	-	-	2 to 6	-
Increased asthma symptoms	≤4	-	-	-	-	-	a	-
Influenza	-	-	-	-	7	-	-	-
Laryngitis	-	-	-	-	1 to 3	-	a	-
Nasal congestion	-	2.7	-	1.8 to 5.5	-	-	-	9

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Nasal disorders	-	-	-	-	-	-	a	-
Nasal irritation	-	-	-	-	-	-	-	1 to <3
Nasopharyngitis	-	9.3	-	-	-	8 to 13	-	-
Oropharyngeal edema	-	-	-	-	-	-	a	-
Pharyngolaryngeal pain	-	-	-	2.4 to 4.7	-	3	-	-
Pharyngitis	5 to 27	2.7	≥3	7.0 to 10.5	16.6 to 17.5	4	-	8 to 13
Respiratory disorder	-	-	-	-	-	-	-	1 to <3
Rhinitis	3 to 8	2.2	7 to 12	3.1 to 5.5	9.0 to 15.7	3	1 to 4	4 to 20
Sinusitis	≤3	≥3	≥3	≥3	4.1 to 8.8	4	4 to 10	5 to 22
Stridor	-	-	1 to <3	-	-	-	-	-
Upper respiratory tract infection	7 to 11	≥3	34 to 38	4.1 to 8.7	-	6	14 to 21	8 to 15
Viral respiratory infection	-	-	-	-	-	-	1 to 5	-
Wheezing	-	a	-	-	-	-	a	a
Other								
Adrenal suppression	a	a	a	a	-	-	a	a
Aphonia	-	-	-	-	-	-	a	-
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	-	3 to 6
Bruising	-	-	-	-	-	-	-	2
Cataracts	a	a	a	a	-	-	a	a
Cervical lymphadenopathy	-	-	1 to <3	-	-	-	-	-
Conjunctivitis	-	-	≤4	≥3	-	-	-	-
Cushingoid features	-	-	-	-	-	-	a	-
Dental caries	-	-	-	-	-	-	a	-
Dysmenorrhea	1 to 3	-	-	-	1 to 3	-	-	4 to 9
Dysphonia	1 to 4	1 to 6	1 to <3	<1	-	3	2 to 6	1 to <3
Earache	-	-	1 to <3	-	1 to 3	-	-	1 to <3
Ear infection	-	-	1 to <3	-	-	-	-	-

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Eye infection	-	-	1 to <3	-	-	-	-	-
Facial edema	-	-	-	≥3	-	-	a	-
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	a	a	a	a	-	-	a	a
Growth effects	a	a	a	a	-	-	a	a
Herpes simplex	-	-	1 to <3	-	-	-	-	-
Hyperglycemia	-	-	-	-	-	-	a	-
Hyposalivation	-	-	-	-	-	-	a	-
Immunosuppression	a	a	a	a	-	-	a	a
Infection	-	1 to 3	-	-	0.9 to 3.7	-	-	1 to <3
Injury	-	-	-	-	-	-	≤5	-
Malaise	-	-	-	-	-	-	>3	-
Muscle injuries	-	-	-	-	-	-	a	-
Musculoskeletal pain	-	-	-	≥3	-	-	2 to 5	4 to 22
Myalgia	-	1 to 3	1 to <3	-	1 to 3	-	a	2 to 3
Neck pain	-	1 to 3	-	-	-	-	-	-
Osteoporosis	-	-	<1	-	-	-	a	-
Otitis media	-	1.3	4 to 12	-	-	-	-	-
Pain	1 to 5	≥3	≥3	0.3 to 3.1	-	-	a	1 to <3
Pneumonia	-	-	-	≥3	-	-	a	-
Purpura	-	-	1 to <3	-	-	-	-	-
Soft tissue injuries	-	-	-	-	-	-	a	-
Sore Throat	-	a	-	-	-	3	3 to 13	1 to <3
Taste perversion	-	1 to 3	-	-	1 to 3	-	-	-
Tooth discoloration	-	-	-	-	-	-	a	-
Toothache	-	-	-	-	3	3	-	-
Urinary tract infection	-	-	-	-	0.9 to 3.5	-	a	2
Vasculitis consistent with Churg-Strauss	-	-	-	-	-	-	a	-

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
syndrome								
Vaginitis	-	-	-	-	1 to 3	-	-	-
Viral infection	-	-	3 to 5	-	-	-	≤2	-
Voice alteration	-	1 to 3	-	-	1 to 3	-	-	-
Weight gain	-	1 to 3	-	-	-	-	a	-

a Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[1-10]

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

Warnings/Precautions

Table 8. Warnings and Precautions[1-10]

Warning/Precaution	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Candida albicans; infections occur in the mouth and pharynx of some patients	a	a	a	a	a	a	a	a
Eosinophilic conditions and Churg-Strauss Syndrome	-	a	a	-	a	-	a	-
Glaucoma, increased intraocular pressure, and cataracts	a	a	a	a	a	a	a	a
Hypercorticism and adrenal suppression; may appear at particularly at higher doses	a	a	a	a	a	a	a	a
Hypersensitivity reactions following transition from systemic corticosteroids	a	a	a	a	a	a	a	a
Inhaled corticosteroids do not provide the mineralocorticoid necessary during times of trauma, surgery or infections	a	a	a	a	a	a	a	a
Infections; persons on immunosuppressive medications are more susceptible to infections than healthy individuals	a	a	a	a	a	a	a	a
Not indicated for relief of acute bronchospasm	a	a	a	a	a	a	a	a
Oral corticosteroid withdrawal; some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular	a	a	a	a	a	a	a	a

Warning/Precaution	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
pain, lassitude and depression, despite maintenance or even improvement of respiratory function								
Paradoxical bronchospasm following administration	a	a	a	a	a	a	a	a
Patients transferred from systemically active steroids to inhaled corticosteroids due to adrenal insufficiency	a	a	a	a	a	a	a	a
Reduction in bone mineral density with long-term use	-	a	a	a	a	a	a	a
Reduction in growth velocity in pediatric patients	-	a	a	a	a	a	a	a
Systemic absorption at recommended doses	a	a	a	a	a	a	a	a

Drug Interactions

Table 8. Drug Interactions[1-10]

Generic Name	Interacting Medication or Disease	Potential Result
Budesonide, fluticasone furoate/ propionate, mometasone furoate	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[1-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Beclomethasone	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy: 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: Meter dose aerosol inhaler (HFA): children five to 11 years of age: initial, 40 µg BID; maximum, 80 µg BID	Inhalation aerosol (HFA inhaler, metered dose): 40 µg 80 µg
Budesonide	Maintenance treatment of asthma	Maintenance treatment of	Dry powder for

Generic Name	Adult Dose	Pediatric Dose	Availability
	as prophylactic therapy: Dry powder inhaler: initial, 360 µg BID (selected patients can be initiated at 180 µg BID); maximum, 720 µg BID	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 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	inhalation (inhaler, breath activated, metered dose): 90 µg 180 µg Suspension for inhalation (nebulizer): 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL
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.	Inhalation aerosol (HFA inhaler, metered dose): 80 µg 160 µg
Flunisolide	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy (≥12 years of age): Meter dose aerosol inhaler (HFA):	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy (age 6 to 11 years):	Inhalation aerosol (HFA inhaler, metered dose): 80 µg

Generic Name	Adult Dose	Pediatric Dose	Availability
	initial, inhale 160 µg (two sprays) twice daily; maximum, 320 µg (four sprays) twice daily	Meter dose aerosol inhaler (HFA): initial, inhale 80 µg (one spray) twice daily; maximum, 160 µg (two sprays) twice daily	
Fluticasone furoate	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy: Aerosol powder: initial, 100 µg inhaled once daily; maintenance, 100 to 200 µg inhaled once daily; maximum, 200 µg inhaled once daily	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy (age 12 to 17 years): Refer to adult dose	Aerosol powder (breath activated inhaler) 100 µg 200 µg
Fluticasone propionate	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy: 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 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	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy: 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 for inhalation (inhaler with blister pack; Flovent Diskus®): 50 µg 100 µg 250 µg Inhalation aerosol (HFA inhaler, metered dose; Flovent HFA®): 44 µg 110 µg 220 µg
Mometasone furoate	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	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 for inhalation (inhaler, metered dose; Asmanex Twisthaler®): 110 µg 220 µg Inhalation powder (HFA

Generic Name	Adult Dose	Pediatric Dose	Availability
	oral corticosteroids; initial, 440 µg BID; maximum, 880 µg daily		inhaler, metered dose, breath activated; Asmanex HFA®):

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)**[68]	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 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.

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

Assessment, treatment and monitoring
· 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>Preferred SABA as</td><td>Preferred Low-dose</td><td>Preferred Low-dose</td><td>Preferred Medium-dose</td><td>Preferred High-dose</td><td>Preferred High-dose</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td>needed</td><td>ICS

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

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

<u>Alternative</u>
Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>ICS+ LABA and consider omalizu-mab for patients who have allergies</td><td>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 and Prevention (2012)[71]</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.
· 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.

<u>Controller medications</u>
· 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</td></tr>
</table>

Clinical Guidelines	Recommendations
	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. 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

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
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="5">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 + LABA</td><td>Oral corticosteroid</td></tr>
<tr><td>Leukotriene modifier</td><td colspan="2">Medium- or high-dose ICS</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td colspan="2">Low-dose ICS +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td colspan="2">Low-dose ICS +sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>

<u>Management of exacerbations</u>
· 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.
</td></tr>
<tr><td>Global Initiative for Chronic Obstructive Lung Disease:</td><td><u>Diagnosis</u>
· A clinical diagnosis of chronic obstructive pulmonary disease (COPD)</td></tr>
</table>

Clinical Guidelines	Recommendations
Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2014)[72]	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. <u>Treatment</u> · 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 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

Clinical Guidelines	Recommendations
	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)**[73]	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 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

Clinical Guidelines	Recommendations
	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. <u>Management of exacerbations</u> · 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.[1-11] Beclomethasone (QVAR®), flunisolide (Aerospan®) and fluticasone propionate (Flovent Diskus®, Flovent HFA®) are also approved for asthmatic patients requiring oral corticosteroid therapy.[1,5,7,8] 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.[12-67] Currently, only budesonide suspension for nebulization is available generically.

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.[68,71] 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.[72,73]

References

1. QVAR® [package insert]. Horsham (PA): Teva Respiratory LLC.; 2014 Jul.
2. Pulmicort Flexhaler® [package insert]. Wilmington (DE): Astra-Zeneca; 2010 Jul.
3. Pulmicort Respules® [package insert]. Wilmington (DE): Astra-Zeneca; 2010 Jul.
4. Alvesco® [package insert]. Marlborough (MA): Sepracor Inc.; 2013 Jan.
5. Aerospan® [package insert]. Marlborough (MA): Acton Pharmaceuticals Inc.; 2014 Sep.
6. Arnuity Ellipta® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2014 Nov.
7. Flovent Diskus® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2014 May.
8. Flovent HFA® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2014 May.
9. Asmanex Twisthaler® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2014 Apr.
10. Asmanex HFA® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2014 Sep.
11. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Truven Health Analytics; Updated periodically [cited 2015 Jan 13]. Available from: http://www.thomsonhc.com/.
12. van den Berge M, Luijk B, Bareille P, Dallow N, Postma DS, Lammers JW. Prolonged protection of the new inhaled corticosteroid fluticasone furoate against AMP hyperresponsiveness in patients with asthma. Allergy. 2010 Dec;65(12):1531-5. doi: 10.1111/j.1398-9995.2010.02414.x.
13. Bleecker ER, Bateman ED, Busse WW, Woodcock A, Frith L, House KW, et al. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. Thorax. 2012 Jan;67(1):35-41. doi: 10.1136/thoraxjnl-2011-200308. Epub 2011 Aug 9.
14. Busse WW, Bleecker ER, Bateman ED, Lötvall J, Forth R, Davis AM, et al. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. Thorax. 2012 Jan;67(1):35-41. doi: 10.1136/thoraxjnl-2011-200308. Epub 2011 Aug 9.
15. Bateman ED, Bleecker ER, Lötvall J, Woodcock A, Forth R, Medley H et al. Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial. Respir Med. 2012 May;106(5):642-50. doi: 10.1016/j.rmed.2012.01.004. Epub 2012 Feb 18.
16. Woodcock A, Bateman ED, Busse WW, Lötvall J, Snowise NG, Forth R, et al. Efficacy in asthma of once-daily treatment with fluticasone furoate: a randomized, placebo-controlled trial. Respir Res. 2011 Oct 6;12:132. doi: 10.1186/1465-9921-12-132.
17. Woodcock A, Bleecker ER, Busse WW, Lötvall J, Snowise NG, Frith L, et al. Fluticasone furoate: once-daily evening treatment versus twice-daily treatment in moderate asthma. Respir Res. 2011 Dec 21;12:160. doi: 10.1186/1465-9921-12-160.
18. Medley H1, Orozco S, Allen A. Efficacy and safety profile of fluticasone furoate administered once daily in the morning or evening: a randomized, double-blind, double-dummy, placebo-controlled trial in adult and adolescent patients with persistent bronchial asthma. Clin Ther. 2012 Aug;34(8):1683-95. doi: 10.1016/j.clinthera.2012.06.024. Epub 2012 Jul 13.
19. Lötvall J, Bleecker ER, Busse WW, O'Byrne PM, Woodcock A, Kerwin EM, et al. Efficacy and safety of fluticasone furoate 100 µg once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial. Respir Med. 2014 Jan;108(1):41-9. doi: 10.1016/j.rmed.2013.11.009. Epub 2013 Nov 19.
20. Bleecker ER, Lötvall J, O'Byrne PM, Woodcock A, Busse WW, Kerwin EM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014 Sep-Oct;2(5):553-61. doi: 10.1016/j.jaip.2014.02.010. Epub 2014 Apr 24.
21. Woodcock A1, Lötvall J, Busse WW, Bateman ED, Stone S, Ellsworth A, et al. Efficacy and safety of fluticasone furoate 100 µg and 200 µg once daily in the treatment of moderate-severe asthma in adults and adolescents: a 24-week randomised study. BMC Pulm Med. 2014 Jul 9;14:113. doi: 10.1186/1471-2466-14-113.
22. O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J. 2014 Mar;43(3):773-82. doi: 10.1183/09031936.00064513. Epub 2013 Oct 17.

23. O'Byrne PM1, Woodcock A, Bleecker ER, Bateman ED, Lötvall J, Forth R, et al. Efficacy and safety of once-daily fluticasone furoate 50 mcg in adults with persistent asthma: a 12-week randomized trial. Respir Res. 2014 Aug 11;15:88. doi: 10.1186/s12931-014-0088-z.
24. Busse WW, Bateman ED, O'Byrne PM, Lötvall J, Woodcock A, Medley H, et al. Once-daily fluticasone furoate 50 mcg in mild-to-moderate asthma: a 24-week placebo-controlled randomized trial. Allergy. 2014 Nov;69(11):1522-30. doi: 10.1111/all.12480. Epub 2014 Aug 22.
25. Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. J Allergy Clin Immunol. 1999;104(6):1215-22.
26. Bronsky E, Korenblat P, Harris AG, Chen R. Comparative clinical study of inhaled beclomethasone dipropionate and triamcinolone acetonide in persistent asthma. Ann Allergy Asthma Immunol. 1998;90:295-302.
27. Nathan RA, Nayak AS, Graft DF, Lawrence M, Picone FJ, Ahmed T, et al. Mometasone furoate: efficacy and safety in moderate asthma compared to beclomethasone dipropionate. Ann Allergy Asthma Immunol. 2001;86:203-10.
28. Bernstein DI, Berkowitz RB, Chervinsky P, Dvorin DJ, Finn AF, Gross GN, et al. Dose-ranging study of a new steroid for asthma: mometasone furoate dry powder inhaler. Respir Med. 1999;93:603-12.
29. van Aalderen WM, Price D, De Baets FM, Price J. Beclomethasone dipropionate extra fine aerosol vs fluticasone propionate in children with asthma. Respiratory Medicine. 2007;101:1585-93.
30. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Pediatrics. 2000;106(1):1-7.
31. Berkowitz R, Rachelefsky G, Harris AG, Chen R. A comparison of triamcinolone MDI with a built-in tube extended and beclomethasone dipropionate MDI in adult asthmatics. Chest. 1998;114:757-65.
32. Raphael GD, Lanier RQ, Baker J, Edwards L, Rickard K, Lincourt WR. A comparison of multiple doses of fluticasone propionate and beclomethasone dipropionate in subjects with persistent asthma. J Allergy Clin Immunol. 1999;103(5):796-803.
33. Tinkelman DG, Bronsky EA, Gross G, Schoenwetter WF, Spector SL. Efficacy and safety of budesonide inhalation powder (Pulmicort Turbuhaler®) during 52 weeks of treatment in adults and children with persistent asthma. J of Asthma. 2003;40(3):225-36.
34. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. NEJM. 2000;343:1064-9.
35. Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jacono J. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department. JAMA. 1999;281(22):2119-26.
36. Sheffer AL, Silverman M, Woolcock AJ, et al. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the inhaled steroid treatment as regular therapy in early asthma (START) study. Ann Allergy Asthma Immunol. 2005;94(1):48-54.
37. Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. Pediatrics. 1999 Feb;103(2):414-21.
38. Corren J, Berkowitz R, Murray JJ, Prenner B. Comparison of once-daily mometasone furoate vs once-daily budesonide in patients with moderate persistent asthma. Int J Clin Pract. 2003;57(7):567-72.
39. Vermeulen JH, Gyurkovits K, Rauer H, Engelstatter R. Randomized comparison of the efficacy and safety of ciclesonide and budesonide in adolescents with severe asthma. Respir Med. 2007;101:2182-91.
40. von Berg A, Engelstätter R, Minic P, Sréckovic M, Garcia ML, Latoś T, et al. Comparison of the efficacy and safety of ciclesonide 160 µg once daily vs budesonide 400 µg once daily in children with asthma. Pediatr Allergy Immunol. 2007;18:391-400.
41. Newhouse M, Knight A, Wang S, Newman K. Comparison of efficacy and safety between flunisolide/AeroChamber® and budesonide/Turbuhaler® in patients with moderate asthma. Ann Allergy Asthma Immunol. 2000;84:313-9.

42. Ferguson AC, Van Bever HP, Teper AM, Lasytsya O, Goldfrad CH, Whitehead PJ. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. Respiratory Medicine. 2007;101:118-29.
43. Ferguson AC, Spier S, Manjra A, Versteegh FG, Mark S, Zhang P. Efficacy and safety of high-dose inhaled steroids in children with asthma: A comparison of fluticasone propionate with budesonide. J Pediatr. 1999;134(4):422-7.
44. Fitzgerald D, Van Asperen P, Mellis C, Honner M, Smith L, Ambler G. Fluticasone propionate 750 µg/day vs beclomethasone dipropionate 1500 µg/day: comparison of efficacy and adrenal function in pediatric asthma. Thorax. 1998;53(8):656-61.
45. Bousquet J, D'Urzo A, Hebert J, Barraza CH, Boulet LP, Suárez-Chacón R, et al. Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler®. Eur Respir J. 2000;16:808-16.
46. Weiss KB, Liljas B, Schoenwetter W, Schatz M, Luce BR. Effectiveness of budesonide administered via dry-powder inhaler vs triamcinolone acetonide administered via pressurized metered-dose inhaler for adults with persistent asthma in managed care settings. Clinical Therapeutics. 2004;26(1):102-14.
47. Vogelmeier CF, Hering T, Lewin T, Sander P, Bethke TD. Efficacy and safety of ciclesonide in the treatment of 24,037 asthmatic patients in routine medical care. Respir Med. 2011 Feb;105(2):186-94.
48. Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma treated previously with inhaled steroids. Clinical Study Report 3030; Marlborough Mass: Sepracor Inc.
49. Meltzer E, Korenblat P, Weinstein S, Noonan M, Karafilidis J. Efficacy and safety evaluation of ciclesonide in mild to moderate persistent asthma previously treated with inhaled corticosteroids [abstract]. Allergy & Asthma Proceedings. 2009;30(3):293-303.
50. Bateman E, Karpel J, Casale T, Wenzel S, Banerji D. Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma. CHEST. 2006;129:1176-87.
51. Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma not treated with steroids. Clinical Study Report 3031; Marlborough Mass: Sepracor Inc.
52. Berger W, Kerwin E, Bernstein D, Pedinoff A, Bensch G, Karafilidis J. Efficacy and safety evaluation of ciclesonide in subjects with mild to moderate asthma not currently using inhaled corticosteroids [abstract]. Allergy & Asthma Proceedings. 2009;30(3):304-14.
53. Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma administered once-daily. Data on File. Clinical Study Report 321; Marlborough, Mass: Sepracor Inc.
54. Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma administered once-daily. Data on File. Clinical Study Report 322; Marlborough, Mass: Sepracor Inc.
55. Efficacy and safety of ciclesonide metered-dose inhaler MDI and fluticasone MDI in adults and adolescents with moderate to severe persistent asthma treated previously with inhaled steroids. Clinical Study Report 323/324; Marlborough Mass: Sepracor Inc.
56. Nelson HS, Busse WW, deBoisblanc BP, Berger WE, Noonan MJ, Webb DR, et al. Fluticasone propionate powder: Oral corticosteroid-sparing effect and improved lung function and quality of life in patients with severe chronic asthma. J Allergy Clin Immunol. 1999;103(2 pt 1):267-75.
57. Condemi JJ, Chervinsky P, Goldstein MF, Ford LB, Berger WE, Ayars GH, et al. Fluticasone propionate powder administered through Diskhaler vs triamcinolone acetonide aerosol administered through metered-dose inhaler in patients with persistent asthma. J Allergy Clin Immunol. 1997;100(4):467-74.
58. Berend N, Kellett B, Kent N, Sly PD; Collaborative Study Group of the Australian Lung Foundation. Improved safety with equivalent asthma control in adults with chronic severe asthma on high-dose fluticasone propionate. Respirology. 2001;6(3):237-46.
59. Sheikh S, Goldsmith LJ, Howell L. Comparison of the efficacy of inhaled fluticasone propionate, 880 µg/day, with flunisolide, 1,500 µg/day, in moderate-to-severe persistent asthma. Ann Allergy Asthma Immunol. 1999;83:300-4.

60. Harnest U, Price D, Howes T, Sussman G. Comparison of mometasone furoate dry powder inhaler and fluticasone propionate dry powder inhaler in patients with moderate to severe persistent asthma requiring high-dose inhaled corticosteroid therapy: findings from a non inferiority trial. Journal of Asthma. 2008;45:215-20.
61. O'Connor B, Bonnaud G, Haahtela T, Luna JM, Querfurt H, Wegener T, et al. Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator. Ann Allergy Asthma Immunol. 2001;86:397-404.
62. Wardlaw A, Larivee P, Eller J, Cockcroft DW, Ghaly L, Harris AG, et al. Efficacy and safety of mometasone furoate dry powder inhaler vs fluticasone propionate metered-dose inhaler in asthma subjects previously using fluticasone propionate. Ann Allergy Asthma Immunol. 2004;93:49-55.
63. Fish JE, Karpel JP, Craig TJ, Bensch GW, Noonan M, Webb DR, et al. Inhaled mometasone furoate reduces oral prednisone requirements while improving respiratory function and health-related quality of life in patients with severe persistent asthma. J Allergy Clin Immunol. 2000;106:852-60.
64. Krouse J, Krouse H, Janisse J. Effects of mometasone furoate administered via dry powder inhaler once daily in the evening on nocturnal lung function and sleep parameters in patients with moderate persistent asthma: a randomized, double-blind, placebo-controlled pilot study [abstract]. Clinical Drug Investigation. 2009;29(1):51-8.
65. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily vs twice-daily dosing of mometasone furoate administered via dry powder inhaler: a randomized open-label study. BMC Pulmonary Medicine. 2010;10(1).
66. Noonan M, Leflein J, Corren J, Staudinger H. Long-term safety of mometasone furoate administered via a dry powder inhaler in children: results of an open-label study comparing mometasone furoate with beclomethasone dipropionate in children with persistent asthma. BMC Pediatrics. 2009;9:43.
67. Kramer S, Rottier BL, Scholten RJ, Boluyt N. Ciclesonide versus other inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev. 2013 Feb 28;2:CD010352. doi: 10.1002/14651858.CD010352.
68. National Heart, Lung, and Blood Institute and National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma full report 2007. [guideline on the internet]. 2007. [cited 2015 Jan 13]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
69. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, et al. Effect of inhaled glucocorticoids in childhood on adult height. N Engl J Med. 2012 Sep 6;367(10):904-12.
70. Roizen J, Alter C, Bamba V. Recent research on inhaled corticosteroids and growth. Curr Opin Endocrinol Diabetes Obes. 2012 Feb;19(1):53-6.
71. Fitzgerald M, Bateman ED, Bousquet J, Cruz A, Haahtela T, O'Byrne P, et al. Global Initiative for Asthma. Global strategy for asthma management and prevention 2012 [guideline on the internet]. 2012. [cited 2015 Jan 13]. Available from: http://www.ginasthma.com.
72. Global Initiative for Chronic Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [guideline on the internet]. Global Initiative for Chronic Lung Disease World Health Organization; 2014 [cited 2015 Jan 13]. Available from: http://www.goldcopd.org/.
73. National Institute for Health and Clinical Excellence. Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). [guideline on the internet]. 2010 [cited 2015 Jan 13]. Available from: www.nice.org.uk/guidance/CG101.
74. Your Metered-dose inhaler is changing to help improve the environment [press release on the Internet]. Rockville, MD: Food and Drug Administration: 2008 May 30 [cited 2015 Jan 13]. Available from: http://www.fda.gov/Drugs/ResourcesForYou/ucm085130.htm.