

Therapeutic Class Overview

Inhaled Corticosteroid and Long-Acting β_2 -Agonist Combination Products

Therapeutic Class

- Overview/Summary:** The combination inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA) products include Advair[®] (fluticasone propionate/salmeterol), Dulera[®] (mometasone/formoterol) and Symbicort[®] (budesonide/formoterol), with Dulera[®] being the most recently Food and Drug Administration (FDA) approved product within the class. All of the products are FDA approved for the treatment of asthma; however, only fluticasone propionate/salmeterol and budesonide/formoterol have FDA approval for use in the treatment of chronic obstructive pulmonary disease. The ICSs exert their anti-inflammatory effect by binding to the glucocorticoid receptors with a subsequent activation of genes involved in anti-inflammatory processes, as well as via the inhibition of pro-inflammatory genes involved in the asthmatic response. These agents have selective action on β_2 receptors which stimulate adenyl cyclase, resulting in an increased intracellular cyclic adenosine monophosphate level, which subsequently triggers bronchial smooth muscles relaxation. The LABA medications also inhibit the release of mediators that are involved in immediate hypersensitivity. All of the combination products are associated with the same adverse events, precautions and contraindications.¹⁻⁴ Moreover, all LABA-containing medications have revised their package labeling to reflect the results of an analysis which reported an increased risk of asthma exacerbations and hospitalizations in pediatric and adult patients, as well as death in some patients with all of the LABA-containing medications.⁵ The combination ICS/LABA products appear to be equally efficacious for their respective indications, with the products differing in available dosage forms, dosing frequency (one vs two inhalations twice daily), pharmacokinetic profiles and ages for their FDA approved indications.¹⁻⁴

Table 1. Current Medications Available in the Therapeutic Class¹⁻⁴

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Budesonide/formoterol (Symbicort [®] HFA)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema*, and treatment of asthma in patients ≥ 12 years of age	Meter dose aerosol inhaler (HFA) (60 or 120 actuations): 80/4.5 μg 160/4.5 μg	-
Fluticasone propionate/salmeterol (Advair Diskus [®] , Advair HFA [®])	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema [†] , treatment of asthma in patients ≥ 4 years of age (Advair Diskus [®]), and treatment of asthma in patients ≥ 12 years of age (Advair HFA [®])	Dry powder inhaler (60 blisters): 100/50 μg 250/50 μg 500/50 μg Meter dose aerosol inhaler (HFA) (60 or 120 actuations): 45/21 μg 115/21 μg 230/21 μg	-
Mometasone/formoterol (Dulera [®])	Treatment of asthma in patients ≥ 12 years of age	Meter dose aerosol inhaler (HFA) (120 actuations): 100/5 μg 200/5 μg	-

HFA=hydrofluoroalkane

* Symbicort[®] 160/4.5 μg is the only strength Food and Drug Administration (FDA) approved for this indication.

† Advair[®] 250/50 μg is the only strength FDA approved for this indication.

Evidence-based Medicine

- The safety and efficacy of mometasone/formoterol were established in two randomized, double-blind, parallel-group, multicenter trials of 12 and 26 week duration (N=1,509).
 - After 26 weeks of treatment, mometasone/formoterol was more effective than monotherapy with the individual components in controlling asthma and reducing the risk of asthma deteriorations in patients with persistent asthma uncontrolled on medium-dose inhaled corticosteroids (ICSs).⁵
 - After 12 weeks of treatment, mometasone/formoterol was more effective than mometasone monotherapy in improving asthma control and reducing nocturnal awakenings.
 - Patients poorly controlled on high dose ICSs experienced significant improvements in asthma control, lung function and symptoms when treated with Dulera[®] compared to mometasone monotherapy.⁶
 - A long term safety trial demonstrated that treatment with Dulera[®] for up to one year is well tolerated.⁷
- A single head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated noninferiority of mometasone/formoterol in regard to the forced expiratory volume in 1 second (FEV₁) area under the curve from 0 to 12 hours. Mometasone/formoterol treatment was also associated with a significantly quicker onset of action and increase in FEV₁ five minutes post dose compared to fluticasone propionate/salmeterol.⁸
- Numerous trials have evaluated the combination ICS/LABA products to their respective individual components as monotherapy, and results have generally demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and achieving control of asthma symptoms. Moreover, there is similar efficacy between the administration of the combination ICS/LABA products to their individual components used in combination.⁹⁻³⁴
- Head-to-head trials comparing budesonide/formoterol and fluticasone propionate/salmeterol have been conducted but have failed to consistently demonstrate “superiority” of one product over the other.³⁵⁻⁴⁴

Key Points within the Medication Class

- According to Current Clinical Guidelines:⁴⁵⁻⁴⁸
 - Inhaled corticosteroids (ICSs) and β_2 -agonists are well established treatment options in the management of both asthma and chronic obstructive pulmonary disease (COPD).
 - The addition of a long-acting β_2 -agonist (LABA) is the preferred treatment option in asthma patients who fail to achieve adequate control with a low to medium dose ICS.
 - β_2 -agonists are among the principal bronchodilators used in the treatment of COPD, and long-acting bronchodilators are more effective and convenient than short-acting bronchodilators.
 - ICSs are recommended as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV₁ \leq 50% predicted and repeated exacerbations.
 - ICS/LABA products are more effective than either component alone in reducing exacerbations or improving lung function in COPD patients.
 - No one ICS/LABA product is preferred over another for the treatment of asthma or COPD.
- Other Key Facts:
 - All LABA-containing medications carry a Black Box Warning regarding an increased risk of asthma-related deaths associated with their use.
 - Budesonide/formoterol has a quicker onset of action (15 minutes) compared to fluticasone propionate/salmeterol (30 to 60 minutes). The onset of action of mometasone/formoterol has not been reported.¹⁻⁴
 - All ICS/LABA products are available for twice daily dosing (two inhalations/dose), except fluticasone propionate/salmeterol (Advair Diskus[®]) which can be administered as one inhalation twice daily for the treatment of asthma.¹⁻⁴
 - For the treatment of asthma, all ICS/LABA products are approved for use in patients \geq 12 years of age, except Advair Diskus[®] which is approved for use in patients \geq 4 years of age.
 - No generic products are available in this therapeutic class.

References

1. Symbicort® [package insert]. Wilmington (DE): AstraZeneca LP; 2010 Jun.
2. Advair Diskus® [package insert]. Research Triangle Park (NC); GlaxoSmithKline: 2011 Sep.
3. Advair HFA® [package insert]. Research Triangle Park (NC); GlaxoSmithKline: 2010 Jun.
4. Dulera® [package insert]. Whitehouse Station (NJ): Schering Corporation; 2011 Jul.
5. Nathan RA, Nolte H, Pearlman DS. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 μ g combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. *Allergy Asthma Proc.* 2010;31:269-79.
6. Weinstein SF, Corren J, Murphy K, Nolte H, White M. Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids (abstract). *Allergy Asthma Proc.* 2010;31:280-9.
7. Maspero JF, Nolte H, Cherrez-Ojeda I. Long-term safety of mometasone furoate/formoterol combination for treatment of patients with persistent asthma. *J Asthma.* 2010;47:1106-15.
8. Bernstein DI, Hebert J, Cheema A, Murphy KR, Cherrez-Ojeda I, Matiz-Bueno CE, et al. Efficacy and Onset of Action of Mometasone Furoate/Formoterol and Fluticasone Propionate/Salmeterol Combination Treatment in Subjects With Persistent Asthma. *Allergy Asthma Clin Immunol.* 2011 Dec 7;7(1):21. [Epub ahead of print]
9. Laloo U, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. *Chest.* 2003;123:1480-7.
10. Tal A, Simon G, Vermeulen, JH, Petru V, Cobos N, Everard ML, et al. Budesonide/formoterol in a single inhaler vs inhaled corticosteroids alone in the treatment of asthma. *Pediatr Pulmonol.* 2002;34:342-50.
11. Zangrilli J, Mansfield LE, Uryniak T, O'Brien CD. Efficacy of budesonide/formoterol pressurized metered-dose inhaler versus budesonide pressurized metered-dose inhaler alone in Hispanic adults and adolescents with asthma: a randomized, controlled trial. *Ann Allergy Asthma Immunol.* 2011 Sep;107(3):258-65.e2
12. Pohl WR, Vetter N, Zwick H, Hrubos V. Adjustable maintenance dosing with budesonide/formoterol or budesonide: double blind study. *Respir Med.* 2006;100(3):551-60.
13. Kuna P, Creemers JPHM, Vondra V, Black PN, Lindqvist A, Nihlen U, et al. Once-daily dosing with budesonide/formoterol compared with twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. *Respir Med.* 2006;100(12):2151-9.
14. Morice AH, Peterson S, Beckman O, Osmanliev D. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. *Int J Clin Pract.* 2007;61(11):1874-83.
15. Jenkins C, Kolarikova R, Kuna P, Caillaud D, Sanchis J, Popp W, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. *Respirology.* 2006;11:276-86.
16. Eid NS, Noonan MJ, Chipps B, Parasuraman B, Miller CJ, O'Brien CD. Once- vs twice-daily budesonide/formoterol in 6- to 15-year old patients with stable asthma. *Pediatrics.* 2010;126:e565-e75.
17. Kerwin EM, Oppenheimer JJ, LaForce C, Parasuraman B, Miller CJ, O'Dowd L, et al. Efficacy and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler in adults and adolescents with asthma previously stable with twice-daily budesonide/formoterol dosing. *Ann Allergy Asthma Immunol.* 2009;103:62-72.
18. Berger WE, Bleecker ER, O'Dowd L, Miller CJ, Mezzanotte W. Efficacy and safety of budesonide/formoterol pressurized medtered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma. *Allergy Asthma Proc.* 2010;31:49-59.
19. Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. *Clin Ther.* 2007 May;29(5):823-43.
20. Rosenhall L, Heinig JH, Lindqvist A, Leegaard J, Ståhl E, Bergqvist PB. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. *Int J Clin Pract.* 2002;56(6):427-33.
21. Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma. *Drugs.* 2006;66(17):2235-54.
22. Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. *Can Respir J.* 1999;6:45-51.
23. Nelson HS, Wolfe JD, Gross G, Greos LS, Baitinger L, Scott C, et al. Efficacy and safety of fluticasone propionate 44 μ g/salmeterol 21 μ g administered in a hydrofluoroalkane metered-dose inhaler as an initial asthma maintenance treatment. *Ann Allergy Asthma Immunol.* 2003;91:263-9.
24. Perrin K, Williams M, Wijesinghe M, James K, Weatherhall M, Beasley R. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β -agonist inhaler therapy in asthma. *J Allergy Clin Immunol.* 2010;126:505-10.
25. Marceau C, Lemiere C, Berbiche D, Perreault S, Blais L. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. *J Allergy Clin Immunol.* 2006;118:574-81.
26. Gappa M, Zachgo W, von Berg A, Kamin W, Stern-Strater C, Steinkamp G. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). *Pediatr Pulmonol.* 2009;44:1132-42.
27. Vaessen-Verberne AAPH, van den Berg NJ, van Nierop JC, Brackel HJL, Gerrits GPJM, Hop WCJ, Duiverman EJ. Combination therapy salmeterol/fluticasone vs doubling dose of fluticasone in children with asthma. *Am J Respir Crit Care Med.* 2010;182:1221-7.
28. Bateman E, Boushey H, Bousquet J, Buss WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med.* 2004;170:836-44.
29. Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone/salmeterol in a single inhaler is stepped down. *J Allergy Clin Immunol.* 2006;117(3):563-70.

30. Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 μg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. *Respir Med*. 2001;95:136-46.
31. Pearlman DS, Peden D, Condemni JJ, Weinstein S, White M, Baitinger L, et al. Efficacy and safety of fluticasone/salmeterol HFA 134A MDI in patients with mild-moderate persistent asthma. *J Asthma*. 2004;41:797-806.
32. Nathan RA, Rooklin A, Schoaf L, Scott C, Ellsworth A, House K, et al. Efficacy and tolerability of fluticasone/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescents and adult patients with persistent asthma: a randomized, double blind, placebo-controlled, 12-week study. *Clin Ther*. 2006;28:73-85.
33. Lundback B, Ronmark E, Lindberg A, Jonsson AC, Larsson LG, Petavy, et al. Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. *Respir Med*. 2006;100:2-10.
34. Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone and salmeterol inhaled from a single inhaler vs separate inhalers. *J Allergy Clin Immunol*. 2003;112:29-36.
35. Dahl R, Chuchalin A, Gor D, Yoxall S, Sharma R. EXCEL: a randomized trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. *Resp Med*. 2006; 100:1152-62.
36. Bousquet J, Boulet Louis-Philippe, Peters MJ, Magnussen H, Quirarte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med*. 2007;101:2437-46.
37. FitzGerald MJ, Boulet LP, Follows RM. The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. *Clin Ther*. 2005;27(4):393-406.
38. Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared with formoterol-budesonide adjustable maintenance dosing: impact on health-related quality of life. *Respir Res*. 2007 Jul 4;8:46.
39. Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ. Evaluation of different inhaled combination therapies (EDICT): a randomized, double-blind, comparison of Seretide (50/250 μg bd Diskus) vs formoterol (12 μg bd) and budesonide (800 μg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. *Respir Med*. 2002;96(11):851-61.
40. Busse WW, Shah SR, Somerville L, Parasuraman B, Martin P, Goldman M. Comparison of adjustable- and fixed-dose budesonide/ formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. *J Allergy Clin Immunol*. 2008;121:1407-14.
41. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinex-Jamenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract*. 2007;61(5):725-36.
42. Aalbers R, Backer V, Kava TT, Omenaas ER, Sandström T, Jorup C, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Opin*. 2004;20(2):225-40.
43. Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lötvall J. Onset of bronchodilation with budesonide/formoterol and salmeterol/fluticasone in single inhalers. *Pulm Pharmacol Ther*. 2001;14(1):29-34.
44. O'Connor PD, Patrick DL, Parasuraman B, Martin P, Goldman M. Comparison of patient-reported outcomes during treatment with adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler vs fixed-dose fluticasone propionate/salmeterol dry powder inhaler in patients with asthma. *J Asthma*. 2010;47:217-23.
45. 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 2012 Feb]. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>.
46. Bateman ED, Bousquet J, FitzGerald M, Haahntela T, O'Byrne P, Ohta K, et al. Global Initiative for Asthma. Global strategy for asthma management and prevention 2009 [guideline on the internet]. 2009. [cited 2012 Feb]. Available from: <http://www.ginasthma.com>.
47. Rodriguez-Roisin R, Anzueto A, Bourbeau J, deGuia T, Hui DSC, Jenkins C, et al. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease updated 2010 [guideline on the internet]. 2010 [cited 2012 Feb]. Available from: <http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intlId=989>.
48. 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 2012 Feb]. Available from: www.nice.org.uk/guidance/CG101.

Therapeutic Class Review

Inhaled Corticosteroid and Long-Acting β_2 -Agonist Combination Products

Overview/Summary

Symbicort[®] (budesonide/formoterol), Advair[®] (fluticasone propionate/salmeterol) and Dulera[®] (mometasone/formoterol) are the available combination inhaled corticosteroid (ICS) and long-acting β_2 -agonist (LABA) products. All are Food and Drug Administration (FDA)-approved for the treatment of asthma, with only budesonide/formoterol and fluticasone propionate/salmeterol being FDA-approved for the treatment of chronic obstructive pulmonary disease (COPD).¹⁻⁴ None of the combination ICS/LABA products are available generically.

Corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils) and mediators (e.g., histamine, cytokines) which are involved in the asthmatic response. The ICSs exert their anti-inflammatory effect by binding to the glucocorticoid receptors with a subsequent activation of genes involved in anti-inflammatory processes, as well as via the inhibition of pro-inflammatory genes involved in the asthmatic response. Inflammation is also a component of COPD pathogenesis.¹⁻⁴ The LABAs are also useful for long-term control of persistent asthma and COPD, and have been proven to help control nocturnal symptoms. These agents have selective action on β_2 receptors which stimulate adenyl cyclase, resulting in an increased intracellular cyclic adenosine monophosphate level, which subsequently triggers bronchial smooth muscles relaxation. The LABA medications also inhibit the release of mediators that are involved in immediate hypersensitivity.¹⁻⁴

The products differ in their available dosage forms, dosing frequency and in their pharmacokinetic profiles. Budesonide/formoterol (Symbicort[®]) has a faster onset of action, at 15 minutes, compared to 30 to 60 minutes with fluticasone propionate/salmeterol (Advair[®]). The onset of action of mometasone/formoterol (Dulera[®]) has not been reported. Fluticasone propionate/salmeterol is available as a dry powered inhaler (DPI) and as a hydrofluoroalkane (HFA) metered dose inhaler (MDI) which are dosed as one inhalation twice-daily (DPI) and two inhalations twice daily (MDI), respectively. Budesonide/formoterol and mometasone/formoterol are only available as HFA MDIs, and both are dosed as two inhalations twice daily.¹⁻⁴

Adverse events are similar among the combination ICS/LABA products with headache, nasopharyngitis, pharyngitis and upper respiratory tract infections being the most commonly reported.¹⁻⁴ Of note, all LABA-containing medications contain a Black Box Warning regarding an increased risk of asthma-related deaths. In February 2010, results from a meta-analysis demonstrated that LABAs were associated with an increased risk of asthma exacerbations and hospitalizations in pediatric and adult patients, as well as death in some patients. Based on the findings, the FDA now requires the product labeling of all LABA-containing medications to include information regarding these risks. In addition, the use of LABAs is now contraindicated without the presence of an asthma controller medication in the therapeutic regimen. The FDA also recommends that LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications, and that LABAs should be used for the shortest duration of time to achieve asthma control. Moreover, the FDA recommends the use of a combination ICS/LABA product in pediatric and adolescent patients who require LABA therapy to ensure compliance with both medications.⁵

There has been a single head-to-head trial comparing mometasone/formoterol (Dulera[®]) to fluticasone propionate/salmeterol (Advair[®]) which demonstrated mometasone/formoterol (Dulera[®]) to be noninferior to fluticasone propionate/salmeterol (Advair[®]) in regard to an improvement in change in forced expiratory volume in 1 second (FEV₁) area under the curve from 0 to 12 hours.⁶ Head-to-head trials comparing budesonide/formoterol (Symbicort[®]) and fluticasone propionate/salmeterol (Advair[®]) have not demonstrated consistent "superiority" of one product over the other.⁷⁻¹⁶ Trials have compared these agents for standard asthma maintenance. Moreover, a fixed dose fluticasone propionate/salmeterol regimen has been compared to a patient/prescriber adjustable dose budesonide/formoterol combination

regimen. Other trials have evaluated the budesonide/formoterol regimen as both maintenance and as needed treatment. This regimen is also known as Symbicort[®] Maintenance and Reliever Therapy (SMART). Of particular importance regarding this regimen is that it has not been approved by the FDA. This dosing regimen has reported significantly greater reductions in the overall number of exacerbations and in severe exacerbations compared to regular maintenance dosing regimens of both budesonide/formoterol and fluticasone propionate/salmeterol; however, the SMART dosing regimen demonstrated equal efficacy to both standard dose budesonide/formoterol and fluticasone propionate/salmeterol in lung function parameters, symptom reduction, and as needed reliever medication.⁷⁻¹⁶

Current treatment guidelines published by the National, Heart, Lung, Blood Institute (NHLBI) recommend against the use of a LABA as monotherapy for long-term asthma maintenance or for acute symptom treatment or exacerbations. These agents should be used in combination with an ICS for long-term control and prevention of symptoms in patients with moderate to severe persistent asthma. Of the adjunctive therapies available, LABAs are the recommended option to be used in combination with an ICS in patients ≥ 12 years of age that have not had adequate asthma symptom control with a low dose ICS. The guidelines recommend that for patients five to 11 years of age with moderate persistent asthma or asthma not controlled adequately on low-dose ICS, the option of a LABA should be weighed equally to potentially increasing the ICS dose. Additionally, the combination of a LABA with an ICS is recommended as preferred therapy in children with severe persistent asthma. The NHLBI guidelines do not specifically select one combination ICS/LABA product as being preferred over the others.¹⁷ The Global Initiative for Asthma (GINA) guidelines also recommend the use of a LABA as add on therapy as the preferred treatment option after the patient has failed to achieve adequate control with medium dose ICS monotherapy. The GINA guidelines also recommend against the use of LABAs as monotherapy. It should be noted that the GINA guidelines recommend that budesonide/formoterol (Symbicort[®]) can be utilized as both a maintenance and rescue medication; however, use of this agent as a rescue medication is not approved by the FDA. The GINA guidelines also do not specifically select one combination ICS/LABA product as being preferred over the others.¹⁸

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline on COPD recommends the use of bronchodilators, administered on an as needed basis or on a regular basis, to prevent or reduce symptoms and exacerbations. Principal bronchodilators include β_2 -agonists, anticholinergics and methylxanthines, used as monotherapy or in combination. The choice of which bronchodilator should be based on availability and individual response in terms of symptom relief and side effects, and based on the evidence that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting agents. ICSs are recommended as add-on therapy to bronchodilator treatment in symptomatic patients with a FEV₁ $< 50\%$ predicted and repeated exacerbations. The guideline also states that an ICS combined with a LABA is more effective than either component alone in reducing exacerbations or improving lung function and health status, but that this combination increases the risk of pneumonia. In addition, there is no evidence to support that ICS/LABA combination therapy has a statistically significant effect on mortality. Combination ICS/LABA therapy can also be combined with an anticholinergic to provide additional benefits in patients with COPD. Like the NHLBI and GINA guidelines, according to the GOLD guidelines, no one combination ICS/LABA product is preferred over the other.¹⁹ The National Institute for Clinical Excellence (NICE) COPD guidelines recommend the use of long-acting bronchodilators (LABAs and/or anticholinergics) to control symptoms in patients who continue to experience symptoms despite the use of a short-acting bronchodilator agent. In patients with stable COPD and an FEV₁ $\geq 50\%$, who remain breathless or who have exacerbations despite management with a LABA, consideration of the addition of an ICS (in a combination inhaler) or a long-acting muscarinic antagonist (when ICSs are not tolerated or declined) should be made. No preferred combination ICS/LABA product is provided within the current NICE guidelines.²⁰

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
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Generic Name (Trade name)	Medication Class	Generic Availability
Budesonide/formoterol (Symbicort [®] HFA)	Inhaled corticosteroid/long-acting β_2 -agonist	-
Fluticasone propionate/salmeterol (Advair Diskus [®] , Advair HFA [®])	Inhaled corticosteroid/long-acting β_2 -agonist	-
Mometasone/formoterol (Dulera [®])	Inhaled corticosteroid/long-acting β_2 -agonist	-

HFA=hydrofluoroalkane.

Indications

None of the combination inhaled corticosteroid/long-acting β_2 -agonist products are indicated for the relief of acute bronchospasm.¹⁻⁴

Table 2. Food and Drug Administration Approved Indications¹⁻⁴

Generic Name	Treatment of Asthma in Adults and Children ≥ 4 Years of Age	Treatment of Asthma in Adults and Children ≥ 12 Years of Age	Maintenance Treatment of Airflow Obstruction in Patients with Chronic Obstructive Pulmonary Disease*
Budesonide/formoterol		✓	✓ [†]
Fluticasone propionate/salmeterol	✓ (Advair Diskus [®])	✓ (Advair HFA [®])	✓ [‡] (Advair Diskus [®])
Mometasone/formoterol		✓	

HFA=hydrofluoroalkane.

*Including bronchitis and/or emphysema.

†Symbicort[®] 160/4.5 μ g is the only strength Food and Drug Administration (FDA) approved for this indication.‡Advair[®] 250/50 μ g is the only strength FDA-approved for this indication.

Pharmacokinetics

Table 3. Pharmacokinetics¹⁻⁴

Generic Name	Onset (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Budesonide/formoterol	0.25	12	60/59 to 62	None	4.7/7.9
Fluticasone propionate/salmeterol	0.5 to 1.0	12	<5/25 to 60	None	5.33 to 7.65/5.50
Mometasone/formoterol	Not reported	Not reported	8/59 to 62	None	25/9 to 11

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the combination inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA) products for their Food and Drug Administration (FDA)-approved indications are outlined in Table 4.^{7-16,21-77} Numerous trials have evaluated the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and achieving control of asthma symptoms.^{23-33,35,46-54,61,62} Additionally, there is similar efficacy between the administration of the combination ICS/LABA products to their individual components used in combination.^{21,25,29,35,42-45} A single head-to-head trial, described below, has been conducted comparing mometasone/formoterol (Dulera[®]) and fluticasone propionate/salmeterol (Advair[®]); however, more head-to-head trials comparing budesonide/formoterol (Symbicort[®]) and fluticasone propionate/salmeterol (Advair[®]) have been conducted. Overall the results of these trials were inconsistent in demonstrating efficacy “superiority” of one product over the other.^{6,7-16}

In an open label, noninferiority study by Bernstein et al, 722 patients ≥ 12 years of age with persistent asthma received mometasone/formoterol (Dulera[®]) or fluticasone propionate/salmeterol (Advair[®]) for 12 weeks following a two week run in period with mometasone. The primary endpoint was the change in forced expiratory volume in 1 second (FEV₁) area under the curve from 0 to 12 hours (AUC_{0 to 12h}) after 12 weeks. At the end of treatment, the change in FEV₁ AUC_{0 to 12h} associated with mometasone/formoterol (Dulera[®]) was noninferior to improvements observed with fluticasone propionate/salmeterol (Advair[®]) (3.43 vs 3.24 L/h, respectively; 95% Confidence Interval, -0.40 to 0.76). Moreover,

mometasone/formoterol (Dulera[®]) was associated with a significantly quicker onset of action ($P < 0.001$) and a greater least squares mean change in FEV₁ (200 vs 90 mL; $P \leq 0.001$) compared to fluticasone propionate/salmeterol (Advair[®]).⁶ There were no differences between the two treatment groups in regard to 24-hour asthma symptom scores, the number of symptom-free days and nights or asthma deterioration over 12 weeks (P values not reported).

The safety and efficacy of mometasone/formoterol, was established in two randomized, double-blind, parallel-group, multicenter clinical trials (N=1,509). Enrolled patients were ≥ 12 years of age with persistent asthma uncontrolled on medium or high dose ICSSs. All patients underwent a two to three week run-in period with mometasone to establish a certain level of asthma control.^{60,61}

The first trial was a 26 week, placebo-controlled trial (N=781) that compared mometasone/formoterol 100/5 μg , mometasone 100 μg , formoterol 5 μg and placebo. A primary endpoint of FEV₁ AUC_{0 to 12h} demonstrated that patients receiving combination therapy had significantly higher increases from baseline at week 12 compared to mometasone (the primary treatment comparison) ($P < 0.001$) and placebo ($P < 0.001$). These differences were maintained through 26 weeks of treatment. A second primary endpoint in this trial was clinically judged deteriorations in asthma or reductions in lung function (any of the following: a 20% decrease in FEV₁, a 30% decrease in peak expiratory flow on two or more consecutive days or emergency treatment, hospitalizations or treatment with systemic corticosteroids or other asthma medications not allowed per protocol) for mometasone/formoterol compared to formoterol. A smaller proportion of patients receiving combination therapy (30%) reported an event (54% with formoterol; $P < 0.001$).⁶⁰

The second trial was a 12 week, double-blind trial (N=728) that compared the efficacy of mometasone/formoterol 200/5 μg , mometasone/formoterol 100/5 μg and mometasone 200 μg . In this trial, the primary endpoint was the mean change in FEV₁ AUC_{0 to 12h} from baseline to week 12. Patients receiving both doses of combination therapy had significantly greater increases from baseline at day one in mean FEV₁ AUC_{0 to 12h} compared to mometasone (P values not reported); the difference was maintained over 12 weeks of treatment. A greater increase in the mean trough FEV₁ from baseline to week 12 was also observed for the higher dose of combination therapy (0.19) compared to the lower dose of combination therapy (0.14; P value not reported) and to mometasone (0.10; P value not reported). Fewer patients in both combination therapy groups reported clinically judged deterioration in asthma or a reduction in lung function compared to mometasone (12 vs 18%; P value not reported).⁶¹

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Rosenhall et al ²¹ Budesonide/formoterol 160/4.5 μg , 2 inhalations BID via MDI vs budesonide 160 μg , 2 inhalations BID via DPI plus formoterol 4.5 μg , 2 inhalations BID via DPI	MC, OL, RCT Patients with moderate persistent asthma (average age, 45)	N=586 6 months	Primary: Safety and efficacy (FEV ₁ , Mini AQLQ, ACQ, exacerbations) Secondary: Not reported	Primary: Patients in both treatment groups had a mean FEV ₁ increase of five to six percent from baseline (<i>P</i> value not reported). There was no significant change in response using the Mini AQLQ and the ACQ from baseline in both treatment groups. Both treatment groups were well tolerated, with asthma exacerbations occurring at a low frequency (<i>P</i> value not reported). The withdrawal rate in both groups was also similar (<i>P</i> =0.085). Secondary: Not reported
Canonica et al ²² Budesonide/formoterol 80/4.5 μg , 2 inhalations BID via MDI-FD vs budesonide/formoterol 160/4.5 μg , 2 inhalations BID via MDI-FD vs budesonide/formoterol 80/4.5 μg , 2 inhalations BID via MDI-AMD vs budesonide/formoterol	RCT Patients with persistent asthma	N=2,358 12 weeks	Primary: Frequency of asthma exacerbations and changes in asthma symptom severity Secondary: Asthma control, safety and health economics	Primary: Both FD and AMD budesonide/formoterol treatment groups had similar low frequency of exacerbations, as well as improved comparable lung function. However, results did not reach statistical significance (<i>P</i> value not reported). Secondary: Both treatment groups had improved lung function, less asthma symptoms and fewer nighttime awakenings compared to the mean value of the run-in period (<i>P</i> value not reported). Patients in the AMD budesonide/formoterol dose group utilized 24% less of the study drug in comparison to those in the FD group (2.95 vs 3.86 daily inhalations, respectively; <i>P</i> <0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>160/4.5 μg, 2 inhalations BID via MDI-AMD</p> <p>Lalloo et al²³</p> <p>Budesonide/formoterol 80/4.5 μg, 1 inhalation BID via DPI</p> <p>vs</p> <p>budesonide 200 μg, 1 inhalation BID</p> <p>Inhaled terbutaline or salbutamol was used as a reliever medication depending on patient preference.</p>	<p>DB, MC, PG, RCT</p> <p>Patients >18 years of age with a diagnosis of asthma assessed by the following: FEV₁ 60 to 90% of predicted normal value and >12% reversibility of basal FEV₁ within 15 minutes of terbutaline or salbutamol inhalation; all patients received ICSs of any brand at a constant dose of 200 to 500 $\mu\text{g}/\text{day}$ for ≥ 1 month prior to study entry</p>	<p>N=467</p> <p>12 weeks</p>	<p>Primary: Morning and evening PEF values</p> <p>Secondary: FEV₁/FVC measurements, symptom free days, reliever free days, nighttime awakenings, time to first mild and severe exacerbation, and safety</p>	<p>Primary: Morning and evening PEF values increased for both treatment groups; however, significantly larger increases were seen with combination therapy than with monotherapy ($P=0.002$ and $P<0.001$, respectively).</p> <p>Secondary: Mean FEV₁ scores increased in both groups but no significant difference was found, additionally, FVC showed no change from baseline.</p> <p>The incidence of asthma control days, symptom free days and reliever medication use ($P=0.025$) all favored combination therapy. Asthma control days favored combination therapy (17 vs 10%; $P=0.002$). Symptom free days were similar between groups (16 vs 10%; $P=0.007$). A reduction of 24 vs 6% and 23 vs 14% favored combination therapy for asthma symptom score and nighttime awakenings, respectively (P values not reported).</p> <p>Fewer patients experienced a mild exacerbation (110/230) in the combination group than the monotherapy group (136/237; P value not reported). Nighttime awakenings also favored combination therapy (75 vs 105; P value not reported).</p> <p>The monotherapy group showed a shorter time to first mild exacerbation compared to the combination group ($P=0.02$). The risk of having a mild exacerbation was estimated to be 26% lower in the combination group ($P=0.02$).</p> <p>The chance of having a severe exacerbation was six percent lower in the combination group ($P=0.85$).</p> <p>No between group differences were noted for the profile and frequency of adverse events. Both treatment groups commonly reported respiratory infection, pharyngitis, and rhinitis. Overall, there were seven severe adverse events, five occurred with combination therapy and two with monotherapy.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Tal et al²⁴</p> <p>Budesonide/formoterol 80/4.5 μg, 2 inhalations BID via DPI</p> <p>vs</p> <p>budesonide 100 μg, 2 inhalations BID via MDI</p>	<p>DB, DD, MC, PG, RCT</p> <p>Children 4 to 17 years of age with a diagnosis of asthma for ≥ 6 months, FEV₁ 40 to 90% of predicted value at visit 1, >15% reversibility of FEV₁ within 15 minutes of inhalation of a SABA, 6 weeks constant dosing with an ICS (budesonide, fluticasone or beclomethasone)</p>	<p>N=286</p> <p>12 weeks</p>	<p>Primary: Morning PEF</p> <p>Secondary: FEV₁, FEV₁ over a 12 hour time period, rescue inhaler use, comparison of nocturnal asthma symptoms, and safety</p>	<p>Primary: Combination therapy resulted in a significantly greater increase in morning PEF than monotherapy ($P < 0.001$). Results were similar for evening PEF (P value not reported).</p> <p>Secondary: FEV₁ scoring ($P < 0.05$), mean improvement of FEV₁ over 12 hours after one dose ($P < 0.05$) and mean improvement of FEV₁ ten minutes after first dose ($P < 0.05$) favored combination therapy.</p> <p>A decrease in rescue inhaler use from 0.71 to 0.60 inhalations/day was seen in the combination therapy group, and a change of 0.50 to 0.41 inhalations was seen with the monotherapy group. There was no statistical significance between the groups (P value not reported).</p> <p>A decrease in the number of nights awakening with asthma symptoms was seen in both groups with no significant difference (combination therapy decreased from 7.2 to 5.5% and monotherapy decreased from 8.5 to 6.6%; P value not reported).</p> <p>Reported adverse events between the two groups were comparable and reported as combination vs monotherapy. Pharyngitis (8 vs 12%), respiratory infection (8 vs 6%), rhinitis (7 vs 4%), coughing (5 vs 5%), headache (6 vs 4%), viral infection (7 vs 3%), fever (6 vs 2%) and aggravated asthma (5 vs 3%). In the combination therapy group, 4.7% of patients had serious adverse side effects.</p>
<p>Zangrilli et al²⁵</p> <p>Budesonide/formoterol 160/4.5 μg, 2 inhalations BID via DPI</p> <p>vs</p> <p>budesonide 160 μg, 2 inhalations BID via MDI</p>	<p>AC, DB, MC, RCT</p> <p>Hispanic patients ≥ 12 years of age with asthma for ≥ 6 months and a pre-bronchodilator FEV₁ of 45 to 85% of predicted normal and reversibility of</p>	<p>N=150</p> <p>12 weeks</p>	<p>Primary: Mean change from baseline in morning (AM) PEF</p> <p>Secondary: Predefined asthma events (decreased FEV₁ $\geq 20\%$ from randomization or FEV₁ <40% of predicted</p>	<p>Primary: The morning PEF value increased from baseline during randomized treatment, in both treatment groups but there was no significant difference between treatments (25.4 vs 19.9% in the combination and monotherapy groups, respectively; $P \geq 0.428$).</p> <p>Secondary: Patients who received combination therapy experienced fewer asthma events compared to patients receiving monotherapy, although the difference was not statistically significant (25.2 vs 31.7%; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	<p>≥12% with albuterol administration and a documented daytime or nighttime asthma symptom scores ≥0 on 3 or more days within 7 consecutive days during a 2-week run-in period on budesonide 160 µg BID</p>		<p>normal, ≥12 inhalations of albuterol per day, decreased morning PEF ≥20% from baseline on ≥3 of 7 consecutive days after randomization, ≥2 nocturnal asthma awakenings requiring rescue medication within 7 days after randomization, or a clinical exacerbation requiring emergency treatment, hospitalization, or use of an excluded asthma medication) and withdrawals caused by these events, pulmonary function assessments and diary-based measures of asthma control</p>	<p>Similarly, 3.1% and 6.5% of patients in the combination and monotherapy treatment groups withdrew from the study due to asthma related events, although the differences in discontinuation rates were not significant (<i>P</i> value not reported).</p> <p>There was no significant difference between patients receiving combination treatment or monotherapy, in regard to the change in daily asthma symptom score, daytime symptom score or nighttime symptom score (<i>P</i>≥0.181 for all comparisons).</p> <p>Rescue medication use decreased, and the percentage of symptom-free days, awakening-free nights, and rescue medication-free days increased in both treatment groups, but no differences in these outcomes were observed between the treatment groups (<i>P</i> values not reported).</p>
<p>Pohl et al²⁶</p> <p>Budesonide/formoterol 160/4.5 µg, 2 inhalations BID, via MDI-AMD</p> <p>vs</p> <p>budesonide 320 µg, 2 inhalations BID, via DPI-AMD</p>	<p>DB, PG, RCT</p> <p>Patients >19 years of age with asthma, FEV₁ reversibility of ≥15% (or 200 mL) within 1 month prior to enrollment, FEV₁ 40 to 85% of predicted normal, requirement with</p>	<p>N=133</p> <p>20 weeks</p>	<p>Primary:</p> <p>Number of patients/ treatment group with ≥1 treatment failure (defined as hospitalization, oral steroids, nebulized β_2-agonists, withdrawal due to lack of efficacy or life-threatening condition)</p> <p>Secondary:</p> <p>Health-related quality of</p>	<p>Primary:</p> <p>The rate of treatment failures were comparable between the two treatment groups with five out of the 63 patients in the budesonide/formoterol group and two out of the 63 patients in the budesonide group experiencing treatment failure throughout the duration of the study.</p> <p>Secondary:</p> <p>Patients in the budesonide/formoterol group had a statistically significant improvement in health-related quality of life and treatment satisfaction (for patients and physicians) vs those in the budesonide group (<i>P</i><0.05).</p> <p>Patients in the budesonide/formoterol group also had a lower use of daily inhalations of study drug vs budesonide (<i>P</i>=0.024). Both groups had</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	an ICS or ICS/LABA combination within given starting dose range		life measured by the SF-36, dose of study medication, days of reliever medication use, and treatment satisfaction	minimal use of reliever medications.
Kuna et al ²⁷ Budesonide/formoterol 80/4.5 μ g, 2 inhalations every evening via MDI vs budesonide/formoterol 80/4.5 μ g, 1 inhalation BID via MDI vs budesonide 200 μ g, 1 inhalation every evening via DPI	AC, DB, DD, PG, RCT Adult patients with mild to moderate persistent asthma who were not optimally controlled on an ICS dose of 200 to 500 μ g/day, mean predicted FEV ₁ at baseline was 78.5%	N=617 12 weeks	Primary: Morning PEF Secondary: Evening PEF, symptom-free days, reliever-free days, asthma control days, and adverse events	Primary: Patients in both budesonide/formoterol regimens showed greater improvements in morning PEF ($P<0.05$). Secondary: Patients in both budesonide/formoterol regimens showed greater improvement in evening PEF, symptom-free days, reliever-free days and asthma-control days compared to the budesonide regimen ($P<0.05$). Both budesonide/formoterol regimens were similar in all efficacy variables, except for evening PEF which was higher with the BID regimen (18.3 vs 9.6 L/minute; $P<0.05$). There were no between-group differences in nighttime awakenings due to asthma, or in the number and nature of adverse events.
Morice et al ²⁸ Budesonide/formoterol 160/4.5 μ g via DPI vs budesonide/formoterol 160/4.5 μ g via MDI vs budesonide 200 μ g via	DB, DD, MC, PG, RCT Outpatients ≥ 12 years of age with asthma for ≥ 6 months with inadequate control on an ICS alone, FEV ₁ of 50 to 90% predicted normal, reversibility of $>12\%$ after	N=680 12 weeks	Primary: Change from baseline in morning PEF Secondary: Changes from baseline in evening PEF, nighttime awakenings, asthma symptom score, symptom-free days and asthma control days	Primary: Patients in the budesonide/formoterol DPI and budesonide/formoterol MDI groups had improved morning PEF compared to those in the budesonide group by 31.4 and 28.6 L/minute, respectively ($P<0.001$). Secondary: Patients in the budesonide/formoterol groups had greater improvements observed compared to those in the budesonide group. End points were similar between the two budesonide/formoterol devices, with the exception of symptom-free and asthma control days, which were slightly improved with the DPI.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MDI	inhalation of terbutaline 1 mg, and daily ICS use history ≥ 3 months			
<p>Jenkins et al²⁹</p> <p>Budesonide/formoterol 320/9 μg, 2 inhalations BID via DPI (treatment 1)</p> <p>vs</p> <p>budesonide 400 μg, 2 inhalations BID plus formoterol 9 μg, 2 inhalations BID (treatment 2)</p> <p>vs</p> <p>budesonide 400 μg, 2 inhalations BID (after 12 weeks this group was randomized to either treatment 1 or 2)</p> <p>Terbutaline 0.5 mg was used throughout the study for as-needed relief.</p>	<p>DB, DD, MC, RCT</p> <p>Outpatients >12 years of age with a diagnosis of asthma for ≥ 6 months, FEV₁ 40 to 85% of predicted, >15% reversibility in increase from baseline FEV₁ after inhalation of a bronchodilator (for patients >18 years of age an increase of >200 mL, 15 to 30 minutes post bronchodilator); all patients used ICSs for >4 months before study entry at a daily dose >750 μg for >4 weeks, patients required an asthma symptoms score of >1 for ≥ 4 of 7 days of the run-in period</p>	<p>N=456</p> <p>24 weeks</p>	<p>Primary: Morning and evening PEF</p> <p>Secondary: Adherence to therapy, FEV₁, symptom free days and nights, total number of reliever inhalations recorded in diary, daytime/nighttime symptom scores via diary, and safety</p>	<p>Primary: Patients receiving combination therapy had greater increases from baseline PEF scoring in both the morning and evening with 37.4 and 4.5 L/minute respectively ($P < 0.001$). There was no significant difference between either of the combination therapies (P value not reported).</p> <p>Secondary: FEV₁ increased over time for all three treatment groups. However, those receiving combination therapy compared to monotherapy showed significant improvement (0.30 vs 0.14 L, respectively; $P < 0.001$).</p> <p>Combination therapy reduced asthma symptom scores significantly better than monotherapy alone ($P = 0.0051$).</p> <p>Patients receiving combination therapy had 16% more symptom free days than budesonide alone ($P < 0.001$), used 0.97 inhalations of reliever medication/day compared to 1.61 for budesonide alone ($P < 0.001$), had 19% more reliever free days ($P < 0.001$) compared to budesonide alone, and resulted in 16% more asthma-control days, which is approximately 58 more days a year with asthma control ($P < 0.001$) compared to budesonide alone.</p> <p>Combination therapy reduced the risk for mild exacerbation by 36% ($P = 0.0032$).</p> <p>Combining budesonide/formoterol in one inhaler reduced the risk of mild exacerbation by 17% compared to separate inhaler therapy ($P = 0.13$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Eid et al³⁰</p> <p>Budesonide/formoterol 40/4.5 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>budesonide/formoterol 80/4.5 μg, 2 inhalations QD via MDI</p> <p>vs</p> <p>budesonide 80 μg, 2 inhalations QD via MDI</p> <p>All patients discontinued their current asthma therapy and received budesonide/formoterol 40/4.5 μg, 2 inhalations BID via MDI and as needed rescue albuterol during a 4 to 5 week run-in period.</p>	<p>AC, DB, MC, PG, RCT</p> <p>Patients 6 to 15 years of age with a documented asthma diagnosis for ≥ 6 months, stable disease based on consistent previous therapy, a prebronchodilator FEV₁ 60 to 90%, bronchodilatory reversibility of $\geq 12\%$ and ≥ 0.20 L in FEV₁ and mild to moderate asthma based on ICS use and pulmonary function</p>	<p>N=521</p> <p>12 weeks</p>	<p>Primary: Evening PEF</p> <p>Secondary: Morning PEF, daytime and nighttime asthma severity scores, nighttime awakenings attributable to asthma, daytime and nighttime rescue medication use, physician and caregiver assessment of overall level of asthma control, PAQLQ, PACQLQ, and safety</p>	<p>Primary: Both combination therapies maintained evening PEF significantly more than monotherapy ($P \leq 0.027$ for both). For combination therapy, mean evening PEF values steadily improved from baseline values with BID administration, whereas they were maintained at the baseline level with QD administration; however, mean changes from baseline were not significantly different between the two groups (P value not reported).</p> <p>Secondary: For morning PEF, both combination therapies were significantly more effective than monotherapy ($P \leq 0.010$), and there were no significant differences noted between the combination therapies ($P < 0.05$). Morning PEF was well maintained during the treatment period with both combination therapies; improvement from baseline values were observed for BID administration.</p> <p>For daytime and nighttime asthma symptoms, symptom-free days, awakening-free nights and asthma control days, the level of asthma control established during the run-in period was well maintained in all treatment groups, and there were no significant between group differences observed.</p> <p>Compared with monotherapy, treatment with combination therapy BID resulted in significantly less daytime and nighttime rescue medication use and more rescue medication-free days ($P \leq 0.023$). For combination therapy, daytime rescue medication use increased and rescue medication-free days decreased with QD administration compared to BID administration ($P \leq 0.039$).</p> <p>The percentage of caregivers whose responses indicated improvements in asthma symptoms or the ease of asthma management was similar across treatment groups (56.7 to 60.4%). Similar results were observed for comparisons of the percentages of physicians whose responses indicated improvements in the patient's asthma symptoms (70.0 to 77.8%). However a significantly greater percentage of physicians' responses indicated improvements in the ease of asthma management with combination therapy BID vs monotherapy (75.0 vs 64.4%; $P = 0.035$), but not those</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>receiving combination therapy QD (70.4%; $P=0.362$).</p> <p>Neither the magnitude of mean changes within each group nor the magnitude of the mean differences between the groups was considered clinically meaningful according to the predefined minimal important difference of 0.5 for any of PAQLQ or PACQLQ overall or domain scores.</p> <p>All treatments were generally well tolerated, with most adverse events being of mild to moderate intensity. The incidence of overall adverse events was similar across the treatment groups.</p>
<p>Kerwin et al³¹</p> <p>Budesonide/formoterol 160/4.5 μg, 2 inhalations QD via MDI</p> <p>vs</p> <p>budesonide/formoterol 80/4.5 μg, 2 inhalations QD via MDI</p> <p>vs</p> <p>budesonide/formoterol 80/4.5 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>budesonide 160 μg, 2 inhalations QD via MDI</p> <p>All patients discontinued their current asthma therapy and received SB budesonide/formoterol</p>	<p>AC, DB, PG, RCT</p> <p>Patients ≥ 12 years of age with asthma for ≥ 6 months, mild to moderate asthma based on pulmonary function and ICS use, received an ICS or ICS/LABA therapy for ≥ 4 weeks before screening, with a FEV₁ 60 to 90% and demonstrated reversibility of FEV₁ $\geq 12\%$ and ≥ 0.20 L from baseline within 15 to 30 minutes of SABA use</p>	<p>N=619</p> <p>12 weeks</p>	<p>Primary: Evening pre-dose FEV₁</p> <p>Secondary: Morning and evening pre-dose PEF, daytime and nighttime asthma symptom scores, daytime and nighttime rescue medication use, nighttime awakenings due to asthma, symptoms-free days, awakening-free nights, asthma control days, rescue medication-free days, patient withdrawals due to predefined criteria for worsening asthma, AQLQ, and safety</p>	<p>Primary: Budesonide/formoterol QD (320/9 $\mu\text{g}/\text{day}$) was significantly more effective than budesonide for evening pre-dose FEV₁ and evening PEF ($P \leq 0.004$). For combination therapy, changes in evening pre-dose FEV₁ and evening PEF were significantly more favorable for BID administration vs QD administration (320/9 $\mu\text{g}/\text{day}$) ($P < 0.001$). Mean morning PEF was maintained throughout the study with budesonide/formoterol QD (320/9 $\mu\text{g}/\text{day}$).</p> <p>Budesonide/formoterol QD (160/9 $\mu\text{g}/\text{day}$) was significantly more effective than budesonide in maintaining evening pre-dose FEV₁ and morning PEF during treatment ($P \leq 0.016$). For combination therapy, changes in evening pre-dose FEV₁ and evening PEF were significantly more favorable for BID administration vs QD administration (160/9 $\mu\text{g}/\text{day}$) ($P < 0.001$).</p> <p>Across all efficacy variables, differences between the two combination therapy QD groups were small and of questionable clinical relevance. The only significant difference noted between the two groups was for evening pre-dose PEF (least squares mean difference, 0.05 L; 95% CI, 0.00 to 0.10) which favored the higher dose QD group (320/9 $\mu\text{g}/\text{day}$) ($P = 0.031$).</p> <p>Secondary: Results for morning and evening pre-dose PEF are reported in the primary outcome section.</p> <p>Changes in rescue medication use and symptom-related variables significantly favored budesonide/formoterol QD (320/90 $\mu\text{g}/\text{day}$) vs</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
80/4.5 μg , 2 inhalations BID via MDI during a 4 to 5 week run-in period.				<p>budesonide ($P \leq 0.045$), except awakening-free nights, asthma control days and daytime rescue medication use. For combination therapy, QD administration (320/9 $\mu\text{g}/\text{day}$) and BID administration were similarly effective for diary variables reflective of the 12 hour period after evening dosing (nighttime asthma symptoms, awakening-free nights and nighttime rescue medication use), with significantly more favorable results for BID administration compared to QD administration (320/9 $\mu\text{g}/\text{day}$) for all other symptom-related and rescue medication use variables.</p> <p>Changes in symptom-related variables were significantly more favorable for budesonide/formoterol QD (160/9 $\mu\text{g}/\text{day}$) compared to budesonide ($P \leq 0.023$), except symptom-free days and daytime rescue medication use. For combination therapy, BID administration was significantly more effective than QD (160/9 $\mu\text{g}/\text{day}$) administration for all symptom-related and rescue medication use variables ($P < 0.01$), except those that reflected the 12 hour period after evening dose.</p> <p>For combination therapy, results for asthma control days significantly favored BID administration compared to QD administration (320/9 and 160/9 $\mu\text{g}/\text{day}$) ($P \leq 0.005$).</p> <p>The percentages of patients withdrawing due to worsening asthma were as follows: 4.6, 6.6, 3.3 and 6.6% for budesonide/formoterol QD (320/9 $\mu\text{g}/\text{day}$), budesonide/formoterol QD (160/9 $\mu\text{g}/\text{day}$), budesonide/formoterol BID and budesonide (P values not reported).</p> <p>Mean changes in AQLQ overall and domain scores were small in all groups and less than the clinically meaningful difference. These changes were significantly more favorable for budesonide/formoterol BID vs budesonide ($P \leq 0.018$), but similar among the combination groups (except for the AQLQ symptoms domain, which significantly favored BID administration vs QD [160/9 $\mu\text{g}/\text{day}$] administration; $P = 0.034$).</p> <p>All treatments were generally well tolerated, with most adverse events being of mild to moderate intensity.</p>
Berger et al ³²	AC, DB, DD, MC,	N=752	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Budesonide/formoterol 80/4.5 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>budesonide/formoterol 160/4.5 μg, 2 inhalations QD via MDI</p> <p>vs</p> <p>budesonide/formoterol 80/4.5 μg, 2 inhalations QD via MDI</p> <p>vs</p> <p>budesonide 160 μg, 2 inhalations QD via MDI</p> <p>vs</p> <p>placebo</p> <p>All patients discontinued their current asthma therapy and received SB treatment with budesonide/formoterol 80/4.5 μg, 2 inhalations BID via MDI and rescue albuterol as needed during a 4 to 5 week run-in period.</p>	<p>PC, RCT</p> <p>Patients ≥ 16 years of age with a documented diagnosis of asthma for ≥ 6 months, mild to moderate persistent asthma based on ICS use and pulmonary function, previous use of low to medium dose ICS during the month prior to enrollment and a prebronchodilator FEV₁ 60 to 90%, with bronchodilator reversibility to albuterol of $\geq 12\%$ and ≥ 0.20 L in FEV₁</p>	<p>12 weeks</p>	<p>Pulmonary function (evening PEF as primary outcome)</p> <p>Secondary: Daytime and nighttime symptom scores, nighttime awakenings, rescue medication use, events of and patient withdrawals from the trial because of predefined criteria for worsening asthma control, and AQLQ</p>	<p>For pulmonary function variables (evening PEF and evening pre-dose FEV₁) at the end of QD administration, all combination therapy groups were significantly ($P < 0.001$) more effective than placebo. Compared with budesonide, results for evening PEF significantly favored combination therapy ($P < 0.001$), whereas results for evening pre-dose FEV₁ significantly favored budesonide/formoterol BID ($P < 0.001$).</p> <p>For both evening PEF and evening pre-dose FEV₁, significant differences were observed between the budesonide/formoterol BID and QD groups, favoring BID administration ($P \leq 0.010$). There were no significant differences in pulmonary function variables between the two combination therapy QD groups.</p> <p>Secondary: Changes from baseline in all rescue medication use and symptom-related variables were significantly better for all combination therapy groups vs placebo ($P < 0.001$ for all). Compared with budesonide, significantly ($P \leq 0.045$) better results were observed for all rescue medication use and symptom-related variables with the combination therapy BID and QD (320/9 $\mu\text{g}/\text{day}$) groups. Over the 12 week period, the percentage of patients with a symptom-free day was greater in all combination therapy groups compared to budesonide and placebo.</p> <p>Nighttime asthma control variables were similar in the budesonide/formoterol QD and BID groups; however, BID administration showed significantly better results than QD (160/9 $\mu\text{g}/\text{day}$) administration for all other asthma control variables ($P \leq 0.020$).</p> <p>For combination therapy, significant differences in favor of BID administration compared with QD administration (320/9 $\mu\text{g}/\text{day}$) were observed for asthma control days ($P = 0.030$) and daytime rescue medication use ($P = 0.050$). Significant differences in favor of the higher QD dose (320/9 $\mu\text{g}/\text{day}$) compared to the lower (160/9 $\mu\text{g}/\text{day}$) QD dose were observed for symptom-free days, asthma control days and rescue medication-free days ($P \leq 0.040$).</p> <p>The percentage of patient with events of or withdrawals due to worsening</p>

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				<p>asthma control were significantly lower for all combination therapy groups compared with placebo ($P<0.001$ for all), and for budesonide/formoterol BID and QD (160/9 $\mu\text{g}/\text{day}$) compared with budesonide ($P\leq 0.028$). In addition, significantly fewer patients in the budesonide/formoterol BID, budesonide/formoterol QD (320/9 $\mu\text{g}/\text{day}$) and budesonide groups met the criterion of clinical asthma exacerbation compared with placebo ($P<0.01$). Results were not significantly different between the combination therapy groups for these variables.</p> <p>Mean changes from baseline in AQLQ overall and all domain scores were significantly more favorable ($P\leq 0.010$), and differences were clinically meaningful, for all combination therapy groups compared to placebo, with the exception of the environmental exposure domain, for which clinically meaningful differences between placebo were observed only for budesonide/formoterol BID.</p>
<p>Corren et al³³</p> <p>Budesonide/formoterol 80/4.5 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>budesonide 80 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>formoterol 4.5 μg, 2 inhalations BID via DPI</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, MC, PC, RCT</p> <p>Patients ≥ 12 years of age with predominantly mild to moderate persistent asthma treated with an ICS for ≥ 4 weeks before screening and with a prebronchodilator FEV₁ 60 to 90% of predicted normal on ICS at screening</p>	<p>N=480</p> <p>12 weeks</p>	<p>Primary: Changes from baseline in morning pre-dose FEV₁ and 12-hour mean FEV₁ after morning dose</p> <p>Secondary: Morning and evening pre-dose PEF, daytime and nighttime symptom scores, nighttime awakenings, daily rescue medication use, and worsening asthma</p>	<p>Primary: The mean change from baseline in pre-dose FEV₁ was greater in patients who received budesonide/formoterol compared to those who received budesonide, formoterol or placebo ($P<0.005$).</p> <p>Observed mean changes from baseline in 12-hour FEV₁ were greater in patients who received budesonide/formoterol compared to those who received budesonide or placebo ($P<0.001$). There was no evidence of diminution of the 12-hour bronchodilatory effect of budesonide/formoterol during the study period.</p> <p>Secondary: Patients who received treatment with budesonide/formoterol had greater mean increases from baseline in morning and evening pre-dose PEF compared to budesonide or formoterol ($P<0.001$).</p> <p>Mean decreases in symptom scores were greater with budesonide/formoterol compared to formoterol and placebo ($P<0.046$). Active treatments were associated with greater mean increases in awakening-free nights compared to placebo ($P<0.012$).</p> <p>Patients who received budesonide/formoterol had a greater mean</p>

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				<p>reduction from baseline in daily rescue medication use compared to formoterol ($P=0.006$).</p> <p>The percentage of patients experiencing worsening asthma was reduced with budesonide/formoterol compared to formoterol or placebo ($P\leq 0.01$).</p>
<p>Murphy et al³⁴</p> <p>Budesonide/formoterol 80/4.5 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>budesonide 80 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>formoterol 4.5 μg, 2 inhalations BID via DPI</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, MC, PC, RCT</p> <p>Patients ≥ 18 years of age with predominantly mild to moderate persistent asthma</p>	<p>N=405</p> <p>12 weeks</p>	<p>Primary: AQLQ, MOS Sleep Scale, asthma control variables (daily asthma symptom score, percentage of symptom free days, percentage of rescue medication free days, percentage of asthma control days), and PSAM</p> <p>Secondary: Not reported</p>	<p>Primary: A significantly greater improvement from baseline in AQLQ overall and domain scores, MOS Sleep Scale domain scores and asthma control variables was seen in the budesonide/formoterol group compared to placebo ($P<0.033$).</p> <p>A significantly greater improvement from baseline in AQLQ overall and domain scores, daily asthma symptom score, percentage of symptom free days, percentage of rescue medication free days and percentage of asthma control days was seen in the budesonide/formoterol group compared to formoterol ($P<0.042$).</p> <p>Significantly greater PSAM scores were reported in the budesonide/formoterol group compared to all other treatment arms ($P<0.004$).</p> <p>Secondary: Not reported</p>
<p>Noonan et al³⁵</p> <p>Budesonide/formoterol 160/4.5 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>budesonide 160 μg, 2 inhalations BID via MDI plus formoterol 4.5 μg, 2 inhalations BID via DPI</p>	<p>DB, DD, MC, PC, RCT</p> <p>Patients ≥ 12 years of age, documented diagnosis of asthma for ≥ 6 months, moderate to high ICS use for ≥ 4 weeks, prebronchodilator</p>	<p>N=596</p> <p>12 weeks</p>	<p>Primary: Mean change from baseline in morning pre-dose FEV₁ and mean change from baseline in 12-hour FEV₁ after administration of morning dose</p> <p>Secondary: PEF, asthma symptoms, rescue medications use,</p>	<p>Primary: Greater improvements in morning pre-dose FEV₁ were obtained in patients treated with budesonide/formoterol (0.19 L) than those treated with budesonide (0.10 L), formoterol (-0.12 L) or placebo (-0.17 L; $P\leq 0.049$).</p> <p>Patients who received budesonide/formoterol also demonstrated a greater improvement in 12-hour FEV₁ than budesonide, formoterol and placebo at two weeks and end of treatment ($P\leq 0.001$). Fewer patients receiving budesonide/formoterol than the individual products or placebo met worsening asthma criteria.</p>

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<p>vs</p> <p>budesonide 160 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>formoterol 4.5 μg, 2 inhalations BID via DPI</p> <p>vs</p> <p>placebo</p>	<p>FEV₁ 45 to 85% of predicted normal</p>		<p>and worsening asthma</p>	<p>Secondary:</p> <p>Budesonide/formoterol treatment resulted in greater improvements in morning and evening PEF, daytime and nighttime symptoms, worsening asthma and percentage of symptom-free days than budesonide, formoterol and placebo ($P \leq 0.05$).</p> <p>Patients receiving budesonide/formoterol demonstrated reduction in asthma symptoms, use of rescue medication and improvement in PEF within the first day and effects were maintained over the course of the 12-week study.</p> <p>Significant reductions in the use of rescue medication were observed in patients with budesonide/formoterol treatment compared to formoterol ($P < 0.001$) and placebo but not with budesonide ($P = 0.066$). Awakenings due to asthma were not significantly different between active treatment groups. Similar results were obtained for treatment arms with combination budesonide/formoterol and concurrent administration of the individual components. No clinically significant differences in adverse events were observed between treatment groups.</p> <p>Patients who received budesonide/formoterol had clinically significant bronchodilation, defined as >15% improvement in FEV₁, within 15 minutes and effect was maintained over 12 hours.</p>
<p>Bateman et al³⁶</p> <p>Budesonide/formoterol 160/4.5 μg, 1 inhalation BID via DPI</p> <p>vs</p> <p>fluticasone 250 μg, 1 inhalation BID via DPI</p> <p>There was a 2 week run-in period in which patients received</p>	<p>DB, DD, PG, RCT</p> <p>Patients with asthma (average age of 42 years, FEV₁ 78% predicted, reversibility 21%)</p>	<p>N=373</p> <p>12 weeks</p>	<p>Primary:</p> <p>Morning PEF</p> <p>Secondary:</p> <p>Evening PEF, clinic FEV₁, use of reliever medication, symptom-free days, asthma control days, night-time awakenings, and risk of having an exacerbation</p>	<p>Primary:</p> <p>Patients in the budesonide/formoterol group had significantly greater increases in morning PEF than those in the fluticasone group (27.4 vs 7.7 L/minute, respectively; $P < 0.001$).</p> <p>Secondary:</p> <p>Those in the budesonide/formoterol group had a significant improvement in their evening PEF and FEV₁ compared to the fluticasone group (P values not reported). Also, patients in the budesonide/formoterol group utilized less reliever medication ($P = 0.04$) and had a greater proportion of reliever-free days ($P < 0.001$).</p> <p>Patients in the budesonide/formoterol group had a 32% risk reduction of having an exacerbation compared to those in the fluticasone group</p>

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budesonide 200 μ g BID.				<p>($P < 0.05$).</p> <p>Although not statistically significant, patients in the budesonide/formoterol group had improvements in regards to symptom-free days, asthma control days and nighttime awakenings vs those in the fluticasone group (60.4 vs 55.5%, 57.8 vs 52.4% and 7.9 vs 9.6%, respectively; P values not reported).</p>
<p>Papi et al³⁷</p> <p>Budesonide/formoterol 200/6 μg, 2 inhalations BID via DPI</p> <p>vs</p> <p>beclomethasone/formoterol 100/6 μg, 2 inhalations BID via MDI</p> <p>There was a 2 week run-in period in which patients were allowed to continue their stable dose of ICS and use salbutamol as needed, except ≥ 6 hours prior to pulmonary function test.</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients 18 to 65 years of age with moderate to severe persistent asthma, an FEV₁ of 50 to 80% of predicted normal, previously treated with an ICS $< 1,000$ μg/day of BDP equivalent, uncontrolled asthma symptoms</p>	<p>N=219</p> <p>12 weeks</p>	<p>Primary: Morning pre-dose PEF measured by patients (weeks 11 to 12)</p> <p>Secondary: FEV₁, FVC, PEF, MEF_{50%}, symptom scores, and time to first exacerbation</p>	<p>Primary: There was no significant difference in morning pre-dose PEF observed between beclomethasone/formoterol and budesonide/formoterol (difference between adjusted means, 0.49 L/minute; CI, -11.97 to 12.95).</p> <p>Secondary: Patients in the beclomethasone/formoterol and budesonide/formoterol groups had a significant improvement from baseline in their morning PEF (mean increase, 29.43\pm52.80 L/minute; 95% CI, 19.31 to 39.54; mean increase, 28.63\pm43.40 L/minute; 95% CI, 20.39 to 36.87). There was no significant difference in evening PEF between the two treatment groups (P value not reported).</p> <p>Patients in both treatment groups had significant improvements in FEV₁, FVC, PEF and MEF_{50%} from baseline beginning at week two of treatment and continuing throughout the study period (P value not reported). There was no statistically significant difference reported between the two treatment groups at the end of the study (P value not reported).</p> <p>There were statistically significant improvements in both daytime and nighttime symptom scores from baseline observed between the two treatment groups ($P < 0.001$),</p> <p>Patients in the beclomethasone/formoterol and budesonide/formoterol groups had a reduction in the daily use of rescue medication in the last week of the run-in period to the last two weeks of the treatment period (2.16\pm1.15 to 0.76\pm0.92 puffs/day and 2.28\pm1.50 to 0.87\pm1.04 puffs/day, respectively).</p> <p>There was no statistically significant difference in the time to first</p>

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<p>Scicchitano et al³⁸</p> <p>Budesonide/formoterol 160/4.5 μg, 2 inhalations QD with additional inhalations as needed via MDI</p> <p>vs</p> <p>budesonide 160 μg, 2 inhalations BID via DPI and terbutaline 0.4 mg inhalations as needed</p>	<p>DB, PG, RCT</p> <p>Patients 11 to 80 years of age with symptomatic asthma, mean FEV₁ 70% of predicted, mean ICS dose 746 $\mu\text{g}/\text{day}$</p>	<p>N=1,890</p> <p>12 months</p>	<p>Primary: Time to first severe exacerbation (defined as hospital/emergency room visit, oral steroids or fall in morning PEF to <70% of baseline for two consecutive days)</p> <p>Secondary: Number of severe exacerbations, use of as needed medication, mean daily ICS dose, and number of asthma control days</p>	<p>exacerbation observed between the two groups (<i>P</i> value not reported).</p> <p>Primary: Patients in the budesonide/formoterol group had prolonged time to first exacerbation, and a 39% lower risk of having a severe exacerbation compared to the budesonide group (<i>P</i><0.001).</p> <p>Secondary: Patients in the budesonide/formoterol group had 45% fewer severe exacerbations resulting in medical interventions/patient compared to those in the budesonide group (<i>P</i><0.001).</p> <p>Patients in the budesonide/formoterol group also had less utilization of as-needed medication (<i>P</i><0.001), and a lower mean daily ICS dose (466 vs 640 $\mu\text{g}/\text{day}$, respectively) compared to those in the budesonide group.</p> <p>Overall, those in the budesonide/formoterol group experienced 31 more asthma control days and 12 more undisturbed nights/patient-year vs those in the budesonide group (<i>P</i> value not reported).</p>
<p>Rabe et al³⁹</p> <p>Budesonide/formoterol 80/4.5 μg, 2 inhalations every evening and additional inhalations as needed via MDI</p> <p>vs</p> <p>budesonide 160 μg, 2 inhalations every evening via DPI and terbutaline 0.4 mg as needed</p> <p>There was a 14 to 18 day run-in period in which patients received</p>	<p>AC, DB, MC, PG, RCT</p> <p>Patients 11 to 79 years of age with an asthma diagnosis for ≥ 6 months, FEV₁ 60 to 100% predicted normal, >12% reversibility of baseline FEV₁ 15 minutes after terbutaline 1 mg inhalation, all patients had received an ICS 200 to 500 $\mu\text{g}/\text{day}$</p>	<p>N=697</p> <p>6 months</p>	<p>Primary: Morning PEF</p> <p>Secondary: FEV₁, evening PEF, as needed inhalations, as needed medication-free days, asthma symptom score, nighttime awakenings, symptom free days, asthma control days, and risk of exacerbation</p>	<p>Primary: Patients in the budesonide/formoterol group had greater improvements in morning PEF from baseline than those in the budesonide group and was maintained throughout the six month treatment period (34.5 vs 9.5 L/minute, respectively; <i>P</i><0.001).</p> <p>Secondary: Both treatment groups were associated with an increase in mean FEV₁, but those in the budesonide/formoterol group had statistically significant greater improvements compared to those receiving budesonide alone (<i>P</i><0.001).</p> <p>Patients in the budesonide/formoterol group also had greater improvements in evening PEF from baseline than those in the budesonide group.</p> <p>Patients in the budesonide/formoterol group had statistically significantly lower asthma symptom scores in comparison to those who were receiving</p>

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<p>budesonide 100 μg BID and terbutaline 0.5 mg as needed, both via DPI.</p>	<p>for ≥ 3 months at a constant dose for ≥ 30 days prior to study and were required to have had ≥ 7 inhalations of as-needed medication during the last 10 days of the run-in period but < 10 inhalations on any single day</p>			<p>budesonide ($P < 0.001$). There was also a statistically significant improvement in both symptom free days and asthma control-days observed in the budesonide/formoterol group vs those in the budesonide group ($P < 0.01$).</p> <p>Those in the budesonide/formoterol group had less utilization of as-needed medication, along with eight percent more as-needed medication-free days vs those in the budesonide group ($P < 0.001$).</p> <p>Patients in the budesonide/formoterol had a 54% lower risk in having an exacerbation in comparison to those in the budesonide group ($P = 0.0011$), as well as 90% fewer hospitalizations/emergency department treatments vs those in the budesonide group ($P = 0.026$).</p>
<p>Louis et al⁴⁰</p> <p>Budesonide/formoterol 160/4.5 μg, 1 inhalation BID with additional inhalations as needed via MDI</p> <p>vs</p> <p>conventional best practice (CBP) treatment (multiple controller therapies allowed, ICS and ICS/LABAs at any dose and add-on oral leukotriene antagonist or xanthenes if warranted)</p> <p>The CBP group was treated in a stepwise approach in accordance with the Global Initiative for Asthma guidelines.</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥ 12 years of age with an asthma diagnosis for > 3 months and prescribed ICS at a dose of ≥ 500 μg/day</p> <p>beclometasone dipropionate equivalent with or without other controller therapies, if a patient was using ICS monotherapy, they needed to use ≥ 3 inhalations of as-needed medication for symptom relief during the last 7 days before</p>	<p>N=908</p> <p>26 weeks</p>	<p>Primary: Time to first severe asthma exacerbation (defined as deterioration in asthma leading to hospitalization, emergency room visit, or equivalent) or oral steroid treatment for ≥ 3 days.</p> <p>Secondary: Number of severe asthma exacerbations, the mean use of as-needed medication (reliever medication) and prescribed asthma medications and scores on ACQ5, SATQ,</p>	<p>Primary: There was no difference in the time to first severe asthma exacerbation for patients treated with budesonide/formoterol compared to CBP ($P = 0.75$).</p> <p>Secondary: Only 2.7% of patients who received budesonide/formoterol and 4.1% of patients treated according to CBP experienced a severe asthma exacerbation during treatment. Twelve patients in the budesonide/formoterol group experienced a total of 14 exacerbations, and 19 patients in the CBP group experienced a total of 25 exacerbations (annual rate including all patients: 0.074 vs 0.13 per patient-year; $P = 0.09$).</p> <p>A similar percentage of patients in both groups had ≥ 1 day during which at least one dose of an as-needed medication was required (58.5 and 63.5% for budesonide/formoterol and CBP groups, respectively; P value not reported).</p> <p>The mean daily dose of inhaled steroid was significantly lower in the budesonide/formoterol group compared to the CBP group (482 vs 589 μg daily, $P < 0.0001$).</p> <p>In the budesonide/formoterol group, the mean ACQ5 score assessing symptom control and activity limitation during the treatment period, decreased by -0.30 compared to -0.17 in the CBP group ($P < 0.01$). Both</p>

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	enrolment.			groups showed similar overall treatment satisfaction (improvement in SATQ overall score) from enrolment to the end of the study (<i>P</i> value not reported).
<p>You-Ning et al⁴¹</p> <p>Fluticasone/salmeterol 125/25 μg, 2 inhalations BID via HFA MDI</p> <p>vs</p> <p>fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus</p>	<p>MC, OL, PG, RCT</p> <p>Patients 18 to 70 years of age with diagnosis of asthma, receiving stable doses of budesonide or beclomethasone up to 1,200 $\mu\text{g}/\text{day}$ or fluticasone up to 600 μg per/day for ≥ 1 month, or required therapy with ICSs, total score of ≥ 8 for daytime and nighttime symptoms and $\geq 15\%$ reversibility and 200 mL elevation in FEV₁ following albuterol</p>	<p>N=270</p> <p>4 weeks</p>	<p>Primary: Morning PEF</p> <p>Secondary: Rescue medication use, daytime and nighttime symptom scores, evening PEF, FEV₁ and patient self-evaluation of efficacy</p>	<p>Primary: Morning PEF improved significantly in both the fluticasone/salmeterol HFA and Diskus groups compared to baseline (<i>P</i><0.05), but the differences between groups was not significant (<i>P</i>>0.05).</p> <p>Secondary: All secondary endpoints improved significantly compared to baseline in both the fluticasone/salmeterol HFA and Diskus groups (<i>P</i><0.05), but the difference between groups was not significant for any secondary endpoint (<i>P</i>>0.05) except patient self-evaluation of efficacy at visit three which was significantly higher in the Diskus group compared to the HFA group (<i>P</i><0.05).</p>
<p>Chapman et al⁴²</p> <p>Fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus plus placebo</p> <p>vs</p>	<p>DB, DD, RCT</p> <p>Individuals 13 to 75 years of age with symptomatic asthma</p>	<p>N=371</p> <p>28 weeks</p>	<p>Primary: Change in PEFR</p> <p>Secondary: Mean daytime symptom score and FEV₁</p>	<p>Primary: Over weeks one to 12, PEFR was 43 L/minute for the combination therapy group and 36 L/minute for the concurrent therapy group respectively. The difference between the two treatment groups was 6 L/minute (CI, -13 to 0; <i>P</i>=0.114), which was within the predefined criteria for clinical equivalence.</p> <p>Secondary: Over weeks one to 12, 35% of the combination therapy group had a mean daytime symptom score of zero compared to 31% of the concurrent</p>

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fluticasone 250 μ g, 1 inhalation BID via Diskus plus salmeterol 50 μ g, 1 inhalations BID via Diskus				therapy group. No statistically significant difference in FEV ₁ between the combination and concurrent therapy groups was noticed (<i>P</i> value not reported).
Nelson et al ⁴³ Fluticasone/salmeterol 50/100, 50/250 or 50/500 μ g, 1 inhalation BID plus placebo vs salmeterol 50 μ g, 1 inhalation BID plus fluticasone 100, 250 or 500 μ g, 1 inhalation BID	MA (4 DB, DD, MC, RCTs) Individuals \geq 4 years of age diagnosed with asthma	N=1,375 All trials were 12 weeks in duration	Primary: Change from baseline in mean PEF over 12 weeks Secondary: Mean change in evening PEF and clinic FEV ₁ , median percentage of symptom-free days, nights or both, and rescue inhaler free	Primary: A significant advantage (5.4 L/minute) was seen for PEF in the combination therapy over the 12 week treatment period (<i>P</i> =0.006). Secondary: There was a difference in favor of the combination therapy in the mean difference in FEV ₁ (0.04 L) compared to the concurrent therapy (<i>P</i> =0.054). The difference was statistically significant (6.11 L/minute) in the mean evening PEF in favor of the combination therapy (<i>P</i> <0.001). There was no significant difference seen in the percentage of symptom-free and/or rescue inhaler free days and nights between treatment groups (<i>P</i> =0.165 and <i>P</i> =0.635).
Perrin et al ⁴⁴ Fluticasone/salmeterol 125/25 μ g, 2 inhalations BID vs fluticasone 125 μ g, 2 inhalations BID plus salmeterol 25 μ g, 2 inhalations BID At each visit, adherence data from each of the three inhalers were uploaded to a computer; therefore, adherence to	RCT Patients 16 to 65 years of age with a diagnosis of asthma currently taking an ICS at a stable dose with or without a separate LABA inhaler	N=111 24 weeks	Primary: Adherence during the final 6 week period (number of doses taken as a percentage of those prescribed) Secondary: Adherence in the first, second and third 6 week periods; percentage of days on which patients were fully adherent in each 6 week period; the proportion of patients who took >50, >80 or >90% of doses prescribed in each 6	Primary: During the final six weeks of therapy, the mean (SD) percent adherence was 73.7 (36.0), 76.7 (30.5) and 82.4% (24.5) for fluticasone, salmeterol and combination therapy. There was no significant difference between combination therapy and fluticasone (-8.7%; 95% CI, -10.6 to 3.3) or combination therapy and salmeterol (-5.6%; 95% CI, -16.4 to 5.1). Secondary: The point estimates of adherence were consistently higher for combination therapy compared to fluticasone or salmeterol in all four six week periods; however, the differences were not statistically significant (<i>P</i> values not reported). There were no significant differences between the different medications (fluticasone/salmeterol, fluticasone and salmeterol) when adherence was expressed as the percentage of days on which patients were fully adherent, taking the prescribed two doses BID. Throughout the study, patients were fully adherent about four days/week.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>the individual inhalers could be recorded.</p> <p>Adherence to the combination ICS/LABA inhaler was compared to the adherence to the fluticasone inhaler and to the salmeterol inhaler.</p>			<p>week period; overuse</p>	<p>The proportion of patients who took >50, >80 and >90% of medication as prescribed was not significantly different among the different medications, although the point estimates consistently favored the combination regimen (<i>P</i> values not reported).</p> <p>Extra doses of medication were taken on about one day/week, with no significant differences among the three medications. Likewise, when expressed as the mean number of extra doses, there was no significant difference among the three medications.</p>
<p>Marceau et al⁴⁵</p> <p>Fluticasone/salmeterol or budesonide/formoterol (all strengths)</p> <p>vs</p> <p>ICS (beclometasone, budesonide or fluticasone) plus a LABA (formoterol or salmeterol)</p>	<p>RETRO</p> <p>Individuals 16 to 44 years of age who have not been on combination or concurrent ICS and LABA therapy within the past year</p>	<p>N=5,118</p> <p>1 year</p>	<p>Primary: Number of prescription renewals during the first year of treatment</p> <p>Secondary: The rate of moderate to severe asthma exacerbations (defined as a filled prescription of an ICS, an emergency department visit or hospitalization for asthma) during the first year of treatment, and weekly number of doses of SABAs</p>	<p>Primary: An estimation of 44.2% of patients started on combination therapy and 51.5% of patients started on concurrent therapy did not renew their prescription during the first year of treatment (<i>P</i>=0.0001).</p> <p>The number of prescriptions filled on average during the first year after treatment initiation was 3.5 for combination therapy and 2.7 for concurrent therapy (<i>P</i> value not reported).</p> <p>Secondary: Concurrent users had more exacerbations (1.1 vs 0.7; <i>P</i><0.0001), emergency department visits (0.4 vs 0.2; <i>P</i><0.0001), hospitalizations (0.03 vs 0.01; <i>P</i>=0.78) and mean number of doses/week of SABAs (7.0 vs 5.7; <i>P</i><0.0001) compared to combination users.</p>
<p>Gappa et al⁴⁶</p> <p>Fluticasone/salmeterol 100/50 μg, 1 inhalation BID</p> <p>vs</p> <p>fluticasone 200 μg, 1</p>	<p>DB, DD, MC, PG, PRO, RCT</p> <p>Patients 4 to 16 years of age with symptomatic persistent seasonal or perennial asthma</p>	<p>N=441</p> <p>8 weeks</p>	<p>Primary: Change in morning PEF</p> <p>Secondary: Patient diaries for asthma symptoms, patient diaries for morning and evening PEF recordings,</p>	<p>Primary: Combination therapy was demonstrated to not be inferior to fluticasone with respect to the change in mean morning PEF after eight weeks of therapy compared to baseline (<i>P</i><0.0004). The mean increase in morning PEF was 30.4\pm34.1 and 16.7\pm35.8 L/minute in the two treatment groups.</p> <p>Secondary: Combination therapy resulted in significantly better asthma control and less frequent symptoms compared to fluticasone therapy. During the eight</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalation BID All patients received fluticasone 100 μ g BID during a 2 week run-in period.	and prior treatment with an ICS with continuous treatment with an ICS for ≥ 4 weeks, consent to change ICS treatment to BID inhalations of fluticasone 100 μ g and consent to no use of a SABA or anticholinergic on a regular basis		spirometry	weeks, combination therapy patients achieved an average of 3.4 ± 2.7 weeks of good asthma control, and had 8.0 to 8.7% more days without asthma symptoms or without use of SABA than the fluticasone therapy patients (<i>P</i> values not reported). After eight weeks, patients receiving combination therapy had no asthma symptoms and required no SABA rescue medication use on more than 60% days. Asthma symptoms scores during the night and day improved in both groups with no significant differences between them (<i>P</i> value not reported). PEF increased in both treatment groups with statistically “superior” results in the combination therapy group compared to the fluticasone group (<i>P</i> value not reported). The percentage of days with a peak flow variability $\geq 20\%$ was -4.7 ± 12.5 and -1.9 ± 12.5 for the combination therapy and monotherapy groups (-1.9 ; 95% CI, -4.1 to 0.25). Spirometry revealed a significantly larger increase in PEF after combination therapy (6.1 L/minute; 95% CI, 1.8 to 10.4), whereas FEV ₁ and FVC increased to a comparable extent in both treatment groups.
Vaessen-Verberne et al ⁴⁷ Fluticasone 200 μ g, BID vs fluticasone/salmeterol 100/50 μ g, BID All patients received fluticasone 100 μ g BID during a 4 week run-in period. A SABA was used for symptom relief during this period	DB, MC, PG, RCT Patients 6 to 16 years of age with asthma who are still symptomatic on conventional doses of ICSs	N=158 26 weeks	Primary: Percentage of symptom-free days during the last 10 weeks of treatment Secondary: Not reported	Primary: The percentage of symptom-free days did not differ between the two treatment groups in any of the treatment periods (zero to six, six to 16 and 16 to 26 weeks). The mean adjusted difference in symptom-free days between fluticasone and combination therapy during the last 10 weeks was 2.6% (95% CI, -8.1 to 13.4 ; <i>P</i> =0.63) in the per-protocol analysis and 0.4% (95% CI, -9.1 to 9.9 ; <i>P</i> =0.93) in the intent-to-treat analysis. Secondary: Not reported
Bateman et al ⁴⁸	DB, MC, PG, RCT	N=3,421	Primary:	Primary:

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<p>Fluticasone/salmeterol 100/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>fluticasone 100 μg, 1 inhalation BID via Diskus</p> <p>All patients “stepped up” every 12 weeks until asthma was totally controlled or the highest dose was reached (fluticasone/salmeterol 500/50 μg or fluticasone 500 μg BID).</p>	<p>Individuals ≥ 12 years of age, categorized into one of three strata based up previous corticosteroid use</p>	<p>12 months</p>	<p>Asthma control (minimal [ideally no] chronic symptoms, minimal [infrequent] exacerbations, no emergency visits, minimal [ideally no] use of as needed β_2-agonist, no limitations on activities including exercise, PEF $< 20\%$ [near] normal and minimal [or no] adverse effects from medication) symptoms and rescue albuterol use</p> <p>Secondary: Dose of ICS, and exacerbations</p>	<p>In the fluticasone/salmeterol group 71% of the patients achieved well controlled asthma compared to 65% in the fluticasone group (P value not reported).</p> <p>Compared to fluticasone, individuals in the fluticasone/salmeterol group were significantly faster to achieve asthma control ($P \leq 0.002$).</p> <p>Secondary: At a lower corticosteroid dose with fluticasone/salmeterol, control was achieved more rapidly than with fluticasone.</p> <p>There were a significantly lower amount of exacerbations requiring oral corticosteroids and or hospitalizations or emergency visits in the fluticasone/salmeterol group in each stratum ($P \leq 0.009$).</p>
<p>Bateman et al⁴⁹</p> <p>Fluticasone/salmeterol 100/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>fluticasone 250 μg, 1 inhalation BID via Diskus</p> <p>All patients were stabilized on fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus during OL treatment for 12 weeks</p>	<p>DB, MC, PG, RCT</p> <p>Patients 12 to 80 years of age with ≥ 6 month history of asthma treated with only a β_2-agonist over the last 6 months; patients had to have ≤ 10 pack year smoking history, FEV₁ 60 to 80% predicted, reversibility in lung function, combined daytime</p>	<p>N=484</p> <p>12 weeks</p>	<p>Primary: Mean morning PEF</p> <p>Secondary: Asthma control (minimal [ideally no] chronic symptoms, minimal [infrequent] exacerbations, no emergency visits, minimal [ideally no] use of as needed β_2-agonist, no limitations on activities including exercise, PEF $< 20\%$ [near] normal and minimal [or no] adverse</p>	<p>Primary: Patients in the fluticasone/salmeterol group maintained the improved PEF values achieved in the OL treatment period compared to those in the fluticasone group, whose PEF values decreased. The difference between the groups (63 L/minute) was statistically significant ($P < 0.001$).</p> <p>Secondary: The portion of patients with well controlled asthma remained higher in fluticasone/salmeterol group compared to the fluticasone group (P value not reported).</p> <p>The odds of a patient achieving total control of their asthma was 62% greater in fluticasone/salmeterol group compared to the fluticasone group ($P = 0.017$).</p> <p>Statistically significant difference in daytime symptom score, daytime and nighttime rescue use, percent symptom free and rescue-free days and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and were “stepping down” therapy.	and nighttime symptom scores of ≥ 2 on ≥ 4 of the last 7 days of the run-in period and no exacerbations in the run-in period		effects from medication) symptoms, and rescue albuterol use	nights were in favor of fluticasone/salmeterol ($P < 0.05$).
<p>Bateman et al⁵⁰</p> <p>Fluticasone/salmeterol 50/25 μg, 2 inhalations BID via HFA MDI and placebo via Diskus</p> <p>vs</p> <p>fluticasone/salmeterol 100/50 μg, 1 inhalation BID via Diskus and placebo via HFA MDI</p> <p>vs</p> <p>fluticasone 50 μg, 2 inhalations BID via CFC MDI and placebo via Diskus</p>	<p>DB, DD, PG, RCT</p> <p>Patients ≥ 12 years of age with diagnosis of reversible airway obstruction, smoking history of < 10 pack-years, using ICSs (beclomethasone, budesonide or flunisolide at a dose of 400 to 500 $\mu\text{g}/\text{day}$ or fluticasone 200 to 250 $\mu\text{g}/\text{day}$) for ≥ 4 weeks prior to randomization, mean morning PEF 50 to 85% of value measured after albuterol during the last 7 days of the run-in period, symptomatic for the last 7 days of the run-in period,</p>	<p>N=497</p> <p>12 weeks</p>	<p>Primary: Mean morning PEF</p> <p>Secondary: Evening PEF, daytime and nighttime symptom scores, albuterol use, and clinic FEV₁ values</p>	<p>Primary: Mean morning PEF values were equivalent between the fluticasone/salmeterol HFA and Diskus groups (P value not reported).</p> <p>There was a significant improvement in mean morning PEF values in the fluticasone/salmeterol HFA group compared to the fluticasone CFC group ($P < 0.001$). Comparisons were not made between the fluticasone/salmeterol Diskus and the fluticasone CFC groups.</p> <p>Secondary: Mean evening PEF improved in all three groups compared to baseline with the greatest improvements seen in the fluticasone/salmeterol HFA and Diskus groups, and the difference was significant in the fluticasone and salmeterol HFA group compared to the fluticasone CFC group ($P < 0.001$).</p> <p>The number of symptom free days and nights increased in all three treatment groups. The proportion of symptom free days and nights were similar in the fluticasone/salmeterol HFA and Diskus groups.</p> <p>The fluticasone/salmeterol HFA group reported significantly more symptom free days compared to the fluticasone CFC group ($P = 0.001$).</p> <p>The fluticasone/salmeterol HFA group reported more symptom free nights compared to the fluticasone CFC group, but this difference was not significant ($P = 0.063$).</p> <p>The increase in albuterol free days and nights was similar in the fluticasone/salmeterol HFA and Diskus groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	<p>taking albuterol ≤ 800 $\mu\text{g}/\text{day}$ and $\text{FEV}_1 > 50\%$ of predicted value</p>			<p>The increase in albuterol free days and nights was significantly higher in the fluticasone/salmeterol HFA group compared to the fluticasone CFC group ($P < 0.033$) for every assessment period except for weeks five through eight ($P = 0.093$).</p> <p>Clinic FEV_1 values improved in all three treatment groups and the differences between groups was not significant (P value not reported).</p>
<p>Pearlman et al⁵¹</p> <p>Fluticasone/salmeterol 44/21 μg, 2 inhalations BID via HFA MDI</p> <p>vs</p> <p>fluticasone 44 μg, 1 inhalation BID via CFC MDI</p> <p>vs</p> <p>salmeterol 21 μg, 1 inhalation BID via CFC MDI</p> <p>vs</p> <p>placebo HFA MDI</p> <p>Patients were stratified into 2 groups based on asthma therapy at baseline: Group 1-history of an ICS ≥ 3 months with no change in regimen for ≥ 1 month prior to screening</p>	<p>DB, PC, PG, RCT</p> <p>Patients ≥ 12 years of age diagnosed with asthma requiring pharmacotherapy over the last 6 months, FEV_1 40 to 85% of predicted value, $\geq 15\%$ increase in FEV_1 within 30 minutes of albuterol administration</p>	<p>N=360</p> <p>12 weeks</p>	<p>Primary: For fluticasone/salmeterol HFA vs fluticasone CFC: AUC of the 12-hour serial FEV_1 relative to baseline</p> <p>For fluticasone/salmeterol HFA vs salmeterol CFC: morning pre-dose FEV_1 at endpoint and the probability of patients remaining in the study without being withdrawn for worsening of asthma</p> <p>Secondary: Morning and evening PEF, patient-rated asthma symptom scores, albuterol use, nighttime awakenings requiring albuterol, and AQLQ scores</p>	<p>Primary: At week 12, the average percent change in serial FEV_1 compared to baseline was significantly greater for fluticasone/salmeterol HFA compared to fluticasone CFC, salmeterol CFC and placebo ($P \leq 0.007$).</p> <p>The AUC of the 12-hour serial FEV_1 was significantly higher on day one (baseline) and week 12 for the fluticasone/salmeterol HFA group compared to the fluticasone CFC and placebo groups ($P < 0.001$), and at week 12 only for the salmeterol CFC group ($P = 0.006$).</p> <p>There was a significant improvement in morning pre-dose FEV_1 from baseline in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups ($P \leq 0.0112$).</p> <p>There were significantly fewer patients withdrawn due to worsening of asthma in the fluticasone/salmeterol group compared to the salmeterol CFC and placebo groups ($P < 0.001$). The difference was not significant when comparing the fluticasone/salmeterol HFA group and the fluticasone CFC group (P value not reported).</p> <p>Secondary: There was a significant increase in mean change from baseline in morning and evening PEF in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups ($P \leq 0.006$).</p> <p>There was a significantly greater percentage of days without asthma symptoms in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups ($P < 0.001$).</p> <p>There was a significant decrease in nighttime awakenings in patients in</p>

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<p>at the following daily doses: beclomethasone 252 to 336 μg, triamcinolone 600 to 800 μg, flunisolide 1,000 μg, fluticasone 176 μg of MDI or 200 μg of DPI or budesonide 400 to 600 μg</p> <p>Group 2-β_2-agonist use for only for 1 week prior to screening (ineligible if treated with an ICS within last month)</p>				<p>the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups ($P \leq 0.007$).</p> <p>There was a significant reduction in the need for albuterol in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups ($P \leq 0.002$).</p> <p>There were no results reported for AQLQ.</p>
<p>Nathan et al⁵²</p> <p>Fluticasone/salmeterol 110/21 μg, 1 inhalation BID via HFA MDI</p> <p>vs</p> <p>fluticasone 110 μg, 1 inhalations BID via CFC MDI</p> <p>vs</p> <p>salmeterol 21 μg, 1 inhalation BID via CFC MDI</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, PG, RCT</p> <p>Patients ≥ 12 years of age diagnosed with asthma requiring pharmacotherapy over the last 6 months, FEV₁ 40 to 85% of predicted value, $\geq 15\%$ increase in FEV₁ within 30 minutes of albuterol administration, history of an ICS ≥ 3 months with no change in regimen for ≥ 1 month prior to screening at the following daily</p>	<p>N=365</p> <p>12 weeks</p>	<p>Primary:</p> <p>For fluticasone/salmeterol HFA vs fluticasone CFC: AUC of the 12-hour serial FEV₁ relative to baseline</p> <p>For fluticasone/salmeterol HFA vs salmeterol CFC: morning pre-dose FEV₁ at endpoint and the probability of patients remaining in the study without being withdrawn for worsening of asthma</p> <p>Secondary:</p> <p>Morning and evening PEF, asthma symptom scores, albuterol use, and nighttime</p>	<p>Primary:</p> <p>The AUC of the 12-hour serial FEV₁ was significantly higher on day one (baseline) and week 12 for the fluticasone/salmeterol HFA group compared to the fluticasone CFC and placebo groups ($P < 0.001$), and at week 12 when compared to the salmeterol CFC group ($P \leq 0.020$).</p> <p>There was a significantly greater improvement in morning pre-dose FEV₁ at endpoint in the fluticasone/salmeterol HFA group compared to the improvements in the fluticasone CFC and salmeterol CFC groups ($P \leq 0.001$). There was a significant decrease in morning pre-dose FEV₁ in patients in the placebo group ($P \leq 0.001$).</p> <p>Significantly fewer patients in the fluticasone/salmeterol HFA group withdrew due to worsening of asthma compared to the salmeterol CFC and placebo groups ($P < 0.001$). The difference was not significant when comparing the fluticasone/salmeterol HFA group and the fluticasone CFC group (P value not reported).</p> <p>Secondary:</p> <p>There was a significant increase in mean change from baseline in morning and evening PEF in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups ($P \leq 0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	<p>doses: beclomethasone 378 to 840 μg, triamcinolone 900 to 1,600 μg, flunisolide 1,250 to 2,000 μg, fluticasone 440 to 660 μg of MDI or 400 to 600 μg of DPI or budesonide 800 to 1,200 μg</p>		<p>awakenings requiring albuterol use</p>	<p>There was a significant improvement in asthma symptom scores in the fluticasone/salmeterol HFA group compared to the placebo group ($P<0.001$), but the difference when compared to the fluticasone CFC and the salmeterol CFC groups was not significant (P value not reported).</p> <p>There was a significant increase in the proportion of days with no asthma symptoms in the fluticasone/salmeterol HFA group compared to the placebo group ($P<0.001$), but the difference when compared to the fluticasone CFC and the salmeterol CFC groups was not significant (P value not reported).</p> <p>The number of nighttime awakenings decreased in the fluticasone/salmeterol HFA group and increased in the fluticasone CFC, salmeterol CFC and placebo groups, but only the difference between the fluticasone/salmeterol HFA and placebo groups was statistically significant ($P<0.001$).</p> <p>There was a significant reduction in the need for albuterol use in the fluticasone/salmeterol HFA group compared to the fluticasone CFC and placebo groups ($P\leq 0.005$), but there was no significant difference when compared to the salmeterol CFC group (P value not reported).</p>
<p>Lundback et al⁵³</p> <p>Fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>fluticasone 250 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>salmeterol 50 μg, 1 inhalation BID via Diskus</p>	<p>DB, PG, RCT</p> <p>Patients 18 to 70 years of age with mild to moderate asthma, symptoms ≥ 2 times/week and ≥ 1 of the following: airway hyper-responsiveness, diurnal variability in PEF $\geq 20\%$ in >3 days during the</p>	<p>N=282</p> <p>12 months</p>	<p>Primary: Number of patients requiring an increase in study medication</p> <p>Secondary: Number of patients experiencing ≥ 2 asthma exacerbations during 12 months, clinic lung function tests (FEV₁ and FVC), airway hyper-responsiveness, diary card data containing information on morning</p>	<p>Primary: Statistically significant lower percentage of patients in the fluticasone/salmeterol group required an increase in study medication compared to fluticasone and salmeterol monotherapy ($P<0.001$).</p> <p>Secondary: Statistically significant lower number of patients having ≥ 2 asthma exacerbations in the fluticasone/salmeterol group compared to the fluticasone monotherapy ($P<0.01$) and salmeterol monotherapy groups ($P<0.001$).</p> <p>Statistically significant improvement in morning PEF values in the fluticasone/salmeterol group compared to the fluticasone and salmeterol monotherapy groups ($P<0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	last 14 days of the run-in, $\geq 30\%$ difference between the highest and second highest PEF reading during any 7 days of the run-in or reversible increase of $\geq 15\%$ in FEV ₁ or PEF after β_2 -agonist administration		PEF, rescue medication use, and daytime and nighttime asthma symptom scores	<p>Statistically significant improvement in FEV₁ ($P < 0.001$) and FVC ($P < 0.05$) from baseline in the fluticasone/salmeterol group compared to the salmeterol monotherapy group.</p> <p>No statistically significant difference in FEV₁ or FVC from baseline in the fluticasone/salmeterol group compared to the fluticasone monotherapy group (P value not reported).</p> <p>Statistically significant improvement in airway hyper-responsiveness in the fluticasone/salmeterol group compared to the fluticasone monotherapy ($P < 0.05$) and salmeterol monotherapy groups ($P < 0.001$).</p> <p>Statistically significant increase in symptom-free days in the fluticasone/salmeterol group and the fluticasone monotherapy group than in the salmeterol monotherapy group ($P < 0.05$).</p> <p>Statistically significant increase in symptom-free nights in the fluticasone/salmeterol group and the fluticasone monotherapy group than in the salmeterol monotherapy group ($P < 0.001$).</p> <p>Statistically significant increase in rescue-medication-free days in the fluticasone/salmeterol group and the fluticasone monotherapy group compared to the salmeterol group ($P < 0.05$).</p> <p>Rescue-medication-free nights was 100% for all treatment groups.</p>
<p>Nelson et al⁵⁴</p> <p>Fluticasone/salmeterol 88/42 μg, 1 inhalation BID via HFA MDI</p> <p>vs</p> <p>fluticasone 88 μg, 1 inhalation BID via CFC MDI</p>	<p>DB, MC, PG, RCT</p> <p>Patients diagnosed with persistent asthma uncontrolled with an as-needed SABA alone</p>	<p>N=283</p> <p>12 weeks</p>	<p>Primary: Area under the FEV₁ curve relative to baseline, withdrawal due to asthma exacerbation, and morning and evening PEF</p> <p>Secondary: Not reported</p>	<p>Primary: Morning pre-dose FEV₁ was significantly improved in the fluticasone/salmeterol HFA group compared to the fluticasone CFC and salmeterol CFC groups ($P \leq 0.016$).</p> <p>Fewer patients in the fluticasone/salmeterol HFA group withdrew due to worsening of asthma compared to the fluticasone CFC and salmeterol CFC groups ($P = 0.024$).</p> <p>Morning and evening PEF values were significantly increased in the fluticasone/salmeterol HFA group compared to the fluticasone CFC and salmeterol CFC groups at endpoint ($P \leq 0.002$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs salmeterol 42 μ g, 1 inhalation BID via CFC MDI				Secondary: Not reported
Postma et al ⁵⁵ Fluticasone/salmeterol 100/50 μ g, 1 inhalation BID vs ciclesonide 160 μ g, 1 inhalation daily in the afternoon vs placebo No ICS, LABA OR other than study medications were permitted for two months prior to randomization and the 12-month study period.	DB, DD, PC, PG, MC, RCT Patients aged 12 to 75 years with a diagnosis of mild persistent asthma (FEV ₁ \geq 80% predicted four hours after rescue medication use (only short-acting b-agonists as required for two months before the start of the study) and randomized to treatment if after a two-week run-in period, they had an FEV ₁ \leq 80% predicted, reversible airway obstruction (change in FEV ₁ \leq 12% or \geq 200 mL after salbutamol inhalation, no nocturnal asthma symptoms, and a total daytime asthma symptom	N=657 52 weeks	Primary: Time to the first severe asthma exacerbation Secondary: Percentage of asthma symptom-free days, asthma symptom scores, rescue medication use, rescue medication-free days, FEV ₁ , PEF, AQLQ	Primary: The time to the first severe asthma exacerbation was significantly prolonged with combination therapy compared to placebo (P=0.0002) but there was no difference between combination therapy and ciclesonide (P=0.24). Secondary: Patients in the ciclesonide and combination treatment groups experienced significantly fewer poorly controlled asthma days than placebo-treated patients (0.8 and 0.6% vs 1.7%, respectively; P \leq 0.0016, for both); however, there was no difference between the two treatments (P=0.14). The median percentages of asthma symptom-free days were significantly higher with ciclesonide and combination treatment compared to placebo (91.5 and 93.6% vs 85.2%, respectively; P \leq 0.001), but there were no significant differences between the treatment groups. (P>0.05). Both active treatments provided significantly more asthma symptom-free days than placebo (P \leq .008, one-sided), rescue medication-free days (P=.0005), and days with asthma control (P \leq 0.003), without significant differences between the active treatment groups. Both ciclesonide and combination therapy provided significant reductions from baseline in asthma symptom scores (-0.31 and -0.32 vs -0.21 points, respectively; P \leq 0.0015). There was no difference in the scores between the active treatments (P=0.75). Patients receiving combination treatment had a significant improvement from baseline in FEV ₁ compared to placebo (0.127 vs -0.022 L; P<0.001), but not compared to the ciclesonide group (P=0.15). Patients receiving combination treatment had a significant improvement

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	score of 2 to 10			<p>from baseline in morning PEF compared to placebo (30.16 vs -9.73 L/min; $P<0.0001$), but not compared to the ciclesonide group ($P=0.80$).</p> <p>Patients receiving combination treatment had a significant improvement from baseline in evening PEF compared to placebo (15.26 vs -15.56 L/min; $P<0.0001$), but not compared to the ciclesonide group ($P=0.86$).</p> <p>Overall, AQLQ scores increased significantly more in both the combination and ciclesonide treatment groups compared to placebo ($P\leq 0.0017$ for both). Compared to combination treatment, ciclesonide was associated with higher AQLQ scores over the course of treatment ($P<0.0001$).</p>
<p>Nguyen et al⁵⁶</p> <p>Fluticasone/salmeterol 100/50 or 250/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>usual care control group (all patients received ICSs at some point during the study)</p>	<p>DB, RCT</p> <p>Pediatric patients 4 to 17 years of age with asthma, parent reported emergency room visits ≥ 5 in the past 2 years or 2 to 3 in the past 2 months, enrolled in Medicaid in Tennessee, Mississippi or Arkansas</p>	<p>N=39</p> <p>12 months</p>	<p>Primary: Reducing the number of emergency department visits and hospitalizations in minority inner-city children</p> <p>Secondary: Not reported</p>	<p>Primary: Statistically significant decrease in the number of emergency department visit/year in the study group compared to the control group (1.2 to 0.8; $P=0.017$).</p> <p>The risk of experiencing at least one hospitalization was reduced by 43% in the treatment group compared to the placebo group (risk ratio, 0.57; 95% CI, 0.19 to 1.71; $P=0.31$).</p> <p>The risk of experiencing an asthma exacerbation was reduced by 23% in the treatment group compared to the placebo group ($P=0.09$).</p> <p>Secondary: Not reported</p>
<p>Ringdal et al⁵⁷</p> <p>Fluticasone/salmeterol 100/50 μg, 1 inhalation BID plus oral placebo</p> <p>vs</p> <p>fluticasone 100 μg, BID plus montelukast 10 mg,</p>	<p>DB, DD, MC, PG RCT</p> <p>Patients 14 to 79 years of age with a diagnosis of asthma, history of receiving ICSs for ≥ 4 weeks prior to randomization,</p>	<p>N=806</p> <p>14 weeks</p>	<p>Primary: Mean morning PEF value</p> <p>Secondary: Evening PEF values, β_2-agonist use, daytime and nighttime symptom scores, changes in asthma medications,</p>	<p>Primary: Statistically significant improvement in morning PEF values in the fluticasone/ salmeterol group compared to the fluticasone plus montelukast group (361 vs 191 L/minute; $P<0.05$).</p> <p>Secondary: Statistically significant improvement in FEV₁ values in the fluticasone/ salmeterol group compared to the fluticasone plus montelukast group (mean treatment difference, 0.11 L; $P<0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD	reversible airway obstruction, $\geq 15\%$ increase in FEV ₁ after β_2 -agonist use, mean morning PEF 50 to 85% predicted, cumulative symptom score ≥ 8 during last 7 days of run-in period and symptoms on ≥ 4 of last 7 days of run-in		FEV ₁ , incidence and severity of asthma exacerbations, patient assessment of satisfaction with treatment, and physician assessment of effectiveness of treatment	<p>The fluticasone/salmeterol group was significantly more likely to have a symptom-free day compared to the fluticasone plus montelukast group (OR, 1.32; 95% CI, 1.05 to 1.65; $P < 0.05$).</p> <p>The fluticasone/salmeterol group was significantly more likely to have a rescue free day compared to the fluticasone plus montelukast group (OR, 1.29; 95% CI, 1.02 to 1.63; $P = 0.03$), but rescue-free nights did not reach statistical significance.</p> <p>A significantly lower number of patients in the fluticasone/salmeterol group had an asthma exacerbation compared to patients in the fluticasone plus montelukast group (9.6 vs 14.6%; $P < 0.05$), but no significant difference between the groups in percentage of patients having moderate or severe asthma exacerbation ($P = 0.07$) was noted.</p> <p>The time to first exacerbation was longer in the fluticasone/salmeterol group compared to the fluticasone plus montelukast group ($P < 0.05$).</p> <p>Patient and physician satisfaction and assessment of treatment was higher in the fluticasone/salmeterol group compared to the fluticasone plus montelukast group ($P < 0.05$).</p>
Lemanske et al ⁵⁸ Fluticasone 250 μg , BID (ICS step up therapy) vs fluticasone/salmeterol 100/50 μg , BID (LABA step up therapy) vs fluticasone 100 μg BID plus montelukast 5 or 10 mg/day (LTRA step up	DB, RCT, XO Patients 6 to 17 years of age with mild to moderate asthma diagnosed by a physician, the ability to perform reproducible spirometry, an FEV ₁ $\geq 60\%$ before bronchodilation, an increase in the FEV ₁ $\geq 12\%$ (bronchodilator reversibility) or a	N=182 48 weeks	Primary: Differential response to each of the 3 step up therapies on the basis of fixed threshold criteria for the following 3 asthma-control measures: the need for treatment with oral prednisone for acute exacerbations, the number of asthma control days and FEV ₁ Secondary: Not reported	Primary: <i>Differential response to the three step up therapies</i> A differential response occurred in 161/165 (98%) patients. The percentage of asthma control days differed according to season in all study groups, ranging from 71 to 79% in the winter and summer months. Asthma exacerbations were most frequent during winter months. The average FEV ₁ varied by less than one percent across seasons. In pairwise comparisons, the proportion of patients who had a better response to LABA step up therapy was higher than the proportion with a better response to LTRA step up therapy (52 vs 34%; $P = 0.02$), and the proportion with a better response to LABA step up therapy was higher than the proportion of with a better response to ICS step up therapy (54 vs 32%; $P = 0.004$), whereas the response to LTRA and ICS step up therapies were similar.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>therapy)</p> <p>All patients received fluticasone 100 μg BID during a 2 to 8 week run-in period.</p> <p>A treatment period was ranked as better than another if the total amount of prednisone received during treatment was \leq180 mg, if the number of annualized asthma control days during the final 12 weeks of the period was increased by \geq31 days or if the FEV₁ at the end of the period was \geq5% higher.</p> <p>If the prednisone threshold was met, the number of asthma control days and FEV₁ were ignored.</p> <p>If the threshold for asthma control days was met, the FEV₁ was ignored.</p> <p>Otherwise the order of response was determined by the FEV₁.</p>	<p>methacholine provocation concentration causing a 20% fall in the FEV₁ of \leq12.5 mg/mL</p>			<p>The primary outcome of the trial, a three-way comparison of step-up therapy with the use of rank-ordered logistic regression, predicted that the response to LABA step up was significantly more likely to be the best response, as compared with the response to LTRA step up (relative probability, 1.6; 95% CI, 1.1 to 2.3; $P=0.004$) and the response to ICS step up therapy (relative probability, 1.7; 95% CI, 1.2 to 2.4; $P=0.002$).</p> <p>Secondary: Not reported</p>
Dahl et al ¹	DB, DD, MC, PG	N=1,769	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>budesonide/formoterol 200/6 μg, 2 inhalations BID via DPI</p>	<p>RCT</p> <p>Patients >18 years of age with a documented clinical history of asthma for ≥ 6 months, receiving 1,000 to 2,000 $\mu\text{g/day}$ beclomethasone or equivalent, reversible increase of >12%, 15 minutes after receiving salbutamol, asthma symptom score of ≥ 2 on ≥ 4 of 7 days of the run-in period</p>	<p>24 weeks</p>	<p>Asthma exacerbation rate</p> <p>Secondary: Morning PEF, FEV₁, percentage of symptom-free days, percentage of symptom-free nights, and percentage of rescue-free days</p>	<p>The adjusted mean rate of all exacerbations over 24 weeks was similar in both treatment groups (2.69 vs 2.79; $P=0.571$). The rate of moderate to severe exacerbations between the treatment groups became significant favoring the fluticasone/salmeterol group (0.105) when compared to the budesonide/formoterol group (0.244) at week 17 to 24 ($P=0.006$).</p> <p>Fluticasone/salmeterol was associated with a 57% reduction in the rate of moderate to severe exacerbations compared to budesonide/formoterol.</p> <p>Secondary: The change from baseline in morning PEF was not statistically different between fluticasone/salmeterol (41.8 L/minute) and budesonide/formoterol (41.4 L/minute; P value not reported).</p> <p>The change from baseline in FEV₁ was not statistically different between fluticasone/salmeterol (0.29 L) and budesonide/formoterol (0.27 L; P value not reported).</p> <p>The change from baseline in percent symptom-free days, nights and rescue free days was not statistically different between fluticasone/salmeterol (63, 85 and 82%) and budesonide/formoterol (60, 86 and 81%; P values not reported).</p> <p>The number of patients who achieved a well controlled week of asthma symptoms was 70% in both treatment groups; the difference was not significant ($P=0.391$).</p> <p>Both treatments were shown to be safe and well tolerated, and the incidence of adverse events was similar in both groups. The proportion of patients with at least one side effect that started during treatment was 55% in the fluticasone/salmeterol group and 54% in the budesonide/formoterol group. One percent of patients in each group reported oral candidiasis; overall only one adverse event was thought to be related to the medications and was hoarseness/dysphonia in the budesonide/formoterol group.</p>
<p>Bousquet et al⁸</p>	<p>DB, MC, PG, RCT</p>	<p>N=2,309</p>	<p>Primary: Time to first severe</p>	<p>Primary: The time to first severe exacerbation was not statistically different between</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Fluticasone/salmeterol 500/50 μg, 1 inhalation BID via Diskus and terbutaline as needed</p> <p>vs</p> <p>budesonide/formoterol 160/4.5 μg, 2 inhalations BID and as needed via DPI</p>	<p>Patients \geq12 years of age with symptomatic asthma, FEV₁ \geq50%, and had experienced an asthma exacerbation in the previous year</p>	<p>6 months</p>	<p>exacerbation (defined as asthma deterioration leading to hospitalization or emergency room visit or use of oral corticosteroids for \geq3 days)</p> <p>Secondary: Rate of severe exacerbations, risk of first hospitalization, rate of hospitalization, FEV₁, morning and evening PEF, as needed medication utilization, asthma control days, symptom free days, and safety</p>	<p>the treatment groups (HR, 0.82; <i>P</i>=0.12).</p> <p>Secondary: There was a 21% reduction in the overall exacerbation rate in the budesonide/formoterol group compared with the fluticasone/salmeterol group (25 vs 31 events/100 patients/year). The difference between groups was significant (<i>P</i>=0.039).</p> <p>The risk of hospitalization or emergency room visit was decreased in the budesonide/formoterol group when compared to the fluticasone/salmeterol group (HR, 0.64; <i>P</i>=0.031).</p> <p>There was a 31% reduction in the rate of hospitalization with budesonide/formoterol compared to fluticasone/salmeterol (9 vs 13 events/100 patients/year; <i>P</i>=0.046).</p> <p>FEV₁ increased in both groups from 2.29 to 2.52 L in the budesonide/formoterol group and from 2.70 to 2.49 L in the fluticasone/salmeterol group. There was no difference between the treatments (<i>P</i> value not reported).</p> <p>Morning and evening PEF scores improved in both treatment groups (for budesonide/formoterol there was an increase from 330.1 to 359.5 L/minute in the morning PEF and an increase from 336.7 to 362.3 in evening PEF; for fluticasone/salmeterol there was an increase from 329.0 to 359.4 in the morning PEF and an increase from 337.7 to 361.7 in the evening PEF; a difference that was not statistically significant (morning; <i>P</i>=0.67, evening; <i>P</i>=0.42 evening).</p> <p>Use of high number as needed medication inhalations of >4, >6 and >8 inhalations/day was reported in 29, 13 and 4% of patients using the fluticasone/salmeterol treatment and in 27, 9 and 3% using the budesonide/formoterol treatment. The differences were not significant (<i>P</i>=0.36).</p> <p>Asthma control days increased in both treatment groups from 6.3 and 5.8% at baseline to 44.0 and 44.9% in the budesonide/formoterol and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>fluticasone/salmeterol groups respectively. The difference was not statistically significant ($P=0.37$).</p> <p>Symptom free days improved from 10.7 and 11.2 at baseline to 47.2 and 48.1 in the budesonide/formoterol and fluticasone/salmeterol groups respectively. The difference was not statistically significant ($P=0.73$).</p> <p>Adverse events were reported in 39 and 40% of patients in the budesonide/formoterol and fluticasone/salmeterol groups respectively. Serious adverse events were three percent in both groups. There were 11 and 20 patients who discontinued the study due to adverse events in the budesonide/formoterol and fluticasone/salmeterol groups respectively. One death occurred in the study due to typhoid fever; however, it was not linked to the study medications.</p>
<p>FitzGerald et al⁹</p> <p>Fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>budesonide/formoterol 200/6 μg, 2 inhalations BID via DPI</p>	<p>DB, DD, RCT</p> <p>Individuals 18 to 70 years of age, with an documented clinical history of asthma and an FEV₁ between 60 to 90% of projected normal</p>	<p>N=706</p> <p>1 year</p>	<p>Primary: Percentage of symptom-free days</p> <p>Secondary: Daily asthma symptom scores, morning PEF, percentage of days free of rescue medication use, and nighttime awakenings due to asthma</p>	<p>Primary: The percentage of symptom-free days was higher with fluticasone/salmeterol compared to budesonide/formoterol (58.8 vs 52.1%; $P=0.034$).</p> <p>The percentage of symptom-free days was significantly higher with fluticasone/salmeterol compared to budesonide/formoterol during weeks five through 52 (73.8 vs 64.9%; $P=0.030$).</p> <p>Secondary: In the fluticasone/salmeterol group there was a significant difference in the adjusted annual mean exacerbation rate compared to the budesonide/formoterol group (0.18 vs 0.33; $P=0.008$).</p> <p>The median value for the percentage of days free of rescue medication over weeks five through 52 was 94.5% in the fluticasone/salmeterol group compared to 90.7% in the budesonide/formoterol group ($P=0.008$).</p> <p>Over the 52-week treatment period the mean morning PEF was significantly higher in the fluticasone/salmeterol group compared to the budesonide/formoterol group (400.1 vs 390.6 L/minute; $P=0.006$).</p>
<p>Price et al¹⁰</p>	<p>DB, DD, MC, PG,</p>	<p>N=688</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus-FD</p> <p>vs</p> <p>budesonide/formoterol 200/6 μg, 2 inhalations BID via DPI-AMD</p> <p>During weeks 1 to 4, patients received either 1 inhalation of fluticasone/salmeterol 250/50 μg BID or 2 inhalations of budesonide/formoterol 200/6 μg and during weeks 5 to 52, those who met the criteria, received budesonide/formoterol-AMD or fluticasone/salmeterol-FD.</p>	<p>RCT</p> <p>Outpatients 18 to 70 years of age, with a clinical asthma history, an FEV₁ 60 to 90% predicted normal, had received an ICS dose equal to 200 to 500 $\mu\text{g}/\text{day}$ of beclomethasone and LABA, or an ICS alone at dose equal to >500 to 1,000 μg beclomethasone (≥ 12 weeks prior to enrollment)</p>	<p>1 year</p>	<p>Symptom-free days (defined as symptom score of zero in a 24-hour period)</p> <p>Secondary: Rate of exacerbations</p>	<p>Patients in the fluticasone/salmeterol group had a significantly greater percentage of symptom-free days (58.8%) over the entire year, compared to patients in the budesonide/formoterol group (52.1%; $P=0.034$).</p> <p>Secondary: The adjusted annual mean exacerbation rate was also significantly lower in the fluticasone/salmeterol group compared to the budesonide/formoterol group (47%; $P=0.008$)</p>
<p>Ringdal et al¹¹</p> <p>Fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>budesonide 800 μg, 1 inhalation BID via DPI and formoterol 12 μg, 1 inhalation BID via DPI</p>	<p>DB, DD, PG, RCT</p> <p>Patients 16 to 75 years of age with a clinical history of reversible airway obstruction, symptomatic on 1,000 to 1,600 $\mu\text{g}/\text{day}$ of budesonide, beclomethasone or flunisolide, or 500 to 800 $\mu\text{g}/\text{day}$</p>	<p>N=428</p> <p>12 weeks</p>	<p>Primary: Mean morning PEF (during week 12 of treatment)</p> <p>Secondary: Morning and evening PEF, day and nighttime symptom scores, nighttime awakenings, FEV₁, rate and severity of exacerbations, and use of rescue medication, withdrawals</p>	<p>Primary: Patients in the per-protocol population had an increase in mean morning PEF of 343 to 386 L/minute with fluticasone/salmeterol compared to an increase of 348 to 389 L/minute observed with budesonide/formoterol (-3.2 L/minute mean difference; 95% CI, -15.0 to 8.6; $P=0.593$).</p> <p>Similar results in mean morning PEF were seen in the intent-to-treat population for both treatment groups.</p> <p>Secondary: The mean rate of exacerbation/patient/84 days of treatment was significantly lower in the fluticasone/salmeterol group in comparison to the budesonide/formoterol group with a risk reduction of 36% (0.472 vs 0.735, respectively; 95% CI, 0.51 to 0.80; $P<0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	of fluticasone, FEV ₁ 50 to 85%, increased symptom scores or reliever use		from study	<p>Over the entire treatment period, patients in the fluticasone/salmeterol group had a statistically significant greater percentage of nights with no awakenings, without symptoms and a symptom score of <2 in comparison to those in the budesonide/formoterol group ($P=0.02$, $P=0.04$ and $P=0.03$, respectively).</p> <p>There was no significant difference in morning and evening PEF, clinic-measured FEV₁, improvement in day-time symptoms and use of relief medication (salbutamol) between the two treatment groups.</p>
<p>Busse et al¹²</p> <p><u>Treatment period I:</u> Fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>budesonide/formoterol 160/4.5 μg, 2 inhalations BID via MDI (FD)</p> <p><u>Treatment period II:</u> fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>budesonide/formoterol 160/4.5 μg, 2 inhalations BID via MDI (FD)</p> <p>vs</p> <p>budesonide/formoterol</p>	<p>MC, OL, RCT,</p> <p>Patients ≥ 12 years of age with an asthma diagnosis for ≥ 6 months and who are in stable condition, required to have a prebronchodilator FEV₁ $\geq 50\%$ of predicted normal and to have been maintained on a daily medium dose ICS or ICS/LABA for ≥ 12 weeks before screening</p>	<p>N=1,225</p> <p>Treatment Period I: 1 month</p> <p>Treatment Period II: 6 months</p>	<p>Primary: Number of exacerbations/patient-treatment year, percentage of patients with ≥ 1 exacerbations, And time from first dose to first exacerbation</p> <p>Secondary: Predose FEV₁, morning PEF, morning and evening asthma symptom scores, nighttime awakenings, daily rescue medication use, average daily symptom scores, symptom-free days, rescue medication-free days, and safety</p>	<p>Primary: There was no significant difference seen in the treatment groups and the time to first exacerbation (P value not reported).</p> <p>There was no significant difference seen in the treatment groups and the percentage of patients with at least one exacerbation, for the AMD budesonide/formoterol group the percentage was 8.0%, 8.8% in the FD budesonide/formoterol group and 9.2% in the fluticasone/salmeterol group (P value not reported).</p> <p>There was no significant difference seen in the treatment groups and the total number of exacerbations/patient treatment year, for the AMD budesonide/formoterol group the value was 0.196, 0.240 in the FD budesonide/formoterol group and 0.189 in the fluticasone/salmeterol group (P value not reported).</p> <p>Secondary: No statistically significant differences were seen in predose FEV₁, for the AMD budesonide/formoterol group the change was 0.13 L, 0.15 L in the FD budesonide/formoterol group and 0.16 L in the fluticasone/salmeterol group (P value not reported).</p> <p>No statistically significant differences were seen in morning PEF, for the AMD budesonide/formoterol group the change was 34.73 L/minute, 30.86 L/minute in the FD budesonide/formoterol group and 33.59 L/minute in the fluticasone/salmeterol group (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
160/4.5 μg AMD (adjustable from 2 inhalations BID to 2 inhalations QD or 4 inhalations BID all via Diskus)				<p>No statistically significant differences were seen in morning and evening asthma symptom scores, for the AMD budesonide/formoterol group the change was -0.39, for the FD budesonide/formoterol group the score was -0.37 and -0.35 L in the fluticasone/salmeterol group (<i>P</i> value not reported).</p> <p>No statistically significant differences were seen in nighttime awakenings. For the adjustable dose budesonide/formoterol group the percent change was 10.03%, 10.02% in the FD budesonide/formoterol group and 7.73% in the fluticasone/salmeterol group (<i>P</i> value not reported).</p> <p>No statistically significant differences were seen in the percentage of symptom-free days, for the AMD budesonide/formoterol group the percent change was 26.59%, 25.80% in the FD budesonide/formoterol group and 25.39% in the fluticasone/salmeterol group (<i>P</i> value not reported).</p> <p>No statistically significant differences were seen in the percentage of rescue medication-free days, for the AMD budesonide/formoterol group the percent change was 41.84%, 41.24% in the FD budesonide/formoterol group and 38.85% in the fluticasone/salmeterol group (<i>P</i> value not reported).</p> <p>All treatment groups were well tolerated. Adverse events were in general mild (56.1%) or moderate (38.4%), and no study medication adverse events were considered serious.</p>
<p>Kuna et al¹³</p> <p>Fluticasone/salmeterol 125/25 μg, 2 inhalations BID</p> <p>vs</p> <p>budesonide/formoterol 320/9 μg, 1 inhalation BID</p> <p>vs</p>	<p>DB, DD, PG, RCT</p> <p>Patients ≥ 12 years of age with an asthma diagnosis ≥ 6 months, using an ICS ≥ 3 months, FEV₁ $\geq 50\%$ predicted normal, and $\geq 12\%$ reversibility following terbutaline and ≥ 1</p>	<p>N=3,335</p> <p>6 months</p>	<p>Primary: Time to first severe exacerbation (defined as asthma deterioration resulting in hospitalization or emergency room visit or the need for oral steroids ≥ 3 days)</p> <p>Secondary: Exacerbation rates, total number of severe</p>	<p>Primary: The budesonide/formoterol 160/4.5 μg group prolonged the time to first severe exacerbation when compared to the fluticasone/salmeterol (<i>P</i>=0.0034) and budesonide/formoterol 320/9 μg groups (<i>P</i>=0.023). There was a 33% reduction in the HR for a first severe exacerbation with the budesonide/formoterol 160/4.5 μg group compared with the fluticasone/salmeterol group (<i>P</i>=0.003), and a 26% reduction when compared to the budesonide/formoterol 320/9 μg group (<i>P</i>=0.026).</p> <p>Secondary: Exacerbation rates were 19, 16 and 12 events/100 patients/six months for the fluticasone/salmeterol group, the budesonide/formoterol 320/9 μg group and the budesonide/formoterol 160/4.5 μg group. The difference</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>budesonide/formoterol 160/4.5 μg, 1 inhalation BID and additional inhalations as needed</p> <p>Both FD treatment groups also had terbutaline as an as needed reliever medication.</p>	<p>asthma exacerbation in previous 1 to 12 months</p>		<p>exacerbations, number of patients having ≥ 1 hospitalization, number of mild exacerbation days, asthma symptom total score, morning and evening PEF, FEV₁, asthma symptom score, asthma induced night-awakenings, symptom-free days, as-needed medication free days, asthma-control days, number of mild exacerbations (defined as a day with any of one the following: morning PEF $\geq 20\%$ below baseline, daily as-needed medication use ≥ 2 inhalations or a night with asthma-related awakenings), and safety</p>	<p>between the budesonide/formoterol 160/4.5 μg group, the fluticasone/salmeterol group ($P < 0.001$) and the budesonide/formoterol 320/9 μg group ($P = 0.0048$) were statistically significant. However the difference between the fluticasone/salmeterol group and the budesonide/formoterol 320/9 μg group was not statistically significant ($P = 0.1$).</p> <p>The total number of severe exacerbations were 208, 173 and 125 in the fluticasone/salmeterol, budesonide/formoterol 320/9 μg and budesonide/formoterol 160/4.5 μg groups, respectively (P value not reported).</p> <p>The percentage of patients having at least one hospitalizations/emergency room visit was 6, 5 and 4% in the fluticasone/salmeterol, budesonide/formoterol 320/9 μg and budesonide/formoterol 160/4.5 μg groups, respectively. The difference was significant between the budesonide/formoterol 160/4.5 μg group and the fluticasone/salmeterol group ($P = 0.047$), but not between the two budesonide/formoterol groups or between the budesonide/formoterol 320/9 μg and fluticasone/salmeterol groups ($P = 0.066$).</p> <p>There were no significant differences seen between the three treatment groups in the number of mild exacerbation days. Overall 59, 63 and 61% in the fluticasone/salmeterol group, the budesonide/formoterol 320/9 μg group and the budesonide/formoterol 160/4.5 μg group experienced a mild exacerbation (P value not reported).</p> <p>There were no significant differences between all three treatment groups in asthma symptom total score (1.03, 1.07 and 1.06), percentage of symptom-free days (46.0, 44.6 and 44.2%), percentage of asthma-control days (43.7, 42.2 and 41.3%), percentage of night-time awakenings (14.0, 14.6 and 14.1%), total number of inhalations/day (0.96, 1.05 and 1.02) for the fluticasone/salmeterol, the budesonide/formoterol 320/9 μg and the budesonide/formoterol 160/4.5 μg groups, respectively (P values not reported).</p> <p>There were no significant differences found between all three treatment</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>groups in FEV₁ (2.67, 2.66 and 2.69 L), morning PEF (367, 362 and 363 L/minute), evening PEF (370, 366 and 368 L/minute) for the fluticasone/salmeterol, the budesonide/formoterol 320/9 μg and the budesonide/formoterol 160/4.5 μg groups, respectively (<i>P</i> values not reported).</p> <p>All three treatment groups reported no significant differences in the number or severity of adverse events. The most frequently reported adverse events were upper respiratory tract infection, pharyngitis and nasopharyngitis.</p>
<p>Aalbers et al¹⁴</p> <p>Fluticasone/salmeterol 250/50 μg, 1 inhalation BID via Diskus-FD</p> <p>vs</p> <p>budesonide/formoterol 160/4.5 μg, 2 inhalations BID via DPI-AMD</p> <p>vs</p> <p>budesonide/formoterol 160/4.5 μg, 2 inhalations BID via DPI-FD</p> <p>During a 4 week DB period, the budesonide/formoterol AMD and FD groups received 2 inhalations BID, and those in the fluticasone/salmeterol group received 1 inhalation BID.</p>	<p>DB (4 weeks), ES (6 months), OL</p> <p>Patients with moderate-severe asthma, mean symptom score 1.5, mean FEV₁ 84% predicted, mean ICS dose 735 μg/day</p>	<p>N=658</p> <p>4 week DB period plus a 6 month OL extension</p>	<p>Primary: Odds of achieving a WCAW</p> <p>Secondary: Exacerbation rate and use of reliever medication</p>	<p>Primary: There was no difference in the OR pertaining to WCAW observed in the FD treatment groups (<i>P</i> value not reported).</p> <p>There was a significant increase in the odds of achieving WCAW observed in the budesonide/formoterol AMD group in comparison to the budesonide/formoterol FD group during the open period, regardless of a 15% decrease in the average use of study drug (OR, 1.335; 95% CI, 1.001 to 1.783; <i>P</i>=0.049).</p> <p>Secondary: Patients in the budesonide/formoterol AMD group had a significantly lower exacerbation rate (40%) compared to those in the fluticasone/salmeterol group, and a 32% lower exacerbation rate compared to those in the budesonide-formoterol FD group (<i>P</i>=0.018 and <i>P</i> value not significant, respectively).</p> <p>Patients in the budesonide/formoterol AMD group used significantly less reliever medication during the open study period vs those in the budesonide/formoterol and the fluticasone/salmeterol FD groups (<i>P</i>=0.001 and <i>P</i>=0.011, respectively).</p>

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<p>During a 6 month extension period, all FD groups remained the same and the budesonide/formoterol AMD group could decrease dose to 1 inhalation BID, or increase dose up to 4 inhalations BID for 7 to 14 days based on asthma symptoms.</p>				
<p>Palmqvist et al¹⁵</p> <p>Fluticasone/salmeterol 250/50 μg, 1 inhalation via Diskus</p> <p>vs</p> <p>budesonide/formoterol 160/4.5 μg, 1 inhalation via DPI</p> <p>vs</p> <p>budesonide/formoterol 160/4.5 μg, 2 inhalations via DPI</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT, XO</p> <p>Adult asthmatic patients (mean predicted FEV₁ of 78%, mean reversibility of 19%)</p>	<p>N=30</p> <p>4 days</p>	<p>Primary: Mean FEV₁ at 15 minutes after inhalation</p> <p>Secondary: Time to bronchodilation (defined as >15% increase in FEV₁ from baseline), absolute FEV₁ at three minutes, and FEV₁ at time points \leq60 minutes</p>	<p>Primary: Both budesonide/formoterol doses demonstrated improvements in FEV₁ compared to fluticasone/salmeterol and placebo at 15 minutes postdose ($P < 0.001$).</p> <p>Secondary: At one hour, bronchodilation was achieved in 47% of patients in the fluticasone/salmeterol group, 73% of those in the budesonide/formoterol one inhalation group and 77% of those in the budesonide/formoterol two inhalations group.</p> <p>Both doses of budesonide/formoterol also demonstrated significant improvements in FEV₁ at three minutes ($P < 0.001$) and at 60 minutes (P values not reported) compared to fluticasone/salmeterol and placebo.</p>
<p>O'Connor et al¹⁶</p>	<p>OL, Phase III, RCT</p>	<p>N=1,225</p>	<p>Primary: AQLQ, ACQ, ATSM and</p>	<p>Primary: For AQLQ, no differences were observed between treatment groups in the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Month 1: Budesonide/formoterol 160/4.5 μg, 2 inhalations BID via PMDI</p> <p>vs</p> <p>fluticasone/salmeterol 250/50 μg, 1 inhalation BID via DPI</p> <p>Months 2 to 7: Patients receiving fluticasone/salmeterol continued therapy (FD), whereas those who received budesonide/formoterol were randomized to continue budesonide/formoterol 160/4.5 μg, 2 inhalations BID via MDI (FD) OR to budesonide/formoterol 160/4.5, 2 inhalations QD or 4 inhalations BID (AMD).</p> <p>All patients received their usual asthma therapy for 10 to 14 days prior to randomization.</p>	<p>Patients ≥ 12 years of age with moderate to severe asthma</p>	<p>7 months</p>	<p>OEQ</p> <p>Secondary: Not reported</p>	<p>percentages of patients with clinical meaningful improvements (≥ 0.5) in overall score. Although improvements were statistically significantly greater ($P \leq 0.04$) in the majority of domains for AMD vs either FD regimens, no clinically meaningful between group differences were noted. There were no statistically significant differences between FD regimens in mean improvement from baseline for overall or individual domain scores at the end of treatment.</p> <p>At the end of treatment, the mean change from baseline for all treatment groups exceeded the minimum important difference (0.5) for the ACQ, with no statistically significant or clinically meaningful between group changes noted (P values not reported).</p> <p>As indicated by the ATSM overall score at the end of treatment, patients reported significantly greater treatment satisfactions with AMD vs FD fluticasone/salmeterol ($P = 0.020$); there was no significant difference between group differences between the budesonide/formoterol FD and fluticasone/salmeterol FD groups. Patients in both budesonide/formoterol groups reported significantly greater treatment satisfaction than those in the fluticasone/salmeterol group for the attributes of timely relief of symptoms ($P \leq 0.037$) and feel medication working ($P \leq 0.020$). Patients in the budesonide/formoterol AMD group reported significantly greater treatment satisfaction for the attribute of dosing management than patients in the fluticasone/salmeterol FD group ($P < 0.001$), and reported significantly greater treatment satisfaction of the attributes of daily activity, leisure activity and dosing management than patients in the budesonide/formoterol group FD ($P \leq 0.048$).</p> <p>For the predefined item "During the past week, you could feel your study medication begin to work right away", 71, 71 and 59% of patients in the budesonide/formoterol AMD, budesonide/formoterol FD and fluticasone/salmeterol FD groups responded positively at the end of treatment. The differences observed between the budesonide/formoterol groups and the fluticasone/salmeterol groups were statistically significant ($P \leq 0.002$). For the predefined item "During the past week, you were satisfied with how quickly you felt your study medication begin to work", 78, 80 and 73% of patients in the budesonide/formoterol AMD,</p>

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				<p>budesonide/formoterol FD and fluticasone/salmeterol FD groups responded positively at the end of treatment. The difference between the FD budesonide/formoterol and fluticasone/salmeterol groups was small but statistically significant ($P=0.025$).</p> <p>Secondary: Not reported</p>
<p>Edwards et al⁵⁹</p> <p>Fluticasone/salmeterol</p> <p>vs</p> <p>budesonide/formoterol</p> <p>vs</p> <p>budesonide/formoterol-AMD</p> <p>vs</p> <p>budesonide</p>	<p>MA (15 trials)</p> <p>Patients with moderate to severe asthma</p>	<p>N=not reported</p> <p>12 to 52 weeks</p>	<p>Primary: Treatment failure</p> <p>Secondary: Hospitalizations, emergency visits, use of oral steroids</p>	<p>Primary: Patients in the budesonide/formoterol group demonstrated 50% less treatment failure in comparison to those who received budesonide monotherapy (RR, 1.50; 95% CI, 1.12 to 2.02; $P=0.007$).</p> <p>Although there seemed to be a favorable trend in the reduction of treatment failure observed in the budesonide/formoterol-AMD group vs the budesonide/formoterol group, there was no significant difference detected (RR, 0.88; 95% CI, 0.77 to 1.02; $P=0.09$).</p> <p>There was no significant difference observed between those in the budesonide/formoterol group and those in the fluticasone/salmeterol group in regards to treatment failure ($P=0.86$).</p> <p>Secondary: Patients in the fluticasone/salmeterol group had a 49% greater risk of hospitalizations/accident and emergency visits compared to those in the FD budesonide/formoterol group (RR, 1.49; 95% CI, 1.07 to 2.08; $P=0.02$). Patients in the budesonide/formoterol-AMD treatment group had a 28% risk reduction in hospitalizations/accident and emergency visits vs those treated with FD budesonide/formoterol (RR, 0.72; 95% CI, 0.52 to 0.99; $P=0.04$).</p> <p>Budesonide alone, was associated with a greater risk (51%) in the use of oral steroids in comparison to budesonide/formoterol (RR, 1.51; 95% CI, 1.10 to 2.09; $P=0.01$). Patients in the budesonide/formoterol-AMD group had a lower requirement for oral steroids than those in the budesonide-formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; $P=0.01$).</p> <p>Patients in the budesonide/formoterol-AMD treatment group experienced a</p>

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<p>Nathan et al⁶⁰</p> <p>Mometasone/formoterol 200/10 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>mometasone 200 μg, 2 inhalations BID</p> <p>vs</p> <p>formoterol 10 μg, 2 inhalations BID</p> <p>vs</p> <p>placebo</p> <p>All patients entered a 2 to 3 week OL, run-in period with mometasone MDI 200 μg, BID.</p>	<p>DB, DD, MC, PC, PG, RCT</p> <p>Patients ≥ 12 years of age with a documented history of asthma for ≥ 12 months on a stable asthma regimen for ≥ 2 weeks at screening and with a history of a medium dose ICS for ≥ 12 weeks, with or without a LABA who met ≥ 1 of the following: an increase in $\text{FEV}_1 \geq 12\%$ or a volume increase of ≥ 200 mL after about 15 to 20 minutes of albuterol/ salbutamol administration or of a nebulized SABA, PEF variability $\geq 20\%$ or a diurnal variation of PEF $\geq 20\%$</p>	<p>N=781</p> <p>26 weeks</p>	<p>Primary: Time to first asthma deterioration for combination therapy vs formoterol and bronchodilatory effect of combination therapy vs mometasone</p> <p>Secondary: Change from baseline AQLQ total score for combination therapy vs placebo, ACQ total score for combination therapy vs placebo and proportion of nocturnal awakenings due to asthma requiring SABA rescue medications; trough FEV_1; changes from baseline in AM PEF and symptom scores; total 24-hour SABA usage; time to first moderate asthma exacerbation; safety and tolerability</p>	<p>19% decreased risk in use of oral steroids vs those in the budesonide/formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; $P=0.01$).</p> <p>Primary: A total of 341 patients experienced asthma deteriorations at some point during the study. The median times to first deterioration were 92 and 131 days for formoterol and placebo, respectively. Because $<50\%$ of patients in the combination and mometasone groups experienced a deterioration, median times could not be determined. Significantly fewer patients receiving combination therapy (30.4%) and mometasone (33.9%) experienced an asthma deterioration compared to formoterol (54.0%) and placebo (55.6%) ($P<0.001$ for all).</p> <p>FEV₁ AUC_{0 to 12h} improved more with combination therapy compared to mometasone ($P<0.001$) or placebo ($P<0.001$) at all time points throughout the study, and to formoterol at week 12 ($P=0.017$).</p> <p>Secondary: There was a statistically significantly greater mean improvement in baseline AQLQ total scores for combination therapy compared to formoterol ($P<0.001$) and placebo ($P=0.004$).</p> <p>There was a statistically significant and clinically important improvement in the ACQ total scores for combination therapy (-0.52 vs -2.0 for formoterol vs -0.22 for placebo; $P<0.001$ for both).</p> <p>At end of treatment, 24 hour asthma symptoms scores were significantly more improved from baseline levels with combination therapy compared to both formoterol and placebo ($P<0.001$); mean changes from baseline were -0.50, -0.41, 0.11 and 0.09 for combination therapy, mometasone, formoterol and placebo, respectively.</p> <p>Both combination therapy and mometasone exhibited “superior” changes from baseline for nocturnal awakenings compared to formoterol ($P<0.001$ for both) and placebo ($P<0.001$ and $P=0.003$).</p> <p>Mean trough FEV_1 values were balanced across the groups at baseline and mean changes from baseline at week 12 were combination therapy,</p>

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				<p>0.13 L; mometasone, 0.07 L; formoterol, 0.00 L and placebo, -0.05 L. Combination therapy was significantly better than treatment with formoterol after week one ($P \leq 0.001$) and placebo at all time points ($P \leq 0.006$). Combination therapy was also statistically better than treatment with mometasone at several time points, including week 26 ($P = 0.023$).</p> <p>At end of treatment, the mean changes from baseline in morning PEF values were 7.0, 3.2, -2.9 and -6.0% for combination therapy, mometasone, formoterol and placebo, respectively. The changes were significantly greater for combination therapy compared to the other groups ($P \leq 0.008$).</p> <p>End of treatment 24 hour SABA use was significantly reduced from baseline levels in both the combination therapy (-61.1%) and mometasone (-22.1%) groups compared to either the formoterol (184.1%) and placebo (79.1%) groups ($P \leq 0.001$).</p> <p>Reductions were seen in the proportion of patients who experienced moderate asthma exacerbations: 46.1, 50.0, 67.3 and 70.9% ($P < 0.001$ for both combination therapy and mometasone vs formoterol and placebo).</p> <p>The most common treatment-emergent adverse events were nasopharyngitis (6.3, 7.8, 6.4 and 3.6%), upper respiratory tract infection (5.8, 8.3, 5.9 and 8.7%) and headache (4.7, 5.2, 3.0 and 3.6%).</p>
<p>Meltzer et al⁶²</p> <p>Mometasone/formoterol 100/10 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>mometasone 100 μg, 2 inhalations BID</p> <p>vs</p>	<p>DB,DD, MC, PC, PG, RCT</p> <p>Patients ≥ 12 years of age with asthma for ≥ 12 months who were on a stable asthma regimen (unchanged dose > 2 weeks prior to screening) and had a history of</p>	<p>N=746</p> <p>26 weeks</p>	<p>Primary: Time to first asthma deterioration (severe asthma exacerbation, defined as lung function reduction or clinically judged deterioration), Mean change in FEV₁ AUC_{0 to 12h}</p> <p>Secondary: Change from baseline in morning FEV₁ pre-dose</p>	<p>Primary: Fewer patients treated with mometasone/formoterol experienced an asthma deterioration event compared to patients treated with formoterol alone (17 vs 45%; $P < 0.001$). In addition, the mometasone/formoterol combination treatment was associated with lower rates of deterioration compared to mometasone monotherapy and placebo (17 vs 28 and 46%, respectively; $P \leq 0.006$). There were fewer asthma deterioration events in the mometasone group compared to formoterol alone (28 vs 45%; $P \leq 0.002$).</p> <p>Improvements from baseline in lung function for both mometasone/formoterol and formoterol groups were apparent as early as five minutes post-dose, peaked at two hours and were sustained</p>

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<p>formoterol 10 μg, 2 inhalations BID</p> <p>vs</p> <p>placebo</p> <p>All patients entered a 2 to 3 week OL, run-in period with mometasone MDI 100 μg, BID.</p>	<p>low-dose ICS use >12 weeks with or without LABA</p>		<p>assessment (trough FEV₁) at each visit and end-point, change in AQLQ total score, change in ACQ total score, change from baseline in proportion of nights with nocturnal awakenings due to asthma requiring SABA use and 24-hr SABA usage</p>	<p>throughout the 12 hour evaluation. The mometasone/formoterol combination was associated with a greater mean FEV₁ AUC_{0 to 12h} improvement from baseline at week 12 compared to mometasone alone (4.00 versus 2.53 L/h, respectively; $P=0.001$). Formoterol was associated with a significantly greater mean improvement in FEV₁ AUC_{0 to 12h} (3.83 L/h) compared to mometasone and placebo (2.53 and 1.11 L/h, respectively; $P\leq 0.004$). Treatment with mometasone/formoterol and mometasone also resulted in a significantly greater mean improvement in FEV₁ AUC_{0 to 12h} at week 12 compared with placebo ($P\leq 0.002$). Mean FEV₁ AUC_{0 to 12h} improvements at week 12 in placebo, formoterol, mometasone and mometasone/formoterol treatment groups corresponded to mean increases in FEV₁ of 0.09 L (4.1%), 0.32 L (12.3%), 0.21 L (9.0%) and 0.33 L (13.8%), respectively.</p> <p>Secondary: Mometasone/formoterol improved morning pre-dose (trough FEV₁) lung function compared to fluticasone alone during treatment ($P=0.029$). Also, mean percentage changes from baseline in morning PEF values were -5.3%, 1.4%, 1.6% and 5.2% for placebo, formoterol alone, mometasone alone and mometasone/formoterol groups, respectively ($P\leq 0.03$ for all groups compared to placebo).</p> <p>Treatment with mometasone/formoterol resulted in a significantly greater mean improvement in ACQ total score at week 26 compared to formoterol and placebo (-0.40 vs -0.12 and -0.11, respectively, $P\leq 0.001$) but not mometasone monotherapy (-0.32).</p> <p>Similarly, treatment with mometasone/formoterol was associated with significantly greater changes from baseline in total AQLQ(S) score at week 26 compared to formoterol monotherapy and placebo (0.44 vs 0.15 and 0.06, respectively; $P\leq 0.003$) but not mometasone alone (0.39).</p> <p>Treatment with mometasone/formoterol, mometasone monotherapy and formoterol monotherapy reduced the proportion of nocturnal awakenings requiring SABA use compared with placebo ($P\leq 0.015$). Treatment with mometasone/formoterol reduced nocturnal awakenings more than formoterol alone ($P=0.035$), but mometasone monotherapy did not</p>

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				<p>($P=0.742$).</p> <p>SABA use over 24 hours was significantly reduced from baseline with mometasone/formoterol and mometasone alone compared to placebo ($P\leq 0.004$). In addition, mometasone alone reduced SABA use significantly more than formoterol alone ($P=0.049$).</p>
<p>Weinstein et al⁶¹</p> <p>Mometasone/formoterol 200/10 μg, BID via MDI</p> <p>vs</p> <p>mometasone/formoterol 400/10 μg, BID via MDI</p> <p>vs</p> <p>mometasone 400 μg, BID via MDI</p> <p>All patients entered a 2 to 3 week OL, run-in period with mometasone MDI 400 μg, BID</p>	<p>DB, MC, PG, RCT</p> <p>Patients ≥ 12 years of age with asthma for ≥ 12 months uncontrolled on high dose ICSs (>1000 mg beclomethasone equivalent) with or without LABA for 12 weeks before screening</p>	<p>N=728</p> <p>12 weeks</p>	<p>Primary: Mean change in FEV₁ AUC_{0 to 12h} for combination therapy (800/20 μg) vs mometasone</p> <p>Secondary: Change from baseline in ACQ, AQLQ, proportion on nocturnal awakenings requiring SABA rescue medication, trough FEV₁, evening PEF and number of asthma deteriorations (any one of the following: $\leq 80\%$ of baseline FEV₁, $\leq 70\%$ of baseline PEF for at least 2 consecutive days or a clinically judged deterioration resulting in emergency treatment, hospitalization, or treatment with additional asthma medication such as systemic glucocorticoid steroids.</p>	<p>Primary: A significant improvement from baseline to week 12 for mean change in FEV₁ AUC_{0 to 12h} occurred with both doses of combination therapy compared to mometasone alone (4.19 and 3.59 L/hour vs 2.04 L/hour; for the combination therapy doses of 200/10 μg, 400/10 μg and mometasone 400 μg, respectively; $P<0.001$). Both doses of combination therapy resulted in rapid (five minutes) and sustained improvement in lung function throughout 12 weeks.</p> <p>Secondary: Both doses of combination therapy were associated with lower ACQ scores after 12 weeks of treatment compared to mometasone alone ($P\leq 0.014$), indicating an improvement in asthma control.</p> <p>The mean AQLQ scores increased in all three treatment groups indicating less impairment on activities; however, differences between the groups were not statistically significant.</p> <p>Both doses of combination therapy significantly reduced the number of nocturnal awakenings due to asthma that required SABA use compared to mometasone alone ($P\leq 0.006$).</p> <p>Mean changes from baseline to week 12 were 0.10 L, 0.14 L and 0.19 L for mometasone 400 μg monotherapy, 200/10 μg combination therapy and 400/10 μg combination therapy, respectively. The 400/10 μg combination dose was significantly more effective at improving trough FEV₁ at week 12 ($P=0.006$) and at all other time points ($P\leq 0.04$) compared to monotherapy, whereas the 200/10 μg combination dose was more effective than monotherapy only at week 4 ($P=0.027$).</p> <p>The improvement from baseline in evening PEF was 11.8%, 13.3%, and</p>

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				<p>6.6% for the 200/10 μg and 400/10 μg combination doses, and 400 μg of monotherapy, respectively. Improvements from baseline in evening PEF were also significantly greater for both combination treatment groups compared to mometasone monotherapy at all time points ($P \leq 0.004$).</p> <p>Patients receiving the 200/10 μg dose of combination therapy had significantly fewer asthma deteriorations compared with the mometasone monotherapy group ($P=0.038$). The difference between the 400/10 μg combination treatment group and the mometasone monotherapy group was not significant ($P=0.053$). A combined analysis of both doses of (400/10 μg and 200/10 μg) showed that combination treatment was significantly better than mometasone monotherapy for reducing asthma deteriorations ($P=0.029$).</p>
<p>Bernstein et al⁶</p> <p>Mometasone/formoterol 200/10 μg, 2 inhalations BID via MDI for 12 weeks</p> <p>vs</p> <p>fluticasone/salmeterol 250/25 μg, 2 inhalations BID via MDI for 12 weeks</p> <p>All patients entered a 2 to 4 week run-in period with with mometasone MDI 100 μg, BID.</p>	<p>AC, EB, MC, NI, OL</p> <p>Patients ≥ 12 years of age with persistent asthma for ≥ 12 months, previous treatment with a medium-dose ICS, alone or with LABA, for ≥ 12 weeks before screening, stable asthma treatment regimen for ≥ 2 weeks before screening; history of ≥ 2 unscheduled asthma-related visits to a physician or emergency department within</p>	<p>N=722</p> <p>12 weeks</p>	<p>Primary: Mean change in FEV₁ AUC_{0 to 12h}</p> <p>Secondary: Onset of action (change from baseline in FEV₁ at 5 minutes post dose on day 1), patient-reported outcomes and asthma deterioration on treatment.</p>	<p>Primary: At week 12, the change in FEV₁ AUC_{0 to 12h} with mometasone/formoterol treatment was noninferior to fluticasone/salmeterol (3.43 vs 3.24 L/h, respectively; 95% CI, -0.40 to 0.76). Noninferiority was demonstrated as early as day one of treatment (3.66 vs 3.29 L/h, respectively; 95% CI, -0.11 to 0.84).</p> <p>Secondary: Copyright 2012 • Review Completed on 02/15/2012 mometasone/formoterol on FEV₁ was significantly greater than the effect of fluticasone/salmeterol at all time points measured up to 30 minutes post dose ($P < 0.001$).</p> <p>Treatment with mometasone/formoterol was noninferior to fluticasone/salmeterol at both week 4 and week 12 in mean total ACQ and AQLQ score changes from baseline. In both groups, ACQ scores improved to levels that were below the “uncontrolled” threshold.</p> <p>Both groups had the same LS mean baseline proportion of nights with nocturnal awakenings due to asthma that required the use of a SABA. There was no significant difference between treatments in reducing SABA use by $>65\%$ at week 12 (-65.5 vs -69.8% for mometasone/formoterol and fluticasone/salmeterol, respectively; P value not reported).</p> <p>There was no significant difference between mometasone/formoterol and</p>

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	<p>the past year, or ≥ 3 unscheduled asthma-related visits within the past 2 years; FEV₁ 60 to 90% predicted at screening and baseline, an increase in absolute FEV₁ of $\geq 12\%$ and ≥ 200 mL within 15 to 20 minutes after administration of SABA or PEF variability $>20\%$</p>			<p>fluticasone/salmeterol in total LS mean 24-hour asthma symptom scores. Both treatments improved (reduced) LS mean symptom scores by $\geq 40\%$ at week 12 (-40.0 vs -49.9%, respectively; <i>P</i> value not reported).</p> <p>The proportion of symptom-free days and nights was not significantly different between the two treatment groups. The percentage of patients with asthma deterioration defined as defined as asthma resulting in emergency treatment, hospitalization, or treatment with additional (excluded) asthma medications was similar between the two treatment groups (5.7%).</p>
<p>Maspero et al⁶³</p> <p>Mometasone/formoterol 100/10 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>mometasone/formoterol 200/10 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>fluticasone/salmeterol 125/25 μg, 2 inhalations BID via MDI</p> <p>vs</p>	<p>MC, OL, PG, RCT, SB</p> <p>Patients ≥ 12 years of age with persistent asthma for ≥ 12 months, an FEV₁ $\geq 50\%$, receiving medium to high dose ICSs with or without a LABA for ≥ 12 weeks before screening, on a stable regimen for ≥ 2 weeks before screening, with evidence of β_2-reversibility and normal</p>	<p>N=404</p> <p>52 weeks</p>	<p>Primary: Number and percentage of patients who reported adverse events</p> <p>Secondary: Assessment of impact on HPA axis function</p>	<p>Primary: The number and percentage of patients reporting any adverse event in each group were as follows: mometasone/formoterol 22/100 μg, 109 (77.3%); fluticasone/salmeterol 250/50 μg, 56 (82.4%); mometasone/formoterol 400/10 μg, 103 (79.2%) and fluticasone/salmeterol 500/50 μg, 50 (76.9%) (<i>P</i> values not reported).</p> <p>No noticeable differences in the nature or frequency of adverse events were observed between the groups. The most common adverse event categories were infections and infestations; nervous system disorders; gastrointestinal disorders and respiratory, thoracic and mediastinal disorders. The majority of adverse events were of mild to moderate severity and about one third of adverse events in each group were judged as likely related to treatment.</p> <p>A total of 21 patients (5.2%) reported severe or life-threatening adverse events (mometasone/formoterol 200/10 μg, 8 [5.7%]; fluticasone/salmeterol 250/50 μg, 4 [5.9%]; mometasone/formoterol, 400/10 μg, 5 [3.8%] and fluticasone/salmeterol, 4 [6.2%]).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>fluticasone/salmeterol 250/25 μg, 2 inhalations BID via MDI</p> <p>Patients were stratified at baseline according to their previous ICS dose (medium or high).</p>	<p>electrocardiogram; clinical laboratory tests and chest radiograph and adequate contraceptive precautions for women of childbearing age</p>			<p>Secondary: Compared to baseline, there were sustained statistically significant reductions in plasma cortisol $\text{AUC}_{0 \text{ to } 24\text{h}}$ in all treatment groups ($P \leq 0.043$) at weeks 26 and 52, with the exception of a nonsignificant reduction for fluticasone/salmeterol 250/50 μg at week 52 ($P = 0.076$). At week 26, the extents of decreases were 37.5, 28.8, 33.3 and 22.3% for mometasone/formoterol 200/10 μg, fluticasone/salmeterol 250/50 μg, mometasone/formoterol 400/10 μg and fluticasone/salmeterol 500/50 μg. At week 52, the corresponding decreases were 2.2, 16.7, 29.6 and 32.2%.</p>
<p>Nelson et al⁷⁴</p> <p>Salmeterol 42 μg, 1 inhalation BID via MDI</p> <p>vs</p> <p>placebo</p> <p>Both groups received this treatment as a supplement, not a replacement to current treatment.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Individuals ≥ 12 years of age with asthma diagnosis and currently using medication to treat it</p>	<p>N=26,355</p> <p>28 weeks</p>	<p>Primary: Occurrence of combined respiratory related deaths or respiratory related life-threatening experiences</p> <p>Secondary: All-cause deaths, combined asthma-related deaths or life-threatening experiences, asthma-related deaths, respiratory-related deaths, combined all-cause deaths or life-threatening experiences, and all-cause hospitalizations</p>	<p>Primary: There were three asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo compared to 13 and 37 in subjects receiving salmeterol, a difference that was statistically significant ($P < 0.05$).</p> <p>Secondary: There was no statistically significant difference seen in Caucasians in the primary or secondary end points (P value not reported).</p> <p>For the primary and two of the secondary end points there were a statistically significant difference in African Americans receiving salmeterol compared to placebo ($P < 0.05$).</p> <p>Between the treatment groups there was a statistically significant difference for time to first serious adverse event causing discontinuation (placebo survival rate, 96.18%; salmeterol survival rate, 95.61%; $P = 0.022$).</p>
<p>Salpeter et al⁷⁵</p> <p>LABAs</p> <p>vs</p> <p>placebo</p>	<p>MA (19 DD, PC, RCTs)</p> <p>Asthma diagnoses, 15% of the participants were African American</p>	<p>N=33,826</p> <p>All trials were at least 3 months</p>	<p>Primary: Severe asthma exacerbations requiring hospitalizations, life-threatening, asthma exacerbations, and asthma-related deaths</p>	<p>Primary: LABAs (formoterol and salmeterol) when compared with placebo resulted in an increase in severe exacerbations that required hospitalization (OR, 2.6; 95% CI, 1.6 to 4.3), life-threatening exacerbations (OR, 1.8; 95% CI, 1.1 to 2.9) and asthma-related deaths (OR, 3.5; 95% CI, 1.3 to 9.3), with similar risks seen in adults and children.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	Not reported
Chronic Obstructive Pulmonary Disease				
<p>Welte et al⁶⁴</p> <p>Budesonide/formoterol 320/9 μg, 1 inhalation BID</p> <p>vs</p> <p>placebo</p> <p>Before enrollment, patients stopped their LABA and ICS medications.</p> <p>During a 2 week run-in period all patients used tiotropium 18 μg QD and a reliever medication.</p>	<p>DB, MC, PG, RCT</p> <p>Patients with COPD, eligible for ICS/LABA combination therapy, with a prebronchodilator $\text{FEV}_1 \leq 50\%$ and a history of exacerbations requiring systemic steroids and/or antibiotics</p>	<p>N=660</p> <p>12 weeks</p>	<p>Primary: Change in pre-dose FEV_1</p> <p>Secondary: Pre- and post-dose spirometry measurements, SGRQ-C, morning lung function, COPD symptoms and morning activities, reliever use, exacerbations, and tolerability</p>	<p>Primary: Treatment with budesonide/formoterol improved FEV_1 to a greater extent than placebo. Over the course of the treatment period, the increase in pre-dose FEV_1 was six percent higher ($P < 0.001$) at clinic visits, corresponding to an absolute difference of 65 mL compared to placebo.</p> <p>Secondary: Budesonide/formoterol increased post-dose FEV_1 compared to placebo, by 123 and 131 mL at five and 60 minutes post-dose, respectively. Improvements in pre- and post-dose FVC and inspiratory capacity were also observed with combination therapy.</p> <p>Over the study period, SGRQ-C total scores improved by 3.8 units with budesonide/formoterol compared to 1.5 units with placebo (mean difference, -2.3; 95% CI, -4.23 to -0.32; $P = 0.023$). Improvements in SGRQ-C total score by more than four units were seen in 49.5 and 40.0% of patients in the combination therapy and placebo groups ($P = 0.016$); a similar proportion of patients in each arm had a deterioration in SGRQ-C total scores by more than four units (27.6 and 29.7%, respectively).</p> <p>Similar to what was observed in clinic visits, lung function measurements at home showed significant improvements in pre- and post-treatment (five and 15 minutes) morning FEV_1 and PEF with budesonide/formoterol compared to placebo after one week of treatment. The improvements in FEV_1 were maintained to week 12 ($P < 0.001$ for all).</p> <p>Treatment difference were demonstrated in all COPD symptom scores (breathlessness, nighttime awakenings, chest tightness and cough) from run-in to full treatment period (day and night) in favor of budesonide/formoterol compared to placebo ($P < 0.001$ for all).</p> <p>Significant improvements in morning, nighttime and daytime reliever use were seen with budesonide/formoterol compared to placebo (P values not</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>reported). These effects were seen after the first week of treatment and were stable over time.</p> <p>Severe exacerbations were experienced by 25 (7.6%) patients in the budesonide/formoterol group compared to 61 (18.5%) in the placebo group. Combination therapy decreased the rate of severe exacerbations by 62% (rate ratio, 0.38; 95% CI, 0.25 to 0.78; $P<0.001$) and decreased the number of hospitalizations/emergency room visit by 65% (rate ratio, 0.35; 95% CI, 0.16 to 0.78; $P=0.011$) compared with placebo. Time to first severe exacerbation (HR, 0.39; 95% CI, 0.24 to 0.62; $P<0.001$) and time to first hospitalization/emergency room visit (HR, 0.39; 95% CI, 0.17 to 0.89; $P=0.026$) were also prolonged with combination therapy. In addition, six and 12% of combination therapy and placebo patients required a prescription of antibiotics for the reason "exacerbation of COPD" (P value not reported).</p> <p>Both treatment arms were well tolerated and the overall incidence and severity of adverse events were comparable between groups. There were three cases of pneumonia within each group.</p>
<p>Rennard et al⁶⁵</p> <p>Budesonide/formoterol 160/4.5 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>budesonide/formoterol 80/4.5 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>formoterol 4.5 μg, 2 inhalations BID via DPI</p> <p>vs</p>	<p>MC, PC, RCT</p> <p>Patients ≥ 40 years of age with moderate to severe COPD and a mean percent predicted FEV₁ at baseline ranging from 33.7 to 35.5%</p>	<p>N=1,964</p> <p>12 months</p>	<p>Primary: Mean improvement in baseline pre-dose FEV₁ and one-hour post-dose FEV₁</p> <p>Secondary: Improvement in morning and evening PEF, exacerbation rates, BCS scores, sleep scores, awakening free nights, use of rescue medications, and safety</p>	<p>Primary: The budesonide/formoterol 160/4.5 μg treatment group, demonstrated significantly greater improvements in pre-dose and one hour post-dose FEV₁ when compared to the formoterol monotherapy group ($P\leq 0.023$).</p> <p>Secondary: Both budesonide/formoterol dose treatment groups had significantly greater improvements in morning and evening PEF when compared to both the formoterol and placebo treatment groups ($P\leq 0.017$).</p> <p>Exacerbation rates were significantly reduced by 25 to 30% in both the budesonide/formoterol dose treatment groups when compared to the formoterol treatment group, and by 40% when compared to placebo ($P\leq 0.004$). Both budesonide/formoterol treatment groups had significantly greater improvements in the sleep score and rescue medication when compared to the formoterol treatment group ($P<0.038$).</p> <p>Only the budesonide/formoterol 160/4.5 μg treatment group had a</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p>				<p>significantly greater improvement in the BCS scores compared to the formoterol treatment group (<i>P</i> value not reported), and only the budesonide/formoterol 80/4.5 μg treatment group had a significant improvement in the awakening-free nights compared to formoterol (<i>P</i><0.038).</p> <p>Both budesonide/formoterol were well tolerated compared to both formoterol and placebo. The incidence of pneumonia related adverse events were similar for all active treatment arms, when compared to placebo. The most common adverse events seen in the budesonide/formoterol treatment groups were oral candidiasis, dysphonia and muscle spasms.</p>
<p>Tashkin et al⁶⁶</p> <p>Budesonide/formoterol 160/4.5 μg, 2 inhalations BID via MDI</p> <p>vs</p> <p>budesonide/formoterol 80/4.5 μg 2 inhalations BID via MDI</p> <p>vs</p> <p>budesonide 160 μg, 2 inhalations BID via MDI and formoterol 4.5 μg, 2 inhalations BID via DPI</p> <p>vs</p> <p>budesonide 160 μg 2 inhalations BID via MDI</p> <p>vs</p>	<p>MC, PC, RCT</p> <p>Patients ≥ 40 years of age with moderate to severe COPD and a mean percent predicted FEV₁ at baseline ranging from 33.5 to 34.7%</p>	<p>N=1,704</p> <p>6 months</p>	<p>Primary: Mean improvement in baseline pre-dose FEV₁ and one-hour post-dose FEV₁</p> <p>Secondary: Improvement in morning and evening PEF, BCS scores, sleep scores, awakening free nights, use of rescue medications when compared to placebo, and safety</p>	<p>Primary: The budesonide/formoterol 160/4.5 μg treatment group demonstrated a significantly greater improvement from baseline in pre-dose FEV₁ (0.08 L, 10.7%) when compared to the formoterol monotherapy group (0.04 L, 6.9%; <i>P</i>=0.026) and placebo group (0.01, 2.2%; <i>P</i> value not reported).</p> <p>Patients receiving the budesonide/formoterol 80/4.5 μg combination therapy did not report a significantly greater improvement in pre-dose FEV₁ when compared to the formoterol monotherapy group.</p> <p>Both combination budesonide/formoterol treatment arms demonstrated a significantly greater improvement in pre-dose FEV₁ and one hour post-dose FEV₁ when compared to the budesonide monotherapy treatment arm (<i>P</i><0.001).</p> <p>The budesonide/formoterol 160/4.5 μg treatment group demonstrated a significantly greater improvement from baseline in one hour post-dose FEV₁ (0.20 L, 22.6%; <i>P</i> value not reported) when compared to the budesonide monotherapy group (0.03 L, 4.9%; <i>P</i><0.001) and placebo (0.03 L, 4.1%; <i>P</i> value not reported).</p> <p>Secondary: Improvements in both morning and evening PEF values were significantly greater in both budesonide/formoterol combination treatment arms, when compared to the budesonide monotherapy, formoterol monotherapy and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
formoterol 4.5 μg 2 inhalations BID via DPI vs placebo				placebo groups ($P \leq 0.016$). Both budesonide/formoterol treatment groups significantly improved BCS scores, sleep scores, awakening free nights and use of rescue medications when compared to placebo ($P < 0.028$). Both budesonide/formoterol treatment doses were well tolerated for the six months of treatment. The most common adverse events reported were oral candidiasis, dysphonia and headache. The incidences of pneumonia-related adverse events were similar across for all active treatment groups compared to placebo.
Mansori et al ⁶⁷ Salmeterol 50 μg , BID vs fluticasone/salmeterol 250/50 μg , BID All patients received theophylline sustained release 200 mg BID and ipratropium 40 μg QID before starting the trial.	RCT Male COPD patients with $\text{FEV}_1 < 65\%$, an $\text{FEV}_1/\text{FVC} < 70\%$, > 2 COPD exacerbations within the previous 2 years, with a smoking history > 20 packs/year but were ex-smokers in the last 2 years	N=40 3 months	Primary: Pulmonary function tests, SABA use, and six minute walk distance Secondary: Not reported	Primary: Changes in six minute walk distance, FVC, FEV_1 , PEF and the frequency of using a SABA with fluticasone/salmeterol were significantly greater compared to those receiving salmeterol ($P < 0.01$ to $P < 0.001$). The number of exacerbations during 90 days in the last year before the trial was not statistically different between the two groups; however, the number of exacerbations during the 90 day treatment period in patients treated with fluticasone was significantly lower compared to the other patients ($P < 0.001$). Secondary: Not reported
Dal Negro et al ⁶⁸ Fluticasone/salmeterol 250/50 μg , 1 inhalation BID via Diskus vs salmeterol 50 μg , 1 inhalation BID via Diskus	DB, PC, PG, RCT Patients 53 to 78 years diagnosed with moderate COPD who were naïve to ICSs, $\text{FEV}_1 \leq 80\%$ predicted value but > 800 mL,	N=18 52 weeks	Primary: FEV_1 , morning PEF values, COPD symptom scores, number of exacerbations, and β_2 -agonist use Secondary: Not reported	Primary: Increase in FEV_1 percent predicted noted in the fluticasone/salmeterol group but this increase was not significant (49.9 to 53.4%; $P = 0.07$). However, if the increase is expressed as a percent over baseline value, it is significant in the fluticasone/salmeterol group (1.1 to 6.6; $P < 0.001$), but not in the salmeterol group ($P = 0.79$). Statistically significant increase in morning PEF values in the fluticasone/salmeterol group compare to the placebo group (180 L/minute to 255.4 L/minute compared to 160.6 L/minute to 173.3 L/minute;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	FEV ₁ / FVC ratio \leq 70% predicted value, FEV ₁ change of \leq 12% following β_2 -agonist administration, receiving regular treatment with oral theophylline 200 mg BID, SABA as needed current or ex-smokers with history of \geq 10 pack years			<p>$P < 0.001$) but values did not change in the salmeterol and placebo groups.</p> <p>Statistically significant reduction in daily symptom scores in the fluticasone/salmeterol group ($P = 0.008$), but not in the salmeterol group (P value not reported).</p> <p>Statistically significant reduction in β_2-agonist use in the fluticasone/salmeterol group (4.2 to 1.9; $P < 0.001$), but not in the salmeterol group (4.1 to 4.2; P value not reported).</p> <p>Statistically significant decrease in exacerbations in fluticasone/salmeterol group ($P < 0.001$), but not in salmeterol group (P value not reported).</p> <p>Secondary: Not reported</p>
Hanania et al ⁶⁹ Fluticasone/salmeterol 250/50 μ g, 1 inhalation BID via Diskus vs fluticasone 250 μ g, 1 inhalation BID via Diskus vs salmeterol 50 μ g, 1 inhalation BID via Diskus vs placebo	DB, MC, PC, RCT Patients 40 to 87 years of age, current or former smokers with \geq 20 pack year history, diagnosed with COPD, FEV ₁ /FVC ratio of \leq 70%, baseline FEV ₁ of $<$ 65% predicted normal value but $>$ 0.70 L (or if \leq 0.70 L, then $>$ 40% predicted)	N=723 24 weeks	Primary: Morning pre-dose FEV ₁ and two hour post-dose FEV ₁ Secondary: Morning PEF values, transition dyspnea index, CRDQ, CBSQ, exacerbations, and supplemental albuterol use	<p>Primary: Statistically significant increase in pre-dose FEV₁ in the fluticasone/salmeterol group compared to the salmeterol group (91 mL; $P = 0.012$) and placebo (one mL; $P < 0.001$). No significant difference between the fluticasone/salmeterol group and the fluticasone group (P value not reported).</p> <p>Statistically significant increase in two hour post-dose FEV₁ in the fluticasone/salmeterol group compared to the salmeterol group (281 vs 200 mL; $P < 0.001$), placebo (281 vs 58 mL; $P < 0.001$) and fluticasone group (281 vs 147 mL; $P < 0.001$).</p> <p>Secondary: Statistically significant increase in morning PEF values in the fluticasone/salmeterol group compared to the salmeterol, placebo and fluticasone groups ($P \leq 0.034$), though improvements were also seen from baseline in the salmeterol and fluticasone monotherapy groups ($P < 0.001$).</p> <p>Statistically significant improvements in dyspnea index observed in the fluticasone/salmeterol group ($P = 0.023$) compared to the placebo group, in addition to improvements in the fluticasone ($P = 0.057$) and salmeterol ($P = 0.043$) monotherapy groups compared to the placebo group (NOTE:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>difference in the fluticasone monotherapy group not significant; <i>P</i> value not reported).</p> <p>Statistically significant reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to the fluticasone monotherapy group (-1.0 vs -0.2; <i>P</i>=0.036) and placebo (-1.0 vs 0.1; <i>P</i>=0.002).</p> <p>Numerical reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to the salmeterol monotherapy group.</p> <p>Statistically significant increase in CBSQ scores in the fluticasone/salmeterol group and the fluticasone monotherapy group compared to placebo (<i>P</i>≤0.017).</p> <p>There was significant difference between treatment groups in terms of exacerbations or time to first exacerbation (<i>P</i> value not provided).</p>
<p>Vestbo et al⁷⁰</p> <p>Fluticasone/salmeterol 500/50 μg, 1 inhalation BID</p> <p>vs</p> <p>fluticasone 500 μg, 1 inhalation BID</p> <p>vs</p> <p>salmeterol 50 μg, 1 inhalation BID</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, PG, RCT</p> <p>Patients diagnosed with COPD, pre-dose FEV₁ 25 to 70% predicted, <10% increase in FEV₁ after β_2-agonist use, pre-bronchodilator FEV₁/FVC ratio ≤70%, smoking history of ≥10 pack years, history of chronic bronchitis, ≥1 COPD exacerbation/year for previous 3</p>	<p>N=1,465</p> <p>12 months</p>	<p>Primary: Time to first observation of treatment effects in each arm of study, analyzed for the first 14 days after initial treatment</p> <p>Secondary: Not reported</p>	<p>Primary: Significant increases in PEF in the fluticasone/salmeterol and salmeterol monotherapy groups over placebo after one day (<i>P</i><0.001). This was also observed in the fluticasone group on day two (<i>P</i><0.001).</p> <p>Increase in PEF values in the fluticasone/salmeterol group was significantly better than the other treatment groups after day one (<i>P</i><0.001). No other mention of comparison between groups.</p> <p>Significant increase in FEV₁ values in all treatment groups compared to placebo by day 14 (<i>P</i><0.001 for the salmeterol monotherapy and fluticasone/salmeterol groups and <i>P</i>=0.016 for the fluticasone monotherapy group). No mention of comparison between groups.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	years, and 1 of them requiring oral corticosteroids, antibiotics, or both			
<p>Calverley et al⁷¹</p> <p>Fluticasone/salmeterol 500/50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>fluticasone 500 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>salmeterol 50 μg, 1 inhalation BID via Diskus</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, PG, RCT</p> <p>Patients diagnosed with COPD, pre-dose FEV₁ 25 to 70% predicted, <10% increase in FEV₁ after β_2-agonist use, pre-bronchodilator FEV₁/FVC ratio \leq70%, smoking history of \geq10 pack years, a history of chronic bronchitis, \geq1 COPD exacerbation/year for previous 3 years, and \geq1 exacerbation in previous year requiring oral corticosteroids, antibiotics, or both</p>	<p>N=1,465</p> <p>12 months</p>	<p>Primary: Pre-dose FEV₁ after 12 months of treatment and after abstaining from bronchodilators for \geq6 hours and from study medication by \geq12 hours</p> <p>Secondary: Pre-dose FVC, post-bronchodilator FEV₁ and FVC, morning PEF, use of relief medication, symptom scores, nighttime awakenings, acute COPD exacerbations and SGRQ scores</p>	<p>Primary: Statistically significant improvement in pre-dose FEV₁ in all treatment groups compared to placebo (P<0.001 for salmeterol, P=0.0063 for fluticasone and P<0.001 for fluticasone/salmeterol) and statistically significant improvement in the fluticasone/salmeterol group compared to the fluticasone and salmeterol monotherapy groups (P<0.001).</p> <p>Secondary: Predose FVC improved significantly in all groups compared to placebo (P=0.0004 for salmeterol, P=0.013 for fluticasone and P<0.001 for fluticasone/salmeterol) and there was a statistically significant improvement in pre-dose FVC in the fluticasone/salmeterol group when compared to the fluticasone and salmeterol monotherapy groups (P=0.006 for salmeterol and P<0.001 for fluticasone).</p> <p>Postbronchodilator FEV₁ improved significantly in the fluticasone and fluticasone/salmeterol groups compared to the placebo group (P=0.013 for fluticasone and P<0.001 for fluticasone/salmeterol), and there was a statistically significant difference between the fluticasone/salmeterol group compared to the salmeterol and fluticasone monotherapy groups (P=0.039 and P=0.0014, respectively).</p> <p>Statistically significant improvement in PEF in all treatment groups compared to placebo (P<0.001), and there was a statistically significant improvement in the fluticasone/salmeterol group compared to the fluticasone and salmeterol monotherapy groups (P<0.001).</p> <p>All active treatment groups significantly decreased the number of exacerbations per patient/year compared to placebo (P=0.003), but there was no significant difference between the groups (P values not reported).</p> <p>Statistically significant reduction in the use of relief medication in the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>fluticasone/salmeterol group compared to the placebo and other treatment groups ($P<0.001$ for placebo, $P=0.004$ for salmeterol and $P=0.003$ for fluticasone).</p> <p>Statistically significant reduction in nighttime awakenings in the fluticasone/salmeterol group compared to the placebo and salmeterol groups ($P=0.006$ and $P=0.011$, respectively), but there was no significant difference between the fluticasone/salmeterol and fluticasone monotherapy groups ($P=0.591$).</p> <p>Fluticasone/salmeterol combination therapy showed significant improvement in SGRQ scores compared to placebo and fluticasone ($P=0.0003$ and $P=0.021$ respectively), but no difference between fluticasone/salmeterol and salmeterol monotherapy ($P=0.071$).</p>
<p>Partridge et al⁷²</p> <p>Budesonide/formoterol 320/9 μg, 1 inhalation BID plus placebo</p> <p>vs</p> <p>salmeterol/fluticasone 50/500 μg, 1 inhalation BID plus placebo</p> <p>The treatment periods were separated by a 1 to 2 week washout period during which the patients used their prescribed ICS in the same manner as during the run-in period.</p>	<p>DB, DD, RCT, XO</p> <p>Patients ≥ 40 years of age with a clinical diagnosis of COPD, symptoms for ≥ 2 years, ≥ 1 COPD exacerbation requiring oral steroids and/or antibiotics in the previous 12 months, a current or previous smokers with a smoking history of ≥ 10 pack years, $\text{FEV}_1 \leq 50\%$ and $\text{FEV}_1/\text{vital capacity} < 70\%$ pre-bronchodilator and who had</p>	<p>N=442</p> <p>2 weeks</p>	<p>Primary: PEF five minutes post-morning dose</p> <p>Secondary: PEF and FEV_1 before and at five and 15 minutes after morning dose and before evening dose, CDLM, CCQ, and SGRQ-C</p>	<p>Primary: The estimated increase from baseline in PEF five minutes post-morning dose was 15.1 vs 14.2 L/minute for the two groups (mean difference, 1.01 L/minute; 95% CI, -2.7 to 4.7; $P=0.603$).</p> <p>Secondary: Mean morning FEV_1 improved more with budesonide/formoterol at five minutes post dose (0.12 vs 0.09 L, respectively; $P=0.090$), and significantly at 15 minutes post dose (0.14 vs 0.10 L, respectively; $P<0.05$). There were no statistically significant differences in morning pre-dose lung function (i.e., PEF measurements). e-Diary recorded morning PEF and FEV_1 showed greater improvements for budesonide/formoterol, indicating a more rapid onset of effect.</p> <p>At five and 15 minutes post-dose, budesonide/formoterol had numerically greater improvements in both symptom variables (breathlessness and chest tightness), with no statistical significance (data not shown). Comparing patients' abilities to perform morning activities, treatment with budesonide/formoterol resulted in statistically significant improvements (total CDLM score, 0.22 vs 0.12, respectively; mean difference, 0.10; 95% CI, 0.01 to 0.19; $P<0.05$). In addition, numerically greater improvements with budesonide/formoterol were observed for the individual morning activities that comprised the total score (getting washed, dried, dressed;</p>

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	previously used a short-acting bronchodilator as reliever medication			<p>eating breakfast, walking around the house early and walking around the house later). Although statistically significant, the observed mean difference between treatments (0.10) was below the minimal important differences of 0.20.</p> <p>Overall CCQ scores and SGRQ-C total scores were comparable between the two groups (data not shown).</p>
<p>Make et al⁷³</p> <p>Fluticasone/salmeterol 250/50 μg, 1 inhalation BID</p> <p>vs</p> <p>ipratropium/albuterol 36/206 μg, 1 inhalation QID</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients 40 to 85 years of age diagnosed with moderate to severe COPD, FEV₁/FVC ratio \leq70%, FEV₁ >0.70 L and \leq70% predicted normal value (or if \leq0.70 L, then \geq40% predicted), smoking history of \geq10 pack years, use of inhaled short acting bronchodilator for COPD for \geq30 days</p>	<p>N=361</p> <p>8 weeks</p>	<p>Primary: Morning pre-dose FEV₁</p> <p>Secondary: Morning PEF values, six-hour FEV₁ AUC, percentage of symptom free nights, dyspnea, and overall combined daytime symptom score</p>	<p>Primary: Statistically significant improvement in morning pre-dose FEV₁ in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (change from baseline, 126 vs -1 mL; P<0.001).</p> <p>Secondary: Statistically significant improvement in mean FEV₁ AUC in the fluticasone/salmeterol group at week eight compared to the ipratropium/albuterol group (change from baseline, 0.38 vs -0.18; P=0.002).</p> <p>Statistically significant improvement in morning PEF values in the fluticasone/salmeterol group compared to the ipratropium/albuterol group at week one and throughout study (change from baseline, 33 vs 1 L/minute; P<0.001).</p> <p>Mean post-administration FEV₁ values significantly higher in the ipratropium/albuterol group at one half, one and two hours compared to the fluticasone/salmeterol group (P<0.001), but higher in the fluticasone/salmeterol group at six hours (P=0.003).</p> <p>Dyspnea scores significantly higher in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (P=0.026), though improvements over baseline observed in both groups.</p> <p>Significantly greater reduction in overall daytime symptom score in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (change from baseline, -46.7 vs -28.1; P=0.024).</p> <p>Statistically significant increase in albuterol-free nights in the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Lee et al⁶</p> <p>Exposure to ICSs, ipratropium, LABAs, theophylline and SABAs</p>	<p>Nested case-control</p> <p>Patients treated in the United States Veterans Health Administration health care system</p>	<p>N=145,020</p> <p>Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004</p>	<p>Primary: All-cause mortality, respiratory mortality, and cardiovascular mortality</p> <p>Secondary: Subgroup analyses of primary outcomes</p>	<p>fluticasone/salmeterol group compared to the ipratropium/albuterol group (change from baseline, 19.0 vs 7.3%; $P<0.001$), and a similar increase in albuterol-free days (change from baseline, 34.7 vs 26.7%; $P=0.021$).</p> <p>Primary: After adjusted for differences in covariates, ICSs and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICSs and 0.92 (95% CI, 0.88 to 0.96) for LABAs was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15).</p> <p>Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared with the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABAs (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICSs (OR, 0.88; 95% CI, 0.79 to 1.00), however, this also did not reach statistical significance.</p> <p>Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABAs (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths.</p> <p>Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICSs, 1.08 for ipratropium and 0.90 for LABAs.</p> <p>Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICSs with ipratropium reduced the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; $P < 0.001$).</p> <p>In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.</p>
<p>Cope et al⁷⁷</p> <p>Indacaterol 150 mg PO QD</p> <p>vs</p> <p>indacaterol 300 mg PO QD</p> <p>vs</p> <p>budesonide/formoterol 9/160 μg, 1 inhalation BID</p> <p>vs</p> <p>budesonide/formoterol 9/320 μg, 1 inhalation BID</p> <p>vs</p> <p>fluticasone/salmeterol 50/250 μg, 1 inhalation BID</p> <p>vs</p> <p>fluticasone/salmeterol</p>	<p>MA (15 PC, RCT)</p> <p>RCTs evaluating patients with COPD who were treated with indacaterol, budesonide/formoterol or salmeterol/fluticasone and reported outcomes of trough FEV₁ (reported predose values) at 12 weeks and 6 months, SGRQ total score at 6 months, and TDI total score at 6 months</p>	<p>N=10,211</p> <p>Up to 6 months</p>	<p>Primary: Trough FEV₁ at week 12 and 6 months, total scores for St. George's Respiratory Questionnaire SGRQ, and TDI.</p> <p>Secondary: Not reported</p>	<p>Primary: Treatment with indacaterol 150 μg resulted in a greater change from baseline in FEV₁ at 12 weeks compared to budesonide/formoterol 160/9 μg (0.11 L; 95% CI, 0.08 to 0.13; P value not reported) and budesonide/formoterol 320/9 μg (0.09 L; 95% CI, 0.06 to 0.11; P value not reported).</p> <p>Indacaterol 150 μg was comparable to fluticasone/salmeterol 250/50 μg (0.02 L; 95% CI, -0.04 to 0.08; P value not reported) and fluticasone/salmeterol 500/50 μg (0.03 L; 95% CI, 0.00 to 0.06; P value not reported). Similar results were observed for indacaterol 300 μg at 12 weeks and indacaterol 150 μg and 300 μg at six months.</p> <p>Indacaterol 150 μg demonstrated a comparable improvement in SGRQ total score at six months compared to both doses of budesonide/formoterol, and a greater improvement compared to fluticasone/salmeterol 500/50 μg (-2.16 point improvement; 95% CI, -4.96 to 0.95; P value not reported).</p> <p>Indacaterol 150 and 300 μg demonstrated comparable TDI scores compared to fluticasone/salmeterol 250/50 μg (0.21 points; 95% CI, -0.57 to 0.99; and 0.39; 95% CI, -0.39 to 1.17, respectively; P values not reported) and fluticasone/salmeterol 500/50 μg at six months.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
50/500 μg , 1 inhalation BID				

Drug regimen abbreviations: AMD=adjustable maintenance dosing, BID=twice daily, FD=fixed dose, QD=once daily, QID=four times daily

Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double-dummy, EB=evaluator blinded, ES=extension study, HR=hazard-ratio, MC=multicenter, MA=meta-analysis, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind, SD=standard deviation, XO=crossover

Miscellaneous abbreviations: ACQ=Asthma Control Questionnaire, AQLQ=standardized Asthma Quality of Life Questioner, ATSM=Asthma Treatment Satisfaction Measure, AUC=area under the curve, BCS=breathlessness, cough and sputum scores, CBP=conventional best practices, CBSQ=chronic bronchitis symptom questionnaire, CCQ=Clinical COPD Questionnaire, CDLM=Capacity of Daily Living During the Morning, CFC= chlorofluorocarbon, COPD=chronic obstructive pulmonary disease, CRDQ=chronic respiratory disease questionnaire, DPI=dry powder inhaler, FEV₁=forced expiratory volume in 1 second, FVC=forced vital capacity, HFA=hydrofluoroalkane, HPA=hypothalamic-pituitary-adrenal, ICS=inhaled corticosteroid, LABA=long-acting β_2 -agonist, LS=least squares, LTRA=leukotriene receptor antagonist, MDI=metered dose inhaler, MEF_{50%}=mid-expiratory flow at 50% vital capacity, MOS Sleep Scale=Medical Outcomes Study Sleep Scale, OEQ=Onset of Effect Questionnaire, PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire, PAQLQ=Pediatric Asthma Quality of Life Questionnaire, PEF=peak expiratory flow, PEFr=peak expiratory flow rate, PSAM=Patient Satisfaction with Asthma Medication questioner, SABA=short acting β_2 -agonist, SF-36=Short-Form Health Survey, SGRQ=Saint George's Respiratory Questionnaire, SGRQ-C=Saint George's Respiratory Questionnaire for COPD patients, WCAW=well-controlled asthma week

Special Populations**Table 5. Special Populations**¹⁻⁴

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Budesonide/ formoterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <12 years of age have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction; use with caution.	C	Unknown; use with caution.
Fluticasone propionate/ salmeterol	No dosage adjustment required in the elderly. Safety and efficacy in children <4 years of age have not been established for the dry powder inhaler. Safety and efficacy in children <12 years of age have not been established for the meter dose aerosol inhaler (HFA).	Not studied in renal dysfunction.	Not studied in hepatic dysfunction; use with caution.	C	Unknown; use with caution.
Mometasone/ formoterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <12 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.

HFA=hydrofluoroalkane.

Adverse Drug Events**Table 6. Adverse Drug Events (%)**¹⁻⁴

Adverse Event	Budesonide/ Formoterol	Fluticasone Propionate/ Salmeterol	Mometasone/ Formoterol
Ear, Nose and Throat			
Candidiasis, oral	1.4 to 3.2	1 to 4	-
Hoarseness/dysphonia	<3	2 to 5	-
Nasal congestion	2.5 to 3.2	-	-
Nasopharyngitis	9.7 to 10.5	-	4.7
Pharyngitis	<3	10 to 13	-
Pharyngolaryngeal pain	6.1 to 8.9	-	-
Sinusitis	4.8 to 5.8	4 to 5	2.0 to 3.3
Upper respiratory infection	7.6 to 10.5	21 to 27	-

Adverse Event	Budesonide/ Formoterol	Fluticasone Propionate/ Salmeterol	Mometasone/ Formoterol
Upper respiratory inflammation	-	6 to 7	-
Lower Respiratory			
Bronchitis	<4	2 to 8	-
Cough	<4	3 to 6	-
Viral respiratory infections	-	4	-
Neurology			
Headache	6.5 to 11.3	12 to 13	2.0 to 4.5
Gastrointestinal			
Gastrointestinal discomfort	1.1 to 6.5	1 to 4	-
Diarrhea	-	2 to 4	-
Influenza	2.4 to 3.2	-	-
Nausea/vomiting	1.4 to 3.2	4 to 6	-
Viral gastrointestinal infections	-	<3	-
Other			
Back pain	1.6 to 3.2	-	-
Candidiasis, unspecified site	-	<3	-
Musculoskeletal pain	-	2 to 4	-

- Event not reported or incidence <1%.

Contraindications/Precautions

The combination inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA) products are contraindicated for the primary treatment of status asthmaticus or in any other acute asthma or chronic obstructive pulmonary disease (COPD) episodes where intensive measures might be required. Budesonide/formoterol (Symbicort[®]) and mometasone/formoterol (Dulera[®]) are additionally contraindicated in patients with hypersensitivity to any ingredient that the combination product consists of, and fluticasone propionate/salmeterol (Advair[®]) is further contraindicated in patients with severe milk protein hypersensitivities.¹⁻⁴

All LABA-containing medications are assigned a Black Box Warning (outlined below) regarding an increased risk of asthma-related deaths. In February 2010, results from a meta-analysis demonstrated that LABAs were associated with an increased risk of asthma exacerbations and hospitalizations in pediatric and adult patients, as well as death in some patients. Use of a LABA medication is contraindicated in patients not receiving an asthma controller medication. Additionally, long-term use of LABA medications is recommended only in patients whose asthma cannot be adequately controlled on asthma controller medications, and LABA medications should be used for the shortest duration of time required to achieve asthma control. Specific to the pediatric and adolescent populations, the use of a combination ICS/LABA product is recommended in these patients who require a LABA in order to ensure compliance with both medications.^{1-4,78}

The combination ICS/LABA products should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. In addition, as with other inhaled drugs containing β_2 -adrenergic agents, these combination products should not be used more often than recommended, at higher doses than recommended or in conjunction with other medications containing LABAs, as an overdose may result.¹⁻⁴

The development of localized infections of the mouth and pharynx with *Candida albicans* has been reported in patients treated with combination ICS/LABA products. If an infection develops, it should be treated with appropriate local and systemic therapy, while treatment with the combination product continues, but at times therapy with the combination product may need to be interrupted. Patients should be instructed to rinse their mouth after inhalation of a combination ICS/LABA product.¹⁻⁴

Physicians should monitor for the development of pneumonia in patients with COPD who are receiving a combination ICS/LABA product as the clinical features of pneumonia and exacerbations frequently overlap. In addition, patients receiving medications that suppress the immune system are more susceptible to infections than healthy patients. ICSs should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections or ocular herpes simplex.¹⁻⁴

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICSs because deaths due to adrenal insufficiency have occurred. After withdrawal from systemic corticosteroids, a number of months are required for recovery of the hypothalamic-pituitary-adrenal (HPA) function. The fluticasone propionate/salmeterol hydrofluoroalkane inhaler should not be used for transferring patients from systemic corticosteroid therapy. Budesonide, fluticasone propionate and mometasone will often help control asthma symptoms with less suppression of the HPA function than therapeutically equivalent doses of oral prednisone. Since ICSs are absorbed into the circulation and can be systemically active at high doses, the beneficial effects of these agents in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Because of the possibility of systemic absorption of ICSs, patients treated with one of the combination ICS/LABA products should be observed carefully for any evidence of systemic corticosteroid effects.¹⁻⁴

As with any inhaled medication, the combination ICS/LABA products can produce paradoxical bronchospasm, which may be life threatening. If this occurs, it should be treated immediately with an inhaled short-acting bronchodilator, and therapy with the combination product should be discontinued and alternative therapy should be initiated.¹⁻⁴

Excessive β -adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise and insomnia. Therefore, the combination ICS/LABA products should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension.¹⁻⁴

Decreases in bone mineral density (BMD) have been observed with long term therapy of products containing ICSs. The clinical significance of small changes in BMD with regard to long term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content should be monitored and treated with established standards of care. Assessment of BMD is recommended prior to starting treatment with fluticasone propionate/salmeterol and periodically thereafter. If significant reductions in BMD are observed and treatment is still required, use of a medication to treat or prevent osteoporosis should be considered.¹⁻⁴

ICSs may cause a reduction in growth velocity when administered in pediatric patients; therefore, growth should be monitored in patients receiving a combination ICS/LABA product. To minimize the systemic effects of an ICS, each patient's dose should be titrated to the lowest dosage that effectively controls their symptoms.

Glaucoma and cataracts have been reported in patients with asthma and COPD following long term administration of ICSs; therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma and/or cataracts.¹⁻⁴

In rare cases, patients receiving a combination ICS/LABA product may present with systemic eosinophilic conditions. These events usually have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of an ICS.¹⁻⁴

Like all medications containing sympathomimetic amines, the combination ICS/LABA products should be used with caution in patients with convulsive disorders thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines.¹⁻⁴

β -adrenergic agonist medications may produce significant hypokalemia in some patients which has the potential to produce adverse cardiovascular effects. The reduction in serum potassium is usually transient and does require supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical trials with the combination ICS/LABA products.¹⁻⁴

Black Box Warning for Symbicort[®] (budesonide/formoterol), Advair[®] (fluticasone propionate/salmeterol) and Dulera[®] (mometasone/formoterol)^{1-4,78}

WARNING

Long-acting β_2 adrenergic agonists such as salmeterol may increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths of 13,176 patients treated for 28 weeks on salmeterol vs three deaths of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma-control drugs mitigates the increased risk of asthma-related death from long-acting β_2 adrenergic agonists. Available data from controlled clinical trials suggest that long-acting β_2 adrenergic agonists increase the risk of hospitalization in children and adolescents.

Therefore, when treating patients with asthma, only prescribe fluticasone/salmeterol for patients not adequately controlled on a long term asthma control medication (e.g., inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and long-acting β_2 adrenergic agonist. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue fluticasone/salmeterol) if possible without loss of asthma control, and maintain the patient on a long-term asthma-control medication, such as an inhaled corticosteroid. Do not use fluticasone/salmeterol for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Drug Interactions

Table 7. Drug Interactions^{1-4,78}

Generic Name	Interacting Medication or Disease	Potential Result
ICSs (budesonide, fluticasone propionate)	Azole antifungals	ICS effects and toxicity may be increased.
ICSs (budesonide)	Barbiturates	Decreased pharmacologic effects of ICSs may be observed.
ICSs (budesonide)	Hydantoins	Decreased ICS effects may occur within days of phenytoin initiation and persist for three weeks after discontinuation.
ICSs (budesonide)	Rifamycins	Decreased pharmacologic effects of ICSs may be observed.
ICSs (budesonide)	Warfarin	ICSs may reduce the anticoagulant dose requirements and occasionally induce hypercoagulation that could oppose the anticoagulant action of warfarin.
LABAs (formoterol, salmeterol)	B-blockers	Pharmacologic effects of sympathomimetic β -agonists may be antagonized by β -blockers, resulting in bronchospasm.

ICS=inhaled corticosteroid, LABAs=long-acting β -agonists

Dosage and Administration

Table 8. Dosing and Administration¹⁻⁴

Generic Name	Adult Dose	Pediatric Dose	Availability
Budesonide/ formoterol	<p><u>Treatment of asthma in adults and children >12 years of age:</u> Meter dose aerosol inhaler (HFA): initial, 2 inhalations BID, with the starting dose based upon the patient's asthma severity; maintenance, for patients who do not respond adequately to the starting dose after 1 to 2 weeks with 80/4.5 μg, consideration to using 160/4.5 μg can be made to provide additional asthma control; maximum, 160/4.5 μg BID</p> <p><u>Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease*[†]:</u> Meter dose aerosol inhaler (HFA): 160/4.5 μg, 2 inhalations BID</p>	Safety and efficacy in children <12 years of age have not been established.	Meter dose aerosol inhaler (HFA) (60 or 120 actuations): 80/4.5 μg 160/4.5 μg
Fluticasone propionate/ salmeterol	<p><u>Treatment of asthma in adults and children >12 years of age:</u> Dry powder inhaler: initial, 1 inhalation BID, with the starting dose based upon the patient's asthma severity; maintenance, failure to respond to the starting dosage after 2 weeks of therapy warrants consideration to using a higher strength to provide additional improvement in asthma control; maximum, 500/50 μg BID</p> <p>Meter dose aerosol inhaler (HFA): initial, 2 inhalations BID, with the starting dose based upon the patient's asthma severity; maintenance, failure to respond to the starting dosage after 2 weeks of therapy warrants consideration to using a higher strength to provide additional improvement in asthma control; maximum, 230/21 μg 2 inhalations BID</p> <p><u>Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease*[†]:</u> Dry powder inhaler: 250/50 μg 1 inhalation BID</p>	<p><u>Treatment of asthma in children >4 years of age:</u> Dry powder inhaler: 100/50 μg 1 inhalation BID (initial dose is indicated for patients not currently on an inhaled corticosteroid and whose treatment warrants the initiation of two maintenance therapies)</p> <p>Safety and efficacy in children <4 years of age have not been established for the dry powder inhaler.</p> <p>Safety and efficacy in children <12 years of age have not been established for the meter dose aerosol inhaler (HFA).</p>	<p>Dry powder inhaler (60 blisters): 100/50 μg 250/50 μg 500/50 μg</p> <p>Meter dose aerosol inhaler (HFA) (60 or 120 actuations): 45/21 μg 115/21 μg 230/21 μg</p>
Mometasone/ formoterol	<p><u>Treatment of asthma in adults and children >12 years of age:</u> Meter dose aerosol inhaler (HFA): initial, 100/5 μg 2 inhalations BID if previous therapy with medium dose inhaled corticosteroid or 200/5 μg 2 inhalations BID if previous therapy with high dose inhaled corticosteroid; maintenance, 2 inhalations BID; maximum, 200/5 μg 2</p>	Safety and efficacy in children <12 years of age have not been established.	Meter dose aerosol inhaler (HFA) (120 actuations): 100/5 μg 200/5 μg

Generic Name	Adult Dose	Pediatric Dose	Availability
	inhalations BID		

BID=twice daily, HFA=hydrofluoroalkane

*Including bronchitis and/or emphysema.

†Symbicort® 160/4.5 μ g is the only strength Food and Drug Administration (FDA) approved for this indication.

‡Advair® 250/50 μ g is the only strength FDA-approved for this indication.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
<p>The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: Guidelines for the Diagnosis and Management of Asthma (2007)¹⁷</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> 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 additional pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. <p><u>Treatment</u></p> <ul style="list-style-type: none"> 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. <p><u>Long-term control medications</u></p> <ul style="list-style-type: none"> 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 low-dose ICSs, the addition of a long-acting β_2-adrenergic agonists (LABAs) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton.

Clinical Guidelines	Recommendations																		
	<ul style="list-style-type: none"> • 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 bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease and has not been studied in the long-term management of asthma. <p><u>Quick-relief medications</u></p> <ul style="list-style-type: none"> • 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. <p><u>Assessment, treatment and monitoring</u></p> <ul style="list-style-type: none"> • 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 border="1" data-bbox="479 1560 1412 1862"> <thead> <tr> <th data-bbox="479 1560 609 1644">Inter-mittent Asthma</th> <th colspan="5" data-bbox="609 1560 1412 1644">Persistent Asthma: Daily Medication</th> </tr> <tr> <th data-bbox="479 1644 609 1675">Step 1</th> <th data-bbox="609 1644 771 1675">Step 2</th> <th data-bbox="771 1644 933 1675">Step 3</th> <th data-bbox="933 1644 1096 1675">Step 4</th> <th data-bbox="1096 1644 1258 1675">Step 5</th> <th data-bbox="1258 1644 1412 1675">Step 6</th> </tr> </thead> <tbody> <tr> <td data-bbox="479 1675 609 1862">Preferred SABA as needed</td> <td data-bbox="609 1675 771 1862">Preferred Low-dose ICS Alternative Cromolyn, leukotriene</td> <td data-bbox="771 1675 933 1862">Preferred Low-dose ICS+LABA or medium-dose ICS Alternative</td> <td data-bbox="933 1675 1096 1862">Preferred Medium-dose ICS+LABA Alternative Medium-</td> <td data-bbox="1096 1675 1258 1862">Preferred High-dose ICS+ LABA and consider omalizu-</td> <td data-bbox="1258 1675 1412 1862">Preferred High-dose ICS+LABA+ oral steroid and consider omalizumab</td> </tr> </tbody> </table>	Inter-mittent Asthma	Persistent Asthma: Daily Medication					Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Preferred SABA as needed	Preferred Low-dose ICS Alternative Cromolyn, leukotriene	Preferred Low-dose ICS+LABA or medium-dose ICS Alternative	Preferred Medium-dose ICS+LABA Alternative Medium-	Preferred High-dose ICS+ LABA and consider omalizu-	Preferred High-dose ICS+LABA+ oral steroid and consider omalizumab
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Clinical Guidelines	Recommendations					
		receptor antagonists, nedocromil, or theophylline	Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	mab for patients who have allergies	for patients who have allergies
<p>Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention (2010)¹⁸</p>	<p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> • Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended. <p><u>Special populations</u></p> <ul style="list-style-type: none"> • 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. <p><u>Diagnosis</u></p> <ul style="list-style-type: none"> • A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough and chest tightness. • Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity, reversibility and variability of airflow limitation and provide confirmation of the diagnosis of asthma. • Asthma has been classified by severity in previous reports. However, asthma severity may change over time, and depends not only on the severity of the underlying disease but also its responsiveness to treatment. <p><u>Treatment</u></p> <ul style="list-style-type: none"> • 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 glucocorticosteroids, leukotriene receptor antagonists, LABAs in combination with ICS, sustained-released theophylline, cromones and anti-immunoglobulin E (IgE). • Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include SABAs, inhaled anticholinergics and short-acting theophylline. <p><u>Controller medications</u></p> <ul style="list-style-type: none"> • ICSs are currently the most effective anti-inflammatory medications for the 					

Clinical Guidelines	Recommendations
	<p>treatment of persistent asthma for patients of all ages.</p> <ul style="list-style-type: none"> • ICSs differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences. • To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of ICS. • Leukotriene receptor antagonists are generally less effective than ICSs and therefore may be used as an alternative treatment in patients with mild persistent asthma. • Some patients with aspirin-sensitive asthma respond well to leukotriene receptor antagonists. • Leukotriene receptor antagonists used as add-on therapy may reduce the dose of ICS required by patients with moderate to severe asthma and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of ICS. • Several studies have demonstrated that leukotriene receptor antagonists 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 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 budesonide and formoterol may be used for rescue and maintenance therapy, this use is not approved by the Food and Drug Administration (FDA). • Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on ICS alone. • Cromolyn and nedocromil are less effective than a low dose of an ICS. • 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 who are uncontrolled on inhaled glucocorticoids. • 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. <p><u>Reliever medications</u></p> <ul style="list-style-type: none"> • SABAs are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise induced bronchospasm in patients of all ages. • SABAs should be used only on an as-needed basis at the lowest dose and frequency required. • Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with ICS, the use of this agent as a rescue inhaler is not approved by the FDA. • Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than SABAs. • Short-acting theophylline may be considered for relief of asthma symptoms.

Clinical Guidelines	Recommendations																																
	<ul style="list-style-type: none"> Short-acting oral β_2-adrenergic agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication; however, they are associated with a higher prevalence of adverse effects. Systemic corticosteroids are important in the treatment of severe acute exacerbations. <p><u>Assessment, treatment, and monitoring</u></p> <ul style="list-style-type: none"> 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, treatment can be stepped down to the lowest step and dose of treatment that maintains control. Asthma control is defined as: no (twice or less/week) daytime symptoms; no limitations of daily activities, including exercise; no nocturnal symptoms or awakening because of asthma; no (twice or less/week) need for reliever treatment; normal or near-normal lung function results and no exacerbations. 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 border="1" data-bbox="483 940 1409 1497"> <thead> <tr> <th data-bbox="483 940 630 972">Step 1</th> <th data-bbox="630 940 797 972">Step 2</th> <th data-bbox="797 940 1013 972">Step 3</th> <th data-bbox="1013 940 1240 972">Step 4</th> <th data-bbox="1240 940 1409 972">Step 5</th> </tr> </thead> <tbody> <tr> <td colspan="5" data-bbox="483 972 1409 1003" style="text-align: center;"><i>Asthma Education and Environmental Control</i></td> </tr> <tr> <td data-bbox="483 1003 630 1056">As Needed SABAs</td> <td colspan="4" data-bbox="630 1003 1409 1056" style="text-align: center;">As Needed SABAs</td> </tr> <tr> <td data-bbox="483 1056 630 1497" rowspan="4" style="text-align: center; vertical-align: middle;">Controller Options*</td> <td data-bbox="630 1056 797 1129" style="text-align: center;">Select One</td> <td data-bbox="797 1056 1013 1129" style="text-align: center;">Select One</td> <td data-bbox="1013 1056 1240 1129" style="text-align: center;">To Step 3 Treatment, Select One or More</td> <td data-bbox="1240 1056 1409 1129" style="text-align: center;">To Step 4 Treatment, Add Either</td> </tr> <tr> <td data-bbox="630 1129 797 1192" style="text-align: center;"><u>Low-dose ICS</u></td> <td data-bbox="797 1129 1013 1192" style="text-align: center;"><u>Low-dose ICS+LABA</u></td> <td data-bbox="1013 1129 1240 1192" style="text-align: center;"><u>Medium- or high-dose ICS+LABA</u></td> <td data-bbox="1240 1129 1409 1192" style="text-align: center;">Oral corticosteroid</td> </tr> <tr> <td data-bbox="630 1192 797 1388" style="text-align: center;">Leukotriene receptor antagonists</td> <td data-bbox="797 1192 1013 1388" style="text-align: center;">Medium- or high-dose ICS Low-dose ICS + leukotriene receptor antagonists</td> <td data-bbox="1013 1192 1240 1388" style="text-align: center;">Leukotriene receptor antagonists Sustained release theophylline</td> <td data-bbox="1240 1192 1409 1388" style="text-align: center;">Anti-IgE treatment</td> </tr> <tr> <td data-bbox="630 1388 797 1497" style="text-align: center;">-</td> <td data-bbox="797 1388 1013 1497" style="text-align: center;">Low-dose ICS + sustained-release theophylline</td> <td data-bbox="1013 1388 1240 1497" style="text-align: center;">-</td> <td data-bbox="1240 1388 1409 1497" style="text-align: center;">-</td> </tr> </tbody> </table> <p data-bbox="483 1497 889 1528">*Preferred controller options are underlined.</p> <ul style="list-style-type: none"> Patients who do not reach an acceptable level of control at Step 4 can be considered to have difficult-to-treat asthma. In these patients, a compromise may need to be reached focusing on achieving the best level of control feasible, with as little disruption of activities and as few daily symptoms as possible, while minimizing the potential for adverse effects. Consideration of utilizing an asthma specialist should occur. <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> Repeated administration of SABAs is the best method of achieving relief for mild to moderate exacerbations. 	Step 1	Step 2	Step 3	Step 4	Step 5	<i>Asthma Education and Environmental Control</i>					As Needed SABAs	As Needed SABAs				Controller Options*	Select One	Select One	To Step 3 Treatment, Select One or More	To Step 4 Treatment, Add Either	<u>Low-dose ICS</u>	<u>Low-dose ICS+LABA</u>	<u>Medium- or high-dose ICS+LABA</u>	Oral corticosteroid	Leukotriene receptor antagonists	Medium- or high-dose ICS Low-dose ICS + leukotriene receptor antagonists	Leukotriene receptor antagonists Sustained release theophylline	Anti-IgE treatment	-	Low-dose ICS + sustained-release theophylline	-	-
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Clinical Guidelines	Recommendations
	<ul style="list-style-type: none"> Systemic corticosteroids should be considered if the patient does not immediately respond to SABAs or if the episode is severe. <p><u>Special populations</u></p> <ul style="list-style-type: none"> LABAs may also be used to prevent exercise induced bronchospasm and because of a more rapid onset of action, formoterol is more suitable for symptom relief as well as symptom prevention over salmeterol. Appropriately monitored use of theophylline, ICS, β_2-adrenergic agonists and leukotriene receptor antagonists, specifically montelukast, are not associated with an increased incidence of fetal abnormalities. ICS has been shown to prevent exacerbations of asthma during pregnancy. Acute exacerbations during pregnancy should be treated with nebulized SABAs and oxygen. Systemic corticosteroids should be instituted when necessary.
<p>Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2010)¹⁹</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease. A diagnosis of COPD should be confirmed by spirometry. The presence of a post-bronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) <0.70 confirms the presence of airflow limitation that is not fully reversible. Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications. A detailed medical history should be obtained for all patients suspected of developing COPD. Severity of COPD is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications such as respiratory failure, right heart failure, weight loss and arterial hypoxemia. Chest radiograph may be useful to rule out other diagnoses and to establish the presence of significant comorbidities such as cardiac failure. Arterial blood gas tension measurements should be considered for all patients with FEV₁ <50% predicted or clinical signs suggestive of respiratory failure or right heart failure. COPD is typically a progressive disease; therefore, lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy. In addition, symptom monitoring is used to determine when to modify therapy and to identify any complications that may develop. Comorbidities are common in COPD and should be actively identified. Comorbidities often complicate the management of COPD, and vice versa. Screening for α_1-antitrypsin deficiency may be valuable in patients of Caucasian descent who develop COPD at a young age (<45 years of age) or who have a strong family history of the disease. In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques and it is assumed that asthma and COPD coexist in these patients. In these instances, current management is similar to that of asthma. Other potential diagnoses (e.g., congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis, and diffuse panbronchiolitis) are usually easier to

Clinical Guidelines	Recommendations
	<p>distinguish from COPD.</p> <p><u>Treatment</u></p> <ul style="list-style-type: none"> • 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 the long term decline in lung function that is hallmark of this disease. Treatment should be focused on reducing symptoms and complications. • Choice of agent within each medication class depends on the availability of medication and the patient's response. • Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. • Inhaled therapy is preferred. • When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. COPD patients may have more problems in effective coordination with a metered dose inhaler compared to healthy patients; alternative breath-activated or spacer devices are available for most formulations. Dry powder inhalers may be more convenient and possibly provide improved drug deposition, although this has not been established in COPD. • Principle bronchodilators include β_2-agonists, anticholinergics and methylxanthines used as monotherapy or in combination. • Regular treatment with long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. • The choice between β_2-agonists, anticholinergics, theophylline or combination therapy depends on availability and individual response in terms of symptom relief and side effects. • The order in which the bronchodilator medications are normally introduced into patient care (based on the level of disease severity and clinical symptoms) is: β-agonists, anticholinergics and methylxanthines. • Regular use of LABAs or short- or long-acting anticholinergics improves health status. • Long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. • Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. All theophylline studies were performed with slow-release preparations. • Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator. • For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. • The addition of regular treatment with ICSs to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV₁ <50% predicted and repeated exacerbations. • Regular treatment with ICSs has been shown to reduce the frequency of exacerbations and thus improve health status for symptomatic patients with an FEV₁ <50% of the predicted value and repeated exacerbations. • Treatment with ICSs increases the likelihood of pneumonia and does not reduce overall mortality. • An ICS combined with a LABA is more effective than the individual components in reducing exacerbations and improving lung function and

Clinical Guidelines	Recommendations
	<p>health status.</p> <ul style="list-style-type: none"> • Combination ICS/LABA therapy increases the likelihood of pneumonia. • Addition of an ICS/LABA to an anticholinergic appears to provide additional benefits. • There is insufficient evidence to recommend a therapeutic trial with systemic corticosteroids in patients with Stage II, Stage III or Stage IV COPD and poor response to an inhaled bronchodilator. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • In COPD patients influenza vaccines can reduce serious illness. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥ 65 years old or for patients < 65 years old with an $FEV_1 < 40\%$ of the predicted value. • Long-term administration of oxygen (> 15 hours/day) increases survival in patients with chronic respiratory failure. <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> • The most common causes of an exacerbation are tracheobronchial tree infections and air pollution. • Inhaled β_2-agonists (particularly inhaled β_2-agonists with or without anticholinergics) and systemic corticosteroids are effective treatments for exacerbations of COPD. • Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.
<p>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)²⁰</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> • 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 $FEV_1/FVC < 70\%$. <p><u>Treatment</u></p> <ul style="list-style-type: none"> • Smoking cessation should be encouraged for all patients with COPD. • Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. • Long-acting bronchodilators (beta₂ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. • Once-daily long-acting muscarinic antagonists are preferred compared to four-times-daily short-acting muscarinic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with a muscarinic antagonist. <ul style="list-style-type: none"> ○ $FEV_1 \geq 50\%$ predicted: long-acting β_2-agonist or long-acting muscarinic antagonist. ○ $FEV_1 < 50\%$ predicted: either long-acting β_2-agonist with an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist. • In patients with stable COPD and $FEV_1 \geq 50\%$ who remain breathless or have exacerbations despite maintenance therapy with a long-acting β_2-

Clinical Guidelines	Recommendations
	<p>agonist, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist when inhaled corticosteroids are not tolerated or declined.</p> <ul style="list-style-type: none"> • Consider a long-acting muscarinic antagonist in patients remaining breathless or having exacerbations despite therapy with long-acting β_2-agonist and inhaled corticosteroids and vice versa. • Choice of drug should take in to consideration the patient’s symptomatic response, preference, potential to reduce exacerbations, and side effects 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 long-acting and short-acting bronchodilators 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. <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> • 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

The combination inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA) products are all Food and Drug Administration (FDA)-approved for the treatment of asthma in adults and children (age varies depending on product). Currently, only budesonide/formoterol (Symbicort[®]) and fluticasone propionate/salmeterol (Advair[®]) are currently FDA-approved for the treatment of chronic obstructive pulmonary disease (COPD).¹⁻⁴ The combination ICS/LABA products are not available generically, and the individual components of each of the products are also commercially available solely as branded products.

In regards to the clinical efficacy of the combination ICS/LABA products, trials have demonstrated that the combination products are “superior” to the individual separate components; furthermore head-to-head trials comparing budesonide/formoterol and fluticasone propionate/salmeterol failed to demonstrate that one product is consistently “superior” over the other. A single head-to-head trial comparing mometasone/formoterol (Dulera[®]) to fluticasone propionate/salmeterol demonstrated noninferiority in regard to forced expiratory volume in 1 second (FEV₁) area under the curve from 0 to 12 hours, in

addition to a significantly faster onset of action and increase in FEV₁. The combination products have been compared to the Symbicort[®] Maintenance and Reliever Therapy (SMART) dosing regimen. The SMART dosing regimen used in these trials demonstrated a greater decrease in asthma exacerbations and hospitalization rates compared to standard dosing regimens for budesonide/formoterol and fluticasone propionate/salmeterol. Again, it is important to note that the SMART dosing regimen has not been approved by the FDA.^{7-16,21-72}

For the treatment of asthma, current guidelines support the use of combination ICS/LABA products for long term control and prevention of symptoms in patients who do not achieve sufficient symptom control with an ICS (low to medium dose) as monotherapy, as LABA medications are the preferred add on therapy in these patients. According to the Global Initiative for Asthma (GINA) guidelines, clinical trials have demonstrated that delivering a LABA and an ICS in a combination inhaler is as effective as giving the two individual agents concomitantly. They also state that fixed combination inhalers are more convenient, may increase compliance and ensure that the LABA is always accompanied by an ICS. A major divergence between the National, Heart, Lung, Blood Institute (NHLBI) and GINA guidelines, is the recommendation of budesonide/formoterol as both maintenance and rescue therapy by the GINA guidelines.^{17,18} As mentioned previously, the use of a combination ICS/LABA product for the relief of acute bronchospasm is not approved by the FDA.¹⁻⁴ Currently, the NHLBI guidelines recommend that LABA medications should not be used for the treatment of acute asthma symptoms or exacerbation.^{17,18} Regarding the treatment of COPD, consensus guidelines from both the Global Initiative for Chronic Obstructive Lung Disease and the National Institute for Health and Clinical Excellence recommend the use of combination ICS/LABA products as second-line, when a patients remain symptomatic and have repeated exacerbations while on an initial short- and long-acting bronchodilator.^{19,20} Finally, none of the current asthma or COPD treatment guidelines recommend the use of one combination ICS/LABA product over another; further reinforcing the lack of any significant clinical difference between the products.¹⁷⁻²⁰

References

1. Symbicort[®] [package insert]. Wilmington (DE): AstraZeneca LP; 2010 Jun.
2. Advair Diskus[®] [package insert]. Research Triangle Park (NC); GlaxoSmithKline: 2011 Sep.
3. Advair HFA[®] [package insert]. Research Triangle Park (NC); GlaxoSmithKline: 2010 Jun.
4. Dulera[®] [package insert]. Whitehouse Station (NJ): Schering Corporation; 2011 Jul.
5. FDA announces new safety controls for long-acting beta agonists, medications used to treat asthma [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2010 Feb 18 [cited 2011 Nov 9]. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm200931.htm>.
6. Bernstein DI, Hebert J, Cheema A, Murphy KR, Cherrez-Ojeda I, Matiz-Bueno CE, et al. Efficacy and Onset of Action of Mometasone Furoate/Formoterol and Fluticasone Propionate/Salmeterol Combination Treatment in Subjects With Persistent Asthma. *Allergy Asthma Clin Immunol*. 2011 Dec 7;7(1):21. [Epub ahead of print]
7. Dahl R, Chuchalin A, Gor D, Yoxall S, Sharma R. EXCEL: a randomized trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. *Resp Med*. 2006; 100:1152-62.
8. Bousquet J, Boulet Louis-Philippe, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med*. 2007;101:2437-46.
9. FitzGerald MJ, Boulet LP, Follows RM. The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. *Clin Ther*. 2005;27(4):393-406.
10. Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared with formoterol-budesonide adjustable maintenance dosing: impact on health-related quality of life. *Respir Res*. 2007 Jul 4;8:46.
11. Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ. Evaluation of different inhaled combination therapies (EDICT): a randomized, double-blind, comparison of Seretide (50/250 μ g bd Diskus) vs formoterol (12 μ g bd) and budesonide (800 μ g bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. *Respir Med*. 2002;96(11):851-61.
12. Busse WW, Shah SR, Somerville L, Parasuraman B, Martin P, Goldman M. Comparison of adjustable- and fixed-dose budesonide/ formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. *J Allergy Clin Immunol*. 2008;121:1407-14.
13. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinex-Jamenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract*. 2007;61(5):725-36.
14. Aalbers R, Backer V, Kava TT, Omenaas ER, Sandström T, Jorup C, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Opin*. 2004;20(2):225-40.
15. Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lötvall J. Onset of bronchodilation with budesonide/formoterol and salmeterol/fluticasone in single inhalers. *Pulm Pharmacol Ther*. 2001;14(1):29-34.
16. O'Connor PD, Patrick DL, Parasuraman B, Martin P, Goldman M. Comparison of patient-reported outcomes during treatment with adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler vs fixed-dose fluticasone propionate/salmeterol dry powder inhaler in patients with asthma. *J Asthma*. 2010;47:217-23.
17. 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 2011 Nov 9]. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>.
18. Bateman ED, Bousquet J, FitzGerald M, Haahtela T, O'Byrne P, Ohta K, et al. Global Initiative for Asthma. Global strategy for asthma management and prevention 2010 [guideline on the internet]. 2010. [cited 2011 Nov 9]. Available from: <http://www.ginasthma.com>.

19. Rodriguez-Roisin R, Anzueto A, Bourbeau J, Calverley P, deGuia T, Fukuchi Y, et al. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease updated 2009 [guideline on the internet]. 2009 [cited 2011 Nov 9]. Available from: <http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=2003>.
20. 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 2011 Nov 9]. Available from: www.nice.org.uk/guidance/CG101.
21. Rosenhall L, Heinig JH, Lindqvist A, Leegaard J, Ståhl E, Bergqvist PB. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. *Int J Clin Pract*. 2002;56(6):427-33.
22. Canonica GW, Castellani P, Cazzola M, Fabbri LM, Fogliani V, Mangrella M, et al; The CAST (Control Of Asthma By Symbicort Turbuhaler) Study Group. Adjustable maintenance dosing with budesonide/formoterol in a single inhaler provides effective asthma symptom control at lower dose than fixed maintenance dosing. *Pulm Pharmacol Ther*. 2004;17(4):239-47.
23. Laloo U, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. *Chest*. 2003;123:1480-7.
24. Tal A, Simon G, Vermeulen, JH, Petru V, Cobos N, Everard ML, et al. Budesonide/formoterol in a single inhaler vs inhaled corticosteroids alone in the treatment of asthma. *Pediatr Pulmonol*. 2002;34:342-50.
25. Zangrilli J, Mansfield LE, Uryniak T, O'Brien CD. Efficacy of budesonide/formoterol pressurized metered-dose inhaler versus budesonide pressurized metered-dose inhaler alone in Hispanic adults and adolescents with asthma: a randomized, controlled trial. *Ann Allergy Asthma Immunol*. 2011 Sep;107(3):258-65.e2
26. Pohl WR, Vetter N, Zwick H, Hrubos W. Adjustable maintenance dosing with budesonide/formoterol or budesonide: double blind study. *Respir Med*. 2006;100(3):551-60.
27. Kuna P, Creemers JPHM, Vondra V, Black PN, Lindqvist A, Nihlen U, et al. Once-daily dosing with budesonide/formoterol compared with twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. *Respir Med*. 2006;100(12):2151-9.
28. Morice AH, Peterson S, Beckman O, Osmanliev D. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. *Int J Clin Pract*. 2007;61(11):1874-83.
29. Jenkins C, Kolarikova R, Kuna P, Caillaud D, Sanchis J, Popp W, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. *Respirology*. 2006;11:276-86.
30. Eid NS, Noonan MJ, Chipps B, Parasuraman B, Miller CJ, O'Brien CD. Once- vs twice-daily budesonide/formoterol in 6- to 15-year old patients with stable asthma. *Pediatrics*. 2010;126:e565-e75.
31. Kerwin EM, Oppenheimer JJ, LaForce C, Parasuraman B, Miller CJ, O'Dowd L, et al. Efficacy and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler in adults and adolescents with asthma previously stable with twice-daily budesonide/formoterol dosing. *Ann Allergy Asthma Immunol*. 2009;103:62-72.
32. Berger WE, Bleecker ER, O'Dowd L, Miller CJ, Mezzanotte W. Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma. *Allergy Asthma Proc*. 2010;31:49-59.
33. Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. *Clin Ther*. 2007 May;29(5):823-43.
34. Murphy K, Nelson H, Parasuraman B, Boggs R, Miller C, O'Dowd L. The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma. *Curr Med Res Opin*. 2008;24(3):879-94.

35. Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma. *Drugs*. 2006;66(17):2235-54.
36. Bateman ED, Bantje TA, Joao Gomes M, Toumbis MG, Huber RM, Naya I, et al. Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone propionate alone in patients with moderate persistent asthma. *Am J Respir Med*. 2003;2(3):275-81.
37. Papi A, Paggiaro PL, Nicolini G, Vignola AM, Fabbri LM. Beclomethasone/formoterol vs budesonide/formoterol combination therapy in asthma. *Eur Respir J*. 2007;29:682-9.
38. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy vs a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin*. 2004;20(9):1403-18.
39. Rabe KF, Pizzichini E, Ställberg B, Romero S, Balanzat AM, Atienza T, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma. *Chest*. 2006;129(2):246-56.
40. Louis R, Joos G, Michils A, Vandenhoven G. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. *Int J Clin Pract*. 2009 Oct;63(10):1479-88.
41. You-Ning L, Humphries M, Du X, Wang L, Jiang J. Efficacy and safety of salmeterol/fluticasone propionate delivered via a hydrofluoroalkane metered dose inhaler in Chinese patients with moderate asthma poorly controlled with inhaled corticosteroids. *Int J Clin Pract*. 2005;59:754-9.
42. Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. *Can Respir J*. 1999;6:45-51.
43. Nelson HS, Wolfe JD, Gross G, Greos LS, Baitinger L, Scott C, et al. Efficacy and safety of fluticasone propionate 44 μ g/salmeterol 21 μ g administered in a hydrofluoroalkane metered-dose inhaler as an initial asthma maintenance treatment. *Ann Allergy Asthma Immunol*. 2003;91:263-9.
44. Perrin K, Williams M, Wijesinghe M, James K, Weatherhall M, Beasley R. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β -agonist inhaler therapy in asthma. *J Allergy Clin Immunol*. 2010;126:505-10.
45. Marceau C, Lemiere C, Berbiche D, Perreault S, Blais L. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. *J Allergy Clin Immunol*. 2006;118:574-81.
46. Gappa M, Zachgo W, von Berg A, Kamin W, Stern-Strater C, Steinkamp G. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). *Pediatr Pulmonol*. 2009;44:1132-42.
47. Vaessen-Verberne AAPH, van den Berg NJ, van Nierop JC, Brackel HJL, Gerrits GPJM, Hop WCJ, Duiverman EJ. Combination therapy salmeterol/fluticasone vs doubling dose of fluticasone in children with asthma. *Am J Respir Crit Care Med*. 2010;182:1221-7.
48. Bateman E, Boushey H, Bousquet J, Buss WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med*. 2004;170:836-44.
49. Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone/salmeterol in a single inhaler is stepped down. *J Allergy Clin Immunol*. 2006;117(3):563-70.
50. Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 μ g twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. *Respir Med*. 2001;95:136-46.
51. Pearlman DS, Peden D, Condemi JJ, Weinstein S, White M, Baitinger L, et al. Efficacy and safety of fluticasone/salmeterol HFA 134A MDI in patients with mild-moderate persistent asthma. *J Asthma*. 2004;41:797-806.
52. Nathan RA, Rooklin A, Schoaf L, Scott C, Ellsworth A, House K, et al. Efficacy and tolerability of fluticasone/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescents and adult patients with persistent asthma: a randomized, double blind, placebo-controlled, 12-week study. *Clin Ther*. 2006;28:73-85.
53. Lundback B, Ronmark E, Lindberg A, Jonsson AC, Larsson LG, Petavy, et al. Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. *Respir Med*. 2006;100:2-10.

54. Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone and salmeterol inhaled from a single inhaler vs separate inhalers. *J Allergy Clin Immunol*. 2003;112:29-36.
55. Postma DS, O'Byrne PM, Pedersen S. Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control. *Chest*. 2011 Feb;139(2):311-8.
56. Nguyen WT, Stewart C, Fisher K, Tolley E, Lew DB, Self TH. Maintenance asthma treatment with fluticasone/salmeterol combination via Diskus: effect on outcomes in inner-city children enrolled in TennCare. *Allergy Asthma Proc*. 2005;26:129-34.
57. Ringdal N, Eliraz A, Pruzinec P, Weber HH, Mulder PG, Akveld M, et al. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. *Respir Med*. 2003;97:234-41.
58. Lemanske RF, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med*. 2010;362:975-85.
59. Edwards SJ, Gruffydd-Jones K, Ryan DP. Systemic review and meta-analysis of budesonide/formoterol in a single inhaler. *Curr Med Res Opin*. 2007 Aug;23(8):1809-20.
60. Nathan RA, Nolte H, Pearlman DS. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 μg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. *Allergy Asthma Proc*. 2010;31:269-79.
61. Weinstein SF, Corren J, Murphy K, Nolte H, White M. Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids. *Allergy Asthma Proc*. 2010;31:280-9.
62. Bernstein DI, Hebert J, Cheema A, Murphy KR, Cherrez-Ojeda I, Matiz-Bueno CE, et al. Efficacy and Onset of Action of Mometasone Furoate/Formoterol and Fluticasone Propionate/Salmeterol Combination Treatment in Subjects With Persistent Asthma. *Allergy Asthma Clin Immunol*. 2011 Dec 7;7(1):21. [Epub ahead of print]
63. Maspero JF, Nolte H, Cherrez-Ojeda I. Long-term safety of mometasone furoate/formoterol combination for treatment of patients with persistent asthma. *J Asthma*. 2010;47:1106-15.
64. Welte T, Miravittles M, Hernandez P, Eriksson G, Perterson S, Polanowski T, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;180:741-50.
65. Rennard SI, Tashkin DP, McElhattan J, Goldman M, Ramachandran S, Martin UJ, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549-65.
66. Tashkin DP, Rennard SI, Martin P, Ramachandran S, Martin UJ, Silkoff PE, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs*. 2008;68(14):1975-2000..
67. Mansori F, Khorasani AN, Boskabady MH and Boskabady M. The effect of inhaled salmeterol, alone and in combination with fluticasone propionate, on management of COPD patients. *Clin Respir J*. 2010;4:241-7.
68. Dal Negro R, Pomari C, Tognella S, Micheletto C. Salmeterol and fluticasone 50 μg /250 μg bid in combination provides a better long term control than salmeterol 50 μg bid alone and placebo in COPD patients already treated with theophylline. *Pulm Pharmacol Ther*. 2003;16:241-6.
69. Hanania N, Darken P, Horstman D, Reisner C, Lee B, Davis S, et al. The efficacy and safety of fluticasone propionate (250 μg)/salmeterol (50 μg) combined in the discus inhaler for the treatment of COPD. *Chest*. 2003;124(3):834-43.
70. Vestbo J, Pauwels R, Anderson J, Jones P, Calverley P. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. *Thorax*. 2005;60:301-4.
71. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. *Lancet*. 2003;361:449-56.

72. Partridge MR, Schuermann W, Beckman O, Persson T, Polanowski T. Effect on lung function and morning activities of budesonide/formoterol vs salmeterol/fluticasone in patients with COPD. *Ther Adv Respir Dis*. 2009;3(4):147-57.
73. Make B, Hanania N, ZuWallack R, Kalberg C, Emmett A, Brown CP, et al. The efficacy and safety of inhaled fluticasone propionate/salmeterol and ipratropium/albuterol for the treatment of chronic obstructive pulmonary disease: an eight week, multicenter, randomized, double blind, double dummy, parallel-group study. *Clin Ther*. 2005;27(5):531-42.
74. Nelson HS, Weiss ST, Bleeker ER, Yancey SW, Dorinsky PM. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15-26.
75. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-Analysis: Effect of long-acting B-agonists on severe asthma exacerbations and asthma-related deaths. *Annals of Internal Medicine*. 2006;144(12):904-14.
76. Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med*. 2008;149:380-90.
77. Cope S, Capkun-Niggli G, Gale R, Jardim JR, Jansen JP. Comparative efficacy of indacaterol 150 μ g and 300 μ g versus fixed-dose combinations of formoterol + budesonide or salmeterol + fluticasone for the treatment of chronic obstructive pulmonary disease--a network meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2011;6:329-44.
78. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2010 [cited 2011 Nov 9]. Available from: <http://online.factsandcomparisons.com>.