Research Review

Symbicort Maintenance and Reliever Therapy (SMART) for asthma

Asthma treatment evolution

Fixed dose therapy with inhaled corticosteroids (ICS) has been the mainstay of asthma treatment for many years. In the past 10 years, the practice of combining an ICS with a long-acting beta 2 agonist (LABA), rather than simply increasing the ICS dose has improved symptom control in patients with persistent asthma.[1-5] This led to the development of combination inhalers such as budesonide/eformoterol containing both an ICS and LABA.

The established benefits of combination inhalers include[6]:

- Convenience – one inhaler vs two
- ICS cannot be discontinued when the LABA is used
- Improved compliance to long-term therapy
- Improved asthma control with lower doses of ICS (vs ICS alone)
- Cost effective
- ICS and LABA may act synergistically at a molecular level.

Emergence of a new approach to asthma management

Usual clinical practice has been to give combination inhalers as a fixed dose once or twice daily (depending on the severity of asthma) and to use a short-acting beta 2 agonist (SABA) inhaler to relieve any breakthrough symptoms.[6]

Local research has shown the vast majority of patients with asthma in New Zealand have poor or very poor asthma control, leading to a huge burden in terms of morbidity and cost.[7-8] We know that ICS and LABA are very effective medications, and so why is control so poor?

One major reason for this mismatch between effective treatments and poor outcomes is poor compliance. It is well known that compliance with most treatments including those for asthma is poor.[9-13] We also know simplifying treatments can have huge benefits in terms of increasing compliance and improving outcomes. A typical patient with asthma may have three inhalers, each with different dosing instructions, some for use with a spacer and alternative instructions for each of them in the event of worsening asthma – its little wonder patients get confused!

These issues have resulted in a new approach to the use of combination inhalers employing them for both regular maintenance treatment and relief of breakthrough symptoms, thereby delivering increased anti-inflammatory activity at the first sign of increased symptoms. The first treatment regimen to be intensely researched for this novel approach to asthma management has been referred to as **S**ymbicort **M**aintenance **A**nd **R**elief **T**herapy, or SMART.

The rationale for SMART is that eformoterol, even though it has a mean duration of action of 12 hours, also has an onset of action of 1-3 minutes - similar to that of a SABA. It is less well known that the onset of action of ICS is also very rapid, with detectable effects within 1-2 hours. Therefore, the budesonide/eformoterol combination can be used as a reliever medication and a maintenance medication: both effects from one inhaler. As patients use the combination inhaler for symptom relief, they automatically take additional ICS, just when it is needed.

Evidence supporting SMART therapy'

Using budesonide/eformoterol for both maintenance and relief therapy has been shown to be more effective at reducing exacerbations and improving daily control than the same fixed maintenance dose of budesonide/eformoterol (plus terbutaline as needed),[14] a higher fixed maintenance dose of budesonide (plus terbutaline as needed)[14-17] and a higher fixed maintenance dose of salmeterol/fluticasone[11]. These key studies and others are reviewed in the following section together with a guiding commentary from Dr Shaun Holt.

The SMART method of maintenance/reliever therapy was recently approved by regulatory authority Medsafe for use in New Zealand. For more details go to www.medsafe.govt.nz.

In addition this new treatment method has recently been incorporated into the World Health Organisation's asthma initiative (GINA – www.ginasthma.com) guidelines.

Budesonide/Eformoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma[14] – 'STAY'

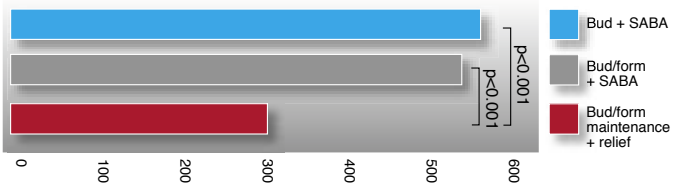
Authors: O'Byrne PM, et al.

Summary: The use of budesonide/eformoterol for regular maintenance therapy and symptom relief was more effective than 2 fixed dose regimens over a 1-year period in this multicentre, double-blind, parallel group study.

Methods: 2760 patients aged 4-80 years with asthma (forced expiratory volume in 1 sec [FEV1] 60-100% predicted) were randomised to 1 of 3 treatments: budesonide/eformoterol 80/4.5mcg twice daily and as required (SMART); budesonide/eformoterol 80/4.5mcg twice daily and terbutaline 0.4mg as required (budesonide/eformoterol and SABA); budesonide 320mcg twice daily and terbutaline 0.4mg as required (budesonide and SABA). All patients a history of at least 1 asthma exacerbation in the past 12 months and had been using a constant dose of ICS for at least 3 months.

Results: SMART therapy significantly prolonged the time to first severe asthma exacerbation compared with the other treatments (both $p < 0.001$) and reduced the risk of severe asthma exacerbation by 45% compared with budesonide/eformoterol and SABA and by 47% compared with budesonide and SABA. Its effect on exacerbation risk remained constant over time. SMART therapy also significantly reduced total severe exacerbations, improved night-time symptoms and lung function compared with the other treatments.[14]

No. of severe asthma exacerbations



Comment: This study is considered one of the largest asthma studies ever conducted involving adults, adolescents, and children as young as 4 years old. The first regimen, SMART therapy, prolonged the time before the first severe exacerbations ($p<0.001$), decreased the overall need for systemic steroids ($p < 0.001$), resulted in 14 extra nights of undisturbed sleep per year ($p < 0.05$), sustained reductions in the rescue medication used for symptom relief ($p < 0.001$), and lowered the risk of experiencing a severe asthma exacerbation by 45%. Lung function was also significantly higher with SMART.

The authors commented in the discussion that the benefits achieved from SMART dosing, despite the lower overall amount of budesonide taken, imply that the reason for the efficacy of SMART therapy lies in the timing of the increase in inhaled steroid dose. Further evidence from this comes from data from studies that have doubled the inhaled steroid dose well into the course of an exacerbation: these studies have generally failed to show benefits from this approach.

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Budesonide/Eformoterol as Maintenance and Reliever Therapy Reduces Asthma Exacerbations versus a Higher Maintenance dose of Budesonide/Eformoterol or Salmeterol/Fluticasone[15] – 'COMPASS'

Authors: Kuna P, et al. for the COMPASS Investigators

Summary: SMART therapy was more effective than a higher maintenance dose of budesonide/eformoterol (plus terbutaline for relief) or a comparable fixed dose of salmeterol/fluticasone (plus terbutaline) in patients with persistent asthma.

Methods: 3335 patients (FEV1 at least 50% of predicted normal, with at least 12% reversibility after terbutaline 1mg) were randomised to use 1 of 3 treatments: Budesonide/eformoterol (160/4.5mcg) twice daily plus an additional inhalation as required (SMART); a higher maintenance dose of budesonide/eformoterol (320/9mcg twice daily) plus terbutaline as needed; or a comparable dose of salmeterol/fluticasone (50/250mcg twice daily) plus terbutaline as needed. Treatment continued for 6 months in a double-dummy manner.

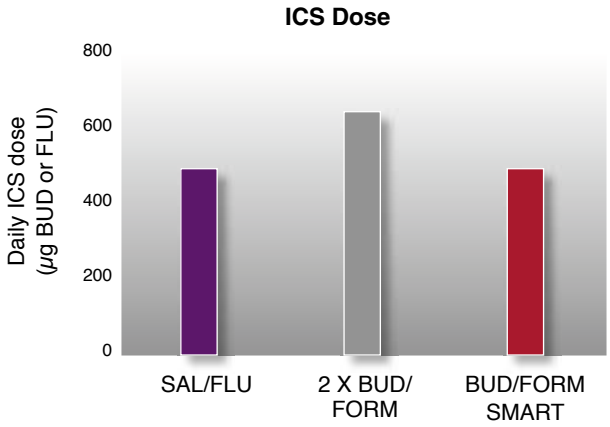
Results: the use of SMART significantly prolonged the time to first severe exacerbation compared with both fixed-dose maintenance treatments, and reduced the total number of severe exacerbations by 28% ($p < 0.01$) and 39% ($p < 0.001$) versus fixed-dose budesonide/eformoterol and salmeterol/fluticasone, respectively. Mean daily ICS use was also lower in SMART recipients (483mcg) than fixed-dose budesonide/eformoterol (640mcg) and salmeterol/fluticasone (500mcg) recipients.[15]

Comment: The aim of COMPASS was to answer the question: Is SMART more effective than a higher maintenance dose of combination inhaler plus conventional reliever? Accordingly this 6-month study had 3 arms: SMART; 2-fold higher fixed budesonide/eformoterol maintenance dose with terbutaline for relief; comparable dose of salmeterol/fluticasone with terbutaline for relief.

In terms of a reduction in exacerbations, SMART did in fact prove to be superior to both of the higher fixed dose treatments. The reduction in exacerbations was 39% when compared to salmeterol/fluticasone fixed dose and 28% when compared to budesonide/eformoterol fixed dose.

This study also addressed one of the key concerns with SMART: the total dose of inhaled steroid taken when budesonide/eformoterol is used as a reliever – no overall increase in inhaled steroid use was seen and the overall inhaled steroid dose was reduced by around 25%.

The authors of this study commented that, given the pressures on the health system caused by exacerbations, the reduction in exacerbations seen with SMART was an important finding.



Efficacy and Safety of Budesonide/Eformoterol Single Inhaler Therapy versus a Higher Dose of Budesonide in Moderate to Severe Asthma[16] – 'STEP'

Authors: Scicchitano R, et al.

Summary: Budesonide/eformoterol for maintenance and relief was at least as effective as a higher dose of budesonide (plus terbutaline as needed) in patients with moderate to severe asthma in this 12-month, randomised, double-blind, double-dummy, parallel group study.

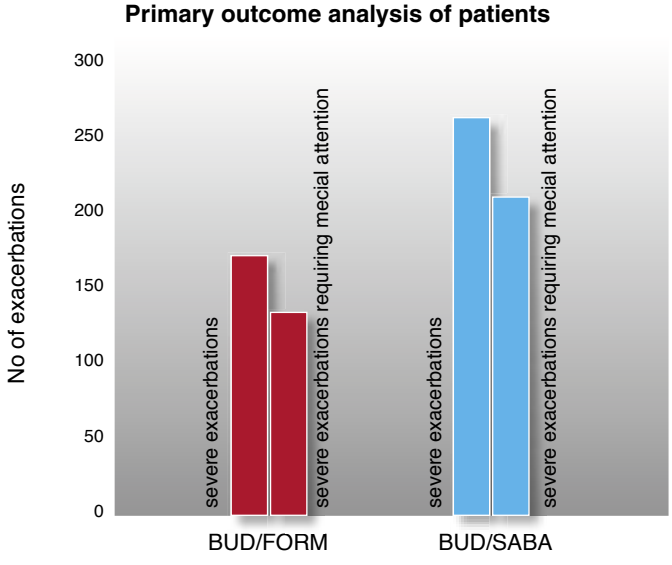
Methods: 1890 male and female patients with moderate to severe asthma (FEV1 50-90% of predicted value, with at least 12% reversibility after terbutaline) received either budesonide/eformoterol single inhaler therapy (160/4.5mcg; 2 inhalations once daily plus an additional inhalation as needed) or a higher dosage of budesonide alone (160mcg; 2 inhalations twice daily plus terbutaline as needed) for 1 year.

Results: Budesonide/eformoterol significantly prolonged the time to first severe exacerbation compared with higher dose budesonide alone ($p < 0.001$). In addition, 170 budesonide/eformoterol recipients versus 259 budesonide monotherapy recipients reported a severe exacerbation (39% risk reduction; $p < 0.001$). Patients receiving single inhaler therapy required fewer hospitalisations or oral steroids and had a lower mean daily ICS dose (466 vs 640mcg).[16]

Comment: This study is of particular interest because it was partially undertaken in several research centres in New Zealand, who contributed around 50 patients to the study. Along with the 'STEAM' study (see later)[17], this was one of the first studies to demonstrate the safety and efficacy of the novel concept of using budesonide/eformoterol as a reliever inhaler, as well as for maintenance.

The patients in this study, referred to as 'STEP', had moderate-to-severe asthma and the patients who took budesonide/eformoterol as a reliever had a reduction in the risk of severe exacerbations (39%) and they also used significantly fewer doses of rescue medication.

The possibility of using the same inhaler for both maintenance of disease and relief of symptoms was a revolutionary idea, with the potential to simplify and improve asthma management, for both patient and Doctor. This study confirmed the efficacy and safety of this novel approach, in patients whose asthma was moderate-to-severe.



Budesonide/Eformoterol in a Single Inhaler for Maintenance and Relief in Mild-to-Moderate Asthma: a randomised double-blind trial[17] – 'STEAM'

Authors: Rabe KF, et al.

Summary: This double-dummy study compared the use of budesonide/eformoterol maintenance and relief therapy with a higher dosage of budesonide (plus terbutaline as required).

Methods: 697 patients aged 11-79 years with mild to moderate asthma (mean baseline FEV1 75% of predicted) were randomised to receive 6 months' treatment with either budesonide/eformoterol (80/4.5mcg two inhalations once daily for maintenance and one inhalation when required for relief) or double-dose budesonide (160mcg two inhalations once daily) plus terbutaline 0.4mg as required.

Results: Morning peak expiratory flow (primary endpoint) showed greater improvement from baseline with budesonide/eformoterol than with double-dose budesonide (+34.5 vs +9.5 L/min, respectively; $p < 0.001$). Budesonide/eformoterol recipients had a 54% lower risk of severe exacerbation ($p < 0.01$) and received a lower mean daily dose of ICS (240 vs 320mcg) during the study compared with double-dose budesonide recipients.[17]

Comment: This was a smaller study and involved patients with milder asthma. SMART therapy was compared to a higher dose of budesonide plus terbutaline for relief.

The results were quite astounding, in that SMART therapy reduced severe exacerbations by 54%. Markers of severe exacerbations including hospitalisations and emergency room visits, and use of oral steroids were all markedly reduced in the group randomised to SMART.

Further, morning peak flow rates were 25 L/min higher in the SMART group. This level of increase is such that patients would notice a huge improvement in their asthma symptoms.

This was the first study in patients with mild-to-moderate asthma which demonstrated that when budesonide/eformoterol is used in this manner, a separate reliever medication is not only not needed, but actually leads to worse outcomes.

Mean Patient Diary Card Efficacy Variables Before and During 6 Months of Inhaled Treatment With Either Budesonide/Formoterol for Both Maintenance and Symptom Relief or Budesonide for Maintenance with Terbutaline as Reliever Medication

	Budesonide/Formoterol, 80ug/4.5 ug, Two Inhalations qd		Budesonide,160 ug Two Inhalations qd			
Efficacy Variable	Baseline, Mean (Range)	Treatment, Mean (Range)	Baseline, Mean (Range)	Treatment, Mean (Range)	Adjusted Between-Group Difference (95% Confidence Interval)	p Value
Morning PEF, L/min	345 (137 to 707)	379 (163 to 828)	335 (127 to 734)	345 (140 to 704)	25.0 (19.4 to 30.6)	<0.001

Budesonide/Eformoterol Maintenance and Reliever Therapy: an Effective Asthma Treatment Option?[18] – 'COSMOS'

Authors: Vogelmeier C et al.

Summary: The use of budesonide/eformoterol maintenance and reliever therapy was at least as effective as salmeterol/fluticasone plus salbutamol in patients with asthma in this open-label study.

Methods: 2143 patients with FEV1 40-90% (mean 73%) predicted who had taken at least 500 mcg/day of budesonide or fluticasone for a month prior to entry were randomised to receive either budesonide/eformoterol (160/4.5mcg, 2 inhalations twice daily and additional inhalations as required) or salmeterol/fluticasone 50/250mcg twice daily plus salbutamol as required. Dosages were adjusted after 4 weeks if necessary.

Results: Budesonide/eformoterol prolonged the time to first severe exacerbation compared with controls ($p = 0.0051$) and reduced the risk of severe exacerbation by 25% (95% confidence interval 7-39%; $p = 0.0076$). Budesonide/eformoterol also reduced unscheduled visits by 24%, the number of oral steroid days by 34%, ER visits by 16% and hospital days by 37%. Fewer budesonide/eformoterol than salmeterol/fluticasone recipients reported a severe exacerbation over the 12-month treatment period (159 vs 204; $p = 0.0076$). Both treatments were well tolerated.[18]

Comment: The strengths of this landmark research lie in its pragmatic, "real-life" study design. Some of the novel aspects of this study were the fact that physicians could titrate maintenance doses according to their normal clinical practice; there was no study entry requirement for the demonstration of reversibility to beta-agonist; patients did not keep symptom or peak flow diaries and, most importantly, the study was open-label.

In order to correctly interpret this study, it is necessary to be absolutely certain what the two groups were taking. Patients were randomised to salmeterol/fluticasone 50/250mcg bid with salbutamol for relief or budesonide/eformoterol 160/4.5mcg, 2 puffs bid with the same inhaler used for symptomatic relief.

The main findings from COSMOS were that several parameters of asthma control were comparable or even improved despite a reduction in the number of different types of inhalers needed by the patient. The reduction in the number of severe exacerbations with the use of budesonide/eformoterol as a single inhaler was an intriguing finding, and the reason could well be that the increased doses of inhaled steroid, taken when extra reliever was used in the early stages of an exacerbation, may have prevented mild exacerbations from becoming

Clinical outcomes

Variable	SAL/FLU + salbutamol	BUD/FORM maintenance + as needed	p-value
Patients n	1076	1067	
All severe exacerbations			
Patients with event n (%)	204 (19)	159 (15)	0.0076

Effect of Budesonide in Combination with Eformoterol for Reliever Therapy in Asthma Exacerbations: a Randomised Controlled, Double-Blind Study[19] – 'SMILE'

Authors: Rabe KF, et al.

Summary: The use of budesonide/eformoterol as required for relief reduced the risk of severe exacerbations compared with eformoterol or terbutaline in patients receiving budesonide/eformoterol maintenance therapy in this multicentre, double-blind study.

Methods: 3394 patients aged 12 years or older (FEV 50-100% of predicted) who were symptomatic despite maintenance therapy with budesonide/eformoterol (160/4.5mcg 1 puff bid) were randomised to receive additional budesonide/eformoterol 160/4.5mcg, eformoterol 4.5mcg or terbutaline 0.4mg as required for relief during the 12-month trial period.

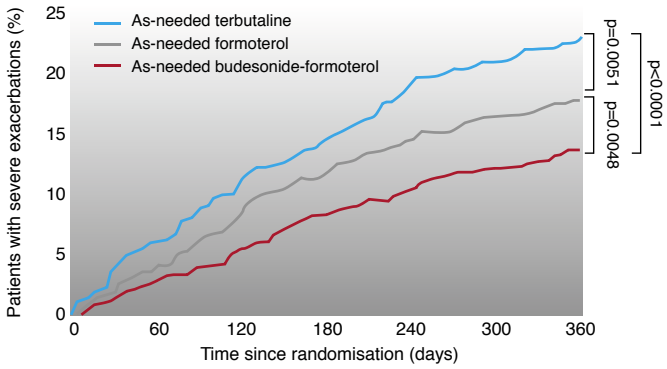
Results: Relief therapy with budesonide/eformoterol prolonged the time to first severe exacerbation compared with additional eformoterol ($p = 0.0048$) or terbutaline ($p < 0.0001$), and relief with eformoterol alone was more effective than terbutaline ($p = 0.0051$). Budesonide/eformoterol relief reduced the instantaneous risk of a severe exacerbation by 27% and 45% versus eformoterol and terbutaline respectively. Asthma control days improved in all three groups to a similar extent. All treatments were well tolerated.[19]

Comment: The SMILE study was another huge study in the series of studies assessing the safety and efficacy of SMART therapy. Over 3,000 adolescents and adults took maintenance doses of budesonide/eformoterol and the 3 groups used eformoterol, terbutaline or budesonide/eformoterol for relief of symptoms.

Overall, the data showed that the use of eformoterol as a reliever was superior to terbutaline, and budesonide/eformoterol was superior to both. The rate of severe exacerbations was 37, 29, and 19 per 100 patients/year with as-needed terbutaline, eformoterol, and budesonide/eformoterol respectively. Similar patterns were seen with a range of important secondary outcome measures, including symptoms, hospitalisations, night-time awakenings due to asthma and mild exacerbations.

The aim of the SMILE study was to assess whether the addition of an inhaled steroid, budesonide, as part of the reliever inhaler would provide any additional clinical benefits, and the results conclusively showed that it does.

Time to first severe asthma exacerbation



Conclusions – Dr Shaun Holt

The Symbicort Maintenance And Relief Therapy asthma studies have demonstrated that the novel concept of a single inhaler to treat asthma is effective, safe and convenient for patients. As such, this approach has the potential to change the way we currently treat asthma as the current complexities of dosing and multiple devices remains a constant management challenge. As better outcomes have been displayed with lower doses of ICS and LABA, it would appear that the reasons for the impressive results seen in the SMART studies lie in the timing of doses taken and perhaps with the increased compliance due to the simplicity of needing only one inhaler.

An initial concern for prescribers would be the safety of 'as required' ICS and LABA, but the studies featured in this review have shown patients achieved better control using lower doses. SMART may not be suitable for all patients particularly those with severe uncontrolled asthma, but for the majority of people it appears SMART therapy can provide better asthma control.

References

1. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ 2000; 320: 1368-1373
2. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. AM J Respir Crit Care Med 20001; 164: 1392-1397.
3. Walters EH, Walters JA, Gibson MD. Inhaled long acting beta agonists for stable chronic asthma. Cochrane Database Syst Rev 2003; 4: CD001385.
4. Pauwels RA, Lofdahl C-G, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med 1997; 337: 1412-1418
5. Kankaanranta H, Lahdensuo A, Moilanen E, Barnes PJ. Add-on therapy options in asthma not adequately controlled by inhaled corticosteroids: a comprehensive review. Respir Res 2004; 5: 17
6. Barnes PJ. Scientific rationale for using a single inhaler for asthma control. Eur Respir J 2007; 29: 587-595
7. Holt S, Bealey R. The burden of asthma in New Zealand. 2002. Wellington: Asthma and Respiratory Foundation of New Zealand
8. Holt S, Kljakovic M, Reid J, for the POMS Steering Committee. Asthma morbidity, control and treatment in New Zealand: results of the Patient Outcomes Management Survey (POMS), 2001. New Zealand Medical Journal 16 May 2003; 116.
9. Cochrane GM. Therapeutic compliance in asthma: its magnitude and implications. Eur Respir J 1992;5:122-4.
10. Bauman LJ, Wright E, Leickly FE et al. Relationship of adherence to pediatric asthma morbidity among inner-city children. Pediatrics 2002;110(1 Pt 1):e6.
11. Williams LK, Pladevall M, Hugo X et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol 2004;114:1288-93.
12. Krishnan JA, Riekert KA, McCoy JV et al. Corticosteroid use after hospital discharge among high-risk adult with asthma. Am J Respir Crit Care Med 2004;170:1281-5.
13. Spector SL, Kinsman RA, Maulinney M et al. Compliance of patients with asthma with an experimental medication. Implications for controlled trials. J Allergy Clin Immunol 1986; 77:65-70.
14. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005; 171: 129-136
15. Kuna P, Peters MJ, Buhl R, for the COMPASS Investigators. Budesonide/formoterol as maintenance and reliever therapy reduces asthma exacerbations versus a higher maintenance dose of budesonide/formoterol or salmeterol/fluticasone. [poster]
16. Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin 2004; 20: 1403-1418
17. Rabe KF, Pizzichini E, Stallberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized double-blind trial. CHEST 2006; 129: 246-256
18. Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? Eur Respir J 2005; 26: 819-828
19. Rabe KF, Atienza T,Magyar P, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006; 368: 744-753

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