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Appendices

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Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over

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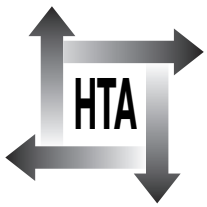

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Appendix 1

Expert advisory group

Members of the expert advisory group were as follows:

Dr Nick Adams, Consultant Physician; Dr Alan Cade, Consultant Paediatrician, Plymouth Hospitals NHS Trust; Dr Chris Cates, Coordinating Editor, Cochrane Airways Review Group; Dr Tim Harrison, Consultant Physician (Pharmacotherapy), Nottingham City Hospital; Professor Stephen Holgate, MRC Clinical Professor of Immunopharmacology, Southampton General Hospital; Ms Emily Lancsar, Lecturer in Economics, University of Newcastle-upon-Tyne; Ms Sarah Lewis, Reader in Medical Statistics, Division of Respiratory Medicine, Nottingham City Hospital; Dr David Mabin, Consultant Paediatrician, RD&E NHS Foundation Trust; Dr David Seamark, GP, Honiton Medical Practice; Dr David Sinclair, Consultant Physician, Respiratory Medicine, Torbay District Hospital; Professor Anne Tattersfield, Emeritus Professor of Respiratory Medicine; Professor John Warner, Professor of Child Health, Department of Child Health, University of Southampton.

Appendix 2

Assessment protocol

Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Final Protocol. 4 May 2006

1. Title of the project

Inhaled corticosteroids and long acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.

2. Name of TAR teams and 'leads'

Southampton Health Technology Assessment Centre (SHTAC); Peninsula Technology Assessment Group (PenTAG).

3. Plain English summary

Chronic asthma is a condition that affects around 5 million children and adults in the UK. The symptoms can include wheezing, shortness of breath and general difficulties in breathing, and can significantly disrupt daytime activity and the ability to sleep well at night. Symptoms occur as a result of tightening of the muscles surrounding the airways and inflammation of the airway lining. People with asthma need to maintain good control of the condition to prevent worsening of symptoms or 'asthma attacks'. This can be achieved by following a healthy lifestyle, reducing contact with substances likely to aggravate asthma and regular and correct use of prescribed drugs. People with mild asthma can usually manage the condition through the use of an inhaler device containing a short-acting beta$_2$ agonist (e.g. salbutamol) on an as-needed basis. Short-acting beta$_2$ agonists are known as bronchodilators and work by relaxing the airway muscles to improve the passage of air into the lungs. When this is not enough to prevent worsening of symptoms, patients may be prescribed one of the five available corticosteroids, usually via a hand-held inhaler. A corticosteroid works to reduce inflammation in the airways. The corticosteroid is usually inhaled twice per day for a given period of months or longer (in addition to the inhaled short-acting beta$_2$ agonist, as needed) until asthma is stabilised, at which time it may be gradually reduced. Often a low, regular dose of inhaled corticosteroid is needed to control symptoms.

Where asthma symptoms continue to be difficult to control, the daily dose of inhaled corticosteroid may be increased, or a third drug may be prescribed. Inhaled long-acting beta$_2$ agonists, of which there are two, are commonly used in these situations. They may be given separately or in a combined inhaler containing the inhaled corticosteroid. Other drugs may be given in cases where control is still not adequate.

There are a number of different inhaled corticosteroids and long-acting beta$_2$ agonists available, in different combinations and via different inhalers. This study will systematically summarise the results of clinical trials which compare the different inhaled corticosteroids with each other; trials which compare inhaled corticosteroids combined with long-acting beta$_2$ agonists with use of inhaled corticosteroids only; and trials which compare the two different combinations of inhaled corticosteroids and long-acting beta$_2$ agonists. The report will include an economic evaluation, to compare the costs and benefits of the different drugs to indicate whether they represent good value for money from the NHS and Personal Social Services (PSS) perspective.

4. Decision problem

The aim of this health technology assessment is to assess the clinical effectiveness and cost-effectiveness of inhaled corticosteroids (ICS), and inhaled corticosteroids in combination with long-acting beta$_2$ agonists (LABA), in the treatment of chronic asthma in adults and children aged 12 years and over.

4.1. Background to asthma

Asthma is a condition characterised by inflammation and narrowing of the bronchial airways leading to wheezing, cough, chest tightness, shortness of breath and general difficulties in breathing. Symptoms vary from mild intermittent wheezing or coughing to severe attacks requiring hospital treatment. Severity can be defined on the basis of symptoms, lung

function and incidence of exacerbations. Definitions vary but a classification system has been proposed by the Global Initiative for Asthma (GINA).[P1,P2] Asthma can be triggered by a number of stimuli, including allergens (e.g. animals, house dust mite), environmental factors (e.g. dust, pollution, tobacco smoke) and exercise. Family history of asthma and low birth weight may predispose people to the condition. Other risk factors include increasing age, lower social class and urban dwelling.[P3] Although common in children and young adults, asthma can affect people at any time of life.

Asthma is distinguished from other related conditions such as chronic obstructive pulmonary disease (COPD) or emphysema through reversible rather than progressive airway narrowing (although evidence is emerging that people with asthma do have some degree of decline in lung function over time). Prevalence has increased considerably over recent decades, in both developed and developing countries. Reasons are complex, reflecting environmental and lifestyle factors. In the UK there are 5.2 million people (9%) with asthma, including 590,000 teenagers. In England and Wales the number of people affected is around 4.7 million. Although severe exacerbations of asthma may cause death, mortality from the condition is relatively low compared with other respiratory diseases such as COPD. Respiratory disease accounts for greater mortality in the UK (24% of total deaths) than coronary heart disease (21%) or non-respiratory cancer (19%). However, asthma is responsible for only 1% of respiratory deaths.[P3]

4.2. Management

The management of asthma includes several inter-linked approaches, including medication (e.g. bronchodilators, corticosteroids), lifestyle modification, environmental changes (e.g. minimising the impact of allergens in the home or workplace), patient education (e.g. to encourage self-management and improve concordance with medication) and regular monitoring to assess disease control. Management is primarily the responsibility of the GP in collaboration with the patient, although specialist intervention may be required in severe cases. The aims of treatment are to relieve symptoms (e.g. wheeze, cough), improve health-related quality of life (including ability to work, study or sleep), improve lung function [i.e. forced expiratory volume 1 (FEV_1); peak expiratory flow rate, (PEF)], minimise the requirement for relief (e.g. short-acting $beta_2$ agonists) and rescue (oral corticosteroids) medication and reduce adverse effects associated with medication.

The British Thoracic Society (BTS),[P4] in collaboration with the Scottish Intercollegiate Guidelines Network (SIGN), have published clinical guidelines on asthma. The guidelines cover a variety of aspects of management, including pharmacological management. They propose a stepwise approach to achieving symptom control (Appendix 9.1). Treatment is initiated at the step most appropriate to the initial severity of asthma and the person's day-to-day needs, with the aim of achieving early control of symptoms. Control is maintained by stepping up treatment as necessary and stepping down when control is good.

First-line treatment in mild intermittent asthma is with an inhaled short-acting $beta_2$ agonist, as required for symptom relief (e.g. salbutamol or terbutaline). Treatment is stepped up with the introduction of regular preventer therapy with ICS in addition to symptomatic use of an inhaled short-acting $beta_2$ agonist (Step 2). If necessary, a LABA is added (Step 3) and if control is still not adequate the dose of the ICS can be increased, in addition to introduction of a fourth drug (such as an oral $beta_2$ agonist or a leukotriene receptor antagonist) (Step 4). If response remains poor, specialist care may be initiated with regular use of oral corticosteroids (e.g. prednisolone), in addition to the other drugs.

4.2.1. Inhaled corticosteroids (ICS)

ICS work to reduce bronchial inflammation. They are recommended for prophylactic treatment of asthma when patients are using a short-acting $beta_2$ agonist more than three times per week or if symptoms disturb sleep more than once per week, or if the patient has suffered exacerbations in the last 2 years requiring a systemic corticosteroid or a nebulised bronchodilator. Corticosteroid inhalers should be used regularly for maximum benefit.

There are currently five ICS licensed in the UK for adults (see Appendix 9.2 for details of delivery devices):

- beclometasone dipropionate [AeroBec (3M), AeroBec Forte (3M), Asmabec Clickhaler (Celltech), Beclazone Easi-Breathe (IVAX), Becloforte (Allen and Hanburys), Beclometasone Cyclocaps (APS), Becodisks (Allen and Hanburys), Becotide (Allen and Hanburys), Easyhaler (Ranbaxy), Filair (3M),

Filair Forte (3M), Qvar (3M) and Pulvinal Beclometasone Dipropionate (Trinity)]
- budesonide [Budesonide Cyclocaps (APS), Novolizer (Viatris), Pulmicort (AstraZeneca)]
- ciclesonide [Alvesco (Altana Pharma)]
- fluticasone propionate [Flixotide (Allen and Hanburys)]
- mometasone furoate [Asmanex (Schering-Plough)].

Beclometasone dipropionate, budesonide and fluticasone propionate have been used for some time, whereas ciclesonide and mometasone are relatively new. There are a variety of delivery systems including pressurised metered-dose inhalers (pMDI), breath-activated pMDIs, dry powdered formulations and nebulisers. Chlorofluorocarbons (CFCs) have been the traditional propellant in pMDIs, but with the phasing out of CFCs they are being replaced by ozone-friendly hydrofluoroalkanes (HFAs). Spacer chambers can be attached to pMDIs to make them easier to use and improve drug delivery to the lungs.

Standard daily recommended doses of ICS are 200 micrograms (µg) twice daily for budesonide and beclometasone dipropionate, 100–250 µg twice daily for fluticasone propionate, 200–400 µg per day for mometasone furoate and 160 µg daily for ciclesonide (BNF, No. 50).[P5] The BTS recommends titrating to the lowest dose at which effective control is maintained. In adults this can be up to 800 µg/day (for budesonide or beclometasone dipropionate).[P4] Fluticasone is considered clinically equivalent to budesonide or beclometasone dipropionate at half the dose (however, HFA-propelled beclometasone dipropionate is regarded as clinically equivalent to fluticasone at the same dose).

If maintenance therapy with an ICS does not adequately control symptoms, there are a number of potential treatment options. One is to continue with the ICS but to increase the dose to the higher end of the recommended range (e.g. up to 800 µg). However, this increases the risk of adverse effects. An alternative is to add a LABA. Adding a LABA may be preferential as results of dose–response studies suggest that higher doses of ICS may worsen the overall therapeutic ratio (that is, the ratio of the maximally tolerated dose of a drug to the minimally curative or effective dose).[P6]

4.2.2. Long-acting beta$_2$ agonists (LABA)

Two LABAs are licensed for use in the UK, salmeterol (Serevent) and formoterol (Foradil; Oxis). Like short-acting beta$_2$ agonists, LABAs have a bronchodilatory action, expanding the bronchial airways to improve the passage of air. They are recommended in addition to existing inhaled corticosteroid therapy, rather than replacing it. They can be used in combination with inhaled corticosteroids in separate inhalers, or combined in one inhaler. There are two licensed combination inhalers in the UK:

- budesonide + formoterol fumarate (Symbicort); available as dry powder only
- fluticasone propionate + salmeterol (as xinafoate) (Seretide); available as dry powder or aerosol.

The two LABAs differ chemically, with formoterol associated with a more rapid onset of action. Standard daily recommended doses vary according to severity. In mild asthma a typical dose of fluticasone propionate/salmeterol is 100/50 µg twice daily. This can be titrated up to 500/50 µg twice daily. Correspondingly, a typical dose of budesonide/formoterol is 80/4.5 µg twice daily, titrated up to 320/9 µg twice daily in severe cases.

As mentioned, clinical guidelines recommend adding a LABA to inhaled corticosteroids as a first-line add-on therapy.[P4] Once a LABA has been added there are three main options:

- Continuing therapy with ICS and LABA if response is adequate following the introduction of LABA. After a period of maintenance therapy, a 'step-down' may be appropriate.
- If there is a response to LABA but control is still not adequate, then the dose of the IC can be increased to the higher end of the range (e.g. up to 800 µg for budesonide or equivalent). Progression to Stage 4 of the pathway is recommended if control is still not achieved.
- If there is no response then the LABA should be withdrawn and the ICS dose should be increased up to the higher end of the dose range (e.g. up to 800 µg for budesonide or beclometasone dipropionate). If control is still not adequate, other therapies could be added on a trial basis (e.g. leukotriene receptor antagonists, theophylline). Progression to Stage 4 of the pathway is recommended if control is still not achieved.

Given the vast range of options available in the pharmacological management of chronic asthma, an assessment of clinical effectiveness and cost-effectiveness of the various strategies is required. Specifically, an assessment is needed of the relative

benefits of the different ICS; and of the two ICS and LABA combination inhalers. It is also necessary to assess the benefits and adverse effects of combined treatment with an ICS and a LABA compared with continuing ICS alone (including increasing the dose of the IC) in situations of worsening asthma control.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1. Search strategy

- A search strategy will be devised and tested by an experienced information scientist. The strategy will be designed to identify two different types of study: (i) studies reporting the clinical effectiveness of inhaled corticosteroids and long-acting beta$_2$ agonists; and (ii) studies reporting the cost-effectiveness of inhaled corticosteroids and long-acting beta$_2$ agonists.
- A number of electronic databases will be searched, including: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE) and the NHS Economic Evaluation Database (NHS EED); MEDLINE (Ovid); EMBASE (Ovid); National Research Register; Current Controlled Trials; ISI Proceedings; Web of Science; and BIOSIS. Bibliographies of related papers will be assessed for relevant studies where possible.
- The manufacturers' submissions to NICE will be assessed for any additional studies.
- Experts will be contacted to identify additional published and unpublished references.
- Searches will be carried out from the inception date of the database until February/March 2006 (for clinical effectiveness and cost-effectiveness studies). All searches will be limited to the English language. The searches will be updated around October 2006.
- Searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see Section 6.5b).

5.2. Inclusion and exclusion criteria

5.2.1. Intervention

Studies reporting evaluations of the following inhaled corticosteroids will be included:

- beclometasone dipropionate
- budesonide
- ciclesonide
- fluticasone propionate
- mometasone furoate.

Studies reporting evaluations of the following inhaled corticosteroids combined with long-acting beta$_2$ agonists in the same inhaler (i.e. combination inhalers) will be included:

- budesonide + formoterol fumarate
- fluticasone propionate + salmeterol (as xinafoate).

Studies reporting treatment duration of 4 weeks or less will not be included

5.2.2. Comparators

- The inhaled corticosteroids will be compared with each other.
- The combination inhalers will be compared with each other and with inhaled corticosteroids only. They will also be compared with inhaled corticosteroids and long-acting beta$_2$ agonists administered in separate inhalers, in terms of any adverse events likely to impact on costs and cost-effectiveness.
- Studies testing different doses of the same agent or the same agent delivered by different inhaler devices will not be included.

5.2.3. Types of studies

- Fully published randomised controlled trials (RCTs) or systematic reviews of RCTs. Double blinding is not a prerequisite for inclusion, although blinding will be assessed as part of critical appraisal (see Section 5.3). Indicators of a 'systematic' review include an explicit search strategy and inclusion/exclusion criteria.
- Studies published as abstracts or conference presentations from 2004 onwards will be included in the primary analysis of clinical and cost-effectiveness only if sufficient details are presented to allow an appraisal of the methodology and assessment of results.

5.2.4. Population

- Adults and children aged 12 years and over diagnosed with chronic asthma. Studies in which the patient group is asthmatics with a specific related co-morbidity (e.g. bronchitis; cystic fibrosis) will not be included, except for chronic obstructive pulmonary disease (COPD) as is requested in the NICE Scope.
- Where data are available, clinical effectiveness and cost-effectiveness will be reported for patient subgroups, in terms of disease severity, age and smokers/non-smokers. Concordance according to different patient subgroups will be assessed where data allow.
- Studies reporting the treatment of acute exacerbations of asthma will not be included.

5.2.5. Outcomes

- Studies reporting one or more of the following outcomes will be included:
  - objective measures of lung function (e.g. FEV_1, PEF)
  - symptom-free days and nights
  - incidence of mild and severe acute exacerbations (e.g. mild – requiring unscheduled contact with healthcare professional; severe – requiring hospitalisation, short-term 'rescue' use of systemic corticosteroids or visit to accident and emergency department)
  - adverse effects of treatment
  - health-related quality of life
  - mortality.
- Titles and abstracts of studies identified by searching will be screened by one reviewer based on the above inclusion/exclusion criteria. A second reviewer will check a random 10% of these with any discrepancies resolved through discussion and involvement of a third reviewer where necessary.
- Full papers of studies which appear potentially relevant on title or abstract will be requested for further assessment. All full papers will be screened independently by one reviewer and checked by a second, and a final decision regarding inclusion will be agreed. Any discrepancy will be resolved by discussion with involvement of a third reviewer where necessary.

5.3. Critical appraisal and data extraction

- A number of recently updated Cochrane systematic reviews of the effectiveness of comparisons of ICS[P7–P9] and ICS with LABA[P10] have been published. Where possible, these and other high-quality systematic reviews will be used to assess clinical effectiveness. RCTs published since the reviews were last updated would be prioritised for data extraction and critical appraisal. The findings of the systematic reviews and the supplemental RCTs will be used together to inform the assessment of clinical effectiveness.
- Data extraction and critical appraisal will be performed by one reviewer using a standardised data extraction form (see Appendix 9.4). A second reviewer will check the form for accuracy and completeness. Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary.
- The quality of included RCTs and systematic reviews (Cochrane or otherwise) will be assessed using NHS CRD (University of York) criteria[P11] (see Appendix 9.5).

5.4. Methods of analysis/synthesis

- Clinical effectiveness studies will be synthesised through a narrative review with tabulation of results of included studies.
- Where data are of sufficient quantity, quality and homogeneity, a meta-analysis of the clinical effectiveness studies will be performed, using appropriate software.
- To minimise clinical heterogeneity, the synthesis will seek to group together studies reporting similar populations and interventions.
  - For example, comparisons of different ICS delivered via pMDI may be considered separately to those comparing different ICS delivered by dry powder formulations.
  - Similarly, comparisons of ICS where a CFC propelled pMDI is used may be grouped separately to those where the propellant is HFA, given suggested differences in potency.[P9]
  - Dose equivalence will need to be taken into account as far as the evidence allows, particularly where a study compares a CFC pMDI ICS with an HFA pMDI ICS.

6. Methods for synthesising evidence of cost-effectiveness

6.1. Search strategy

Refer to Appendix 9.3 for details of the draft search strategy for MEDLINE. The sources to be searched are similar to those used in the clinical-effectiveness review (see Section 5.1). All searches will be limited to the English language.

6.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical with those for the systematic review of clinical effectiveness, except that:

- Non-randomised studies may be included (e.g. decision model-based analyses or analyses of patient-level cost and effectiveness data alongside observational studies).
- Full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost–consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data.)

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

6.3. Study quality assessment

The methodological quality of the economic evaluations will be assessed using accepted frameworks such as the international consensus-developed list of criteria developed by Evers and colleagues[P12] and Drummond and colleagues.[P13] For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling of Philips and colleagues.[P14] We will examine recent published studies which are carried out from the UK NHS and PSS perspective in more detail.

6.4. Data extraction strategy

Data will be extracted by one researcher into two summary tables: one to describe the study design of each economic evaluation and the other to describe the main results.

- The following data will be extracted into the study design table: author and year; model type or trial based; study design [e.g. cost-effectiveness analysis (CEA) or cost–utility analysis (CUA)]; service setting/country; study population; comparators; research question; perspective, time horizon and discounting; main costs included; main outcomes included; sensitivity analyses conducted; and other notable design features.
- For modelling-based economic evaluations, a supplementary study design table will record further descriptions of model structure (and note its consistency with the study perspective, and knowledge of disease/treatment processes), sources of transition and chance node probabilities, sources of utility values, sources of resource use and unit costs, handling of heterogeneity in populations and evidence of validation (e.g. debugging, calibration against external data, comparison with other models).
- For each comparator in the study, the following data will be extracted into the results table: incremental cost; incremental effectiveness/utility and incremental cost-effectiveness ratio(s). Comparators excluded on the basis of dominance or extended dominance will also be noted. The original authors' conclusions will be noted, and also any issues they raise concerning the generalisability of results. Finally, the reviewers' comments on study quality or generalisability (in relation to the NICE scope) will be recorded.

6.5. Synthesis of evidence on costs and effectiveness

(a) Published and submitted economic evaluations

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base from published economic evaluations and sponsor submissions to NICE.

(b) Economic modelling

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and PSS using a decision analytic model. The evaluation will be constrained by available evidence. If possible, the incremental cost-effectiveness of the intervention drug classes and the specified comparators will be estimated in terms of cost per quality-adjusted life-year (QALY) gained, as well as the cost per acute exacerbation avoided.

Model structure will be determined on the basis of research evidence and clinical expert opinion of:

- the biological disease process of chronic asthma in adults (i.e. knowledge of the natural history of the disease)
- the main diagnostic and care pathways for patients in the UK NHS context [both with and without the intervention(s) of interest] and
- the disease states or events that are most important in determining patients' clinical outcomes, quality of life and consumption of NHS or PSS resources.

For example, we will need to consider developing a natural history model of chronic asthma which could reflect factors such as: patient age, asthma severity (e.g. FEV_1, PEF, frequency of acute exacerbations), whether their asthma is predominantly self-managed or GP/primary care nurse managed. The extent to which the model **is able** to reflect these various factors fully will depend upon the available research literature. The extent to which the model **needs to** reflect these factors will depend on how plausible it is that they impact on either the effectiveness or cost impacts of the interventions.

Parameter values will be obtained from relevant research literature, including our own systematic review of clinical effectiveness. Where required parameters are not available from good-quality published studies in the relevant patient group we may use data from sponsor submissions to NICE or expert clinical opinion. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS in 2005 (this is the most recent year for which NHS National Schedule of Reference Cost data will be available). Cost data will be identified from NHS and PSS reference costs or, where these are not relevant,

they will be extracted from published work or sponsor submissions to NICE as appropriate. If insufficient data are retrieved from published sources, costs may be obtained from individual NHS Trusts or groups of Trusts.

To capture health-related quality of life effects, utility values will be sought directly from the relevant research literature. Ideally utility values will be taken from studies that have been based on 'public' (as opposed to patient or clinician) preferences elicited using a choice-based method.

Analysis of uncertainty will focus on cost–utility, assuming the cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented both using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

The simulated population will be defined on the basis of both the published evidence about the characteristics of UK adult population with asthma, and the populations for which good-quality clinical effectiveness is available. The base-case results will be presented for the population of UK adults with asthma. The time horizon for our analysis will be between 1 and 5 years, sufficiently long to reflect both the chronic nature of the disease and estimate differences in rare outcomes, such as asthma-related deaths. The perspective will be that of the NHS and PSS. Both cost and outcomes (QALYs) will be discounted at 3.5%.[P15]

Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be conducted as required (e.g. health-related quality of life, epidemiology and natural history). This is in accordance with the methodological discussion paper produced by InterTASC in January 2005.

7. Handling the company submission(s)

All information submitted by the manufacturers/sponsors as part of the NICE appraisal process will be considered if received by the TAR team no later than 2 August 2006. Information arriving after this date will not be considered.

Economic evaluations included in sponsors' submission will be assessed against the NICE guidance for the Methods of Technology Appraisals (NICE, 2004)[P15] and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used.

Incremental cost-effectiveness ratios (ICERs) estimated from consultee models will be compared with results from the Assessment Group's analysis, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

Any 'commercial-in-confidence' data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name, e.g. in brackets).

8. Competing interests of authors

There are no competing interests.

9. Appendices

9.1. SIGN/BTS pharmacological management pathway for chronic asthma.

9.2. Inhaled steroids and devices.

9.3. MEDLINE search strategy.

9.4. Data extraction form (RCTs and systematic reviews).

9.5. Quality assessment criteria (RCTs and systematic reviews).

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Appendix 3

Systematic reviews: search strategies

Clinical effectiveness search strategy: corticosteroids in asthma

The following databases were searched:
The Cochrane Database of Systematic Reviews (CDSR)
The Cochrane Central Register of Controlled Trials
CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE)
NHS Economic Evaluation Database (NHS EED)
MEDLINE (Ovid)
EMBASE (Ovid)
National Research Register
Current Controlled Trials
Web of Knowledge Science Citation Index and ISI Proceedings
BIOSIS

Ovid MEDLINE 1966–2006. Run on 15 February 2006; update search run on 26 September 2006:

1 exp asthma/
2 asthma.ti,ab.
3 1 or 2
4 exp randomized controlled trials/
5 exp random allocation/
6 controlled clinical trials/
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 exp double blind method/
10 exp single blind method/
11 (randomiz$ or randomis$).
12 placebo.ti,ab.
13 (singl$ or doubl$ or tripl$ or trebl$ or blind$).ti,ab.
14 (trial$ or study or studies or method$).ti,ab.
15 13 or 14
16 meta analysis/
17 (meta analys?s or metaanalys?s).ab,pt,ti.
18 (systematic$ adj2 (review$ or overview$)).ti,ab.
19 or/16-18 28348
20 or/4-12,15,19
21 (letter or editorial or comment).pt.
22 20 not 21
23 3 and 22
24 beclomethasone/
25 bdp.ti,ab.
26 budesonide/
27 (beclomet?asone or budesonide or ciclesonide or fluticasone or mometasone).mp.
28 (asmabec or belclazone or cyclocaps or becodisks or becotide or filair or qvar or pulvinal or pulmicort or flixotide or aerobec or becloforte or novoliser or viatris or alvesco or asmanex or novolizer or easyhaler or symbicort or seretide or serevent or atimos or foradil).mp.
29 exp glucocorticoids/
30 (corticosteroid$ or glucocorticoid$ or steriod$).ti,ab.
31 or/24-30
32 31 not 21
33 23 and 32
34 limit 33 to (humans and english language)
35 or/24-28
36 35 not 21
37 23 and 36
38 limit 37 to (humans and english language)

Cost-effectiveness search strategy: corticosteroids in asthma

The search strategy was translated and run in:
MEDLINE (Ovid)
MEDLINE in Process (Ovid)
EMBASE (Ovid)
Cochrane Database of Systematic Reviews (CDSR)
Cochrane Central Register of Controlled Trials (CCTR)
Science Citation Index (Web of Knowledge)
CRD NHS Economic Evaluation Database, DARE and HTA databases and EconLit.

Ovid MEDLINE 1966 to March Week 1 2006. Searched on 09 March 2006; update search on 6 October 2006:

1 exp Asthma/)
2 asthma.ti,ab
3 1 or 2
4 exp ECONOMICS/
5 exp ECONOMICS, HOSPITAL/
6 exp ECONOMICS, PHARMACEUTICAL/
7 exp ECONOMICS, NURSING/
8 exp ECONOMICS, DENTAL/
9 exp ECONOMICS, MEDICAL/
10 exp "Costs and Cost Analysis"/

11 Cost-Benefit Analysis/
12 VALUE OF LIFE/
13 exp MODELS, ECONOMIC/
14 exp FEES/ and CHARGES/
15 exp BUDGETS/
16 (economic$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharma economic$).tw.
17 (cost$ or costly or costing$ or costed).tw.
18 (cost$ adj2 (benefit$ or utilit$ or minim$ or effective$)).tw.
19 (expenditure$ not energy).tw.
20 (value adj2 (money or monetary)).tw.
21 budget$.tw.
22 (economic adj2 burden).tw.
23 "resource use".ti,ab.
24 or/4-22
25 news.pt.
26 letter.pt.
27 editorial.pt.
28 comment.pt.
29 or/25-28
30 24 not 29
31 3 and 30
32 Beclomethasone/
33 budesonide/
34 bdp.ti,ab.
35 (beclometasone or beclomethasone or budesonide or ciclesonide or fluticasone or mometasone).mp.
36 (pulmicort or flixotide or asmanex or novoliser or becotide or asmabec or belclazone or cyclocaps or becodisks or filair or qvar or pulvinal or aerobec or becloforte or viatris or alvesco).mp.
37 32 or 33 or 34 or 35 or 36
38 31 and 37
39 limit 38 to (humans and english language)

Quality of life search strategy: asthma in adults and children

This search strategy was translated and run in:
MEDLINE (Ovid)
MEDLINE in Process (Ovid)
EMBASE
Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CDSR and CCTR)

Ovid MEDLINE 1966 to May Week 1 2006.
Searched on 11 May 2006; update search run on 6 October 2006:

1 exp Asthma/
2 asthma.ti,ab.
3 1 or 2
4 value of life/
5 quality adjusted life year/
6 quality adjusted life.ti,ab.
7 (qaly$ or qald$ or qale$ or qtime$).ti,ab.
8 disability adjusted life.ti,ab.
9 daly$.ti,ab.
10 health status indicators/
11 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
12 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
13 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.
14 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
15 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
16 (euroqol or euro qol or eq5d or eq 5d).ti,ab.
17 (hql or hqol or h qol or hrqol or hr qol).ti,ab.
18 (ACQ or asthma control questionnaire$).ti,ab.
19 (AQLQ or asthma quality of life questionnaire$).ti,ab.
20 (SGRQ or (St George$ adj5 Respiratory Questionnaire$)).ti,ab.
21 (hye or hyes).ti,ab.
22 health$ year$ equivalent$.ti,ab.
23 health utilit$.ab.
24 (hui or hui1 or hui2 or hui3).ti,ab.
25 disutil$.ti,ab.
26 rosser.ti,ab.
27 quality of well being.ti,ab.
28 quality of wellbeing.ti,ab.
29 qwb.ti,ab.
30 willingness to pay.ti,ab.
31 standard gamble$.ti,ab.
32 time trade off.ti,ab.
33 time tradeoff.ti,ab.
34 tto.ti,ab. (221)
35 (index adj2 well being).mp.
36 (quality adj2 well being).mp.
37 (health adj3 utilit$ ind$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
38 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp.
39 quality adjusted life year$.mp.
40 (15D or 15 dimension$).mp.
41 (12D or 12 dimension$).mp.

42 rating scale$.mp.
43 linear scal$.mp.
44 linear analog$.mp.
45 visual analog$.mp.
46 (categor$ adj2 scal$).mp.
47 or/4-46
48 (letter or editorial or comment).pt.
49 47 not 48
50 3 and 49
51 limit 50 to english language

Adverse events searches: corticosteroids for asthma

This search strategy was translated and run in:
MEDLINE (Ovid)
MEDLINE in Process (Ovid)
EMBASE
Cochrane Database of Systematic Reviews
Cochrane Central Register of Controlled Trials and DARE

Ovid MEDLINE 1966 to May Week 3 2006.
Searched on 26 May 2006:

1 exp Asthma/
2 asthma.ti,ab.
3 1 or 2
4 (beclometasone or beclomethasone or budesonide or ciclesonide or fluticasone or mometasone).mp.
5 (pulmicort or flixotide or asmanex or novoliser or becotide or asmabec or belclazone or cyclocaps or becodisks or filair or qvar or pulvinal or aerobec or becloforte or viatris or alvesco).mp.
6 Beclomethasone/ae, po, to
7 budesonide/ae, po, to
8 Adrenal Cortex Hormones/ad, ae, po, to [Administration & Dosage, Adverse Effects, Poisoning, Toxicity]
9 exp *Pregnenediones/ae, to [Adverse Effects, Toxicity]
10 steroid$.ti,ab.
11 (inhal$ or oral).ti,ab.
12 (toxicity or poisoning or adverse effects).fs.
13 10 and 11 and 12
14 4 and 12
15 5 and 12
16 6 or 7 or 8 or 9 or 13 or 14 or 15
17 (safe or safety).ti,ab.
18 side effect$.ti,ab.
19 tolerability.ti,ab.
20 toxicity.ti,ab.
21 (adverse adj3 (effect or effects or reaction or reactions or event or events or outcome or outcomes or consequence$)).ti,ab.
22 exp Dose-Response Relationship, Drug/
23 17 or 18 or 19 or 20 or 21 or 22
24 long term.ti,ab. (296250)
25 short term.ti,ab. (79427)
26 16 and 23 and 24 and 3
27 16 and 23 and 25 and 3

Healthcare resource use and asthma severity or symptom control searches

This search strategy was translated and run in Ovid MEDLINE, Ovid MEDLINE in Process and Ovid EMBASE.

Ovid MEDLINE 1966 to July Week 4 2006.
Searched on 2 August 2006:

1 "healthcare resource use".mp.
2 exp Health Care Costs/
3 economics/ or exp resource allocation/
4 hcru.ab,ti.
5 health care utilisation.mp
6 1 or 2 or 3 or 4 or 5
7 "Anti-Asthmatic Agents"/
8 Asthma/
9 asthma$.ti,ab.
10 Asthma, Exercise-Induced/
11 7 or 8 or 9 or 10
12 "Drug Administration Schedule"/
13 "Needs Assessment"/
14 "Severity of Illness Index"/
15 (severe$ or severity).ti,ab.
16 (symptom$ adj3 control$).mp
17 (asthma adj3 control$).mp
18 exp disease management/
16 or/12-18
17 6 and 11 and 16

Appendix 4

Systematic review of clinical effectiveness: data extraction forms

Study	Treatment	Participants	Outcomes
Ref.: 248 **Author:** Aalbers *et al*. **Year:** 2004 **Country:** Denmark, Finland, Germany, Norway, Sweden, The Netherlands **Study design:** Double-dummy, double-blind/ open-extension, parallel group, RCT **Number of centres:** 93 **Funding:** Sponsored by AZ (manufacturers of BUD + FF)	**Group A:** *n* = 219 Drug(s): BUD + FF Dose: 320 + 9 μg b.d. (adjustable to 160–640 μg BUD + 4.5–18 μg FF b.d. *in open extension period* [months 2–7]) Delivery: DPI Duration: 1 month (double-blind) + 6 months (open-label) **Group B:** *n* = 215 Drug(s): BUD + FF Dose: 320 + 9 μg b.d. Delivery: DPI Duration: 1 month (double-blind) + 6 months (open-label) **Group C:** *n* = 224 Drug(s): FP + SAL Dose: 250 μg FP + 50 μg SAL b.d. Delivery: DPI Duration: 1 month (double-blind) + 6 months (open-label) **Run-in period:** Duration: 10–14 days ICS: any LABA: not allowed Relief: terbutaline sulfate or salbutamol **Additional treatment allowed:** • Relief: terbutaline sulfate or salbutamol • Other: none (inhaled cromones, leukotriene modifiers, additional β_2-agonists, xanthines, β-blockers and inhaled anticholinergics explicitly disallowed)	**Number randomised:** 658 **Sample attrition/drop-out:** *n* = 83 (25 for AEs; 18 ineligible; 6 lost to follow-up; 34 other) **Inclusion criteria:** • At study entry: – age ⩾12 years – history of asthma for ⩾6 months – FEV_1 ⩾50% predicted – maintained on ICS for ⩾3 months, with stable dosage of 500–1200 μg in previous 1 month • During last 7 days of run-in: – total asthma symptom score ⩾1 on 4 days – PEF 50–85% of post-bronchodilatory PEF – compliant **Exclusion criteria:** • Respiratory tract infection within previous 1 month • Smoking history ⩾10 pack-years • Systemic steroids in previous 1 month **Baseline characteristics:** • Male:female = 299:359 • Mean age (range) = 46 (12–85) years • Median duration of asthma (range) = 12–13 years (0–73) (range of values across groups) • Asthma daytime symptom score (range) = 1.6 (0.1–5.0) • ICS dose at entry (range) = 735 (400–1600) • LABA use at entry = 183 (28%) • Combinations of ICS + LABA at entry = 298 (45%) • FEV_1: litres (range) = 2.73 (0.98–6.11); % predicted (range) = 84% (45–156%) • Mean PEF after bronchodilator, l/minute (range) = 467 (167–951) • Reliever use, occasions/day (range) = 1.8 (0–12.5) • Reliever-free days (range) = 27% (0–100%)	**Primary measure:** Odds of having a well-controlled asthma week (WCAW), defined as: • No night awakenings • No exacerbations • No change in treatment due to AEs • At least two of the following: – asthma symptom score >1 on ⩽2 days – ⩽2 days with reliever use – ⩽4 reliever uses – a.m. PEF ⩾80% of predicted every day **Secondary measures:** • a.m. and p.m. PEF • Daytime symptom score • Nocturnal awakenings • Reliever use • FEV_1 • Total asthma control weeks, defined as: – asymptomatic – no night awakenings – no exacerbations – no reliever use – no change in treatment due to AEs – a.m. PEF ⩾80% of predicted every day • Exacerbations (oral steroids for ⩾3 days, ER visits and/or hospitalisation) **Method of assessing outcomes:** • Daily patient diaries: – PEF (a.m. and p.m.) – symptoms, effects and extra medication • Spirometry (study entry; post run-in; after 1 month blinded Rx; after 6 months open extension) **Length of follow-up:** None beyond 7 months study period

continued

Results

Outcomes	Group A (n = 219)	Group B (n = 215)	Group C (n = 224)	p-Value
FEV_1				
A.m. PEF				
Mean change, baseline to month 7 – l/minute:	27.5[a]	34[a]	35[a]	NS[b,c,d]
SFDs				
Nocturnal awakenings – (%):	12.5%[a]	19.5%[a]	16%[a]	<0.05[b]
Mean difference (95% CI)		4.7%[b] (0.3 to 9.2%)[b]		
Acute exacerbations – n	35[a]	50[a]	59[a]	NS[b,d]; 0.018[c]
Rate (n/months)	0.024	0.036	0.041	
Rate reduction (95% CI)		32.0%[b] (–4.8 to 55.9%)[b]	39.7%[c] (8.3 to 60.3%)[c]	
Systemic corticosteroids, ⩾3 days courses of oral steroids – n	33[a]	46[a]	52[a]	
Use of reliever, mean times/day	0.58[a]	0.94[a]	0.80[a]	<0.01[b]; <0.05[c]
Mean difference (95%CI)		0.30[b] (0.12 to 0.48)[b]	0.23[c] (0.05 to 0.41)[c]	
Mortality				
QoL				
AEs – n (%):				
Any	124 (57%)	124 (58%)	147 (66%)	0.847[b,f]; 0.064[c,f]; 0.095[e,f]
Serious	8 (4%)	11 (5%)	5 (2%)	0.490[b,f]; 0.412[c,f]; 0.130[e,f]
Oral candidiasis	(1%)	(2%)	(3%)	0.446[b,g]; 0.175[c,g]; 0.545[e,g]
Dysphonia	(1%)	(1%)	(7%)	1.000[b,g]; 0.001[c,g]; 0.001[e,g]
Headache	(3%)	(2%)	(4%)	0.544[b,g]; 0.800[c,g]; 0.261[e,g]
Discontinuation due to AEs	27 (12%)	31 (14%)	25 (11%)	0.574[b,f]; 0.768[c,f]; 0.320[e,f]
Other:				
Well-controlled asthma weeks (week 32)	49%[a]	66%[a]	56%[a]	

[a] Values estimated from graphs.
[b] Group A vs Group B.
[c] Group A vs Group C.
[d] Reported as "no significant difference" in text, but no p-values provided.
[e] Group B vs Group C (primary efficacy comparison).
[f] Two-tailed Fisher's exact test, *calculated by reviewer*.
[g] Two-tailed Fisher's exact test, *calculated by reviewer (incidence approximated to nearest integer; proportions only reported in paper)*.

Comments

- ORs (95% CI) for WCAWs:
  - over entire treatment period: Group B vs Group C = 1.289 (0.981 to 1.694; p = NS)
  - over open extension phase (months 2–7): Group A vs Group B = 1.335 (1.001 to 1.783; p = 0.049); Group A vs Group C = 1.048 (0.791 to 1.391; p = NS)
- One-fifth of patients across all groups failed to achieve a single WCAW throughout the study period
- 18–21% of patients achieved a TACW throughout the study period, with no differences between groups
- NNT to avoid 1 exacerbation over 1 year, Group A vs Group C = 4.9
- P.m. PEF was significantly lower in Group A. Mean differences, l/minute (95% CI): Group A vs Group B = 9.6 (1.8 to 17.5; $p < 0.05$); Group A vs Group C = 8.4 (0.7 to 16.1; $p < 0.05$)
- FEV_1 only reported for initial 4-week treatment period
- In Group A during adjustable dosage phase (months 2–7): 95 (45%) were able to step down to lower dosage; 91 (43%) required at least one step-up to higher dosage; 67% of step-up periods resulted in regained asthma control within 7 days
- For use of reliever and nocturnal awakenings, mean differences (reported in text) correspond poorly with apparent difference in mean values (shown in figures)

continued

Methodological comments

- **Allocation to treatment groups**: block randomisation according to schedule computer-generated by a third party
- **Blinding**: double-blind, double-dummy for initial 1 month; subsequently open-label (NB. all extracted data relate to open-label extension, as does primary efficacy variable)
- **Comparability of treatment groups**: the groups are reported to be comparable with regard to demographic and baseline disease characteristics; however, no measures of variability are reported for baseline variables (ranges only)
- **Method of data analysis**: WCAW odds and treatment differences estimated using generalised estimating equation with a logistic link function, an exchangeable dependency model and subject as cluster. Exacerbation data compared between groups using a Poisson regression model with the time in the study as an offset variable. Changes in diary card variables were analysed using ANOVA models with adjustments for country and baseline values
- **Sample size/power calculation**: designed to detect (with 80% power; $\alpha = 0.05$) an OR of 1.41, assuming the odds of a WCAW were 0.67 (i.e. an increase from 40 to 48.5%)
- **Attrition/drop-out**: 4 patients were excluded from analysis for primary end-point (no diary card data). All randomised patients included in safety analyses. Unclear which patients are included in other analyses. 12% of Group A, 14% of Group B and 11% of Group C discontinued treatment. Withdrawals due to unspecified ("other") reasons in 7, 5 and 4% of Groups A, B and C, respectively

General comments

- **Generalisability**: relatively inclusive eligibility criteria
- **Outcome measures**: primary efficacy variable is a composite measure, incorporating objective (e.g. PEF) and subjective (e.g. symptom scores) measures. Physician-assessed efficacy variable (FEV_1) is only reported for initial 4-week treatment period (hence excluded from this analysis). All other efficacy variables are patient-reported
- **Inter-centre variability**: not reported; unclear whether randomisation was stratified by centre; ANOVA analyses used country as a covariate
- **Conflict of interests**: study sponsorship and one author from AZ (manufacturers of BUD + FF)

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Inadequate
5. Was the care provider blinded?	Inadequate
6. Was the patient blinded?	Inadequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Partial

ER, emergency room; NNT, number-needed-to-treat; NS, not significant; QoL, quality of life; TACW, Total Asthma Control Week.
From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 233 **Author:** Aubier *et al*. **Year:** 1999 **Country:** Not specified; investigators are from France, Germany and The Netherlands **Study design:** Multi-centre, parallel-group, double-blind, double-dummy, RCT **Number of centres:** Multi-centre, but units involved not specified (investigators are from 4 separate centres) **Funding:** sponsored by GlaxoWellcome (SFCB3019)	**Group A:** *n* = 167 Drug(s): FP + SAL (combination) + placebo Dose: 500 μg FP + 50 μg SAL b.d. Delivery: 2 separate DPIs (FP + SAL and placebo) Duration: 28 weeks **Group B:** *n* = 171 Drug(s): FP + SAL (concurrent) Dose: 500 μg FP + 50 μg SAL b.d. Delivery: 2 separate DPIs (FP and SAL) Duration: 28 weeks **Group C:** *n* = 165 Drug(s): FP + placebo Dose: 500 μg FP b.d. Delivery: 2 separate DPIs (FP and placebo) Duration: 28 weeks **Run-in period:** Duration: 2 weeks before randomisation ICS: continued treatment "with the same dose of their inhaled steroids" Relief: inhaled salbutamol only **Additional treatment allowed:** • Relief: inhaled salbutamol only • Other: "regular therapy" (e.g. anticholinergics, theophyllines, sodium cromoglycate) continued unchanged throughout the study period"	**Number randomised:** 503 **Sample attrition/drop-out:** *n* = 100 (54 for AEs; 16 lost to follow-up; 9 non-compliant; 1 not eligible; 20 not specified) **Sample crossovers:** None **Inclusion/exclusion criteria:** • Age >12 years • Documented clinical history of reversible airways disease • Treated with any ICS continuously for 12 weeks before run-in • Treated with BDP or BUD 1500–2000 μg/day or FP 750–1000 μg/day for 4 weeks before run-in • At the end of the 2-week run-in period: – symptom score ⩾2 on ⩾4 of the last 7 consecutive days – mean morning PEF >50% and <85% of maximum PEF 15 minutes after inhaled salbutamol 400 μg – FEV_1 50–100% of predicted value **Baseline characteristics:** • Male:female = 269:234 • Mean age (range) = 48 (12–79) years • Smoking history: current = 71 (14%); ex-smoker = 195 (39%); never smoked = 237 (47%) • Duration of asthma (years): <1 = 13 (3%); >1 to 5 = 116 (23%); >5 to 10 = 100 (20%); >10 = 274 (54%) • History of atopy = 260 (52%) • FEV_1: absolute mean = 2.36; % predicted = 73%; % reversibility = 17% • Mean morning PEF during run-in week 2 (l/minute) = 352	**Primary measure:** Mean morning PEF during weeks 1–12 **Secondary measures:** • Evening PEF • SFDs and SFNs • Days and nights when 'rescue' salbutamol was not required • FEV_1 (absolute and predicted) • Serum cortisol levels and 24-hour urinary cortisol excretion (assessed in a subset of 318 patients) • AEs • Compliance **Method of assessing outcomes:** • Clinic assessments in weeks –2, 0, 2, 4, 12, 20, 28 and 28 + 2 • Daily diary card, recording – (weeks –2 to 12) morning and evening PEF (highest reading of 3) – (weeks –2 to 28) changes in concomitant medication and AEs • At assessments in weeks 0, 12 and 28: – ECG – oropharyngeal examination – fasting morning venous blood samples • Compliance = number of doses used divided by the expected use **Length of follow-up:** 28-week treatment period + follow-up visit at week 28 + 2

continued

Results

Outcomes	Group A (*n* = 167)	Group B (*n* = 171)	Group C (*n* = 165)	*p*-Value
FEV_1, mean change from baseline to week 28 – l:	0.25[d]	0.15[d]	0.18[d]	0.454[b]; 0.061[c]
PEF, mean[a] change from baseline, l/minute (SE):				
a.m.: weeks 9–12	38 (3.9)	36 (3.8)	22 (4.0)	0.771[b]; 0.003[c]
a.m.: weeks 1–12	35 (3.1)	33 (3.1)	15 (3.1)	0.535[b]; <0.001[c]
p.m.: weeks 9–12	31 (3.8)	26 (3.7)	13 (3.9)	0.27[b]; <0.001[c]
p.m.: weeks 1–12	29 (3.1)	23 (3.0)	9 (3.1)	0.16[b]; <0.001[c]
SFDs – mean % (weeks 1–12)	38[d]	38[d]	28[d]	NS[b,e]
SFNs – mean % (weeks 1–12)	58[d]	55[d]	51[d]	NS[b,e]
Acute exacerbations				
Use of systemic corticosteroids				
Mortality				
QoL				
Patients experiencing AEs – *n* (%):	28 (17%)	24 (14%)	32 (19%)	0.547[b,f]; 0.570[c,f]
Asthma	4 (2%)	6 (4%)	3 (2%)	0.750[b,f]; 1.0[c,f]
Breathing disorders	5 (3%)	1 (<1%)	4 (2%)	0.118[b,f]; 1.0[c,f]
Cough	2 (1%)	0	5 (3%)	0.243[b,f]; 0.281[c,f]
Hoarseness/dysphonia	4 (2%)	2 (1%)	6 (4%)	0.444[b,f]; 0.541[c,f]
Throat irritation	2 (1%)	2 (1%)	5 (3%)	1.0[b,f]; 0.282[c,f]
Headaches	3 (2%)	1 (<1%)	2 (1%)	0.367[b,f]; 1.0[c,f]
Patients withdrawing because of AEs	16 (10%)	16 (9%)	22 (13%)	1.0[b,f]; 0.305[c,f]
Other				

[a] Adjusted mean, according to ANCOVA, with baseline data as a covariate.
[b] Group A vs Group B.
[c] Group A vs Group C.
[d] Values estimated from graphs.
[e] Reported as "no significant difference" in text, but no *p*-values provided.
[f] Two-tailed Fisher's exact test, *calculated by reviewer*.

Comments

- Mean compliance during weeks 1–28 was 93–94% for all treatment groups
- No clinically significant changes in laboratory values, physical examinations or vital signs were observed in any of the three treatment groups
- According to the specified analysis of the primary efficacy outcome (see 'Method of data analysis' in Methodological comments, below), FP + SAL combination and FP + SAL concurrent were deemed to be clinically equivalent

Methodological comments

Allocation to treatment groups: randomisation methods not specified
Blinding: "double-blind, double-dummy"; primary outcome assessed by (blinded) participants; identity and blinding of assessors of clinical parameters not reported
Comparability of treatment groups: the three treatment groups are reported to be "well balanced for demographic and baseline characteristics". From table of baseline characteristics the groups appear comparable although no statistical tests are reported
Method of data analysis:

- Mean PEF and FEV_1 were adjusted according to ANCOVA, with baseline data as a covariate
- Equivalence of Group A vs Group B was based on 90% CI (unstratified Wilcoxon rank sum) for mean difference in a.m. PEF between groups (Δ = 15 l/minute)
- Superiority of Group A vs Group C was based on *p*-values
- Symptom scores and salbutamol usage were compared using the van Elteren extension to the Wilcoxon rank sum test (*p*-values not reported)
- Common AEs were compared using the two-sided Fisher exact test (*p*-values not reported)

Sample size/power calculation: none reported
Attrition/drop-out: partially reported: AE-related withdrawals are described, but only incomplete details of the distribution of and reasons for other withdrawals are provided

continued

General comments	
• **Generalisability**: relatively inclusive eligibility criteria; not applicable to ICS-naïve population • **Outcome measures**: appropriate and relatively objective • **Inter-centre variability**: not reported; no stratification of randomisation by centre described • **Conflict of interests**: study was sponsored by manufacturers	
Quality criteria for assessment of experimental studies	
1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Primary outcome: adequate other outcomes: unknown
5. Was the care provider blinded?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Partial
From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.	

Study	Treatment	Participants	Outcomes
Ref.: 243 **Author:** Bateman *et al*. **Year:** 1998 **Country:** 4 countries (South Africa, UK, Spain and Portugal) **Study design:** Multi-centre, randomised, double-blind, double-dummy, parallel-group **Number of centres:** 44 **Funding:** GlaxoWellcome Research and Development	**Group A:** *n* = 121 Drug(s): FP/SAL + placebo Dose: 100/50 μg b.d. + placebo b.d. Delivery: FP/SAL combination via one Diskus inhaler + placebo via another Diskus inhaler Duration: 12 weeks **Group B:** *n* = 123 Drug(s): FP + SAL Dose: 100 + 50 μg b.d. Delivery: concurrent therapy via separate Diskus inhalers Duration: 12 weeks **Run-in period:** Duration: 2 weeks ICS: continued to take their ICs Relief: any bronchodilator therapy was replaced by salbutamol via a Diskhaler inhaler or a pressurised metered-dose inhaler	**Number randomised:** 244 **Sample attrition/drop-out:** • A total of 35 withdrawals: 18 (15%) from group A and 17 (14%) from group B. This difference is not significant • 20 of the withdrawals were due to an AE: 11 (9%) from group A and 9 (7%) from group B • Of the 20, 7 were asthma related: 4 from group A and 3 from group B • 2 patients (both combination) were withdrawn as they were pregnant • No differences between the two treatments in AEs resulting in treatment withdrawal **Sample crossovers:** NA **Inclusion criteria:** • Age ⩾12 years with symptomatic asthma • History of documented reversible airways obstruction and receiving BDP or BUD 400–500 μg/day or FP 200–250 μg/day for ⩾4 weeks prior to the start of treatment • Have recorded a symptom score[a] totalling ⩾2 on at least 3 of the last 7 consecutive days during the run-in period • Have a mean morning PEF (calculated from the last 7 days of the run-in period) between 50 + 85% of their PEF measured 15 minutes after administration of salbutamol 400 μg at the start of treatment	**Primary measure:** Mean a.m. PEF **Secondary measures:** • p.m. PEF • FEV_1 • Use of rescue salbutamol • Day- and night-time symptom score **Method of assessing outcomes:** • Clinician visits at 2, 4, 8 and 12 weeks after the start of treatment and 2 weeks after cessation of treatment. Not to take their medication on the morning of, and to avoid taking rescue medication within 6 hours of, any clinic visit • FEV_1 (3 measurements and the highest one was recorded) • AEs reported spontaneously by the patient or as a result of non-suggestive questioning by the clinician were recorded

continued

Study	Treatment	Participants	Outcomes
	Additional treatment allowed: • Relief: salbutamol in the form of a pressurised metered-dose inhaler for symptomatic use. • Other: unknown	**Exclusion criteria:** • Receiving (or having received in the 4 weeks prior to the start of treatment) either salmeterol or any other inhaled LABA • A lower respiratory tract infection within 4 weeks of the run-in period • Taking oral, depot or parenteral corticosteroids within 4 weeks of the run-in period, or • Taking two or more courses of oral depot or parenteral corticosteroids within 12 weeks of the run-in period • An acute exacerbation of reversible airways obstruction that required hospitalisation within 12 weeks of the run-in period • A smoking history of 10 pack years (i.e. 10 cigarettes/day for 20 years or 20 cigarettes/day for 10 years or 40 cigarettes/day for 5 years) **Baseline characteristics:** • Age: mean (range) = 33 (12–78) years • Male:female = 104:140 • Smoking history – current = 19 – ex-smoker = 46 – never = 179 • Mean PEF (l/minute) predicted – morning = 366.5 – evening = 378.5 • Mean FEV_1 (litres), % predicted = 2.38 • Median daytime symptom score of 0, range (no. of patients) = 18–21 • Median night-time symptom score of 0, range (no. of patients) = 37–42 • >75% SFDs, mean (no. of patients) = 4 • >75% SFNs, mean (no. of patients) = 15.5 • >75% of days salbutamol not required, mean (no. of patients) = 20.5 • >75% of nights salbutamol not required, mean (no. of patients) = 43 • Patients using concurrent asthma medication – methylxanthines = 20 – ipratropium bromide = 9 • Mean morning serum cortisol concentrations, nmol/l = 286.5	• Systolic and diastolic blood pressure and pulse rate • Oropharynx examined for any clinical evidence of candidiasis • Fasting blood sample taken between 8 and 10 a.m. at the beginning and end of the treatment for biochemical and haematological analysis and the measurement of morning serum cortisol level • Patient's record • PEF a.m. and p.m. (3 measurements with the highest value recorded) • Use of rescue salbutamol • Day- and night-time symptom score **Length of follow-up:** 14 weeks

[a] Daytime: 0 = no symptoms during the day, 5 = symptoms so severe that they affected work/school and normal daily activity. Night-time: 0 = no symptoms during the night, 4 = symptoms so severe the patient did not sleep.

continued

Results

Outcomes	Group A (n = 121)	Group B (n = 123)	p-Value
FEV_1[a]:			
• Adjusted mean change at week 12 (litres)	0.20	0.17	NR
• Adjusted mean change from baseline at week 12 (% predicted)	6	6	NA
PEF:			
• Adjusted change in mean morning PEF (l/minute)			
– Week 1	34	30	0.374
– Week 2	36	33	0.610
– Week 3	41	31	0.061
– Week 4	41	31	0.051
– Weeks 5–8	44	33	0.049
– Weeks 9–12	47	39	0.220
– Weeks 1–12	42	33	0.098
• Adjusted change in mean evening PEF (l/minute)			
– Week 1	30	27	0.561
– Week 2	32	29	0.587
– Week 3	35	31	0.429
– Week 4	36	28	0.135
– Weeks 5–8	37	30	0.177
– Weeks 9–12	39	34	0.393
– Weeks 1–12	36	30	0.241
>75% SFDs, [no. of patients (%)]	48 (40)	52 (43)	
>75% SFNs, [no. of patients (%)]	65 (54)	69 (57)	
Nocturnal awakenings			
Acute exacerbations			
Use of systemic corticosteroids			
Use of reliever medication:			
– >75% of days salbutamol not required	65 (54)	68 (56)	
– >75% of nights salbutamol not required	82 (68)	87 (72)	
Mortality			
QoL			
Adverse events, drug related – n (%):			
Candidiasis (mouth/throat)	2 (2)	1 (<1)	
– Candidiasis (non-specific site)	0	2 (2)	
– Throat irritation	2 (2)	3 (2)	
– Hoarseness/dysphonia	0	2 (2)	
– Headaches	2 (2)	0	
– Tachycardia	0	2 (2)	
Median daytime symptom score of 0 [no. of patients (%)]	73 (60)	78 (64)	
Median night-time symptom score of 0 [no. of patients (%)]	85 (70)	89 (74)	
End of treatment cortisol (nmol/L)	351	299	

[a] FEV_1 and FEV_1 % predicted value at weeks 2, 4, 6, 8 and 10 can be roughly estimated from Figure 1 in the paper.

Methodological comments

- **Allocation to treatment groups**: treatment numbers were obtained from a computer-generated randomisation code and were assigned in blocks of four to each centre
- **Blinding**: double-dummy, double-blind
- **Comparability of treatment groups**: reported as the two treatment groups were similar for demographic and baseline characteristics
- **Method of data analysis**: mean morning PEF and FEV_1 values were analysed using ANCOVA, and symptom score and use of rescue medication were analysed using the Wilcoxon rank sum test; $p < 0.05$ was classified as significant
- **Sample size/power calculation**: not reported
- **Attrition/drop-out**: all analyses were performed on an ITT basis

continued

General comments	
• **Generalisability**: relatively inclusive eligibility criteria. Not applicable to steroid-naïve patients • **Outcome measures**: appropriate and objective • **Inter-centre variability**: not reported • **Conflict of interests**: study supported by, and one author from, Glaxo Wellcome Research and Development	
Quality criteria for assessment of experimental studies	
1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate
NA, not applicable; NR, not reported. From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.	

Study	Treatment	Participants	Outcomes
Ref.: 234 **Author:** Bateman *et al*. **Year:** 2004 **Country:** 44 **Study design:** Randomized, stratified, double-blind, parallel-group **Number of centres:** 326 **Funding:** Supported by GlaxoSmithKline R&D Limited	**Stratum 1** (No ICS) ***Group A:*** *n* = 548 Drug(s): FP/SAL Dose: • Phase I: dose 100/50, 250/50 or 500/50 μg b.d., step-up until total control or the highest dose was reached • Phase II: continued on the final dose in phase I until the end of the trial Delivery: dry powder inhalers Duration: 52 weeks ***Group B:*** *n* = 550 Drug(s): FP Dose: • Phase I: dose 100, 250 or 500 μg b.d., step-up until total control or the highest dose was reached • Phase II: continued on the final dose in phase I until the end of the trial Delivery: dry powder inhalers Duration: 52 weeks **Stratum 2** (≤ 500 μg BDP or equivalent daily) ***Group A:*** *n* = 585 Drug(s): FP/SAL	**Number randomised:** 3421 **Sample attrition/drop-out:** Withdrawals in phase I = 377 (11%) from baseline, in phase II = 525 (15%) from baseline **Sample crossovers:** Not reported **Inclusion criteria:** • Patients from general practice and hospital clinics • Aged ≥12 and <80 years • At least a 6 months history of asthma • Reversibility: an increase in FEV_1 ≥15% (and ≥200 ml) after inhalation of short-acting β_2-agonists documented within the previous 6 months or as assessed during run-in • A smoking history of <10 pack-years • No use of long-acting inhaled or oral β_2-agonists within the previous 2 weeks	**Primary measure:** Proportion of patients who achieved well-controlled asthma with FP/SAL vs FP during phase I **Secondary measures:** • Cumulative proportion of patients achieving control in phase II • Dose of ICS and time to achievement of the first well-controlled asthma week • Proportion of patients and dose to achieve totally controlled asthma • Time to achieve the first totally controlled week • Asthma quality of life (using AQLQ) • Exacerbation rates (requiring oral corticosteroids, hospitalisations or information or emergency visits) • Morning predose FEV_1 • AEs

continued

Study	Treatment	Participants	Outcomes
	Dose: • Phase I: dose 100/50, 250/50 or 500/50 μg b.d., step-up until total control or the highest dose was reached • Phase II: continued on the final dose in phase I until the end of the trial Delivery: dry powder inhalers Duration: 52 weeks ***Group B:*** *n* = 578 Drug(s): FP Dose: • Phase I: dose 100, 250 or 500 μg b.d., step-up until total control or the highest dose was reached • Phase II: continued on the final dose in phase I until the end of the trial Delivery: dry powder inhalers Duration: 52 weeks **Stratum 3** (>500 to ⩽1000 μg BDP or equivalent daily) ***Group A:*** *n* = 576 Drug(s): FP/SAL Dose: • Phase I: dose 100/50, 250/50 or 500/50 μg, b.d., step-up until total control or the highest dose was reached • Phase II: continued on the final dose in phase I until the end of the trial Delivery: dry powder inhalers Duration: 52 weeks ***Group B:*** *n* = 579 Drug(s): FP Dose: • Phase I: dose 100, 250 or 500 μg b.d., step-up until total control or the highest dose was reached • Phase II: continued on the final dose in phase I until the end of the trial Delivery: dry powder inhalers Duration: 52 weeks **Run-in period:** Duration: 4 weeks ICS: continued on their usual dose (if any) Relief: NR **Additional treatment allowed:** • Relief: NR • Other: NR	**Exclusion criteria:** • Having well-controlled asthma on ⩾3 of the 4 weeks during run-in **Baseline characteristics:** • Mean age (range) = 40 (9–83) years • Male:female (%) = 42:58 • Mean atopy (%) = 58 • Mean pre-bronchodilator FEV_1, l/minute = 2.4 • Mean pre-bronchodilator FEV_1 % predicted = 77 • Mean a.m. PEF, l/minute = 345.83 • Mean a.m. PEF % predicted = 76.67 • Rescue medication, mean occasions/day = 1.8 • Mean daily symptom score[a] = 1.8 • Night-time awakenings, mean occasions/night = 0.5 • Mean exacerbation rate[b] = 0.53 • Duration of asthma (% patients): – 6 months to <1 year = 3.67 – ⩾1 to <10 years = 38 – ⩾10 years = 58.33 • Smoking status (% patients): – current smoker = 7.83 – former smoker = 14.50	**Method of assessing outcomes:** • Clinic visit at weeks 12, 24, 36 and 52; control assessed over an 8-week period before each clinic visit • No other details reported **Length of follow-up:** 52 weeks

[a] 0 = none, 5 = severe.
[b] Documented episodes of hospitalisation and/or course of oral steroids or antibiotics for the treatment of an exacerbation of asthma during the past 12 months.

continued

Results

Outcomes	Group A	Group B	*p*-Value
FEV_1: *see additional table*			
PEF:			
Symptom-free days			
Nocturnal awakenings			
Acute exacerbations[a]			
Use of systemic corticosteroids			
Use of reliever medication			
Mortality			
QoL: *see additional table*			
AEs – *n* (%)[b]			
Other: *see additional table*			

[a] Mean rate of exacerbations requiring either oral steroids or hospitalisation/emergency visit per patient per year over weeks 1–52: can be roughly estimated from Figure 3 in the paper.

[b] Serious AEs during the 1-year period were 4% in FP/SAL arm and 3% in FP arm. Overall incidence of drug-related AEs was 10% in each group. No statistical differences between treatments at week 52 ($p = 0.318$, 95% CI 0.92 to 1.31).

Methodological comments

- **Allocation to treatment groups**: randomisation was done telephonically from a computer-generated allocation schedule balance per stratum and per country
- **Blinding**: investigators and patients were blinded to treatment
- **Comparability of treatment groups**: the FEV_1 at baseline in stratum 1 was 2.48 (95% CI 2.408 to 2.552) for Group A vs 2.52 (95% CI 2.448 to 2.592) for Group B, in stratum 2 was 2.42 (95% CI 2.352 to 2.488) for Group A vs 2.38 (95% CI 2.314 to 2.446) for Group B and in stratum 3 was 2.28 (95% CI 2.212 to 2.348) for Group A vs 2.33 (95% CI 2.264 to 2.396) for Group B; therefore, there appears no significant difference at baseline in terms of FEV_1 between Group A and Group B in each stratum. Similarly, there was no significant difference between Group A and B in each stratum in the mean overall AQLQ score at baseline: in stratum 1 was 4.4 (95% CI 4.283 to 4.517) for Group A vs 4.5 (95% CI 4.382 to 4.618) for Group B, in stratum 2 was 4.7 (95% CI 4.583 to 4.817) for Group A vs 4.5 (95% CI 4.445 to 4.555) for Group B and in stratum 3 was identical for Group A and Group B. However, there was no detail on how this subgroup for which these data were collected was defined (*95% CIs were calculated by the reviewers*)
- **Method of data analysis**: the primary end-point was assessed by use of maximum likelihood logistic regression. Dose of ICS at which control was achieved was assessed using proportional odds logistic regression; both were adjusted for gender, country, age and baseline pre-bronchodilator FEV_1. Model and interaction tests were performed to confirm model validity. The time to achieve the first well-controlled week was analysed using the log-rank test, stratified by country. FEV_1, AQLQ and cortisol were analysed using ANCOVA adjusted as for the primary end-point with baseline covariate. Cortisol data was log transformed prior to analysis. Exacerbation rates were analysed over the 1-year period using Poisson regression and this was adjusted for the primary end-point
- **Sample size/power calculation**: the study was powered to show a 10% difference between treatment groups (significance level 5%, power 80%). Sample size was increased from 400 to 480 per group for each stratum to compensate for potentially unassessable patients
- **Attrition/drop-out**: withdrawals at phase I = 377 (11%), at phase II from baseline = 526 (15%). The study was analysed on an ITT basis by individual strata; the ITT analysis was defined based on a baseline number of patient of 3416 excluding 5 patients who were randomised but not treated

General comments

- **Generalisability**: inclusive eligibility criteria
- **Outcome measures**: appropriate and objective
- **Inter-centre variability**: allocation schedule balanced per stratum and per country based on the ICS dose during the 6 months before screening
- **Conflict of interests**: study supported by GlaxoSmithKline R & D Limited

continued

Quality criteria for assessment of experimental studies	
1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Baseline reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Additional table

Outcomes	Stratum 1		Stratum 2		Stratum 3		*p*-Value
	Group A (*n* = 533)	**Group B (*n* = 531)**	**Group A (*n* = 572)**	**Group B (*n* = 564)**	**Group A (*n* = 561)**	**Group B (*n* = 555)**	
FEV_1:							
% predicted (SD)	76 (18.14)	79 (18.83)	78 (18.17)	77 (18.34)	75 (18.55)	76 (17.44)	
Phase I:							
adjusted mean change (SE)	0.45 (0.02)		0.35 (0.02)		0.29 (0.02)		
Group A minus Group B (SE)[a]	0.14 (0.03)		0.13 (0.02)		0.12 (0.02)		<0.001[a]
Phase II:							
adjusted mean change (SE)	0.52 (0.02)	0.31 (0.02)	0.37 (0.02)	0.22 (0.02)	0.32 (0.02)	0.17 (0.02)	
Group A minus Group B (SE)[a]	0.17 (0.03)	0.34 (0.02)	0.13 (0.02)	0.24 (0.02)	0.14 (0.03)	0.18 (0.02)	
	Group A (*n* = 282)	**Group B (*n* = 275)**	**Group A (*n* = 339)**	**Group B (*n* = 331)**	**Group A (*n* = 346)**	**Group B (*n* = 345)**	
Mean overall AQLQ score[b]							
Phase I:							
adjusted mean change (SE)	1.5 (0.1)		1.3 (0.1)		1.1 (0.1)		
Group A minus Group B (SE)[a]	0.2 (0.1)		0.3 (0.1)		0.2 (0.1)		
Phase II:							
adjusted mean change (SE)	1.6 (0.1)	1.3 (0.1)	1.3 (0.1)	1.0 (0.1)	1.2 (0.1)	0.8 (0.1)	
Group A minus Group B (SE)[a]	0.1 (0.1)	1.4 (0.1)	0.2 (0.1)	1.2 (0.1)	0.2 (0.1)	(0.1)	
Proportion of patients who achieved near-maximal mean overall AQLQ scores at week 52 (%)	62	62	64	53	57	45	

[a] Group A vs Group B.
[b] Obtained at selected sites. No detail on how the subgroup was defined.

Study	Treatment	Participants	Outcomes
Ref.: 199 **Author:** Bousquet *et al.* **Year:** 2000 **Country:** 17 countries **Study design:** Randomised, evaluator-blind, active-controlled, multi-centre **Number of centres:** 57 **Funding:** Schering Plough Research Institute	**Group A:** *n* = 185 Drug(s): MF + placebo Dose: 100 µg b.d. Delivery: DPI Duration: 12 weeks **Group B:** *n* = 176 Drug(s): MF + placebo Dose: 200 µg b.d. Delivery: DPI Duration: 12 weeks **Group C:** *n* = 188 Drug(s): MF + placebo Dose: 400 µg b.d. Delivery: DPI Duration: 12 weeks **Group D:** *n* = 181 Drug(s): BUD Dose: 400 µg b.d. Delivery: Pulmicort Turbuhaler Duration: 12 weeks **Run-in period:** Duration: not defined ICS: as previously prescribed inhaled ICS Relief: not reported **Additional treatment allowed:** • Relief: salbutamol • Other: theophylline permitted throughout the study if a stable dose was an established part of the patient's therapeutic regime prior to the screening visit	**Number randomised:** 730 **Sample attrition/drop-out:** 101 (14%) **Sample crossovers:** Not reported **Inclusion criteria:** • Age ⩾12 years • History of asthma for ⩾6 months • Using an inhaled glucocorticoid daily for ⩾30 days • Have been maintained on a stable regimen of inhaled CIS • FEV_1 60–90% of predicted • Reversibility: an increase in FEV_1 ⩾12.0% and absolute volume increase of at least 200 ml within 30 minutes after 2 inhalations of salbutamol • Non-smoker or had stopped smoking ⩾6 months prior to screening • 12-lead ECGs and vital signs were all clinically acceptable • Free of any clinically significant disease other than asthma **Exclusion criteria:** • Pre-menarche • Pregnancy • Lactation • Requiring allergen-specific immunotherapy • Oral corticosteroids >14 days in 6 months prior to screening, unless on a stable maintenance schedule • Methotrexate, ciclosporin or gold within 3 months • Systemic steroids or another investigational drug in the month prior to screening • Daily nebulised β_2 adrenergic agonists >1 mg • Any LABA <2 weeks prior to screening • Ventilator support in the past 5 years • Hospitalisation for asthma in the last 3 months • >12 puffs/day of salbutamol on any ⩾2 occasions in the past 6 months • Clinical evidence of significant pulmonary disease other than asthma • History or glaucoma and/or posterior sub-capsular cataracts • Increase or decrease in FEV1 of ⩾20% between screening and baseline visits • Clinical abnormal baseline vital sign • Significant abnormal ECG or chest radiograph at screening or within the previous month • Respiratory tract infection during the 2 weeks prior to screening • Clinically significant oropharyngeal candidiasis • Acceptable method of birth control for all women of childbearing potential **Baseline characteristics:** • Mean age (range) = 41(12–76) years • Male:female = 315:415	**Primary measure:** change from baseline to end-point in FEV_1 **Secondary measures:** • FVC • PEF • Symptom scores • Nocturnal awakenings requiring salbutamol use as rescue medication • Daily salbutamol use • Physician evaluation of response to therapy • AE **Method of assessing outcomes:** • Daily patient diaries: – PEF (a.m. and p.m.) (highest of 3 efforts) – salbutamol use – asthma symptoms – number of night-time awakenings requiring salbutamol use – AEs – use of study drug and concomitant medications • Treatment visits after 1, 2, 3, 4, 8 and 12 weeks of treatment: – pulmonary function (FEV_1 and FVC) by spirometry – oropharyngeal examination for the presence of candidiasis, reviewed diary cards, and assessed response to therapy – at each visit someone other than the blinded evaluator evaluated treatment compliance (by direct inquiry of the patient and review of the diary data) and compliance in the use of rescue medication (objective assessment of doses used and review of the patient's diary data reports) **Length of follow-up:** 12 weeks

continued

Study	Treatment	Participants	Outcomes
		• White:African:Hispanic:Asian:other = 555:9:160:5:1 • Mean weight (kg) = 71.5 (range 34–144) • Smoking history – *n* (%): never 510 (70), not in past 6 months 216 (30) • Mean duration of asthma years (range) = 15.75 (1–64) • Mean FEV_1 (% predicted) = 76.8 • Prior ICS (mean dose μg/mean *n*): BDP = 699.25/93, BUD = 662/66, flunisolide =659/4, FP = 437.5/21, triamcinolone acetonide = 416.67/2 (not applicable in BUD group) • Theophylline use (yes/no – *n*) = 19/163 • Salbutamol use (μg/day) = 262.25	

Results

Outcomes[a]	Group A (*n* = 185)	Group B (*n* = 176)	Group C (*n* = 188)	Group D (*n* = 181)	*p*-Value
FEV_1 (litres)	0.10 ± 0.03	0.016 ± 0.03	0.16 ± 0.03	0.06 ± 0.03	<0.05[b,c]
PEF: (a.m., l/minute) change from baseline to end-point ± SE	18.20 ± 5.3	37.84 ± 5.4	37.3 ± 5.2	24.75 ± 5.3	<0.05[d,e]
SFDs					
Nocturnal awakenings: change from baseline to end-point	–0.06	–0.09	–0.16	–0.07	
Acute exacerbations					
Use of systemic corticosteroids					
Use of reliever medication: change of salbutamol use in μg/day from baseline to end-point	–45.8	–90.66	–72.13	–33.90	<0.05[b]
Mortality					
QoL					
AEs – *n* (%):					
• Dysphonia (*n*)	8	5	9	4	
• Oral candidiasis (*n*)	4	6	4	3	
Physician-evaluated response to therapy: change from baseline to end-point	2.43	2.33	2.25	2.53	<0.05[b,c]
Patient self-report – mean score of wheezing a.m.	–0.07	–0.17	–0.27	–0.10	<0.05[c,e]
Patient self-report – mean score of difficulty breathing a.m.	–0.01	–0.20	–0.24	–0.14	<0.05[e]
Patient self-report – mean score of cough a.m.	–0.10	–0.16	–0.19	–0.19	

[a] Values are presented as change from baseline to end-point (the last treatment visit) (± SE).
[b] Group B vs Group D.
[c] Group C vs Group D.
[d] Group B vs Group A.
[e] Group C vs Group A.

Comments
- The incidence of AEs judged by investigators to be related to treatment was similar for all treatment groups (17–20%). Serious AEs were noted for 11 patients but none was related to the treatment
- There were no significant differences in cortisol values among treatment groups at screening or week 12

continued

Methodological comments

- **Allocation to treatment groups**: randomisation was generated in a 1:1:1:1 ratio with a block size of 4. A random code was generated for each country and patients were assigned sequentially as they entered each study centre within the country
- **Blinding**: patients randomised to the FP DPI were instructed to take one inhalation from each DPI (i.e. either one active and one placebo, or two active DPIs); evaluators were blinded to whether a patient received MF–DPI or BUD Turbuhaler
- **Comparability of treatment groups**: the groups are reported to be comparable with regard to demographic and baseline disease characteristics
- **Method of data analysis**: changes from baseline primary and secondary efficacy variables were analysed using a two-way ANOVA that extracted sources of variation due to treatment and centre and treatment-by-centre interaction. Each ANOVA was followed by Duncan's multiple range test to compare all treatment groups. The results of these tests are considered significant at the 0.05 level. Response to therapy as percentage of patients showing improvement or much improvement from baseline was analysed by Fisher's exact test
- **Sample size/power calculation**: designed to enrol ⩾600 patients, or 150 patients per treatment group, to allow detection of a clinical meaningful difference in FEV_1 of approximately 6% of the baseline value between any two groups, with 80% power and 5% significance level, assuming a pooled standard deviation of 0.45 units for FEV_1 change from baseline
- **Attrition/drop-out**: 101/730 patients (14%) did not complete the treatment: 15% in MF–DPI 100 μg group, 10% and 18% in MF–DPI 200 and 400 μg group, and 14% in BUD group, respectively. The analyses of efficacy and safety were based on all the randomised patients who received at least one dose of study mediation and who had post-baseline data (ITT principle)

General comments

- **Generalisability**: relatively inclusive eligibility criteria; not applicable to ICS-naïve population
- **Outcome measures**: appropriate and objective
- **Inter-centre variability**: ANOVA analysis used centre as a covariate
- **Conflict of interests**: study support by and two authors from Schering-Plough

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the care provider blinded?	Inadequate
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Reported
9. Were withdrawals and drop-outs completely described?	Reported

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 200 **Author:** Buhl *et al*. **Year:** 2005 **Country:** Multi-national **Study design:** RCT, non-inferiority, double-blind, double-dummy, parallel group **Number of centres:** 57 **Funding:** Altana Pharma AG	**Group A: CIC** *n* = 266 Drug(s): CIC Dose: 160 μg *ex*-actuator dose q.d. in the evening Delivery: HFA MDI Duration: 12 weeks **Group B: FP** *n* = 263 Drug(s): FP Dose: 88 μg *ex*-actuator dose b.d. Delivery: HFA MDI Duration: 12 weeks **Run-in period:** Duration: 1–4 weeks ICS: none Relief: salbutamol (100 μg/puff) **Additional treatment allowed:** • Relief: not stated but presumably salbutamol (100 μg/puff) • Other:	**Number randomised:** 529 **Sample attrition/drop-out:** *n* = 45 (8.5%): 24 for CIC; 21 for FP **Sample crossovers:** NA **Inclusion criteria:** • 12–75 years of age • Diagnosis of asthma according to American Thoracic Society guidelines for at least 6 months • Maintained on a constant dose of ICS up to 500 μg/day BDP or equivalent • FEV_1 of 80–100% • At randomisation (following run-in period), patients were required to have an FEV_1 between 50% and 90% predicted after rescue medication was withheld for at least 4 hours + a decrease in FEV_1 ⩾10% after ICS withdrawal • All patients had to demonstrate a reversibility of FEV_1 ⩾15% after inhaling 200–400 μg of salbutamol, or have shown a diurnal PEF fluctuation of at least 15% during the baseline period **Exclusion criteria:** • Required systemic steroids within 4 weeks of the baseline period or more than 3 times during the last 6 months • An asthma exacerbation, lower respiratory tract infection or hospitalisation for asthma 4 weeks before baseline entry • Other relevant lung diseases, such as COPD • Smoking history of ⩾10 pack-years **Baseline characteristics:** • ITT population • The treatment groups were balanced with regard to prior use of ICS and other asthma medications • Median age (range) (years): CIC 41 (12–74), FP 38 (12–74) • Female:male (%): CIC 61/39, FP 54/46 • Mean FEV_1, litres (SD): CIC 2.383 (0.61), FP 2.44 (0.73) • Mean FEV_1, % predicted (range): CIC 75 (51–108), FP 75 (48–92) • FEV_1 % predicted, *n* (%) – ⩾80% CIC 77 (29), FP 74 (28) – >60% or <80% CIC 173 (65), FP 174 (66) – ⩽60% CIC 16 (6), FP 15 (6) • Reversibility – change in FEV_1, % predicted (range): CIC 23 (2–77), FP 23 (0–64) • Mean FVC, litres (SD): CIC 3.183 (0.91), FP 3.312 (0.98) • Morning PEF (diary), l/minute (SD): CIC 358 (6), FP 369 (7)	**Primary measure:** Change in FEV_1 from baseline to end of treatment **Co-primary measures:** Change in FVC Change in a.m. PEF **Secondary measures:** • Mean $FEF_{25–75\%}$ • PEF p.m. • Others: • Asthma symptom scores • Use of rescue medication • Number of days without asthma symptoms • Rescue medication-free days • Nights without awakenings due to asthma • Asthma exacerbations **Method of assessing outcomes:** FEV_1, FVC and mean $FEF_{25–75\%}$ were recorded at baseline and at weeks 1, 2, 4, 8 and 12. A.m. and p.m. PEF (mini-Wright peak flow meters) and use of rescue medication were recorded daily in patient diaries The day- and night-time asthma symptom scores were based on a 5-point scale (0 represented no symptoms and 4 the highest level of asthma discomfort). The scoring system is not referenced in the text and may have been devised specifically for the study AEs experienced by a patient or observed by an investigator were recorded at each study visit **Length of follow-up:** 12 weeks
No further information was provided on the methods used to assess outcomes or on treatment protocols/rescue medication			

continued

Results						
Outcomes	**ITT**			**PP**		
	CIC (*n* = 266)	**FP (*n* = 263)**	***p*-Value**	**CIC (*n* = 230)**	**FP (*n* = 221)**	***p*-Value**
FEV_1, litres:						
Baseline, mean	2.391	2.447		2.354	2.462	
Change from baseline, LS mean (SE)	0.489 (0.029)	0.499 (0.029)		0.506 (0.032)	0.536 (0.032)	
Change from baseline, LS mean (SE)	0.489 (0.029)	0.499 (0.029)		0.506 (0.032)	0.536 (0.032)	
Difference of LS mean (95% CI)	–0.01 (–0.085 to 0.066)		0.801	–0.03 (–0.113 to 0.053)		0.477
Morning PEF, l/minute:						
Baseline, mean	360	371		362	372	
Change from baseline, LS mean (SE)	33 (4)	36 (4)		29 (4)	36 (4)	
Difference of LS mean (95% CI)	–3 (–13 to 7)		0.582	–8 (–18 to 3)		0.162
FVC, litres						
Baseline, mean	3.195	3.322		3.161	3.355	
Change from baseline, LS mean (SE)	0.53 (0.032)	0.499 (0.032)		0.531 (0.035)	0.523 (0.034)	
Difference of LS mean (95% CI)	0.031 (–0.053 to 0.115)		0.486	0.008 (–0.082 to 0.099)		0.857
Use of rescue medication (not clearly defined in text)						
Baseline, median	1.43	1.71		1.43	1.86	
Change[a]	–1.0	–1.21		–0.9	–1.21	
Change vs FP point estimate (95% CI)[a]	0.14 (–0.0 to 0.43)		0.13	0.29 (0.0 to 0.57)		0.053
% of SFDs[b] (median)	58%	65%	NR			
% of nights without nocturnal awakenings[b] (median)	100%	100%	NR			
Total asthma symptom score						
Baseline, median	1.48	1.57		1.55	1.5	
Change[a]	–0.75	–0.86		–0.78	–0.82	
Change vs FP point estimate (95% CI)[a]	0.07 (–0.11 to 0.29)		0.387	0.0 (–0.14 to 0.26)		0.778
Daytime symptom score						
Baseline, median	0.86	1.0		0.93	1.0	
Change[a]	–0.43	–0.5		–0.44	–0.5	
Change vs FP point estimate (95% CI)[a]	0.0 (–0.0 to 0.14)		0.317	0.0 (–0.14 to 0.14)		0.722
Night-time symptom score						
Baseline, median	0.5	0.5		0.5	0.5	
Change[a]	–0.29	–0.33		–0.27	–0.29	
Change vs FP point estimate (95% CI)[a]	0.0 (0.0 to 0.1)		0.53	0.0 (0.0 to 0.1)		0.520
Mortality	0	0				
AEs, *n* (%):						
Any	97 (36)	89 (34)				
Upper respiratory tract infection	20 (8)	21 (8)				
Pharyngitis	11 (4)	7 (3)				
Bronchitis	10 (4)	8 (3)				
Asthma	9 (3)	3 (1)				
Headache	9 (3)	10 (4)				
Rhinitis	7 (3)	8 (3)				
Flu syndrome	5 (2)	8 (3)				
Oral candidiasis/voice alteration	0	3 (1)				
Other	26 (10)	21 (8)				

LS, least squares.
[a] Hodges–Lehman point estimate (NB The differences presented are not simple subtractions).
[b] Estimated by reviewer from graph.

continued

Comments

- The PP population did not include 78 patients with major protocol reorganisation violations; $n = 36$ for ciclesonide, $n = 42$ for fluticasone. The most common violations were of inclusion or randomisation criteria
- It is not specified how people who dropped out of the study were analysed in the ITT group. It is also unclear how many were included in the PP analysis or if they were all excluded for protocol violations, etc.
- The change from baseline for each treatment group for FEV_1, FVC, morning PEF, rescue medication and symptom scores were significant ($p < 0.0001$)
- Incomplete data were presented in the text for evening PEF and $FEF_{25–75\%}$. Evening PEF values significantly improved over the 12 weeks following treatment with ciclesonide and fluticasone. $FEF_{25–75\%}$ increased in both ciclesonide and fluticasone groups by 0.519 and 0.601 l/s, respectively ($p < 0.0001$ for both), and no significant differences were observed between treatment groups ($p = 0.264$). PP analysis revealed comparable results
- Analysis of asthma symptom scores and use of rescue medication by diary revealed that the onset of treatment effect was within 24 hours of administration in the ciclesonide and fluticasone groups ($p < 0.0001$). Morning PEF increased statistically significantly on the second day of treatment in both groups ($p = 0.004$ and $p < 0.001$, respectively)
- The number of asthma exacerbations and rescue medication-free days were not reported on

Methodological comments

Allocation to treatment groups: no details reported
Blinding: "double-blind" but no details reported
Comparability of treatment groups: the groups appear comparable but no statistical data is provided. The text noted there was a higher proportion of women in the ciclesonide group
Method of data analysis:

- A PP analysis, based on valid cases, and an ITT analysis, based on the full analysis set, were performed. The lower limit of the two-sided 95% CI of the between-treatment difference was compared with the non-inferiority acceptance limit. The non-inferiority acceptance limits for FEV_1, FVC and morning PEF were –0.2, –0.2 and –25 l/minute, respectively; the rationale for the choice of these values or if they were predefined was not stated
- The lung function end-points were evaluated by ANCOVA, including baseline value at randomisation visit and age as covariates, and treatment, gender and country as factors. Least-square means, 2-sided *p*-values and 95% CIs were used for comparisons within and between treatment groups
- The change in sum of asthma symptom scores and number of inhalations of rescue medication at the end of treatment were analysed by non-parametric methods using Pratt's modification of the Wilcoxon signed rank test for differences within groups and Mann–Whitney *U*-tests for differences between treatment groups
- Mann–Whitney *U*-tests were also used for the between-treatment comparison of the proportion of days without asthma symptoms for which non-inferiority acceptance limits could not be stipulated
- The onset of treatment effect for both CIC and FP was determined by applying a step-down procedure defining the last interval end-point for which statistical significance was observed to morning and evening PEF, sum of asthma symptom scores and use of rescue medication

Sample size/power calculation: based on a between-treatment difference of at most 0.05 litres and a standard deviation of 0.425 litres for the FEV_1 changes, a sample size of 170 PP (230 ITT) patients per treatment group was required to provide a power of 90% to demonstrate non-inferiority
Attrition/drop-out: 45 patients discontinued participation in the study prematurely. 24 patients in the CIC group dropped out – 6 due to AEs, 4 due to lack of efficacy and 14 for other medical and non-medical reasons. 21 patients in the FP group dropped out – 3 due to AEs and 18 for other medical and non-medical reasons

General comments

- **Generalisability**: participants appear to be representative of patients with mild to moderate asthma
- **Outcome measures**: the outcomes are appropriate
- **Inter-centre variability**: not documented
- **Conflict of interests**: two authors are from Altana Pharma AG

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Partial
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 244 **Author:** Chapman *et al*. **Year:** 1999 **Country:** Canada, Norway, Denmark, Sweden, Finland **Study design:** Multi-centre, randomised, double-blind, double-dummy, parallel-group, RCT **Number of centres:** 43 **Funding:** Glaxo Wellcome	**Group A:** *n* = 180 Drug(s): FP/SAL Dose: 250/50 μg b.d. Delivery: Diskus inhaler (Seretide) + placebo Duration: 28 weeks **Group B:** *n* = 191 Drug(s): FP + SAL Dose: 250 + 50 μg b.d. Delivery: Diskus DPI inhaler Duration: 28 weeks **Run-in period:** Duration: 2 weeks continuing ICS: BDP or BUD 800–1200 μg or FP 400–600 μg q.d. Relief: salbutamol **Additional treatment allowed:** • Relief: salbutamol • Other: **Trial aim:** To determine whether Groups A and B are clinically equivalent. Secondary aim to assess safety of Group A over 28-week treatment period	**Number randomised**: 371 **Sample attrition/drop-out**: 36 were withdrawn: 20 (11%) from Group A, 16 (8%) from Group B (*p* = NS). Most common reason for withdrawal was AEs (see Results); lost to follow-up (*n* = 6); non-compliance (*n* = 2), violation entry criteria (*n* = 2) **Sample crossovers:** None reported **Inclusion criteria:** • Aged ⩾12 years with symptomatic asthma despite inhaled corticosteroids • Documented clinical history of reversible airways obstruction • Treatment with BDP, BUD (both 800–1200 μg/day) or FP (400–600 μg/day) for ⩾4 weeks before • Symptom score (day- + night-time) totalling ⩾2 on ⩾4 of the last 7 consecutive days of run-in • Mean PEF (from last 7 days of run-in) of 50–85% of PEF measured 15 minutes after 400 μg salbutamol at the start of treatment **Exclusion criteria:** • Treatment with salmeterol or other long-acting β_2-agonist in 4 weeks before recruitment; lower respiratory tract infection or treatment with corticosteroids (oral, depot, parenteral) within 4 weeks of run-in; treatment with 2 or more courses of oral, depot or parenteral corticosteroids within 12 weeks of run-in; acute exacerbations of reversible airways obstruction requiring hospitalisation within 12 weeks of run-in; smoking history of 10 pack-years or greater **Baseline characteristics:** • Sex, *n* (%) female/male: Group A 88 (49)/92 (51); Group B 109 (57)/82 (43) • Mean age (range) (years): Group A 42.8 (13–73); Group B 41.4 (15–75) • Smoking history, *n* (%): Group A, current 27 (15), ex 53 (29), never 100 (56); Group B, current 25 (13), ex 69 (36), never 97 (51) • Mean baseline PEF, l/minute (% predicted), *n* (%): Group A morning 398 (84), evening 415 (88); Group B morning 391 (85), evening 415 (89) • Mean baseline FEV_1 (litres) (% predicted): Group A 2.51 (75); Group B 2.55 (77) • Use of concurrent asthma medication, *n* (%): Group A methylxanthines 7 (4), ipratropium bromide 2 (1); Group B methylxanthines 6 (3), ipratropium bromide 1 (<1)	**Primary measure:** PEF (a.m. and p.m.) **Secondary measures:** • FEV • Use of salbutamol • Day- and night-time symptom score • Compliance • AEs **Method of assessing outcomes:** • PEF (mini-Wright peak flow meter) best of three recorded in diary card • FEV: highest value of at least 3 maximal and reproducible efforts • Rescue salbutamol • Day- and night-time symptom score in daily record card (daytime score ranged from 0 to 5 from no symptoms to so severe to affect work/school. Night-time score ranged from 0 to 4 from no symptoms to so severe no sleep) • Compliance: number of doses used divided by expected use **Length of follow-up:** 30 weeks (efficacy measurements recorded for first 12 weeks of study only) Patients assessed at start of run in and treatment periods, and at 2, 4, 8, 12, 20 and 28 weeks after randomisation and 2 weeks after cessation of double-blind treatment

continued

Results			
Outcomes	**Group A (n = 180)**	**Group B (n = 191)**	***p*-Value**
PEF: mean morning adjusted changes from baseline, l/minute, 12 weeks [?average of measurements]	43	36	See next row
PEF: difference in mean morning change from baseline, l/minute between Group A and Group B, 12 weeks	–6, (90% CI –13 to 0) within equivalence definition of 15 l/minute. The 95% CI (–14 to 2) also within the equivalence definition		
PEF: mean morning predicted adjusted mean change from baseline, 12 weeks	9%	7%	See next row
PEF: mean morning treatment difference in predicted score between Group A and Group B, 12 weeks	–2% (90% CI –3 to 0%), $p = 0.052$		
PEF: mean evening adjusted changes from baseline, l/minute, 9–12 weeks/1–12 weeks	36 35	26 25	See next row
PEF: difference in mean evening change from baseline, l/minute between Group A and Group B, 9–12 weeks/1–12 weeks	–10 l/minute (90% CI –17 to –3 l/minute), $p = 0.020$ –10 l/minute (90% CI –16 to –4 l/minute), $p = 0.008$		
PEF: mean evening predicted adjusted mean change from baseline, 9–12 weeks/1–12 weeks	8% 7%	5% 5%	See next row
PEF: mean evening treatment difference in predicted score between Group A and Group B, 9–12 weeks/1–12 weeks	–2% (90% CI –4 to –1), $p = 0.009$ –2% (90% CI –4 to –1), $p = 0.002$		
FEV_1: adjusted mean change from baseline, l/minute, 28 weeks	0.26	0.24	See next row
FEV_1: treatment difference	–0.02 (90% CI –0.09 to 0.05)		
SFDs, change from baseline in proportion with median zero score, n (%)	Baseline 1 (1) 12 weeks 63 (35)	Baseline 4 (2) 12 weeks 61 (32)	
SFNs, change from baseline in proportion with median zero score, n (%)	Baseline 61 (34) 12 weeks 111 (62)	Baseline 58 (30) 12 weeks 101 (53)	
For both median day- and night-time symptom scores, there were no significant differences between the treatment groups			
Percentage patients with ⩾75% SFDs, n (%)	Baseline 1 (1) 12 weeks 39 (22)	Baseline 1(1) 12 weeks 29 (15)	See next row
Median difference between Group A and Group B	0% (90% CI –4 to 0%)		
Percentage patients with ⩾75% SFNs, n (%)	Baseline 41 (23) 12 weeks 86 (48)	Baseline 39 (20) 12 weeks 80 (42)	See next row
Median difference between Group A and Group B	–3% (90% CI –9 to 0%)		
Acute exacerbations			
Use of systemic corticosteroids			
Did not require salbutamol on ⩾75% of days, n (%):			
Baseline	10 (6)	21 (11)	See next row
During first 12 weeks	72 (40)	64 (34)	
Median difference between Group A and Group B	–4%, 90% CI –11 to 0%		
Did not require salbutamol on ⩾75% of nights, n (%)			
Baseline	85 (47)	90 (47)	See next row
During treatment period	125 (69)	118 (62)	
Median difference between Group A and Group B	–3%, 90% CI –6 to 0%		
Mortality			
QoL			
Drug-related AEs – n (%) over 28-week period (⩾2% frequency):			
Headaches	9 (5%)	10 (5%)	
Candidiasis: mouth/throat	8 (4%)	7 (4%)	
Candidiasis: non-specific site	3 (2%)	1 (<1%)	
Hoarseness or dysphonia	7 (4%)	7 (4%)	
Throat irritation	5 (3%)	5 (3%)	
Upper respiratory tract infection	4 (2%)	3 (2%)	
Asthma	4 (2%)	3 (2%)	

continued

Outcomes	Group A (n = 180)	Group B (n = 191)	p-Value
Palpitations	4 (2%)	2 (1%)	
Tremors	4 (2%)	1 (<1%)	
Dizziness	3 (2%)	1 (<1%)	
Chest symptoms	3 (2%)	0	
Patients reporting AEs, *n* (%)	160 (89)	164 (86)	
Withdrawals due to AEs, *n* (%)	12 (7)	9 (5)	
Compliance (mean medication use expressed as % of expected use), weeks 1–12/weeks 1–28	96/95%	95/94%	NR

Comments:
Mean serum cortisol concentrations not significantly different between treatments before or during therapy

Methodological comments

- **Allocation to treatment groups**: states randomised, no further details reported
- **Blinding**: states double-blind and placebo inhaler given to Group A but no details of similarities in device given, no details of any blinding of outcome assessors
- **Comparability of treatment groups**: states randomised patients were similar for the two treatment groups, no statistical analysis used but groups do appear to be similar
- **Method of data analysis**: states ITT analysis but no further details; ANCOVA, Wilcoxon rank sum test, χ^2 test. Treatment equivalence was tested using the 90% CI of the difference between the combination and concurrent therapies in mean morning PEF. A **priority** equivalence was regarded as a 90% CI within ±15 l/minute (reference given) and considered to represent a difference of potential clinical relevance. Results discuss 'adjusted' mean changes but no description given
- **Sample size/power calculation**: not reported
- **Attrition/drop-out**: numbers and reasons given

General comments

- **Generalisability**: patients with symptomatic moderate asthma despite inhaled corticosteroids (800–1200 μg/day BDP or equivalent)
- **Outcome measures**: appropriate although style of reporting makes it difficult to establish which is the end-point data on some outcomes
- **Inter-centre variability**: not reported
- **Conflict of interests**: sponsored by GlaxoWellcome and one author is affiliated with GlaxoWellcome

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Partial
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 198 **Author:** Corren *et al*. **Year:** 2003 **Country:** USA **Study design:** Randomised, multi-centre, double-blind, double-dummy, placebo- and active-controlled, parallel-group, clinical study **Number of centres:** 17 **Funding:** Study supported in part with funding from Schering-Plough	**Group A:** *n* = 51 Drug(s): placebo Dose: NA Delivery: PDI Duration: 8 weeks **Group B:** *n* = 104 Drug(s): MF Dose: 440 μg (metered dose, delivering approximately 320 μg *ex*-mouthpiece) q.d. Delivery: DPI Duration: 8 weeks **Group C:** *n* = 106 Drug(s): BUD Dose: 400 μg q.d. Delivery: DPI Duration: 8 weeks **Run-in period:** Duration: not reported ICS: not reported Relief: not reported **Additional treatment allowed:** • Relief: theophylline (if patients had been taking a stable dose for 2 weeks before screening • Other: no	**Number randomised:** 262 **Sample attrition/drop-out:** 19% **Sample crossovers:** NA **Inclusion criteria:** • Age ⩾12 years • A history of asthma for ⩾6 months • Daily use ICS for ⩾30 days and stable ICS regimen within recommended dose ranges for 2 weeks prior screening (flunisolide 1000–2000 μg/day, BUD 400–800 μg/day; triamcinolone acetonide 600–1600 μg/day; BDP 252–840 μg/day and FP 200–500 μg/day) • FEV_1 ⩾50% and ⩽85% of normal predicted values for age, gender and height after all restricted medications had been withheld for appropriate intervals • An increase in FEV_1 of ⩾12% of pre-bronchodilator value, with an absolute volume increase of ⩾200 ml at screening or within the past 12 months **Exclusion criteria:** • Required oral ICS treatment for more than a total of 14 days during the 6 months immediately prior screening • Required a burst of systemic steroids within 1 month prior screening • Treatment with leukotriene modifiers within 2 weeks prior screening • Treatment with methotrexate, cyclosporine, gold or other immunosuppressive agents within the past 3 months • Emergency hospital treatment for asthma twice in the previous 6 months • Hospitalised for an asthma exacerbation within the previous 3 months • Required ventilatory support for asthma within the previous 5 years • Other respiratory or clinically significant disease other than asthma • Smokers within the previous 6 months or demonstrated a clinical condition requiring daily use of nebulised β_2-adrenergic agonists • Women: pre-menarchal, pregnant, breast-feeding or of childbearing potential required to use an acceptable method of birth control **Baseline characteristics:** • Age (mean) = 37.67 years • Sex (male/female) = 96/165 • Caucasian:black:other = 233:16:12 • Mean weight (lb) = 171.67 • Mean duration of asthma = 19.67 years • Mean (least-squares mean) % predicted FEV_1 = 73.37	**Primary measure:** • FEV_1 • PEF (a.m. and p.m.) **Secondary measures:** • $FEF_{25–75\%}$ • FCV • Asthma symptoms • Albuterol use • Nocturnal awakenings • Physician-evaluated response-to-therapy scores and compliance • % of asthma SFDs[a] • AEs **Method of assessing outcomes:** • Visits during treatment on day 1 (baseline) and weeks 1, 3, 5 and 8: – pulmonary function tests – vital sign assessment – response to therapy evaluation by investigators – diary cards review – compliance assessment by questioning patients and/or parents/guardians on if all medications had been taken as directed and by reviewing diary cards • Patient daily diary: – PEF (a.m. and p.m.) – nebulised β_2-adrenergic agonists treatment – number of albuterol inhalations – asthma symptoms – number of nocturnal awakenings requiring albuterol – AEs – daily use and time of use of study medication – concomitant medication **Length of follow-up:** 8 weeks

[a] Defined as a day where both the total a.m. and p.m. scores (rating wheezing, difficulty breathing) were zero.

continued

Results

Outcomes[a]	Group A (n = 51) placebo	Group B (n = 104)	Group C (n = 106)	p-Value
FEV_1[b]:				
change at end-point ± SE		0.19 ± 0.04	0.03 ± 0.04	<0.01[c]
% change at end-point ± SE		8.9 ± 1.8	2.1 ± 1.8	<0.01[c]
PEF[b]: change at end-point ± SE (l/minute)				
a.m.		19.96 ± 4.15	0.54 ± 4.08	<0.01[c]
p.m.		19.4 ± 4.19	4.93 ± 4.13	<0.05[c]
SFDs, %		39.7 ± 3.4	26.8 ± 3.3	<0.01[c]
Nocturnal awakenings: patients with no nocturnal awakenings due to asthma, %		78.8	81.1	NS
Acute exacerbations				
Use of systemic corticosteroids				
Use of reliever medication: albuterol use (puffs/day)		–0.91 ± 0.23	–0.21 ± 0.23	<0.05[c]
Mortality				
QoL				
Adverse events – n (%):[d]				
$FEF_{25–75\%}$ (l/s)[a]: change at end-point		0.24 ± 0.06	–0.03 ± 0.06	<0.01[c]
Physician-evaluated response to therapy: mean score at end-point		2.3 ± 0.1	2.7 ± 0.1	<0.01[c]

[a] Outcome in terms of asthma symptoms: wheezing score (a.m. and p.m.), difficulty breathing score (a.m. and p.m.) and total asthma score (a.m. and p.m.) are available in Table 4 in the paper.
[b] Least-squares mean change from baseline at end-point from two-way ANOVA.
[c] Group B vs Group C.
[d] "There was no differences among groups in overall incidence of AEs".

Methodological comments

- **Allocation to treatment groups**: patients were assigned in a 2:2:1 ratio according to a computer-generated randomisation schedule to one of the three groups (B, C and A, respectively)
- **Blinding**: double-blind, double-dummy with respect to the study drug
- **Comparability of treatment groups**: reported as no significant differences among groups with respect to most demographic and baseline asthma-related characteristics. There is some variety in FEV_1 at baseline in the two active comparison groups: 2.33 (95% CI 2.21 to 2.45) for Group B vs 2.48 (95% CI 2.36 to 2.60) for Group C. Similarly, PEF (p.m.) was higher in Group C – 401.22 (95% CI 383.31 to 419.13) than Group B – 375.03 (95% CI 353.84 to 393.22) [*All 95% CIs calculated by reviewer*]. Baseline imbalances were adjusted for in the ANOVA analysis
- **Method of data analysis**: efficacy variables were analysed by using the same two-way ANOVA that extracted sources of variation due to treatment, centre and treatment-by centre interaction. ANCOVA model was used if significant baseline variations were observed with respect to potential covariates. Pair-wise comparisons were based on least-square means from the ANOVA using a 0.05 significance level
- **Sample size/power calculation**: designed to enrol 100 patients per active treatment group and 50 in the placebo group in order to detect a 0.20 litre (approximately 8%) difference in the change in FEV_1 from baseline to endpoint between treatment groups with 80% power
- **Attrition/drop-out**: 19%. Primary efficacy analyses were based on ITT (defined as basing on all randomised patients receiving at least one dose of study medication and having post baseline data)

General comments

- **Generalisability**: relatively inclusive eligibility criteria; not applicable to ICS-naïve populations
- **Outcome measures**: appropriate and objective
- **Inter-centre variability**: not reported; unclear whether randomisation was stratified by centre; ANOVA analyses used centre as a covariate
- **Conflict of interests**: study was supported in part with funding from Schering-Plough

continued

Quality criteria for assessment of experimental studies	
1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Partial
9. Were withdrawals and drop-outs completely described?	Partial

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 182 **Author:** Dal Negro *et al*. **Year:** 1999 **Country:** Not specified; investigators are from Italy **Study design:** Single-centre, parallel-group, RCT (apparently unblinded) **Number of centres:** 1 **Funding:** None specified	**Group A:** *n* = 16 Drug(s): BDP Dose: 200 μg q.d.s. Delivery: DPI (Pulvinal) Duration: 8 weeks **Group B:** *n* = 16 Drug(s): BUD Dose: 200 μg q.d.s. Delivery: DPI (Turbuhaler) Duration: 8 weeks **Run-in period:** Duration: 2 weeks before randomisation ICS: 2 weeks wash-out; however, all had treatment with BDP MDI 1000 μg for previous 8 weeks Relief: not reported **Additional treatment allowed:** • Relief: inhaled salbutamol • Other: inhaled sodium cromoglycate or nedocromil sodium in patients already receiving them	**Number randomised:** 32 ("were enrolled and completed the study period"; unreported drop-outs may have occurred) **Sample attrition/drop-out:** No withdrawals reported **Inclusion criteria:** • Age 18–65 years • Clinical diagnosis of moderate persistent asthma • Treated with 1000 μg BDP MDI at constant daily dose for previous 8 weeks • Stability of lung function (i.e. diurnal variation of PEF <20%) in previous 4 weeks • Documented reversibility to inhaled β_2-agonists in a recent history • Ability to be trained in the correct use of both powder inhalers and to fill in the diary cards properly • Providing of written informed consent **Exclusion criteria:** • Evidence of symptomatic infective exacerbation in the previous 4 weeks • Likelihood of exposure to allergens or sensitising agents for the total study period • History of clinically significant cardiac, renal, neurological, hepatic or endocrine disease • Pregnancy, lactation or risk of pregnancy • History of hypersensitivity to ICS • Inability to follow the management of concomitant medications **Baseline characteristics:** • Male:female = BDP 9:7, BUD 6:10 • Mean age (years ± SD) = BDP 42.3 ± 13.9, BUD 41.6 ± 8.4 • Smoking history: current = BDP (31.2%), BUD (37.5%); ex-smoker = BDP (12.5%), BUD (12.5%); never smoked = BDP (56.2%), BUD (50%)	**Primary measure:** Not specified **Secondary measures:** • FEV_1 (absolute and predicted) • FVC • PEF (a.m. and p.m.) • $FEF_{25–75\%}$ • $MEF_{50\%}$ • Rescue salbutamol consumption • Incidence of bronchospasm attacks • Symptoms • AEs • Serum ECP • A.m. serum cortisol • Standing heart rate • Blood pressure **Method of assessing outcomes:** • Clinic assessments at weeks –2, 0, 2, 4, 6 and 8: – FEV_1 (highest reading of 3), FVC, PEF, $FEF_{25–75\%}$, MEF_{50} – AEs reported • Daily diary card, recording – a.m. and p.m. PEF (highest of 3) – rescue salbutamol consumption – bronchospasm attacks – symptoms (patient-rated scores for wheezing at rest, wheezing after exercise, coughing

continued

Study	Treatment	Participants	Outcomes
		• Duration of asthma (mean years ± SD): BDP 26.2 ± 6.3, BUD 26.6 ± 9.9 • History of atopy = BDP 75%, BUD 81.2% • FEV_1, (% predicted ± SD) = BDP 65.5 ± 13.4, BUD 67.6 ± 8.5 • PEF (% predicted ± SD) = BDP 72.7 ± 21.5, BUD 70.6 ± 14.8	attacks at rest, coughing attacks after exercise and chest tightness) • At weeks 0, 4 and 8 – serum ECP • At weeks 0 and 8 – morning serum cortisol – standing heart rate – systolic and diastolic blood pressure **Length of follow-up:** 8 weeks

Results

Outcomes	Group A (BDP) (*n* = 16)	Group B (BUD) (*n* = 16)	*p*-Value
FEV_1 – l ± SD:			
Baseline	2.20 ± 0.6	1.91 ± 0.4	NS[a]
Week 2	2.67 ± 0.8	1.99 ± 0.5	<0.05[b]; NS[a,c]
Week 4	2.68 ± 0.7	2.08 ± 0.6	<0.05[b]; NS[a,c]
Week 6	2.71 ± 0.8	2.15 ± 0.5	<0.05[b,c]; NS[a]
Week 8	2.68 ± 0.6	2.13 ± 0.6	<0.05[b]; NS[a,c]
FEV_1 – mean % predicted normal ± SD:			
Baseline	65.5 ± 13.4	67.6 ± 8.5	
Week 4	78.9 ± 9.8	73.8 ± 18.6	
Week 8	79.2 ± 10.3	75.6 ± 19.7	
PEF – l/minute ± SD:			
Baseline	5.80 ± 1.9	5.01 ± 1.4	NS[a]
Week 2	7.04 ± 2.0	5.28 ± 1.7	NS[a,b,c]
Week 4	6.88 ± 1.5	5.53 ± 1.9	NS[a,b,c]
Week 6	7.07 ± 1.9	5.32 ± 1.5	<0.05[b]; NS[a,c]
Week 8	7.49 ± 1.6	5.88 ± 2.0	<0.05[b]; NS[a,c]
Morning PEF – l/minute ± SD:			
Baseline	400 ± 115[d]	360 ± 90[d]	NS[a]
Week 2	435 ± 100[d]	365 ± 90[d]	NS[a,b,c]
Week 4	440 ± 80[d]	380 ± 90[d]	NS[a,b,c]
Week 6	460 ± 80[d]	385 ± 90[d]	<0.05[b,c]; NS[a,c]
Week 8	470 ± 85[d]	400 ± 95[d]	<0.05[b]; NS[a,c]
Evening PEF – l/minute ± SD:			
Baseline	425 ± 95[d]	375 ± 80[d]	NS[a]
Week 2	445 ± 85[d]	385 ± 90[d]	NS[a,b,c]
Week 4	455 ± 75[d]	395 ± 90[d]	NS[a,b,c]
Week 6	465 ± 80[d]	400 ± 80[d]	<0.05[c]; NS[a,b]
Week 8	490 ± 90[d]	410 ± 60[d]	<0.05[c]; NS[a,b]
SFDs			
Nocturnal awakenings			
Acute exacerbations			
Use of reliever medication, number of puffs/day:			
Baseline	2.3 ± 0.3	2.3 ± 0.3	NS[a]
Week 2	2.1 ± 0.3	2.2 ± 0.4	NS[a,b,c]
Week 4	1.6 ± 0.3	2.3 ± 0.5	NS[a,b,c]
Week 6	1.1 ± 0.3	1.8 ± 0.5	NS[a,b,c]
Week 8	0.7 ± 0.3	1.6 ± 0.5	<0.05[b]; NS[a,c]
Use of systemic corticosteroids			
Mortality			

continued

Outcomes	Group A (BDP) (n = 16)	Group B (BUD) (n = 16)	p-Value
QoL			
AEs – n (%)	None	None	See comments
Other			
Bronchospasm attacks in 24 hours – number ± SE:			
Baseline	1.1 ± 0.3	1.1 ± 0.3	NS[a]
Week 2	0.9 ± 0.2	1.1 ± 0.3	NS[a,b,c]
Week 4	0.8 ± 0.3	1.0 ± 0.3	NS[a,b,c]
Week 6	0.8 ± 0.3	0.9 ± 0.3	NS[a,b,c]
Week 8	0.3 ± 0.1	0.8 ± 0.3	<0.05[b]; NS[a,c]

[a] Group A vs Group B.
[b] Group A vs baseline.
[c] Group B vs baseline.
[d] Estimated from graph by reviewer.

Comments

- Point data for morning PEF and evening PEF extrapolated from graph. Statistics from text
- A significant ($p < 0.05$) reduction in the use of salbutamol PRN was reported in the BDP group at week 8 (graphical data and text)
- No statistically significant difference between groups was reported in clinical symptoms or use of rescue salbutamol (text only)
- Negligible increases in morning serum cortisol were reported in both groups (text only)
- 3 patients in Group A and 2 in Group B had upper airways infection thought to be unrelated to treatment
- No significant variations within or between groups were reported in heart rate and systolic and diastolic blood pressure (text only)

Methodological comments

- **Allocation to treatment groups**: randomisation methods not specified
- **Blinding**: apparently not blinded; however, objective measurements (pulmonary function and laboratory tests) were done by technicians blinded to the assigned treatment
- **Comparability of treatment groups**: no statistical significance between groups in baseline characteristics
- **Method of data analysis**:
  - Unpaired Student's t-test used to assess homogeneity of groups at baseline and comparison between groups of lung function, serum ECP, serum cortisol and vital signs
  - Wilcoxon's 2-sample test was used for the same evaluations with regards to symptom score and daily salbutamol consumption
  - Paired t-test was used for comparison within lung function group, serum ECP, serum cortisol and vital signs
  - Wilcoxon's signed rank test was used for the within group comparison of the sum of the symptom score and daily salbutamol consumption.
  - χ^2 test to compare the distribution of AEs
  - Spearman's coefficient to assess the correlation between FEV_1 and ECP values
- Sample size/power calculation: none reported
- **Attrition/drop-out**: no withdrawals reported; ambiguous phrasing of sample description ("Thirty-two patients … were enrolled and completed the study period") suggests the possibility of unreported drop-outs being excluded from analysis

General comments

- **Generalisability**: relatively inclusive eligibility criteria; not applicable to ICS-naïve population
- **Outcome measures**: appropriate and relatively objective
- **Inter-centre variability**: NA
- **Conflict of interests**: not reported; 1 author is from Chiesi (Italian manufacturers of BDP)

continued

Quality criteria for assessment of experimental studies	
1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Unknown
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	NR
9. Were withdrawals and drop-outs completely described?	NA

ECP, serum eosinophilic catatonic protein; PRN, pro re nata.
From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 246 **Author:** FitzGerald *et al*. **Year:** 2005 **Country:** 15 countries (Australia, Austria, Belgium, Bulgaria, Macedonia, Canada, Estonia, Finland, Germany, Ireland, Latvia, The Netherlands, New Zealand, Spain and UK) **Study design:** Multi-centre, parallel-group, double-blind, double-dummy, RCT **Number of centres:** 91 **Funding:** Sponsored by GlaxoSmithKline	**Group A:** *n* = 344 Drug(s): FP/SAL + placebo Dose: 250/50 μg b.d. Delivery: FP/SAL via DISKUS and placebo via Turbuhaler DPI Duration: 52 weeks **Group B:** *n* = 344 Drug(s): BUD/FF + placebo Dose: 400/12 μg b.d. (adjustable within range 200 μg BUD/6 μg FF q.d. to 800 μg BUD/24 μg FF b.d. *after week 4*) Delivery: 2 separate BUD/FF via Turbuhaler and placebo via DISKUS DPI Duration: 52 weeks **Run-in period:** Duration: 2 weeks before randomisation ICS: continued "to take their current asthma medication" Relief: as needed salbutamol **Additional treatment allowed:** • Relief: inhaled salbutamol only	**Number randomised:** 706 **Sample attrition/drop-out:** *n* = 191 (*18 excluded from ITT population due to absent efficacy data and/or took no study medication*; 101 did not meet step-down criteria; 17 due to AEs; 17 consent withdrawn; 6 lost to follow-up; 11 due to protocol violation; 2 did not meet eligibility criteria; 7 due to lack of efficacy; 12 other reasons) **Sample crossovers:** None **Inclusion criteria:** • Age ⩾18 years and <70 years • Documented clinical history of asthma • FEV_1 60–90% predicted • Treated with any ICS at dose equivalent to 200–500 μg/day BDP combined with a LABA, or an ICS alone at a dose equivalent to >500 to 1000 μg/day BDP for ⩾12 weeks before enrolment • Ability to use peak flow meter and correctly record values on diary card At the end of the 2-week run-in period: – total daily symptom score ⩾2 on ⩾4 of the last 7 consecutive days **Exclusion criteria:** • Lower respiratory tract infection or use of systemic corticosteroids within 1 month of study entry • ⩾10 pack-year smoking history • Changes to regular asthma therapy within 12 weeks of study entry • Significant disorder that in the investigator's opinion might put the patient at risk or influence the study outcomes	**Primary measure:** Mean % of symptom-free days (over 24-hour period) on daily record card **Secondary measures:** • % rescue-free days • Daily rescue medication use • Daily asthma symptom score • % nights awoken due to asthma • Mean morning PEF • % well-controlled asthma weeks • Incidence of asthma exacerbations, defined as: – deterioration requiring hospital treatment or treatment with oral corticosteroids, either in the opinion of the investigator or based on a morning PEF <70% of the mean of the last 7 days in weeks 1–4 for >2 consecutive days • AEs • Compliance **Method of assessing outcomes:** • Clinic visits at baseline, weeks 0, 4, 16, 28, 40 and 52, recording: – FEV_1 – AEs

continued

Study	Treatment	Participants	Outcomes
	• Other: oral steroids in event of insufficient asthma control not alleviated by study drugs; inhaled cromones, leukotriene modifiers, β_2-agonists (other than rescue salbutamol), xanthines and inhaled anticholinergics explicitly disallowed	**Baseline characteristics:** • Male:female = SAL/FP 140:204, FF/BUD 128:216 • Mean age (years ± SD) = SAL/FP 46 ± 14, FF/BUD 44 ± 14 • Smoking history: not reported • Duration of asthma ⩾10 years (number and %) = SAL/FP 197 (57%), FF/BUD 200 (58%) • FEV_1 (absolute value litres ± SD) = SAL/FP 2.53 ± 0.80, FF/BUD 2.52 ± 0.70 • FEV_1 (% predicted ± SD) = SAL/FP 82 ± 21, FF/BUD 81 ± 13 • Morning PEF (l/minute ± SD) = SAL/FP 357 ± 103, FF/BUD 362 ± 100 • Daily asthma symptom score (mean ± SD) = SAL/FP 1.9 ± 0.6, FF/BUD 1.9 ± 0.5	• Daily diary card, recording: – asthma symptom score for previous 24 hours – number of nocturnal awakenings due to asthma – number of occasions of salbutamol use during previous 24 hours – number of Turbuhaler inhalations in previous 24 hours – PEF (highest reading of 3) • Compliance (deemed compliant if actual number of doses taken was ±30% of the expected number) **Length of follow-up:** 52 weeks + follow-up visit at week 52 + 2

Results

Outcomes	Group A (*n* = 344)	Group B (*n* = 344)	*p*-Value
FEV_1			
PEF:			
A.m. mean, weeks 1–52 – l/minute (SD)	395 (104)	390 (100)	
Adjusted[a] a.m. mean – l/minute	400.1	390.6	0.006
Symptom-free days, weeks 1–52 – median % (IQR)	58.8 (1.5, 90.6)	52.1 (0, 83.5)	0.034
Nocturnal awakenings, weeks 1–52 – median % (IQR)	1.1 (0, 6.3)	1.4 (0, 6.3)	NS
Asthma exacerbations:			
Patients – *n* (%)	39 (11.3%)	61 (17.7%)	
Events – *n*	50	96	
Adjusted annual mean exacerbation rate	0.18	0.33	0.008
Use of rescue medication, weeks 1–52:			
Days without salbutamol – median % (IQR):	90.5 (66.5, 98.3)	85.6 (58.5, 96.7)	0.008
Daily puffs of salbutamol – median (IQR):	0.11 (0.02, 0.43)	0.18 (0.04, 0.59)	0.006
Exposure to oral corticosteroids (days)	301	559	0.026
Mortality			
QoL			
Patients experiencing AEs – *n* (%):	169/348 (48.6%)	185/354 (52.3%)	
Patients experiencing drug-related AEs – *n* (%)	22 (6.3%)	21 (5.9%)	
Patients experiencing serious AEs – *n* (%)	9 (2.6%)	9 (2.5%)	
Patients withdrawing because of AEs	6	11	
Other			
Adjusted mean daily symptom score	0.8	0.9	NS
Well-controlled asthma weeks – median %	82.7%	71.2%	
Daily ICS exposure – mean μg (SD)	463 (81)	480 (238)	

[a] Adjusted according to ANCOVA allowing for treatment, baseline, group country, sex and age.

continued

Comments
The proportion of patients who were compliant with each device was similar in the two treatment arms: with the Diskus, 80.8% of the SAL/FP group and 82.6% of the FF/BUD group were compliant; with the Turbuhaler, 66.9% of the SAL/FP group and 68.3% of the FF/BUD group were compliant

Methodological comments

- **Allocation to treatment groups**: centralised randomisation employing interactive voice response system
- **Blinding**: "double-blind, double-dummy"; primary outcome assessed by (blinded) participants; identity and blinding of assessors of clinical parameters not reported
- **Comparability of treatment groups**: the two treatment groups are reported to be "well balanced with regard to demographic and baseline characteristics". From table of baseline characteristics the groups appear comparable although no statistical tests are reported
- **Method of data analysis**:
  - Stated ITT analysis (*18 participants were randomised but excluded from ITT population due to absent efficacy data and/or took no study medication*)
  - Percentage of SFDs was analysed using the van Elteren extension to the Wilcoxon rank sum test using grouped country as the stratification variable
  - Percentage of rescue-free days, mean daily rescue medication use and percentage of nights awoken due to asthma were analysed using the van Elteren extension to the Wilcoxon rank sum test using grouped country as the stratification variable
  - Mean asthma symptom score, mean morning PEF were analysed using ANCOVA allowing for treatment, baseline, group country, sex and age
  - Rate of asthma exacerbations was analysed using a maximum likelihood based analysis assuming the negative binomial distribution with time on treatment as offset variable
- **Sample size/power calculation**: it was expected that a sample size of 347 patients per group would be sufficient to detect a difference in the primary end point based on a Mann–Whitney U-test with a 5% two-sided significance level and 90% power
- **Attrition/drop-out**: fully reported

General comments

- **Generalisability**: relatively inclusive eligibility criteria; not applicable to ICS-naïve population
- **Outcome measures**: most (including primary outcome measure) reliant on subjective judgement of participants (e.g. symptom scores) and/or investigators (e.g. exacerbations)
- **Inter-centre variability**: not reported
- **Conflict of interests**: study was sponsored by manufacturers of FP + SAL

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were outcome assessors blinded to the treatment allocation?	Primary outcome and secondary outcomes: adequate FEV1: unknown
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 186 **Author:** Jäger *et al*. **Year:** 2000 **Country:** Germany **Study design:** Multi-centre, randomised, open-label, cross-over **Number of centres:** 6 **Funding:** Not specified	**Group A:** *n* = 79 Drug(s): BDP Dose: 400 μg b.d. Delivery: DPI (Easyhaler) Duration: 8 weeks **Group B:** *n* = 79 Drug(s): BUD Dose: 400 μg b.d. Delivery: DPI (Turbohaler) Duration: 8 weeks **Run-in period:** Duration: 2 weeks prior randomisation ICS: continued treatment with either BDP or BUD 800–1000 μg q.d. Relief: not reported **Additional treatment allowed:** • Relief: salbutamol 100 μg MDI rescue medication permitted p.r.n. • Other: 1-week course of oral steroid permitted if asthma deteriorated	**Number randomised:** 79 **Sample attrition/drop-out:** *n* = 10 (3 for AEs; 2 for withdrawal of informed consent; 2 for violation of entry criteria; 2 for protocol violation; 1 lost to follow-up) **Sample crossovers:** 8 weeks BDP followed by 8 weeks BUD 8 weeks BUD followed by 8 weeks BDP **Inclusion/exclusion criteria:** • Age >18 years • Stable bronchial asthma controlled by daily use of BDP or BUD inhalation aerosols during previous 4 months • No previous experience with Easyhaler or Turbuhaler MDPIs • No respiratory infection or asthma exacerbation during previous 8 weeks • No oral steroids during previous 8 weeks **Baseline characteristics:** • Male:female = BDP 21:18, BUD 18:22 • Mean age (± SD) (years) = BDP 51 ± 16, BUD 50 ± 14 • Smoking history: not reported • Duration of asthma (years ± SD): BDP 9.4 ± 7.7, BUD 11.4 ± 10.6 • History of atopy = BDP 38.5%, BUD 42.5% • FEV_1 (absolute value litres ± SD) = BDP 2.31 ± 0.84, BUD 2.37 ± 0.60 • FEV_1 (% predicted ± SD) = BDP 75 ± 18, BUD 78 ± 18 • Morning PEF (l/minute ± SD) = BDP 365 ± 110, BUD 346 ± 115 • Evening PEF (l/minute ± SD) = BDP 378 ± 112, BUD 367 ± 121 • Severity of asthma = mild (%) BDP 23.1%, BUD 12.5%; = moderate (%) BDP 76.9%, BUD 87.5%	**Primary measure:** PEF (a.m.) **Secondary measures:** • FEV_1 (absolute) • PEF (p.m.) • FVC • Diurnal variation in PEF • Day- and night-time asthma symptom scores • Patient-rated treatment efficacy scores • Patient-rated acceptability of device • Salbutamol inhalations per day • Serum cortisol levels • AEs **Method of assessing outcomes:** • Follow-up visits before crossover (weeks 9–10) and last follow-up visit (weeks 17–18) are primary time points for evaluation of efficacy – FEV_1, FVC – patient-rated treatment efficacy on VAS – patient's assessment of device acceptability on VAS – serum cortisol • Daily patient diary recording: – a.m. and p.m. PEF (highest reading of 3) – number of salbutamol inhalations per day – severity scores for asthma symptoms (dyspnoea, wheezing and cough) during day and night – AEs **Length of follow-up:** 2 weeks run-in period plus two 8-week treatment periods = 18 weeks

continued

Results

Outcomes	BDP (n = 79)	BUD (n = 79)	95% CI for treatment difference; p-value
FEV_1 – litres:			
treatment period	2.47	2.39	0.01 to 0.17; p = NS[a]
A.m. PEF – l/minute:			
treatment period	372	372	–8.3 to 4.8; p = NS[a]; p = 0.01[b]
P.m. PEF – l/minute:			
treatment period	382	381	–7.0 to 7.1; p = NS[a]
SFDs			
Nocturnal awakenings			
Acute exacerbations (n)	6	3	See comments
Use of reliever medication – puffs/day ± SD	2.8 ± 2.1	2.9 ± 2.1	p = NS[a]
Use of systemic corticosteroids			
Mortality			
QoL			
Patients experiencing AEs – n (%):	2	1	
Cough	1	1	
Dysphonia	1		
Oropharyngeal mucosal irritation	8	9	

[a] Group A vs Group B.
[b] Total patient population vs baseline.

Comments

- In the 10-item acceptability questionnaire, three questions revealed significant difference between devices in favour of Group A (BDP Easyhaler): confidence in taking complete dose, determining the number of remaining doses, device they would choose to use
- VAS scores for device acceptability, p = 0.001 in favour of Group A (BDP Easyhaler)
- In five out of the seven patients who had exacerbations during the treatment period, they were related to upper or lower respiratory tract infection

Methodological comments

- **Allocation to treatment groups**: randomisation methods not specified
- **Blinding**: open-label
- **Comparability of treatment groups**: the two treatment groups are reported to be "comparable with respect to age, weight, height and respiratory function". From table of baseline characteristics the groups appear comparable, although no statistical tests are reported.
- **Method of data analysis**:
  - ANOVA with two-sided 5% level of significance was used on measurements of lung function and serum cortisol levels at weeks 10 and 18. Model included terms for treatment, period, sequence, centre and treatment-by-centre interaction
  - Asthma symptom scores were analysed by computing patient-wise percentage scores (sum score of period of interest divided by theoretical maximum score for that period)
  - Patients' assessment of devices using VAS was analysed using Wilcoxon's signed rank test
  - Analysis was ITT
- **Sample size/power calculation**: designed to enrol 58 patients per treatment group to detect (with 90% power; α = 0.05) a difference between groups of 30 l/minute in a.m. PEF (assuming mean of 450 l/minute and SD 70 l/minute)
- **Attrition/drop-out**: reported

General comments

- **Generalisability**: relatively inclusive eligibility criteria
- **Outcome measures**: appropriate and relatively objective
- **Inter-centre variability**: not reported; no stratification of randomisation by centre described
- **Conflict of interests**: none specified; 3 named authors are from Orion Pharma, Finland

continued

Quality criteria for assessment of experimental studies	
1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Open label
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were outcome assessors blinded to the treatment allocation?	Inadequate
5. Was the care provider blinded?	Inadequate
6. Was the patient blinded?	Inadequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partial
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 203 **Author:** Kaur *et al*. **Year:** 2005 **Country:** India **Study design:** Double-blind, randomised crossover **Number of centres:** 1 **Funding:** None specified	**Group A:** *n* = 15 Drug(s): BDP Dose: 1000 μg b.d. Delivery: MDI + spacer Duration: 6 weeks **Group B:** *n* = 15 Drug(s): BUD Dose: 1000 μg b.d. Delivery: MDI + spacer Duration: 6 weeks **Run-in period:** Duration: 1 week ICS: none specified Relief: none specified **Additional treatment allowed:** • Relief: salbutamol as needed • Other: none specified	**Number randomised:** 15 **Sample attrition/drop-out:** *n* = 2 ("One patient opted out of study during second drug phase and other during the first drug phase") **Sample crossovers:** 6 weeks BDP, wash-out 1 week followed by 6 weeks BUD; or 6 weeks BUD, wash-out 1 week followed by 6 weeks BDP **Inclusion/exclusion criteria:** • Age 14–45 years • Newly diagnosed patients with asthma (diagnosis based on history of recurrent cough and wheezing and documentation of >12% and 200 ml increase in FEV_1:FVC after inhalation of 200 μg inhaled Salbutamol • Non-smokers • No other systemic disease **Baseline characteristics:** • Age, years (SD): 28.6 (8.0) • Males:females: 14:1 • Height, cm (SD): 160.4 (6.7) • Weight, kg (SD): 51.2 (9.0)	**Primary measure:** Not specified **Secondary measures:** • Serum cortisol (9 a.m.), μg/100 ml • Serum cortisol (4 p.m.), μg/100 ml • 24 h urinary steroids, mg/24 hours • FVC (litres) • FEV_1 (litres) **Method of assessing outcomes:** • Patient diary for recording: – symptoms – drugs • Beginning and end of treatment periods: – samples of blood (9 a.m. and 4 p.m.) and urine (24 hour) for cortisol – spirometry (FVC, FEV_1) **Length of follow-up:** None beyond two 6-week periods

continued

Results

Outcomes	Group A BDP (n = 15)	Group B BUD (n = 15)	p-Value
FEV_1 (litres) (SD)			
Baseline	1.86 (0.88)	2.14 (0.79)	
Week 6	2.44 (0.76)	2.69 (0.82)	<0.05[b,c]
FVC (litres)			
Baseline	2.89 (0.80)	3.04 (0.87)	
Week 6	3.18 (0.72)	3.71 (0.62)	<0.05[c]; NS[b]
Serum cortisol 9 a.m. (µg/100 ml)			
Baseline	19.27 (4.41)	19.63 (3.58)	
Week 6	19.67 (4.10)	18.78 (3.26)	NS[b,c]
Serum cortisol 4 p.m. (µg/100 ml)			
Baseline	12.46 (2.95)	12.53 (2.03)	
Week 6	12.42 (2.73)	11.57 (2.35)	NS[b,c]
24-hour urinary steroids (mg/24 hours)			
Baseline	16.20 (4.92)	15.63 (4.02)	
Week 6	15.80 (3.73)	15.49 (3.19)	NS[b,c]

[a] Group A vs Group B.
[b] Group A vs baseline.
[c] Group B vs baseline.

Comments

- Study included 10 healthy subjects of either sex, age range 18–35 years, to establish normal range of serum and urinary cortisol. Absolute and mean values of serum cortisol for all patients were found to be within normal range with both BDP and BUD
- Treatment with either BUD or BDP produced a significant ($p < 0.05$) rise in $FEV_{25–75\%}$
- Treatment with BDP produced a slight fall in PEF; treatment with BUD caused a statistically insignificant increase

Methodological comments

- **Allocation to treatment groups**: computer-generated random numbers
- **Blinding**: "double-blind"; identity and blinding of assessors of biochemical and clinical parameters not reported
- **Comparability of treatment groups**: crossover
- **Method of data analysis**: Student's *t*-test for paired samples
- **Sample size/power calculation**: not specified
- **Attrition/drop-out**: 2. No reasons provided. Drop-outs excluded from data analyses

General comments

- **Generalisability**: limited to young patients (<45 years)
- **Outcome measures**: appropriate and objective
- **Inter-centre variability**: NA
- **Conflict of interests**: none specified

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	NA
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Partial
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Inadequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 236 **Author:** Koopmans *et al*. **Year:** 2006 **Country:** Not stated; all authors from The Netherlands **Study design:** Double-blind parallel group RCT **Number of centres:** Not stated (assumed 1) **Funding:** GlaxoSmithKline	**Group A: FP** *n* = 27 Drug(s): FP Dose: 250 μg b.d. Delivery: DPI Diskus Duration: 52 weeks **Group B: FP/SAL** *n* = 27 Drug(s): FP/SAL Dose: 250/50 μg b.d. Delivery: DPI Diskus Duration: 52 weeks **Run-in period:** Duration: 4 weeks ICS: FP 250 μg b.d. Relief: Not stated whether the salbutamol 200 μg rescue medication also applied to run-in period **Additional treatment allowed:** • Relief: salbutamol 200 μg • Other: none stated **Objective:** To investigate whether adding salmeterol to fluticasone has a prolonged effect on the bronchial inflammatory process in asthma	**Number randomised:** 54 **Sample attrition/drop-out:** *n* = 4 (7%), all in FP group (1 due to worsening asthma, 1 lost to follow-up, 2 for personal reasons) **Sample crossovers:** None **Inclusion criteria:** • Mild to moderate persistent allergenic asthma (GINA II and III) • Aged 18–60 years • FEV_1 ⩾70% of predicted value after maximal bronchodilation • Sensitisation to cat, dust mite and/or grass pollen allergens • Bronchial hyperresponsiveness to histamine, PC20 histamine ⩽8.0 mg/ml at end of run-in period • Clinically stable disease without exacerbations within 3 months requiring oral steroids and/or antibiotics prior to entry into study • No changes to asthma medication during 4 weeks prior to entry • Ability to use Diskus inhaler and perform reproducible lung function tests **Exclusion criteria:** • Co-morbidity likely to interfere with the study (undefined) • Lower respiratory tract infection or use of antibiotics during 4 weeks before study entry • Use of the following during the study: theophylline, sodium cromoglycate, nedocromil sodium or antileukotrienes; or antibiotics 4 weeks prior to study • Current smokers, or regular smokers within 6 months before study entry, or a smoking history of >10 pack-years • Pregnant or lactating females • Inability to follow therapy instructions • Participation in another clinical trial within 4 weeks prior to the study **Baseline characteristics:** • Median age (range) (years): FP 32 (19–57), FP/SAL 32 (21–59) • Male:female (%): FP 30:70, FP/SAL 37:63 • Median (range) ICS use before study (μg/day): FP 593 (200–1200), FP/SAL 619 (200–1000) • FEV_1 (% predicted) at start of run-in, geometric mean (± SD): FP 89.9 (14), FP/SAL 88.8 (18) • FEV_1 (% predicted) at end of run-in, geometric mean (± SD): FP 92.6 (16), FP/SAL 93.1 (16.1) • Mean (± SD) morning PEF (l/minute) at end of run-in: FP 422 (102), FP/SAL 418 (102) • Mean (± SD) evening PEF (l/minute) at end of run-in: FP 435 (110), FP/SAL 431 (106) • Mean (± SD) morning symptom score at end of run-in: FP 0.2 (0.3), FP/SAL 0.3 (0.5) • Mean (± SD) evening symptom score at end of run-in: FP 0.6 (0.6), FP/SAL 0.6 (0.7)	**Primary measure:** Sputum eosinophil numbers and eosinophilic cationic protein concentrations **Secondary measures:** • Neutrophil-related sputum parameters • Respiratory membrane permeability • FEV_1 • Bronchial allergen challenge • Responsiveness to histamine • IgE counts • PEF • Symptom scores • Rescue medicine use **Method of assessing outcomes:** • Patient diary cards completed for14 days prior to each clinic visit: – PEF – rescue medicine use – symptom scores • Measurement of FEV_1 (spirometry), allergy responsiveness and biochemical parameters in clinic visits **Length of follow-up:** None beyond the 52-week treatment period

continued

Study	Treatment	Participants	Outcomes
		• Mean (± SD) short-acting β_2-agonist use in second half of run-in (puffs/day): FP 1.4 (1.8), SFC 1.0 (1.3) • Geometric mean (± SD) PC20 histamine at start of run-in (mg/ml): FP 0.14 (0.16), SFC 0.5 (1.5) • Geometric mean (± SD) PC20 histamine at end of run-in (mg/ml): FP 1.0 (1.5), SFC 1.6 (1.3) • Note: morning and evening symptom scores use scales 0–4 and 0–5, respectively, but no further details given	

Results

Outcomes	FP (n = 27)	FP/SAL (n = 27)	p-Value
Mean (± SE) morning PEF (l/minute) at month 12	From chart[a]	From chart[a]	Not given
Mean short-acting β_2-agonist use (puffs/day) at month 12	From chart[b]	From chart[b]	Not given
	Mean (SE) difference FP/SAL – FP over the 1-year study period[c]		
Morning PEF (l/minute)	29 (9)		<0.001
Evening PEF (l/minute)	36 (9)		<0.001
Morning symptom score (scale 0–4)	–0.1 (0.1)		0.02
Evening symptom score (scale 0–5)	–0.2 (0.1)		0.01
Short-acting β_2-agonist use (puffs/day)	–0.9 (0.3)		<0.001
FEV_1 (% predicted)	2.7 (1.5)		0.07
Mortality	NR		
QoL	NR		
AEs – n (%):			
None reported (apart from one drop-out due to worsening asthma)			
Other			

[a] Estimated from Fig. 2A: FP 419 (13), FP/SAL 459 (13).
[b] Estimated from Fig. 2B: FP 0.32, FP/SAL 0.38 (SE bars for FP and FP/SAL overlap; separate SE values are not extractable).
[c] Means for each treatment are not given; only the mean difference is presented.

Comments
- For PEF and short-acting β_2-agonist use, data are available also for months 0, 1, 3, 6, 9 and 11 (in Fig. 2)
- Results have been extracted for the relevant outcomes only
- Difference between FP and FP/SAL in mean morning PEF over the whole treatment period was significant ($p < 0.01$)
- Difference between FP and FP/SAL in mean short-acting β_2-agonist use over the whole treatment period was significant ($p < 0.01$)
- There were no differences in numbers or severity of exacerbations between FP and FP/SAL (results not shown)

Methodological comments

- **Allocation to treatment groups**: no details of the randomisation method are given
- **Blinding**: the study is described as "double blind" but no other information on blinding is given
- **Comparability of treatment groups**: no information given on the ethnic composition of patient populations. The groups appear comparable at baseline with regard to demographic and disease characteristics; stated that there were no significant differences between FP and FP/SAL at baseline
- **Method of data analysis**: it is not stated whether analyses were performed on ITT populations. The majority of results are reported without indication of the n; in the few cases where n is stated (e.g. for allergen-induced inflammation), drop-outs are excluded from the results, suggesting that analysis did not follow an ITT basis. Differences within and between the treatment groups were determined using mixed model ANOVA adjusted for differences at baseline. However, details of the ANOVA models and null hypotheses were not reported. All p-values are 2-sided; level of significance $\alpha = 0.05$
- **Sample size/power calculation**: it is stated that the study was designed to have 80% power to detect a 50% difference in geometric means of the primary outcomes between the groups with a sample size of 54 subjects. This might have been a *post hoc* power calculation, as the required n and actual n appear identical. The primary outcomes (hence also power calculations) are not relevant for data extraction as only the secondary outcomes are clinically significant
- **Attrition/drop-out**: 4 patients (7%) withdrew from the study, all of them from the FP treatment (i.e. 15% of FP patients), 1 due to worsening asthma, 1 lost to follow-up, 2 for personal reasons

continued

General comments

- **Generalisability**: results would be applicable to a patient population with mild to moderate persistent allergic asthma but inapplicable to a drug-naïve population
- **Outcome measures**: the primary outcome measures are surrogate end-points (various biochemical and allergen-inducible markers). Only a small proportion of the results concerns objective and appropriate clinically relevant end-points (PEF, FEV_1, symptom scores and rescue medicine use)
- **Inter-centre variability**: the number and identity of centres and their location are not reported. (The study probably involved one centre in The Netherlands, but this is a guess, as it is not explicitly stated)
- **Conflict of interests**: GlaxoSmithKline provided financial support. The four authors are from academic departments (in the University of Amsterdam) that receive funding from GlaxoSmithKline, Nimico and AstraZeneca to conduct clinical trials. (It is not stated whether the reported work was carried out at the authors' institution)

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partial
8. Did the analyses include an ITT analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 241 **Author:** Kuna *et al*. **Year:** 2006 **Country:** 8 countries (lead author, Poland; also Finland, Germany, Mexico, New Zealand, Norway, Russia, Sweden) **Study design:** Double-blind, double-dummy parallel group RCT **Number of centres:** 61 **Funding:** AstraZeneca	**Group A:** *n* = 202 Drug(s): BUD + FF Dose: 160/9 μg 2 puffs q.d. (181/10.2 μg *ex*-valve) Delivery: Turbuhaler Duration: 12 weeks **Group B:** *n* = 207 Drug(s): BUD + FF Dose: 160/9 μg[a] b.d. (181/10.2 μg *ex*-valve) Delivery: Turbuhaler Duration: 12 weeks **Group C:** *n* = 207 Drug(s): BUD Dose: 200 μg p.m. q.d.[a] Delivery: Turbuhaler Duration: 12 weeks **Run-in period:** Duration: 2 weeks ICS: BUD 100 μg b.d. Relief: none stated	**Number randomised:** 617 but 1 patient did not receive any study medication → 616 in ITT population **Sample attrition/drop-out:** *n* = 61 (10%), comprising 26 due to asthma deterioration, 10 due to other AEs and 25 for other reasons **Sample crossovers:** None **Inclusion criteria:** • Men or women aged: ⩾18 years • Asthma of minimum duration 6 months, not optimally controlled despite a daily dose of 200–500 μg ICS for ⩾30 days prior study entry • Baseline FEV_1 60–90% of predicted normal, with a demonstrated reversibility of FEV_1 of ⩾12% upon inhalation of terbutaline sulfate 1 mg or salbutamol 0.4 mg **Exclusion criteria:** • Use of any systemic corticosteroids within the previous 30 days • Seasonal asthma (defined as asthma exacerbated by seasonal increases in aeroallergens)	**Primary measure:** Mean change a.m. PEF from baseline to end of 12-week treatment **Secondary measures:** P.m. PEF, asthma symptoms, use of reliever, nocturnal waking, FEV_1 **Method of assessing outcomes:** Patient diary cards recording: • A.m. and p.m. PEF Mini-Wright peak flow meter use • Symptom scores (4-point scale: 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe) • Reliever use • Study drug intake • Awakenings due to asthma • AEs (any): – 76 (38%) of patients on 1/day BUD + FF – 78 (38%) of patients on 2/day BUD + FF – 74 (36%) of BUD patients

continued

Study	Treatment	Participants	Outcomes
	Additional treatment allowed: • Relief: terbutaline sulfate or another preferred short-acting β_2-agonist (dose not stated) • Other: none stated	• Respiratory infection in the 4 weeks prior study entry • Severe cardiovascular or any other significant disease • Used β-blocker therapy (including eye drops) • History of heavy smoking (⩾10 pack-years) • Pregnant women • Women of child-bearing potential who failed to use acceptable contraceptive measures • Patients unable to use a peak-flow meter or adequately complete diary cards during the run-in period **Baseline characteristics:** • *n*: Group 1 1/day (*n* = 202), Group 2 2/day (*n* = 207), Group 3 (*n* = 207) • Mean (years) age (range): Group 1 45.8 (18–80), Group 2 43.9 (19–80), Group 3 45.1 (18–78) • Male:female: Group 1 40:60, Group 2 38:62, Group 3 44:56 • Asthma duration (range) (years): Group 1 11.5 (1–63), Group 2 12.2 (0–50), Group 3 10.6 (1–58) • ICS dose (μg/day) (range): Group 1 363 (200–500), Group 2 371 (200–500), Group 3 368 (200–500) • FEV_1 at baseline (litres): Group 1 2.36, Group 2 2.32, Group 3 2.36 • FEV_1 % of predicted normal (range): Group 1 79.3 (37–115), Group 2 77.9 (23–123), Group 3 78.3 (38–119) • Reversibility of FEV_1 (%) upon inhalation of terbutaline sulfate 1 mg or salbutamol 0.4 mg (range): Group 1 23.5 (12–91), Group 2 23.4 (12–75), Group 3 23.2 (12–95) • Morning PEF (l/minute) (range): Group 1 356 (115–684), Group 2 351 (173–692), Group 3 358 (98–740) • Evening PEF (l/minute) (range): Group 1 366 (112–670), Group 2 362 (181–738), Group 3 371 (112–753) • % nocturnal waking due to asthma: Group 1 15.8, Group 2 14.6, Group 3 17.9 • % SFDs: Group 1 37.8, Group 2 36.1, Group 3 38.1 • % asthma control days: Group 1 33.9, Group 2 32.5, Group 3 35.1	• Serious AEs (not related to treatment): – 2 patients on 1/day BUD + FF – 1 patient on 2/day BUD + FF – 4 patients on BUD • Comprising: – 3 aggravated asthma – 1 acute vertigo – 1 lung carcinoma – 1 chest pain – 1 thyroiditis • FEV_1 assessed in clinic by spirometry at start of run-in, end of run-in (2 weeks), and at 4, 8 and 12 weeks into randomised treatment. AEs also assessed at clinic visits by interviewer questioning patients and if reported spontaneously by patient • Patient records to obtain composite measures • SFDs (a day and night with no asthma symptoms or asthma-induced waking) • Reliever-free days (a day and night without reliever medication use) • Asthma control days (a day and night without symptoms, asthma-induced waking or reliever use) **Length of follow-up:** None beyond 12 weeks reported

[a] BUD/FF doses reported as *ex*-actuator, single BUD dose reported as *ex*-valve.

continued

Results

Outcomes (mean values)	Symbicort once daily (n = 202)	Symbicort twice daily (n = 207)	BUD (n = 207)	p-Value
Mean (95% CI) morning PEF change from baseline (l/minute)	23.4 (18.1 to 28.6)		5.5 (0.3 to 10.6)	<0.001
		24.1 (19.0 to 29.2)	5.5 (0.3 to 10.6)	<0.001
Mean (95% CI) evening PEF change from baseline (l/minute)	9.6 (4.4 to 14.8)		–1.7 (–6.8 to 3.5)	<0.01
		18.3 (13.2 to 23.4)	–1.7 (–6.8 to 3.5)	<0.001
Mean (95% CI) % of SFDs	50.0 (46.0 to 54.0)		43.4 (39.4 to 47.3)	<0.05
		50.3 (46.3 to 54.3)	43.4 (39.4 to 47.3)	<0.05
Mean (95% CI) % of nocturnal awakenings	11.3 (9.0 to 13.6)		12.0 (9.8 to 14.3)	NS
		9.9 (7.7 to 12.2)	12.0 (9.8 to 14.3)	NS
Mean (95% CI) % of reliever-free days	61.8 (58.1 to 65.4)		55.5 (52.0 to 59.1)	<0.05
		66.3 (62.7 to 69.9)	55.5 (52.0 to 59.1)	<0.001
Mean (95% CI) % of asthma control (asthma-free) days	47.3 (43.4 to 51.3)		40.0 (36.2 to 43.9)	<0.01
		47.3 (43.4 to 51.1)	40.0 (36.2 to 43.9)	<0.01
Mean FEV_1 change from baseline (litres)[a]	0.08		–0.01	<0.05
		0.12	–0.01	<0.05
Use of systemic corticosteroids				
Mortality				
QoL				
AEs – no. of patients (%) (most frequently reported end-points):				
All AEs	76 (38%)	78 (38%)	74 (36%)	p-Values not given for AEs
Respiratory infection	23 (11.4)	32 (15.5)	25 (12.1)	
Asthma aggravated	12 (5.9)	6 (2.9)	10 (4.8)	
Viral infection	6 (3.0)	7 (3.4)	5 (2.4)	
Pharyngitis	4 (2.0)	7 (3.4)	5 (2.4)	
Rhinitis	4 (2.0)	4 (1.9)	4 (1.9)	
Bronchitis	2 (1.0)	6 (2.9)	3 (1.4)	
Headache	4 (2.0)	4 (1.9)	2 (1.0)	
Pharynx disorder	4 (2.0)	2 (1.0)	1 (0.5)	
Serious AEs (no. of patients) (see Comments)	2	1	4	
Other				

NS, not statistically significant ($p \geqslant 0.05$).
[a] Calculated from baseline and 12-week FEV_1 values given in the text.

Comments
- Once- and twice-daily Symbicort resulted in significantly (about 7%) more asthma control days (26 days per year) compared with BUD ($p < 0.01$; from text)
- Increase in evening PEF differed significantly ($p < 0.05$) between the two Symbicort cohorts
- AEs were asthma-aggravated (n = 3), acute vertigo (n = 1), lung carcinoma (n = 1), chest pain (n = 1), and thyroiditis (n = 1). None was considered to be related to study treatment (not stated which treatment groups the different AE types were observed in)

Methodological comments

- **Allocation to treatment groups**: no details of the randomisation method are reported
- **Blinding**: reported as a double-blind study although no details are given about how the researchers were blinded. The patients were blinded using a double-dummy approach in which each patient received four successively numbered Turbohalers such that treatment and placebo were indistinguishable. Patients were instructed to inhale once from the first inhaler in the morning and then once from each of the other three inhalers in the evening
- **Comparability of treatment groups**: the groups appear comparable with regard to demographic and baseline characteristics. No statistical comparisons of baseline data are reported

continued

- **Method of data analysis**: analyses were performed on the ITT population, defined (by inference) as all the randomised patients who entered the treatment phase of the study who received at least some study medication. 95% CIs are provided and treatment comparisons were analysed using ANOVA (treatment and country as factors; baseline values as covariates; other details not specified). The data from which the mean and 95% CIs were derived do not appear to have been checked for normality. Percentages of symptom-free days, reliever-free days and asthma control days are stated only as being calculated using an "additive model", without further details
- **Sample size/power calculation**: a required sample size of 130 patients per treatment group was calculated on the basis of 80% power in order to detect an 18 l/minute difference in PEF between treatments at $\alpha = 0.05$, assuming an SD of 50 l/minute
- **Attrition/drop-out**: 61/616 randomized and treated patients withdrew from the study:
  - 26 asthma deterioration (10, 5, 11 for once-daily Symbicort, twice-daily Symbicort, BUD, respectively)
  - 10 due to other (unspecified) AEs (5, 3, 2)
  - 25 for other reasons (6, 8, 11)

General comments

- **Generalisability**: with the exception of pregnant women, drug-naïve patients or those with major illnesses in addition to asthma, the patients would appear to be clinically representative of adults with mild-to-moderate (excluding seasonal) asthma. However, the geographical disposition of the patient population among the 61 centres in eight countries is not stated, so the possibility of geographical bias cannot be ruled out (UK not among the included countries). The relatively limited duration of follow-up (maximum 12 weeks) would limit the temporal generality of the findings
- **Outcome measures**: appropriate and objective
- **Inter-centre variability**: not reported (despite large geographical scale and large number of centres)
- **Conflict of interests**: AstraZeneca funded the study. Two members of AstraZeneca (not the authors) were acknowledged for their contribution to the manuscript and the statistical analysis. An independent contractor was acknowledged for providing writing services on behalf of AstraZeneca

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Partial
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 237 **Author:** Lundbäck *et al*. **Year:** 2006 **Country:** Sweden **Study design:** double-blind, parallel-group, RCT **Number of centres:** 1 **Funding:** GlaxoSmithKline	**Group A: FP/SAL** *n* = 95 Drug(s): FP/SAL Dose: FP/SAL 250/50 μg b.d. Delivery: Diskus inhaler Duration: 52 weeks **Group B: FP** *n* = 92 Drug(s): FP Dose: 250 μg b.d. Delivery: Diskus inhaler Duration: 52 weeks **Group C: SAL** *n* = 95 Drug(s): Salmeterol Dose: 50 μg b.d. Delivery: Diskus inhaler Duration: 52 weeks NB. Only Groups A and B are of interest **Run-in period:** Duration: 2 months ICS: 1-month pre-run-in period on "previous therapy", and 1-month run-in period where daily ICS dose was reduced to a maximum of BUD 400 μg q.d. or equivalent Relief: not reported **Additional treatment allowed:** • Relief: salbutamol DPI (0.2 mg) or salbutamol MDI (0.1 mg) • Other: none	**Number randomised:** 282 **Sample attrition/drop-out:** *n* = 19 (7%) (5 for AEs; 5 for non-compliance; 2 treatment failures; 3 pregnancies; 1 remission of asthma; 1 failure to return to clinic; 1 did not want to continue; 1 personal reasons) **Sample crossovers:** NA **Inclusion criteria:** • Aged 18–70 years • Mild-to-moderate persistent asthma, with symptoms at least twice/week • AHR demonstrated by methacholine challenge with PC20 < 8 mg/ml[a] • Diurnal variation in PEF of ⩾20% on >3 days during last 14 days of run-in, ⩾30% difference between highest + 2nd lowest PEF reading during any 7 days in run-in period • Reversible increase of ⩾15% in FEV_1 or PEF after 0.8 mg salbutamol inhalation **Exclusion criteria:** • Daily doses of ICS ⩾1200 μg • ⩾1 life-threatening exacerbations requiring hospitalisation during previous 12 months • Hypersensitive to β-agonists or ICS • Pregnant or lactating • Respiratory tract infection during the 4 weeks prior to run-in **Baseline characteristics:** • Mean age (years): FP/SAL 39.9, FP 39.1 • Male:female (%): FP/SAL 34:66, FP 42:58 • Proportion with asthma >10 years (%): FP/SAL 58, FP 58 • Smokers (%): FP/SAL 14, FP 12 • Weight (kg): FP/SAL 72.9, FP 75.3 • Height (cm): FP/SAL 168.8, FP 169.7 • FEV_1 % predicted (%): FP/SAL 92.1, FP 93 • Mean methacholine PC20 (mg/ml): FP/SAL 0.5, FP 0.6 • Methacholine PC20 <8 mg/ml[a] (%): FP/SAL 97.8, FP 97.8 • + reversibility test[b] (%): FP/SAL 22.1, FP 17.4 • PEF variability (%): FP/SAL 16.8, FP 17.4 • Previous medication (%): SABA, FP/SAL 93, FP 95; LABA, FP/SAL 20, FP 22; corticosteroids, FP/SAL 73, FP 62; other[c], FP/SAL 5, FP 3	**Primary measure:** Number of patients requiring an increase in study medication **Secondary measures:** • Number of patients experiencing ⩾2 exacerbations[d] • Morning PEF • PEF diurnal variation • FEV_1 • FVC • AHR • Day- and night-time symptom scores • Rescue medication use • AEs **Method of assessing outcomes:** • Patient diary cards (used for 7 days prior to randomisation and for 14 days prior to each clinic visit): – PEF (a.m. and p.m.) – asthma symptom scores – rescue medication use – AEs • Clinic assessments at baseline, 1, 3, 6, 9 and 12 months after randomisation: – lung function (FEV_1 and FVC) – AHR (at baseline and after 12 months) – physician recording of AEs **Length of follow-up:** None beyond 12 months treatment period (there was a 2-year open-label follow-up period, but results are not reported in this paper)

AHR, airway hyper-responsiveness.

[a] Concentration required to provoke a 20% reduction in FEV in 1 second (FEV_1).

[b] Medications (not mutually exclusive) used prior to randomisation.

[c] Sodium cromoglycate, montelukast sodium or corticosteroids and bronchodilators combined.

[d] Exacerbations were defined as any deterioration in asthma that required an increase in rescue medication use (β-agonist) over that used during the run-in period of >6 puffs/day for ⩾2 consecutive days, or an increase of ⩾2 doses/day in regular inhaled medication (study medication or additional ICS) for ⩾2 days by the patient's own decision, or ⩾2 days when asthma symptoms prevented the patient's work or normal activities. If rescue medication was insufficient, exacerbations were treated with oral prednisolone (25 mg) for 5 days. A total of 192 patients (68%) had previously received ICS (the median dosage was BUD 500 μg/day or equivalent).

continued

Results

Outcomes	FP/SAL (*n* = 95)	FP (*n* = 92)	*p*-Value
Number requiring increase in study medication, *n* (%)	10 (10.5%)	32 (34.8%)	$p < 0.001$
Morning PEF[a] (l/minute)	38	21	Difference + 16.9, $p < 0.01$
PEF diurnal variation[a]	–2.5	–1.6	Difference –0.9, p = NS
FEV_1[a] (litres)	0.09	0.02	Difference +0.07, p = NS
FVC[a] (litres)	0.07	0.05	Difference +0.01, p = NS
Improvement in AHR after 12 months (mean[a] methacholine PC20) (mg/ml)	1.8	1.1	$p < 0.05$
⩾2 acute exacerbations (%)	4.2	17.4	$p < 0.01$
Median proportion of SFDs (%)	66.7	67.9	
Median SFNs (%)	100	100	
Median proportion of rescue medication-free days (short-acting β_2 agonists) (%)	85.7	85.7	
Median proportion of rescue medication-free nights (short-acting β_2 agonists) (%)	100	100	
Use of systemic corticosteroids			
Mortality			
QoL			
AEs[b] – *n* (%):			
Any	92 (97%)	88 (96%)	NR
RTI[c]	70 (74%)	72 (78%)	
Musculoskeletal pain	9 (9%)	11 (12%)	
Gastroenteritis	11 (12%)	5 (5%)	
Hoarseness/dysphonia	10 (11%)	8 (9%)	
Sinusitis	8 (8%)	5 (5%)	
Headaches	2 (2%)	6 (7%)	
Tonsillitis	4 (4%)	4 (4%)	
Bronchitis	5 (5%)	3 (3%)	
Cough	2 (2%)	3 (3%)	
Chest symptoms	1 (1%)	5 (5%)	
Muscle cramps and spasms	6 (6%)	0 (0)	
Hypertension	0 (0)	5 (5%)	
Candidiasis	6 (6%)	0 (0)	
Other			

[a] Mean change from baseline, adjusted for baseline value, stratum, age and sex.
[b] Most frequently occurring (⩾5%) AEs.
[c] Upper respiratory tract infections plus viral respiratory infections.

Comments
- Results have been presented for FP/SAL and FP groups only
- The main reason for patients increasing their study medication was ⩾2 exacerbations

Methodological comments

- **Allocation to treatment groups**: no details reported of randomisation method
- **Blinding**: both the patients and the investigators administering the medications were blinded. Blinded medication packs were assigned to patients at randomisation; the investigator was supplied with individual sealed envelopes. Blinding for all individuals directly associated with the conduct of the study lasted until either the end of the 12 months or a 2nd asthma exacerbation, which demanded a change in medication
- **Comparability of treatment groups**: the groups appear comparable at baseline with regard to demographic and disease characteristics. No statistical data were reported

continued

- **Method of data analysis**: analyses were performed on an ITT population defined as all patients who were randomised to treatment and received at least one dose of study medication. The pair-wise χ^2 test was used to compare proportions, the ANCOVA adjusted for age, sex and stratum, and the van Elteren extension to the Wilcoxon rank sum test, stratified by stratum, for lung function measurements. Two-sided probability levels ≤5% were considered significant. Any data recorded after unblinding were not included in the analysis. Thus, for assessments recorded at each clinic visit and those derived over the last 2 weeks before each clinic visit, a last observation carried forward approach was used to account for any missing data
- **Sample size/power calculation**: a sample size of 300 patients was calculated on the basis of 80% power to detect a difference of 20% between any pair of treatment groups (FP/SAL vs FP or SAL) in the percentage of patients requiring an increase in dose in any one year
- **Attrition/drop-out**: 19 (7%) withdrew from the study [9 (9%) FP/SAL; 5 (5%) FP]. 2% in the FP/SAL group and 2% in the FP group withdrew due to AEs. Compliance with medication was >70% for all patients throughout the study period
- **Other**: an increase in study medication was required if patients' asthma was not controlled, defined as if they had experienced ≥2 exacerbations during the 12-month treatment period, or if they had any 2 of the following during the 2 weeks prior to the 12-month clinic visit: night symptoms requiring rescue medication >twice; daily symptoms requiring rescue medication >every other day; diurnal variability of mean morning PEF ≥20% on >4 days; a reduction in PEF of ≥15%; or a decrease in clinic FEV_1 ≥10%. Patients randomised to SAL were transferred to FP/SAL (50 μg/250 μg), patients on FP (250 μg) had their dose increased to FP 500 μg, and patients on FP/SAL (50 μg/250 μg) were given FP/SAL (50 μg/500 μg). Patients who needed an increase in study medication as a result of an exacerbation during the 12-month treatment period stopped the blinded phase of the study and continued in the study on an open-label basis

General comments

- **Generalisability**: patients appear to be clinically representative of patients with mild-to-moderate asthma
- **Outcome measures**: appropriate and objective
- **Inter-centre variability**: single-centre study
- **Conflict of interests**: GlaxoSmithKline provided financial support, the study drugs and mini-Wright peak flow meters. Two authors are from GlaxoSmithKline.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Partial
2. Was the treatment allocation concealed?	Inadequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the care provider blinded?	Partial
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 191 **Author:** Medici *et al.* **Year:** 2000 **Country:** Switzerland **Study design:** Multi-centre, double-blind, parallel group RCT **Number of centres:** 7 **Funding:** Glaxo Wellcome R&D, UK	**Group A: FP400** *n* = 22 Drug: FP Dose: 400 μg (200 μg b.d.) Delivery: MDI + spacer Duration: 12 months **Group B: BDP800** *n* = 21 Drug: BDP Dose: 800 μg (400 μg b.d.) Delivery: MDI + spacer Duration: 12 months **Group C: FP750** *n* = 13 Drug: FP Dose: 750 μg (375 μg b.d.) Delivery: MDI + spacer Duration: 12 months **Group D: BDP1500** *n* = 13 Drug: BDP Dose: 1500 μg (750 μg b.d.) Delivery: MDI + spacer Duration: 12 months **Run-in period:** Duration: 4 weeks ICS: BDP 800 or 1500 μg q.d. depending on the dose of ICS use prior to entry Relief: salbutamol as required; most patients also used LABA (not specified) **Additional treatment allowed:** • Relief: none reported • Other: none reported • All other asthma medication "remained unchanged". 4 patients had oral steroids during the treatment period **Study aim:** To compare the effects of treatment with low and high doses of inhaled FP and BDP over 1 year on bone mass and metabolism	**Number randomised:** 69 **Sample attrition/drop-out:** *n* = 4 (6%) (AE 1, non-compliance 1, no reason specified 2) **Sample crossovers:** NA **Inclusion criteria:** • Mild-to-moderate asthma • Aged 20–55 years for men and 20–45 years for women (premenopausal) • 6 months prior use of ICS (400–1600 μg q.d.) **Exclusion criteria:** • A change in regular asthma medication (other than ICS) treatment with antibiotics for infections of upper or lower respiratory tract • Hospital admission during previous 4 weeks • Treatment with systemic corticosteroids during previous 8 weeks • >3 short courses of oral steroids or depot corticosteroids in previous 12 months • Excessively overweight or underweight[a] • Immobilisation • Fractures occurring in 6 months preceding start of study • Disorders of bone metabolism such as osteoporosis or Paget's disease • Pregnancy, lactation, inadequate contraceptive precautions • Amenorrhoea or history of irregular menstrual cycles in 12 months preceding start of study • Treatment with any medication likely to influence bone metabolism **Baseline characteristics:** • Mean age (years): 38–40 across groups • Male:female, *n* (%): 46:23 (67–33%) • Caucasian, *n* (%): 66 (96%) • Mean height (cm): 170–174 across groups • Mean weight (kg): 64–75 across groups • Mean baseline % predicted FEV_1: 75.0–90.2 across groups • Mean baseline % predicted PEF: 78.4–97.8 across groups • Duration of asthma, *n*: <12 years, 2; ⩾12 years, 67 • History of smoking, *n* (%): never 36 (52%); ex-smoker 23 (33%); current smoker 10 (14%)	**Primary measure:** BMD of the distal radius **Secondary measures:** • Cortisol • Biochemical markers of bone metabolism[b] • Lung function: PEF and FEV_1 • AEs **Method of assessing outcomes:** • Clinic visits at start and end of run-in and every 2 months through treatment period: – BMD (at 0, 6 and 12 months) by pQCT and DXA – cortisol by chemoluminescence immunoassay – bone markers by radioimmunoassay, enzyme immunoassay and HPLC using blood/urine samples – FEV_1 at each clinic visit – AEs at each clinic visit • Diary cards before taking study medication, daily during last 2 weeks of run-in and during the 2 weeks preceding each clinic visit: – PEF a.m. and p.m. using mini-Wright peak flow meter **Length of follow-up:** 12 months treatment period + additional follow-up visit 2 weeks after completion of study

DXA, dual-energy X-ray absorptiometry of lumbar spine, evaluating a mixture of cortical and trabecular bone; HPLC, high-performance liquid chromatography; pQCT, peripheral quantitative computed tomography of radius and tibia, evaluating trabecular, total (integral) and compact bone.

[a] Not defined.

[b] Markers of bone metabolism – serum osteocalcin (OC), alkaline phosphatase (bone specific), pro-collagen type I carboxy-terminal propeptide (P1CP), creatinine, calcium, carboxy-terminal crosslinked telopeptide of type I collagen (ICTP).

continued

Results

Outcomes	FP 400 (n = 22)	BDP 800 (n = 21)	FP750 (n = 13)	BDP 1500 (n = 13)	p-Value
PEF					
FEV_1					
SFDs					
Nocturnal awakenings					
Acute exacerbations, n (%)[a]	0	1 (5%)	2 (15%)	1 (8%)	p = ns
Use of systemic corticosteroids					
Mortality					
QoL					
AEs – n (%):					
Hoarseness/dysphonia	1 (5%)	1 (5%)	1 (8%)	0	
Allergic skin reactions	0	0	0	0	
Oral candidiasis	0	0	0	0	
Rash/skin eruptions	0	0	0	0	
Other:					
Mean serum cortisol concentration (nmol/l)[b]					
Baseline	466	474	424	370	
n	22	21	13	13	
Coefficient of variation (%)	29	35	59	54	
12 months	532	486	299	406	
n	21	19	12	12	
Coefficient of variation (%)	41	50	122	41	

[a] Requiring a short course of oral corticosteroids.
[b] Reference range is 138–635.

Comments

BMD

- pQCT: there was no significant difference in change from baseline in BMD of the distal radius for either of the 2 treatment comparisons at 6 or 12 months. Overall, compared with baseline values, there was no loss of trabecular or integral bone in the radius or tibia in any patients over the 12 months. Some negative changes were recorded in the median bone density of compact bone of the radius (FP750 patients) and tibia (BDP800 and FP750 patients); results were not clinically significant (no change exceeded –2%).
- pQCT, non-parametric analyses: the only result of borderline significance was derived from the high-dose comparison of compact bone density of the radius at 12 months (p = 0.048) in patients taking FP750 and BDP1500. While the decrease in bone density was greater in patients taking FP750, negative changes in bone density were recorded in just 3/12 patients, and no change was >–1%. It was therefore not clinically significant
- DXA: there were no significant differences in change from baseline in the bone density of lumbar vertebrae for either of the 2 treatment comparisons at 6 or 12 months, nor was there any difference at 12 months between patients taking FP or BDP in the high-dose comparison. In the low-dose comparison, there was evidence of a significant difference between treatments, patients taking BDP800 showing a negative change from baseline compared with those taking FP400 (p = 0.02). In addition, there was no significant difference in the median change from baseline in bone mineral content of the lumbar spine for either of the 2 treatment comparisons (low and high dose) at 6 and 12 months

Bone markers

- With the exception of the bone resorption marker urine phosphate, all median baseline values for all parameters were within the normal range in all treatment groups. No consistent pattern emerged from the analysis of changes from baseline after 6 and 12 months treatment. In the low-dose comparison group, a statistically significant difference in the change from baseline in osteocalcin at 12 months (p = 0.047) suggested lower bone formation activity in patients taking BDP800 compared with FP400 patients. Likewise, in the high-dose comparison a significant difference from baseline in the bone resorption marker ICTP at 6 months (p = 0.031) suggested greater bone resorption activity in FP750 patients compared with BDP1500 patients. There were no clinically significant changes

Lung function

- Mean daily a.m. and p.m. PEF values taken for 2 weeks before each clinic visit and mean FEV_1 values taken at bimonthly intervals throughout the 12-month study showed that the patients were well controlled on all treatments. Mean values either remained similar or tended to increase slightly above baseline values

continued

AEs
- AE were reported by a similar number of patients in both treatment groups and were comparable between groups. The most common events were infections of the upper respiratory tract and rhinitis. There were no reports of serious AEs
- All geometric mean cortisol values remained within the normal range throughout the 12-month study period

Methodological comments

- **Allocation to treatment groups**: randomisation methods not specified. Allocation to treatment groups depended on whether patients were in the low- or high-dose run-in group, which in turn depended on their regular ICS dose prior to entry
- **Blinding**: just states that study is double-blind – no further details on medications. All scans were performed under blinded conditions
- **Comparability of treatment groups**: states that the demographic and baseline characteristics were well matched in both treatment groups (*p*-values not reported)
- **Method of data analysis**: states that the analysis was ITT, but no further details reported. Differences between treatments in changes from baseline in BMD were analyses using the Wilcoxon rank sum test. Similar methods of analysis were applied to bone markers. All statistical tests performed were 2-sided with *p*-values of 0.05 considered significant. No formal analysis was applied to serum cortisol, daily diary card (PEF, symptom scores or use of additional bronchodilator) or clinic lung function data
- **Sample size/power calculation**: taking the SD of 1.55 for % change in trabecular BMD (obtained in a previous pQCT study), 92 evaluable subjects (23 per treatment group) were required to ensure a power of 80% to detect a 1.3% difference between treatments in change from baseline. *Reviewer*: this was not achieved for any of the groups, and the high-dose groups had only 13 patients each
- **Attrition/drop-out**: 4 patients (6%) (1 from each group) withdrew from the study: AE ($n = 1$, BDP1500), non-compliance ($n = 1$, BDP800), no reason specified ($n = 1$, FP400; $n = 1$, FP750)

General comments

- **Generalisability**: includes patients with mild-to-moderately severe asthma; not applicable to ICS-naïve populations
- **Outcome measures**: focus is on bone density, which is measured objectively by 2 different methods
- **Inter-centre variability**: not reported
- **Conflict of interests**: Glaxo Wellcome R&D provided financial support; 2 authors are from Glaxo Wellcome

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the care provider blinded?	Partial
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 196 **Author:** Niphadkar *et al*. **Year:** 2005 **Country:** India **Study design:** Multi-centre, double-blind, double-dummy (CIC groups) or open-label (BUD group) **Number of centres:** 11 **Funding:** Supported by a grant from Altana Pharma	**Group A:** *n* = 140 Drug(s): CIC a.m. + placebo p.m. Dose: 200 μg q.d. (≈160 μg *ex*-actuator) Delivery: HFA-MDI Duration: 12 weeks **Group B:** *n* = 131 Drug(s): CIC p.m. + placebo a.m. Dose: 200 μg q.d. (≈160 μg *ex*-actuator) Delivery: HFA–MDI Duration: 12 weeks **Group C:** *n* = 134 Drug(s): BUD Dose: 200 μg b.d. Delivery: HFA–MDI Duration: 12 weeks **Run-in period:** Duration: 2–2.5 weeks ICS: BUD 200 μg b.d. Relief: inhaled salbutamol (100 μg/puff) **Additional treatment allowed:** Relief: inhaled salbutamol (100 μg/puff) Other: 1 other concomitant medication (including LABA, oral β_2-agonist, leukotriene antagonist, theophylline, inhaled disodium cromoglycate, nedocromil) **Trial aim:** To assess the non-inferiority of Group B vs Group C	**Number randomised:** 405 **Sample attrition/drop-out:** *n* = 37 [1 did not receive allocated intervention; 1 excluded because randomised twice; 35 discontinued intervention (2 for AEs; 10 for lack of efficacy; 23 other)] **Inclusion criteria:** • At enrolment: – age 18–69 years – persistent asthma for ⩾6 months – constant dose of BDP (⩽500 μg/day), FP (200–250 μg/day), BUD (400 μg/day) or equivalent ICS for previous ⩾4 weeks – FEV_1 ⩾70% predicted ⩾4 hours after last rescue medication and 24 hours after withholding other medication • After run-in: – *stable asthma*, defined as: (a) no fluctuation ⩾20% in diurnal PEF, no need for >4 puffs/day of rescue medication and no night symptom score ⩾2 on any consecutive 2 of previous 10 days (b) no need for oral steroids (c) FEV_1 >69% predicted ⩾4 hours after last rescue medication and 24 hours after withholding all medication except BUD • Either after run-in or during last year: – FEV_1 reversibility ⩾12% after 200–400 μg salbutamol or – positive hyperresponsiveness test (PC20) **Exclusion criteria:** • Any prior use of systemic steroids • Exacerbation/hospitalisation in previous 4 weeks • COPD • Disease states contraindicating ICS • Smoking history of ⩾10 pack-years • Pregnancy or breastfeeding • Abnormal laboratory values **Baseline characteristics:** • Male:female = 213:190 • Median age (range) (years) = 29–32 (18–69)[a] • Median weight, kg = 55–57[a] • Smoking history = 380 (94%) non-smokers, 23 (6%) ex-smokers • ICS pretreated = 356 (88%) • Concomitant medication before entry, *n* (%): LABA = 105 (26%); xanthines = 62 (15%); ICS + LABA = 54 (13%); antihistamines = 37 (9%); nasal corticosteroids = 24 (6%) • Mean FEV_1, litres = 2.2–2.3[a] • Mean FEV_1, % predicted = 92–94[a] • FEV_1 (% predicted), no. (%): ⩾80% = 314 (78%); >60%, <80% = 85 (21%); ⩽60% = 1 (<1%) • Mean reversibility: change in FEV_1, % predicted (range) = 23–28 (–17 to 341)[a] • Mean morning PEF, l/minute = 318.1–324.8[a] • PEF fluctuation, % (range) = 6.9–7.3 (0–34)[a]	**Primary measure:** Change in FEV_1 at the end of treatment **Secondary measures:** • Difference in FEV_1 between randomisation and study visits • FVC • PEF • Diurnal PEF fluctuation • Asthma symptom scores • Rescue medication use • AEs **Method of assessing outcomes:** • Clinic assessments at baseline and weeks 0, 2, 4, 8 and 12: – FEV_1, FVC and PEF (highest reading of 3; ⩾4 hours after last use of salbutamol and ⩾24 hours after last use of any other concomitant asthma medication) • At the start of the baseline period and at the end of treatment: – physical examination, including vital signs and ECG • Throughout treatment, patients recorded: – 3 PEF readings a.m. and p.m. – symptom scores – rescue medication use **Length of follow-up:** None beyond 12-week treatment period

[a] Range of values across all 3 arms.

continued

Results

Outcomes	Group A (n = 139[a])	Group B (n = 131)	Group C (n = 133[a])	p-Value
FEV_1, mean[b] change from baseline:	–0.036	0.022		0.383[c]; 0.598[d]
difference – litres (95% CI)	(–0.120 to 0.045)[c]	(–0.061 to 0.105)[d]		
p-Value (baseline vs week 12)	0.001	NS[e]	0.035	
PEF, mean[b] change from baseline:				
A.m. – l/minute (95%CI)	–5.7	8.0	–1.3	NS[c,e]; NS[d,e]
Difference, a.m. – l/minute (95% CI)	–4.4	9.3		0.464[c]; 0.131[d]
	(–16.4 to 7.5)[c]	(–2.8 to 21.5)[d]		
Difference, p.m. – l/minute (95% CI)	–1.1	4.0		0.855[c]; 0.490[d]
	(–12.4 to 10.3)[c]	(–7.5 to 15.5)[d]		
SFDs – %	89	91	93	NS[c,e]; NS[d,e]
Nocturnal awakenings – %	0	0	0	
Acute exacerbations:				
discontinuations – n (%)	7 (5.0%)	1 (0.8%)	2 (1.5%)	0.067[c,f]; 1.000[d,f]
Use of systemic corticosteroids				
Use of reliever medication				NS[c,d,e]
Mortality				
QoL				
AEs – n (%):				
At least 1 AE	24 (17.1%[g])	32 (24.4%)	28 (21.1%)	0.443[c,f]; 0.558[d,f]
mild or moderate	17 (12.1%[g])	31 (23.7%)	26 (19.5%)	0.099[c,f]; 0.456[d,f]
severe	7 (5.0%[g])	1 (0.8%)	2 (1.5%)	0.174[c,f]; 1.000[d,f]
Asthma aggravated	13 (9.3%[g])	13 (9.9%)	14 (10.5%)	0.840[c,f]; 1.000[d,f]
Upper respiratory tract infections	3 (2.1%[g])	4 (3.1%)	5 (3.8%)	0.492[c,f]; 1.000[d,f]
Rhinitis	2 (1.4%[g])	1 (0.8%)	4 (3.0%)	0.437[c,f]; 0.370[d,f]
Discontinuation due to AEs	1 (0.7%)	0	1 (0.8%)	1.000[c,f]; 1.000[d,f]
Other				

[a] 1 randomised patient excluded from analyses.
[b] Least-squares mean.
[c] Group A vs Group C.
[d] Group B vs Group C.
[e] Reported as "no significant difference" in text, but no p-values provided.
[f] Two-tailed Fisher's exact test, *calculated by reviewer*.
[g] n = 140 (includes patient who was randomised twice and excluded from other analyses).

Comments

- Chart in published paper showing absolute FEV_1 levels at baseline and study end (Fig. 2) appears to be based on erroneous data [data points for all arms are identical (2.11 ± 0.27 l)]; hence *data not extracted*
- During treatment, 44% took concomitant medication (20% LABAs, 11% antihistamines, 7% xanthines and 5% nasal corticosteroids), with similar distribution across trial arms
- Days with control of asthma symptoms and days without PEF fluctuation were maintained versus baseline, with no significant differences between the treatment groups
- No oropharyngeal AEs were reported in any of the 3 treatment groups

Methodological comments

- **Allocation to treatment groups**: central randomisation by computer-generated list
- **Blinding**: patients and investigators were blinded in Groups A and B using double-dummy method with indistinguishable placebo. BUD was administered in an open-label fashion
- **Comparability of treatment groups**: the three treatment groups are reported to be balanced with regard to demographic and baseline disease characteristics. The frequency of previous or concomitant disease and concomitant medication use were comparable in all 3 groups. There were no significant differences in use of allowable concomitant medication during treatment
- **Method of data analysis**:
  - The primary non-inferiority test used 2-sided 95% CI for differences in FEV_1 between groups (Δ = –0.20 litres)
  - Least-squares means and 2-sided 95% CIs presented for differences within and between the groups
  - Two-sided p-values presented for superiority comparisons to confirm differences between treatment groups

continued

– FVC (Δ = –0.20 litres) and PEF (Δ = –25 l/minute) analysed as per FEV_1
– Changes in asthma symptom scores and use of rescue medication compared within treatments by Pratt's modification of the Wilcoxon signed rank test and between treatments by Mann–Whitney *U*-tests
– Between-treatment comparisons for SFDs days free of rescue medication, days free of nocturnal awakening and control of asthma symptoms as perceived by patients (i.e. no symptoms and no rescue medication use) analysed by Mann–Whitney *U*-tests
– Primary and secondary efficacy end-points evaluated by ANCOVA

- **Sample size/power calculation**: designed to have 90% power to establish the non-inferiority of Group B vs Group C, requiring $n > 100$ per treatment
- **Attrition/drop-out**: all patients who received at least 1 dose of study medication were included in the ITT population. Withdrawals related to lack of efficacy and AEs are described; 23 participants discontinued because of unspecified "medical and non-medical reasons"

General comments

- **Generalisability**: relatively inclusive eligibility criteria; not applicable to older and ICS-naïve populations
- **Outcome measures**: appropriate and objective
- **Inter-centre variability**: not reported; unclear whether randomisation was stratified by centre
- **Conflict of interests**: study was sponsored by manufacturers

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unclear
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate for Group A vs Group B; inadequate for Group C (open label)
5. Was the care provider blinded?	Adequate for Group A vs Group B; inadequate for Group C (open label)
6. Was the patient blinded?	Adequate for Group A vs Group B; inadequate for Group C (open label)
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partial
8. Did the analyses include an ITT analysis?	Partial
9. Were withdrawals and drop-outs completely described?	Partial

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 231 **Author:** O'Byrne *et al*. **Year:** 2005 **Country:** International (22 countries) **Study design:** Randomised, parallel group, double-blind **Number of centres:** 246 **Funding:** AstraZeneca (Lund, Sweden)	**Group A:** *n* = 925 Drug(s): BUD/FF Dose: 80/4.5 μg b.d. 80/4.5 μg as needed Delivery: Turbuhaler Duration: 52 weeks **Group B:** *n* = 909 Drug(s): BUD/FF Dose: 80/4.5 μg b.d. + terbutaline 0.4 mg as needed Delivery: Turbuhaler Duration: 52 weeks **Group C:** *n* = 926 Drug(s): BUD Dose: 320 μg b.d. + terbutaline 0.4 mg as needed Delivery: Turbuhaler Duration: 52 weeks **Run-in period:** Duration: 14–18 days ICS: as previously prescribed Relief: terbutaline **Additional treatment allowed:** • Nasal glucocorticoids; antihistamines (except terfenadin); disodium cromoglycate and/or nasal nedocromil sodium; immunotherapy (at constant dose during 90 days pre-enrolment); other medication given at investigators' discretion. Severe exacerbations treated with 10 days of oral prednisone (30 mg/day)	**Number randomised:** 2760 **Sample attrition/drop-out:** *n* = 412 (67 AEs; 111 eligibility criteria not fulfilled; 47 lost to follow-up; 187 other) **Sample crossovers:** NR **Inclusion criteria:** • Age ⩾4 years • ⩾1 exacerbations in previous year • ICS 400–1000 μg/day in previous year • Constant dose of ICS ⩾3 months • FEV_1 60–100% predicted • Reversibility: FEV_1 ⩾12 • For Rx ⩾12 inhalations for adults during last 10 days of run-in **Exclusion criteria:** • During run-in: • For Rx ⩾10 inhalations reliever medication on any one day • Additional exacerbations **Baseline characteristics:** • Mean age (range) (years) = 36 (4–79) • Male:female = 1231:1529 • 4–11 years, *n* (%): 341 (12%) • Mean duration of asthma = 9 years (range: 0–69) • FEV_1 (litres): 2.12 (range: 0.62–4.50) • FEV_1 (% predicted): 73 (range: 43–108) • FEV_1 reversibility: 21% (range: 2–89%) • ICS dose at entry (μg/day): 598–620[a] • LABA use at entry (*n*): 250–258 (28%)[b] • Reliever use, number of inhalations/day: 1.69–1.74 (range: 0.0–9.4) • Reliever use, number of inhalations/night: 0.72 (range: 0.0–6.6) • Asthma symptom scale score (0–6): 1.5 (range: 0.0–6.0) • SFDs (%): 23.5 (range: 0.0–100) • Reliever-free days (%): 8.4 (range: 0.0–100) • Asthma control days (%): 5.6 (range: 0.0–90) • Awakenings (% of nights): 20.9 (range: 0.0–100)	**Primary measure:** Time to first severe exacerbation (defined as hospitalisation emergency room treatment); oral steroid treatment (or an increase in ICS and/or other additional treatment for children aged 4–11 years) or a.m. PEF ⩽ 70% of baseline on 2 consecutive days) **Secondary measures:** • PEF (a.m. and p.m.) • FEV_1 • Time to first mild exacerbation (defined as a.m. PEF ⩽ 80% of baseline, ⩾2 reliever inhalations/day above baseline or awakenings caused by asthma) • Asthma symptom scores (day/night) • Rescue medication use (day/night) • SFDs • Rescue medication free days • Asthma control days • Nocturnal awakenings • Mild exacerbation days • AEs **Method of assessing outcomes:** • Clinic assessments at beginning and end of run-in and 1, 3, 6, 9 and 12 months – PEF (a.m. and p.m.), mini-Wright PEF meter • FEV_1 (spirometry at clinic visits) • Daily patient diaries (symptoms, awakenings, effects and extra medication) • Electrocardiogram, a.m. plasma cortisol, vital signs (at clinic visits) **Length of follow-up:** None beyond 12-month treatment period

[a] Values = combination of metered and delivered doses.
[b] Includes combinations of ICS/LABA and LABA.

continued

Results

Outcomes	Group A (n = 925)	Group B (n = 909)	Group C (n = 926)	p-Value
FEV_1, mean[a] over 12-month treatment period	2.51	2.43	2.41	<0.001[b]; <0.001[c]; 0.09[d]
PEF (l/minute), mean[a] over 12-month treatment period				<0.001[b]; <0.001[c]; <0.001[d]
A.m.	355	346	339	<0.001[b]; <0.001[c];
P.m.:	360	349	345	<0.001[d]
SFDs (%) mean[a] over 12-month treatment period	54	53	46	0.52[b]; <0.001[c]; <0.001[d]
Nocturnal awakenings, (% of nights) mean[a] over 12-month treatment period	9	12	12	<0.001[b]; <0.001[c]; 0.60[d]
Severe exacerbations including PEF falls: patients with event (%)[e]	16	27	28	<0.001[b]; <0.001[c]; 0.74[d]
Severe exacerbations resulting in medical intervention: patients with event (%)[e]	11	21	19	<0.001[b]; <0.001[c]; 0.37[d]
Use of reliever (puffs/day) mean over 12 months	0.73	0.84	1.03	<0.001[b]; <0.001[c]; <0.001[d]
Use of reliever (puffs/night) mean over 12 months	0.28	0.37	0.43	<0.001[b]; <0.001[c]; 0.003[d]
Use of systemic corticosteroids (courses per patient)				
Children (4–11 years)	0.05	0.30	0.38	NR
Adults (12–80 years)	0.19	0.42	0.25	
Mortality				
QoL				
⩾1 AEs – n (%):	496 (54%)	475 (52%)	528 (57%)	0.58[b]; 0.99[c]; 0.03[d]
⩾1 serious AEs – n (%)	46 (5%)	62 (7%)	48 (5%)	
Pharyngitis – n (%)	88 (10%)	88 (10%)	86 (9%)	0.93[b]; 0.99[c]; 0.87[d]
Respiratory infection – n (%)	158 (17%)	144 (16%)	182 (20%)	0.49[b]; 0.15[c]; 0.03[d]
Rhinitis – n (%)	80 (9%)	72 (8%)	76 (8%)	0.61[b]; 0.80[c]; 0.86[d]
Bronchitis – n (%)	51 (6%)	61 (7%)	76 (8%)	0.29[b]; 0.02[c]; 0.25[d]
Sinusitis – n (%)	43 (5%)	39 (4%)	33 (4%)	0.74[b]; 0.29[c]; 0.47[d]
Headache – n (%)	31 (3%)	35 (4%)	42 (5%)	0.62[b]; 0.19[c]; 0.49[d]
Tremor – n (%)	20 (2%)	18 (2%)	19 (2%)	0.87[b]; 0.99[c]; 0.99[d]
Palpitation – n (%)	10 (1%)	11 (1%)	3 (<0.5%)	0.83[b]; 0.09[c]; 0.03[d]
Tachycardia – n (%)	5 (0.5%)	4 (<0.5%)	3 (<0.5%)	0.99[b]; 0.73[c]; 0.72[d]
Candidiasis – n (%)	9 (1%)	6 (1%)	10 (1%)	0.61[b]; 0.82[c]; 0.45[d]
Dysphonia – n (%)	11 (1%)	13 (1%)	12 (1%)	0.69[b]; 0.84[c]; 0.84[d]
Discontinuation due to respiratory events – n (%)	7 (1%)	15 (2%)	14 (2%)	0.80[b]; 0.13[c]; 0.85[d]
Other: asthma control days (%)[f]	45	44	37	0.64[b]; <0.001[c]; <0.001[d]

[a] Least squares mean from two-way ANOVA.
[b] Group A vs Group B.
[c] Group A vs Group C.
[d] Group B vs Group C.
[e] p-Values based on the instantaneous risk of experiencing at least one severe exacerbation (Cox proportional hazards model).
[f] Defined as a day with no symptoms (day or night), no awakenings caused by asthma and no as-needed medication use.

Comments

- Time to first medically managed severe exacerbation was significantly longer in the BUD/FF maintenance + relief group (Group A) compared with the BUD/FF + SABA (Group B) and BUD + SABA groups (Group C); HR = 0.50 (95% CI: 0.40 to 0.64) and 0.55 (95% CI: 0.43 to 0.70), respectively
- The RR of severe exacerbation requiring medical management was reduced by 53% for BUD/FF maintenance + relief compared with BUD/FF + SABA; HR = 0.47 (95% CI: 0.39 to 0.57) and by 46% compared with BUD + SABA; HR = 0.54 (95% CI: 0.44 to 0.66). The effect of using BUD/FF for maintenance + relief remained constant over time
- Symptom measures improved in all groups compared in baseline in requirement for reliever medication treatment and night-time awakenings
- No clinically important differences in ECG, haematology, clinical chemistry or urinalysis were observed between the treatment groups or over time

continued

Methodological comments

- **Allocation to treatment groups**: block randomisation by computer-generated list with treatment stratified by age group in an 8:1 ratio (adults:children)
- **Blinding**: double-blind with respect to treatment group; unclear whether the outcome assessors were blinded
- **Comparability of treatment groups**: the groups are reported to be comparable with regard to demographic and baseline disease characteristics. There appeared to be no baseline imbalance in patient characteristic across the treatment groups
- **Method of data analysis**: the primary efficacy analysis of time to first severe asthma exacerbation was described using Kaplan–Meier plots and a log-rank test, with analysis of instantaneous risk described using a Cox proportional hazards model. Total numbers of severe exacerbations were compared using a Poisson regression model, with adjustments for over-dispersion. Secondary efficacy end-points were evaluated by ANCOVA, with the baseline value as covariate and the mean daily data over the 12-month treatment period as the treatment mean. All hypothesis testing was two-sided, with *p*-values of <5% considered significant
- **Sample size/power calculation**: designed to have 80% power to detect a 23% reduction in exacerbation rate in any of the treatment groups
- **Attrition/drop-out**: all patients who received at least 1 dose of study medication were included in the ITT analysis (for both efficacy and safety). The attrition rate was 15%, with 4% of randomised patients failing to meet the criterion for as-needed medication during the run-in period. Reasons for discontinuations were AEs 2% ($n = 67$); eligibility criteria not fulfilled 4% ($n = 111$); lost to follow-up 2% ($n = 47$); and other (not specified) 7% ($n = 187$). The total *n* analysed for primary end-point and safety was 2753, with LOCF for missing data. LOCF was not undertaken for three patients in Group A, one in Group B and one in Group C

General comments

- **Generalisability**: relatively inclusive eligibility criteria; not applicable to ICS-naïve populations or patients with mild asthma
- **Outcome measures**: appropriately defined and objective
- **Inter-centre variability**: not reported; unclear whether randomisation was stratified by centre and whether centre was analysed as a covariate in the ANCOVA model
- **Conflict of interests**: study support and one author had received previous funding from AstraZeneca

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Unknown
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Partial
9. Were withdrawals and drop-outs completely described?	Partial

HR, hazard ratio; LOCF, last observation carried forward.
From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 202 **Author:** O'Connor *et al*. **Year:** 2001 **Country:** International (mostly Europe and Latin America) **Study design:** Randomised, parallel-group, double-blind (dosage)/ evaluator-blind (medication) **Number of centres:** 60 **Funding:** Schering-Plough Research Institute	**Group A:** *n* = 182 Drug(s): MF Dose: 100 μg b.d. Delivery: DPI Duration: 12 weeks **Group B:** *n* = 182 Drug(s): MF Dose: 200 μg b.d. Delivery: DPI Duration: 12 weeks **Group C:** *n* = 184 Drug(s): MF Dose: 400 μg b.d. Delivery: DPI Duration: 12 weeks **Group D:** *n* = 184 Drug(s): FP Dose: 250 μg b.d. Delivery: DPI Diskhaler Duration: 12 weeks **Run-in period:** Duration: 1–2 week ICS: as previously prescribed Relief: albuterol (MDI or DPI) **Additional treatment allowed:** • Relief: albuterol; nebulised albuterol • Other: theophylline, if already established	**Number randomised:** 733 **Sample attrition/drop-out:** *n* = 102 (1 before receiving any study Rx; 4% due to treatment failure) **Inclusion criteria:** • Age ⩾12 years • History of asthma for ⩾6 months • Maintained on ICS for ⩾30 days – dosage limits (μg): BDP 400–1000; BUD 400–800; flunisolide 500–1000; FP 200–500; triamcinolone acetonide 600–800 • FEV_1 60–90% predicted • Reversibility: FEV_1 ⩾12% and absolute volume increase ⩾200 ml within 30 minutes of albuterol ×2 **Exclusion criteria:** • Smoking within previous 6 months • Methotrexate, ciclosporin or gold Rx in previous 3 months • Oral steroids >14 days in previous 6 months • Systemic steroids or investigational Rx in previous 1 month • >1 mg q.d. nebulised BA/any LABA • Immunotherapy, unless on a stable maintenance schedule • Inpatient hospitalisation for asthma in previous 3 months • Intubation for asthma in previous 5 years • ⩾2 emergency hospital treatments in previous 6 months • Between screening and baseline: – FEV_1 increase/decrease ⩾20% – >12 inhalations of albuterol on any 2 consecutive days • Respiratory tract infection within previous 2 weeks • Pregnant, breastfeeding or premenarcheal women • Significant oral candidiasis • Other clinically significant disease • Abnormal laboratory values **Baseline characteristics:** • Mean age (range) (years) = 41 (12–79) • Male:female = 295:437 • White:black:other = 555:4:173 • Mean duration of asthma = 15 years • Mean FEV_1 (% predicted) = 75% • Previous ICS – *n* (%) at mean dose, μg: BDP = 362 (49%) at 614; BUD = 230 (31%) at 623; flunisolide = 34 (5%) at 774; FP = 103 (14%) at 462; triamcinolone acetonide = 1 (0%) at 149	**Primary measure:** Mean change in FEV_1 from baseline to end-point **Secondary measures:** • PEF • $FEF_{25–75\%}$ • FVC • Asthma symptom scores • Rescue medication use • Nocturnal awakenings • Physician evaluation • AEs **Method of assessing outcomes:** • Clinic assessments at screening, baseline, day 4 and weeks 1, 2, 4, 8 and 12: – spirometry (highest readings of 3) – oropharyngeal examination • Daily patient diaries: – PEF (a.m. and p.m.) (highest readings of 3) – symptoms, effects and extra medication **Length of follow-up:** None beyond 12-week treatment period

continued

Results

Outcomes	Group A (*n* = 182)	Group B (*n* = 182)	Group C (*n* = 184)	Group D (*n* = 184)	*p*-Value
FEV_1, mean[a] change from baseline to last evaluable visit – litres ± SE	0.07 ± 0.04	0.16 ± 0.04	0.19 ± 0.04	0.16 ± 0.04	0.02[b]; NS[c,d,e]
PEF, mean[a] change from baseline to last evaluable visit – l/minute (SE)	15 ± 5	29 ± 6	30 ± 5	32 ± 5	≤0.05[b,d,e]
SFDs					
Nocturnal awakenings, mean[a] change from baseline to last evaluable visit	0.07	0.01	–0.06	–0.14	≤0.05[e]; NS[c,b,d]
Acute exacerbations					
Use of reliever, mean difference – µg/day	–13.23	–94.84	–38.10	–52.06	<0.01[d]; NS[c,b,e]
Use of systemic corticosteroids					
Mortality					
QoL					
AEs – *n* (%)	(20%)	(26%)	(30%)	(29%)	0.029[b,i]; 0.051[e,i]; >0.2[d,f,g,h,i]
Oral candidiasis	(1%)	(7%)	(10%)	(10%)	<0.01[b,d,e,i]; >0.3[f,g,h,i]
Pharyngitis					NS[c] for all comparisons
Dysphonia					NS[c] for all comparisons
Discontinuation due to AEs	9 (5%)	6 (3%)	9 (5%)	8 (4%)	>0.5[j] for all comparisons
Other					

[a] Least-squares mean from two-way ANOVA.
[b] Group A vs Group C (primary efficacy comparison).
[c] Reported as "no significant difference" in text, but no *p*-values provided.
[d] Group A vs Group B.
[e] Group A vs Group D.
[f] Group B vs Group C.
[g] Group B vs Group D.
[h] Group C vs Group D.
[i] Two-tailed Fisher's exact test, *calculated by reviewer (incidence approximated to nearest integer; proportions only reported in paper)*.
[j] Two-tailed Fisher's exact test, *calculated by reviewer*.

Comments

- Results of PEF (p.m.) "similar" to those of PEF (a.m.).
- Symptom measures: improvements in all groups compared to baseline in a.m. wheezing and a.m. and p.m. coughing. Breathing difficulty (a.m.) scores were significantly better with FP (Group D) compared with lower dose MF (Groups A and B) ($p \leq 0.05$) but not Group C
- Physician-evaluated improvement was significantly higher in Groups B, C and D than A ($p < 0.03$)
- Time-to-event (Kaplan–Meier) analysis showed no significant differences in time to worsening of asthma between all treatments

Methodological comments

- **Allocation to treatment groups**: randomisation by computer-generated code (not reported whether central)
- **Blinding**: double-blind with respect to dosage of MF (Groups A, B and C) and evaluator-blind with respect to FP (Group D)
- **Comparability of treatment groups**: the groups are reported to be comparable with regard to demographic and baseline disease characteristics. There is some variety in absolute FEV_1 at baseline, especially in primary comparison groups: 2.53 litres (95% CI 2.43 to 2.63) for Group A vs 2.38 litres (95% CI 2.28 to 2.48) for Group C. Similarly, PEF was higher in Group A – 383 l/minute (95% CI 365 to 401) – compared with Group C – 362 l/minute (95% CI 344 to 380) [*All 95% CIs calculated by reviewer*]. However, these differences appear to fall below conventional significance levels, and % predicted FEV_1 is reported to be similar
- **Method of data analysis**: efficacy analyses use two-way ANOVA, extracting sources of variation due to treatment, centre and treatment-by-centre interaction. Pairwise comparisons performed with no adjustment for multiple comparisons

continued

- **Sample size/power calculation**: designed to enrol 150 patients per treatment group to detect (with 80% power; $\alpha = 0.05$) a 6% change in FEV_1 from baseline to end-point in any pair-wise comparison
- **Attrition/drop-out**: analyses are based on all participants who received at least one dose of study medication and who had post-baseline data. 19% of Group A and 12% each of Groups B, C and D discontinued treatment. Reasons for discontinuations are incompletely reported: 7, 4, 3 and 4% of Groups A, B, C and D, respectively, withdrew because of treatment failure; 5, 3, 5 and 4% of Groups A, B, C and D, respectively, withdrew because of AEs. No reasons are specified for remaining withdrawals

General comments

- **Generalisability**: relatively inclusive eligibility criteria; not applicable to ICS-naïve populations
- **Outcome measures**: appropriate and objective
- **Inter-centre variability**: not reported; unclear whether randomisation was stratified by centre; ANOVA used centre as a covariate
- **Conflict of interests**: study support by and one author from Schering-Plough

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Partial

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 230 **Author:** Pohl *et al*. **Year:** 2006 **Country:** Austria **Study design:** Double-blind, parallel-group, RCT **Number of centres:** 16 across Austria **Funding:** AstraZeneca	**Group A: ICS**[a] *n* = 68 Drug(s): BUD Dose: 320 μg, 2 puffs b.d. first 4 weeks, then AMD[b] Delivery: Pulmicort Turbuhaler Duration: 20 weeks **Group B: ICS/LABA**[c] *n* = 65 Drug(s): BUD/FF Dose: 160/4.5 μg, 2 puffs b.d., first 4 weeks, then AMD[b] Delivery: Symbicort Turbuhaler Duration: 20 weeks **Run-in period:** Not reported **Additional treatment allowed:** • Relief: terbutaline (Bricanyl Turbuhaler) (0.4 mg[e]) as needed for symptom relief • Other: Any medication necessary for patient's safety and well being, given during the study at discretion of the investigator – no other details	**Number randomised:** 133, 126 in ITT population **Recruitment:** Between June 2001 and October 2002 **Sample attrition/drop-out:** *n* = 7 (5%) (5 for Group 1 and 2 for Group 2) due to no efficacy measurement on treatment – eliminated from the ITT population *n* = 24 (19%) of ITT population (15 for Group 1 and 9 for Group 2) withdrew after week 2 **Sample crossovers:** NA **Inclusion criteria:** • Aged ⩾19 years • With asthma indicated by FEV_1 of a short-acting bronchodilator of ⩾15% or 200 ml within 1 month prior to enrolment • FEV_1 of 40–85% of predicted normal • Requirement for ICS or ICS/LABA within the given starting dose range **Exclusion criteria:** • Experience of an asthma exacerbation requiring oral steroids during the 4 weeks prior to study entry • Upper respiratory tract infections in the 6 weeks prior to study entry • Current smokers • Severe cardiovascular disease • Significant concomitant disease • Receiving another investigational drug • Pregnant or planning a pregnancy • Receiving any anti-asthma therapy treatment (other than oral steroids) unless it ceases on study entry **Baseline characteristics:** • Mean age (range) (years): Group 1 = 45 (20–82), Group 2 = 45 (20–80) • Male:female (%): Group 1 59:41, Group 2 48:52 • Median (range) asthma duration (years): Group 1 = 4.5 (0–30), Group 2 = 10 (0–35) • Documented smoking habit, *n* (%): Group 1 = 21 (33), Group 2 = 24 (38) • Previous ICS treatment, *n* (%): Group 1 = 40 (63), Group 2 = 40 (63) • Mean (range) FEV_1 % predicted: Group 1 = 65 (39–85), Group 2 = 67 (35–88)	**Primary measure:** Number of patients per treatment group who experienced ⩾1 treatment failure[f] **Secondary measures:** • HRQoL • Patient and physician treatment satisfaction • Dose of medication • % of days on which patients required reliever medication • FEV_1 • PEF **Method of assessing outcomes:** • Medial Outcomes Study • SF-36 • Patient and physician assessment with treatment satisfaction measured week 20 using VAS[g] • Daily patient diaries – PEF (a.m. and p.m.) – use of terbutaline symptom relief – night-time awakening due to asthma – respiratory symptoms – use of other medications to treat asthma • Safety assessments recorded throughout study • Clinical assessments at 2, 4, 8, 12, 16 and 20 weeks **Length of follow-up:** None beyond 20-week treatment period

continued

Results

Outcomes	Group A – ICS 320 μg (*n* = 63)		Group B – ICS/LABA 160/45 μg (*n* = 63)		*p*-Value
PEF morning: mean (l/minute) change from baseline	398		407		
PEF evening: mean (l/minute) change from baseline	404		411		
FEV_1: mean (litres) change from baseline	0.37		0.36		
Mean number of inhalations per day of ICS	3.4 (1072 μg dose)		3.1 (494 μg dose)		0.024
SFDs	NR		NR		
Nocturnal awakenings	NR		NR		
Exacerbations during last 12 weeks, *n* (%)	1 (1)		2 (3)		
Median inhalations per day (ICS dose)[e]	3.6 (1152 μg)		2.8 (448 μg)		
Use of rescue medication, mean % of days used	17.4		16.2		0.040
Use of systemic corticosteroids, *n* (%)[h]	2 (3)		5 (8)		
Mortality	NR		NR		
HRQoL (means), SF-36:	Wk 0	Wk 20	Wk 0	Wk 20	
Physical functioning	80.7	87.2	77.6	85.9	0.0.25[i]
Physical role functioning	75.0	81.3	73.8	88.5	NR
Bodily pain	82.0	88.4	78.8	89.6	NR
General functioning	64.8	69.3	61.7	68.7	NR
Vitality	56.9	66.4	55.4	63.4	NR
Social functioning	86.2	92.7	87.6	93.7	NR
Emotional role functioning	85.2	83.4	86.0	90.5	0.035[j]
Mental health	70.0	78.0	71.3	73.5	NR
Satisfaction with treatment (VAS scores, mm):					
Patient assessment	75.6		85.4		0.013
Physician assessment	71.1		83.6		0.001
Number of AEs	81		74		
Other					

[a] Inhaled corticosteroids.
[b] Fixed starting dosage was for first 4 weeks only, then dose was adjusted to 2–4 inhalations daily during weeks 5–8, and 1–4 inhalations daily during weeks 9–20. Patients were allowed to step up their dosage if, on 2 consecutive days, a short-acting bronchodilator was required for symptom relief on 2 occasions during the day or a night-time awakening due to asthma was experienced.
[c] Inhaled corticosteroids/long-lasting β_2 agonist.
[d] Reported group difference of ~700 μg (61%) in the ICS dose.
[e] Defined as a severe exacerbation requiring 1 or more of: hospitalisation, nebulised β_2 agonists, oral steroids, or withdrawal owing to lack of efficacy or a life-threatening/fatal condition.
[f] VAS 0–100 mm (0 mm = not satisfying, 100 mm = very satisfying).
[g] Group 1 were treated with oral steroids; Group 2 used nebulised β_2 agonists.
[h] For 6 units.
[i] For 12.1 units – no explanations given for units.

Comments

- For patients with diary assessments on at least 5 clinic visits, a total of 36/47 (77%) patients in Group 2 and 25/42 (60%) patients in Group 1 stepped down their medication during the study
- 75% of Group 2 patients used reliever for symptom relief less than 1 day per week, 50% of Group 2 patients were reliever-free on 99% of the days in the study, compared with 96% of study days being reliever-free for 50% of Group 1 patients
- Although patients in Group 2 used reliever medication on a significantly lower percentage of days, it was reported that there were no difference between the two treatment groups in the percentage of days on which patients used reliever medication for symptom relief
- There were no treatment-related serious AEs
- 20 AEs were regarded as being treatment-related: 3 reports of candidiasis and 2 reports of dysphonia, and 1 instance each of cheilitis, stomatitis, asthma and laryngitis each in Group 1; 3 cases each of myalgia and nervousness, and 1 instance each of heart disorder, dyspnea, rhinitis, pruritis, and taste alterations in Group 2
- 3 patients reported serious AEs in connection with hospitalisation (1 accident, 1 planned cardiac examination in Group 2 and 1 evaluation of hypertension in Group 1)

continued

Methodological comments

- **Allocation to treatment groups**: computer-generated randomised initial treatment regime on day 0 (baseline)
- **Blinding**: double-blind reported, but no details reported. However, it is noted that clinicians were able to increase and decrease doses and it is therefore likely that they were aware of which treatment patients were assigned to
- **Comparability of treatment groups**: the groups appear comparable at baseline, apart from the median asthma duration (Group 1 = 4.5 years, Group 2 = 10 years, no significance values reported)
- **Method of data analysis**: analyses were performed on ITT population, defined as all patients who had received at least one dose of study medication and had a baseline assessment together with at least one post-baseline evaluation. The safety population comprised all randomised patients (n = 126 out of 133 randomised). Baseline and demographic characteristics and all efficacy and safety end-points were analysed using standard descriptive statistical analysis. No replacement of missing data was performed. The proportion of patients with treatment failure was compared using the Cochran–Mantel–Haenszel test, stratified by gender. Exploratory comparisons of changes from baseline in SF-36 questionnaire scores, patient/physician satisfaction ratings, study/reliever medication use, FEV_1 and PEF were compared using the Mann–Whitney *U*-test. Differences between baseline scores and values at week 20 used for analysis. No SDs or CIs given
- **Sample size/power calculation**: assuming that the incidence of treatment failure (primary end-point) with ICS is 25%, a sample size of 80 patients per group was required to give 80% power to demonstrate superiority of ICS/LABA vs ICS, given a true incidence of failure with ICS/LABA of 8.5% (5% significance level, two-sided alternative hypothesis). Due to recruitment difficulties, fewer patients enrolled and the study was not powered to test the hypotheses for the primary efficacy end-point
- **Attrition/drop-out**: n = 133, 7 (5%) drop-outs due to no efficacy measurement on treatment (Group 1 1%, Group 2 4%). ITT population n = 126, 24 (19%) withdrew week 2 [Group 1 n = 15 (12%), Group 2 n = 9 (7%)]. Of these 11 (9%) were lost to follow-up, 4 (3%) withdrew owing to an AE (1 of which was serious), 9 (8%) withdrew for other reasons (no details reported)
- **Compliance**: no details reported
- **Other**: patients were allowed to step up their dosage if, on 2 consecutive days, a short-acting bronchodilator was required for symptom relief on 2 occasions during the day or a night-time awakening due to asthma was experienced. Doses were only stepped down to 1 inhalation daily at the investigator's discretion. The study used an adjustable maintenance dosing regime, adjusting the starting dosage after 4 weeks to 2–4 inhalations daily for ICS (maximum 640 μg) during weeks 5–8 and 1–4 inhalations daily (maximum 1280 μg) during weeks 9–20. ICS/LABA higher dose budesonide only (maximum 320 μg)

General comments

- **Generalisability**: patients appear to be clinically representative of patients with mild-to-moderate asthma
- **Outcome measures**: appropriate and objective
- **Inter-centre variability**: multi-centre study
- **Conflict of interests**: AstraZeneca provided financial and editorial support

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Unknown
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Partial

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 242 **Author:** Ringdal *et al*. **Year:** 2002 **Country:** 11 European countries **Study design:** Randomised, double-blind, double-dummy, parallel-group study **Number of centres:** 11 **Funding:** Glaxo Wellcome	**Group A:** *n* = 212 Drug(s): FP/SAL Dose: 250/50 μg b.d. Delivery: Diskus (Seretide) + 2 placebo DPI Turbuhalers Duration: 12 weeks **Group B:** *n* = 216 Drug(s): BUD/FF Dose: 800/12 μg b.d. Delivery: DPI Turbuhalers + 2 placebo Diskus Duration: 12 weeks **Run-in period:** Duration: 2 weeks ICS: continued with pre-study ICS Relief: **Additional treatment allowed:** • Relief: salbutamol • Other: • Trial aim: to compare safety and efficacy of Group A versus Group B, to demonstrate similar efficacy between treatments but using < one-third of ICS dose in Group A	**Number randomised:** 520 recruited, 428 randomised **Sample attrition/drop-out:** 49 were withdrawn before completing treatment but all included in ITT analysis. 50 (29/21, respectively) were protocol violators prior to unblinding treatment allocation **Sample crossovers:** **Inclusion criteria:** • Patients aged 16–75 years with a clinical history of reversible airways obstruction and who were symptomatic on 1000–1600 μg/day of BUD, BDP or flunisolide, or 500–800 μg/day FP • Reversibility was defined as an increase in FEV_1 of ⩾15% from baseline, 15 minutes after inhaling 400 μg of salbutamol • To be randomised to treatment at visit 2, patients also had to have a predicted FEV_1 of 50–85%, and either a symptom score (day and night combined) of ⩾2 or use of salbutamol for symptomatic relief (not prophylaxis) on ⩾2 occasions, on ⩾4 of the last 7 evaluable days of the run-in period **Exclusion criteria:** • Changed their inhaled steroid dose or received oral corticosteroids, leukotriene modifiers or nasal corticosteroids (other than FP) in the 4 weeks before visit 1, or any LABAs in the 2 weeks before visit 1. Had a recent history of upper or lower respiratory tract infection • Smokers with a history of 10 pack-years or more or had an acute asthma exacerbation within 1 month before visit 1 **Baseline characteristics:** Mean age (± SD) (years): SAL/FP 46.5 (14.0), FF + BUD 48.1 (13.9) Male % (± SD): SAL/FP 84 (40), FF + BUD 105 (49) PEF a.m. (l/minute): SAL/FP 349 (101), FF + BUD 348 (101) PEF p.m. (l/minute): SAL/FP 368 (103), FF + BUD 367 (103) FEV_1 (litres): SAL/FP 2.18 (0.62), FF + BUD 2.20 (0.63) FEV % predicted: SAL/FP 69.2 (10.7), FF + BUD 69.0 (10.1) FEV % reversibility: SAL/FP 26.0 (14.1), FF + BUD 25.0 (11.5) Mean inhaled steroid dose (μg/day): FP: SAL/FP 549 (88), FF + BUD 546 (81); BDP: SAL/FP1165 (66), FF + BUD 1124 (66); BUD: SAL/FP1404 (45), FF + BUD 1409 (64); Flunisolide: SAL/ FP 1214 (7), FF + BUD 1167 (3)	**Primary measure:** Mean PEF a.m. **Secondary measures:** • PEF a.m. and p.m. and at other time points • PEF % diurnal variation • Clinical FEV_1, rate • Severity of exacerbations • Day- and night-time symptom scores • Night-time awakenings • Use of rescue salbutamol • Withdrawals from study • Asthma-related healthcare resource utilisation (Norwegian healthcare system and costs, not data extracted) • AEs **Method of assessing outcomes:** • Diary record cards for daily PEF and asthma symptom score • Daily PEF best of three before taking any rescue medication • Mean PEF calculated over the 12 weeks of treatment. FEV_1 (highest of three technically acceptable measurements) at each clinic visit • Exacerbations (mild, moderate, severe; see below) assessed by physicians reviewing diary card entries and patient history at clinic visit (day symptom scores range from 1 to 6 with 1 = no symptoms to 6 = symptoms so severe that could not go to work/ perform normal activities. Night symptom score range from 1 to 5 with 1 = no symptoms during the night to 5 = symptoms so severe that I did not sleep at all) • AEs defined as any untoward medical occurrence irrespective of causality. All classified by investigator as serious or non-serious, and the cause assessed as unrelated, unlikely, possibly, probably

continued

Study	Treatment	Participants	Outcomes
			or almost certainly related to study drugs **Length of follow-up:** 12 weeks Clinic run-in (visit 1) start of treatment (visit 2) and 4 (visit 3), 8 (visit 4), 12 (visit 5) weeks after start of treatment

Results

Outcomes	Group A (n = 212)	Group B (n = 216)	p-Value
PEF (ITT population), l/minute change from baseline	43	47	Not reported
PEF (per protocol population), l/minute change baseline	N = 157 43	N = 167 41	Difference –3.2 l/minute (95% CI –15.0 to 8.6, p = 0.593)
Median % diurnal variation PEF	N = 187 Baseline 7.8 End-point 4.7	N = 192 Baseline 8 End-point 5.1	Difference –0.3, 95% CI –1.0 to 0.3, p = 0.295
Mean FEV_1 increase from baseline	N = 189 0.27	N = 194 0.26	Difference –0.01, 95% CI –0.09 to 0.07, p = 0.796
SFDs (was an outcome but data not reported)[a]			
Nights without awakenings, % median of nights (proportions for each treatment estimated from figure)	80	60	Difference 4.9, 95% CI 0.0 to 12.0, p = 0.02[a]
Nights without symptoms, % median (proportions for each treatment estimated from figure)	85	72	Difference 2.7, 95% CI 0.0 to 8.4, p = 0.04[a]
Nights with a symptom score <2 median (proportions for each treatment estimated from figure)	98	97	Difference 0.0, 95% CI 0.0 to 1.2, p = 0.03[a]
Acute exacerbations (total number during treatment)	129	206	
No. of mild exacerbations (estimated from graph)	105	175	
No. of moderate exacerbations (estimated from graph)	22	28	
No. of severe exacerbations (estimated from graph)	2	2	
Rate of exacerbations, all severities (estimated from graph)	0.45	0.7	p < 0.001
Mean rate of exacerbation (mild, moderate and severe) per patient per 84 days of treatment	N = 211 0.472	N = 215 0.735	Ratio: 0.64, 95% CI 0.51 to 0.80, p < 0.001[b]
Use of systemic corticosteroids			
Mortality			
QoL			
AEs – total n (%):	91 (43)	78 (36)	
Of these: upper respiratory tract infection	26 (12)	18 (8)	
AE causing 1% or more patients to withdraw (asthma resurgence/loss of control)	1 (<1%)	6 (3%)	
Possible drug-related AEs	18	23	
Of these:			
Oral candidiasis	1	9	
Hoarseness/dysphonia	6	2	

continued

Outcomes	Group A (n = 212)	Group B (n = 216)	p-Value
Throat irritation	4	1	
Worsening asthma control	0	4	
Tremors	0	3	
Tachycardia	3	0	
Muscle cramps and spasms	0	3	
Serious AEs	2	3	
Mean exposure to study treatments, days (SD)[c]	79 (17.6)	79 (17.8)	
Number of asthma-related hospital/GP visits for patients with moderate-to-severe asthma:			
Accident and Emergency visits	1	1	
Hospital days on general ward	7	18	
Outpatient visits	6	17	
GP home visits	15	7	
GP clinic visits	12	11	
GP telephone contacts	13	11	

Exacerbation definitions:
Mild – a deterioration in asthma requiring an increase in relief medication use, which the investigator deemed clinically relevant, or PEF a.m. >20% below baseline (mean of last 10 days of run-in) for ⩾2 consecutive days, or >3 additional reliever inhalations per 24-hour period with respect to baseline for ⩾2 consecutive days, or awakening at night due to asthma for ⩾2 consecutive days.
Moderate – PEF a.m. >30% below baseline on ⩾2 consecutive days, or a deterioration in asthma requiring administration of additional ICS (over and above study medication) and/or oral corticosteroids
Severe – a deterioration in asthma requiring emergency hospital treatment

[a] Discrepancy between difference as reported in the paper, and estimated by reviewers from the graph.
[b] Corresponding to a 31% risk reduction.
[c] Almost 90% of patients were exposed for 77 days (11 weeks) or above.

Comments
- Patients in both groups showed similar improvements in daytime symptoms with no significant differences (no data reported).
- Similar use of salbutamol in both groups with no significant differences noted.
- Data for PEF p.m. not reported but authors report that it followed a similar pattern to PEF a.m. over 12 weeks.

Methodological comments

- **Allocation to treatment groups**: a randomisation code was generated by Glaxo Wellcome computer program and non-overlapping sets of treatment numbers were allocated to each centre. Treatment numbers were allocated at Visit 2 in consecutive order. The randomisation codes were not revealed to the investigators or other study participants until after recruitment, treatment, data collection and analyses were complete
- **Blinding**: numbered treatment packs of study drugs labelled to ensure that both patients and investigators were blinded to the treatment allocation. Patients were instructed to take one inhalation from each inhaler, using the Diskus first followed by the two Turbuhalers. Placebo devices were rendered externally identical with active ones by teaselling but contained no active contents, only lactose (Diskus) or desiccant (Turbuhaler)
- **Comparability of treatment groups**: treatment groups were reported to be well matched at baseline, with the exception of higher median night-time awakenings in the FF + BUD group. No statistical significance value reported
- **Method of data analysis**: analysis based on ITT population. For mean PEF a.m. the analysis was also repeated on the PP population. For PEF variables ANCOVA used adjusted for age, sex, country and baseline value. Analysis of exacerbations Poisson model, adjusting for age used. Other secondary efficacy measures analysed using the Wilcoxon rank sum test, adjusted for country. Treatment differences calculated as the median of all the pairwise differences with the 95% CIs calculated.
- **Sample size/power calculation**: the primary objective was to demonstrate that SAL/FP was non-inferior to FF and BUD. This was defined as the lower limit of the 95% CI for the difference in mean PEF a.m. over week 12 being –15 l/minute or above. Assuming a residual standard deviation of 50 l/minute for PEF a.m. in either treatment group, a total of 470 evaluable patients was expected to provide approximately 90% power for assessing this
- **Attrition/drop-out**: numbers and reasons for withdrawals reported. The 50 protocol violators (assume) remained in the analysis

continued

General comments	
• **Generalisability**: patients with moderate to severe asthma, on daily ICS dose 1000–1600 μg/day (BDP or equivalent) • **Outcome measures**: appropriate and valid, some not fully reported in Results section • **Inter-centre variability**: not reported • **Conflict of interests**: funded by grant from Glaxo Wellcome. One co-author affiliated with Glaxo Wellcome	
Quality criteria for assessment of experimental studies	
1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Adequate
From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.	

Study	Treatment	Participants	Outcomes
Ref.: 245 **Author:** Rosenhall *et al*. **Year:** 2002 **Country:** Sweden, Norway, Finland, Denmark **Study design:** Open-label RCT, parallel-group **Number of centres:** Not stated **Funding:** AstraZeneca, Sweden **NB.** Two further publications describe results from 6 months extension study in a subset of centres (in Sweden, *n* = 321 patients). As this subset only represents a proportion of those originally randomised, results have not been extracted	**Group A:** *n* = 390 Drug(s): BUD/FF Dose: 320/9 μg b.d. Delivery: DPI Turbuhaler (Symbicort) Duration: 6 months **Group B:** *n* = 196 Drug(s): BUD + FF Dose: 320 + 9 μg b.d. Delivery: DPI (Pulmicort and Oxis Turbuhaler) Duration: 6 months **Run-in period:** Not reported **Additional treatment allowed:** • Relief: terbutaline sulfate (0.25 mg/dose) or alternative short-acting β_2 agonist • Other: oral corticosteroids for exacerbations, on maximum of 2 occasions (up to 14 days for each). Also allowed: anticholinergics, nebulised β_2 agonists or intravenous corticosteroids at emergency visits, nasal corticosteroids, antihistamines (other than terfenadine), ocular/nasal cromone formulations **Trial aim:** To assess the longer term safety and efficacy of the single inhaler, particularly in terms of HRQoL	**Number randomised:** 586 **Sample attrition/drop-out:** 47 (8%) discontinuations, 26 (6.6%) in Group A, and 21 (10.7%) in Group B **Sample crossovers:** None reported **Inclusion criteria:** • Age: ⩾18 years • Perennial asthma (minimum duration 6 months) • FEV_1 ⩾50% predicted normal • Requiring treatment with an ICS (400–1200 μg) • Patient selection also took into account need for short- and long-acting β_2 agonist **Exclusion criteria:** • Unstable asthma (e.g. respiratory infection, need for oral corticosteroids within 30 days before randomisation) • Use of: leukotriene antagonists, inhaled cromones, oral bronchodilator therapy, inhaled anticholinergics • Severe cardiovascular disorders, or requiring concurrent β-blocker therapy **Baseline characteristics:** • Male:female = 257:329 • Age (range) (years) = 45.0 (18–81) • Time since asthma diagnosis, (range) (years) = 15.0 (1–67) • Smokers/ex-smokers, *n* = 74/159 • ICS (range) (μg/day) = 709 (400–1600) • FEV_1 (range) (litres) = 2.85 (0.9–5.5) • FEV_1 % predicted normal (range) 94.5 (37–155) • FVC (range) (litres) = 3.79 (1.3–6.5) • Mean ACQ score[a] = 1.5–1.6 (range 0–4) across groups • Mean overall MiniAQLQ score[b] = 5.3–5.4 (range 2–7) across groups	**Primary measure:** AEs **Secondary measures:** FEV_1 FVC Exacerbations HRQoL/symptoms **Method of assessing outcomes:** • Patients assessed in clinic at four visits: visit 1 at baseline, visit 2 at 4 weeks, visit 3 at 13 weeks, visit 4 at 26 weeks) • Information on AEs collected at each visit via questionnaire • Blood and urine samples taken at visit 1 (baseline), 3 and 4 • ECG, pulse rate, blood pressure performed at visit 1, 3 and 4 • Spirometry (FEV/FVC) performed at all visits • HRQoL and asthma control assessed at all visits • HRQoL measured using the MiniAQLQ[b] • Control (symptoms, reliever medication and lung function) measured by the self-administered ACQ[a] **Length of follow-up:** Lung function, MiniAQLQ and ACQ analysed as change from baseline (visit 1) to average of values at visits 3 and 4

[a] ACQ, asthma control questionnaire, contained 7 items: 5 items about asthma-related symptoms, 1 item on reliever mediation usage and 1 item on lung function, all relating to preceding week.
[b] MiniAQLQ, mini asthma quality of life questionnaire, consisted of 15 items related to 4 domains: symptoms, activity limitations, emotional function and environmental stimuli.

continued

Results

Outcomes	Group A (n = 389)	Group B (n = 196)	p-Value
PEF:			
FEV_1 (litres) (mean change from baseline to visits 3–4)[a]	0.14	0.17	
FVC (litres) (mean change from baseline to visits 3–4)[a]	0.09	0.10	
SFDs			
Nocturnal awakenings			
Symptoms: ACQ score, mean change from baseline[b]	–0.50	–0.46	NS
(95% CI)	(–0.50 to –0.42)	(–0.57 to –0.35)	
Acute exacerbations – mean dose of oral corticosteroids (mg/study day)[c]	1.1[d]	1.3	
Acute exacerbations – withdrawals due to asthma (%)	2.3[d]	3.1	
Use of systemic corticosteroids (%)	15[d]	14	
Mortality			
QoL – mean change from baseline in overall MiniAQLQ[e] score	0.48	0.45	NS
(95% CI)	(0.39 to 0.57)	(0.33 to 0.56)	
AEs[f] – n (%)	77	69	
Serious AEs – n (%)	13 (3.3)	5 (2.6)	
Discontinuations due to AEs	11	9	
Discontinuations due to deterioration in asthma	7	5	
AEs (%), incidence ⩾3% patients			
Respiratory infection	35.7	30.6	
Viral infection	10.0	8.7	
Bronchitis	5.9	7.7	
Pharyngitis	6.4	4.1	
Headache	5.9	4.6	
Sinusitis	4.9	6.1	
Tremor	4.1	4.6	
Rhinitis	4.9	2.6	
Dysphonia	4.6	2.0	
Back pain	3.1	2.0	
Prevalence of pharmacologically predictable AEs (%)			
Tachycardia	1.0	1.0	
Tremor	4.1	4.6	
Throat irritation	6.7	4.1	
Hoarseness/dysphonia	4.6	2.0	

NS, no statistically significant difference between groups.

[a] Converted by reviewer from % increase from baseline into mean increase in litres. FEV_1: Group A based on a 5% increase, Group B based on a 6% increase. FVC: both groups based on a 2.5% increase.

[b] Scored on a scale from 0 to 7, where 0 = high levels of asthma control.

[c] Dose equivalent ratio was 20:3 for prednisolone to BDP and 5:4 for prednisolone to methylprednisolone.

[d] n = 390 for Group A.

[e] Scored on a scale from 0 to 7 where 0 = severe asthma problems.

[f] One patient in Group A did not receive any medication and was excluded from the safety analysis.

Comments

- Both treatments resulted in increases in mean FEV_1 of approximately 5–6% compared with baseline
- Improvements in FVC of approximately 2.5% compared with baseline also occurred in each treatment group
- No evidence of a reduction in the beneficial effects of each treatment on lung function was apparent over the 6-month treatment period
- Scores for individual MiniAQLQ domains of symptoms, activity limitation, emotional function and environmental stimuli were presented but not extracted. In terms of individual domain and overall scores there was no statistically significant difference between treatments. Improvements are described as being clinically significant despite relatively low levels of quality of life impairment at study entry
- Baseline ACQ scores were considered low (1.5–1.6 across groups), indicating few patients had poor asthma control at entry. The highest score recorded was 4 on this scale. The mean score was reduced by 30% in each treatment group

continued

- AEs:
  - After adjustment for differences in total treatment exposure, the number of AEs was similar (0.009 vs 0.008 per treatment day in Group A and Group B, respectively)
  - All serious AEs except one (unspecified eye symptoms in Group B) were considered by the investigator to be unrelated to treatment
  - Authors report that both treatments were well tolerated and overall there were no clinically important differences between the two treatment groups regarding the proportion, nature or intensity of the AEs

Methodological comments

- **Allocation to treatment groups**: procedure not reported. Randomisation was biased 2:1 in favour of the single inhaler with the aim of recruiting >300 patients in this group (Group A)
- **Blinding**: study described as an open randomised trial. No details of any attempts to blind patients, care providers or any investigators provided
- **Comparability of treatment groups**: groups appear similar on demographic and prognostic factors, no significance values reported
- **Method of data analysis**: ITT, including all randomised patients who received at least one dose of study medication. Safety variables were analysed by descriptive statistics and assessed by safety experts. Lung function variables were analysed as the change from baseline (visit 1), to the average of the values at visits 3 and 4. A multiplicative model was used, i.e. the logarithms of the pulmonary values were analysed in an ANOVA model. The values at baseline were used as covariates and the factors in the model were treatment and country. MiniAQLQ and ACQ scores were analysed as the average of values at visits 3 and 4. An additive ANOVA model with the same factors and covariates as described for lung function was used
- **Sample size/power calculation**: not reported, but see above under Allocation to treatment groups
- **Attrition/drop-out**: after randomisation 47 patients (8%) withdrew from the study, 26 in Group A, 21 in Group B. During the second half of the study a trend for a reduced withdrawal rate emerged in Group A compared with Group B (overall withdrawal rates 6.7 vs 10.7%, $p = 0.085$)

General comments

- **Generalisability**: patients described as having "moderate" asthma, receiving an average ICS dose of around 700 μg/day, with a relatively high baseline % predicted FEV_1. Not applicable to ICS-naïve population, or patients with unstable asthma (e.g. requiring oral corticosteroids)
- **Outcome measures**: appear to be relatively comprehensive
- **Inter-centre variability**: not reported
- **Conflict of interests**: one of the authors is affiliated with AstraZeneca, Sweden. Study funded by AstraZeneca

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Inadequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 232 **Author:** Scicchitano *et al*. **Year:** 2004 **Country:** Argentina, Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Mexico, The Netherlands, New Zealand, Norway, Portugal, Russia, South Africa, Turkey **Study design:** Double-blind, double-dummy, parallel group RCT **Number of centres:** 211 **Funding:** Supported by AstraZeneca (manufacturers of BUD + FF)	**Group A:** *n* = 947 Drug(s): BUD + FF Dose: 320[a] + 9 μg[b] q.d. Delivery: DPI Relief: ⩽10 extra puffs/day of BUD + FF p.r.n. Duration: 52 weeks **Group B:** *n* = 943 Drug(s): BUD Dose: 320 μg[a] b.d. Delivery: DPI Relief: ⩽10 puffs/day of terbutaline DPI 0.4 mg[c] p.r.n. Duration: 52 weeks **Run-in period:** Duration: 2 weeks ICS: any Relief: terbutaline DPI 0.4 mg[c] p.r.n. **Additional treatment allowed:** • Relief: see above • Other: severe exacerbations treated with oral prednisolone 30 mg/day for 10 days; no details of any allowable additional maintenance treatment	**Number randomised:** 1890 **Sample attrition/drop-out:** *n* = 317 (62 AEs; 72 ineligible; 32 lost to follow-up; 151 other) **Inclusion criteria:** • At study entry: – age 12–80 years – history of asthma for ⩾6 months – ⩾1 clinically important exacerbation in previous 2–12 months – Maintained on ICS at a dosage of 400–1600 μg for ⩾3 months, with stable dosage in previous 30 days – FEV_1 50–90% predicted – FEV_1 reversibility after 1 mg inhaled terbutaline ⩾12% (and ⩾200 ml for aged ⩾18 years) • After run-in: – symptomatic, moderate-to-severe asthma **Exclusion criteria:** • Systemic steroids or inhaled cromones in previous 30 days • ⩾3 courses of systemic steroids in previous 6 months • Cardiovascular disease or other significant disorder • Respiratory tract infection affecting asthma within previous 1 month • Smokers with history ⩾10 pack-years • >10 puffs of reliever on any day of run-in **Baseline characteristics:** *mean (range) except where specified* • Male:female = 798:1092 • Age (years) = 43 (11–80) • Median duration of asthma (range) (years) = 12 (1–71) • FEV_1 predicted = 70% (37–102%); FEV_1 reversibility = 24% (7–171%) • ICS dose at entry (μg) = 746 (250–2000) • LABA use at entry – *n* (%) = 656 (35%) • ICS + LABA combined use at entry – *n* (%) = 178 (9%) • Reliever use (puffs/day) = 1.9 (0–16) • Asthma symptom score = 1.8 (0–6) • SFDs = 10% (0–100%) • Asthma control days = 8% (0–100%)	**Primary measure:** Time to first severe exacerbation = ER visit • Hospitalisation need for systemic steroids • Morning PEF ⩽70% of baseline on 2 consecutive days **Secondary measures:** • Severe exacerbations requiring medical intervention • Mild exacerbation days = – nocturnal awakening; – morning PEF ⩽80% of baseline; and/or – ⩾2 puffs/24 hours reliever more than at baseline • Mild exacerbations (= 2 mild exacerbation days of same type consecutively) • PEF (a.m. and p.m.) • Symptom scores (day-, night-time and total) • Nocturnal awakenings • SFDs (= asymptomatic day and undisturbed night) • Reliever use • Reliever-free days • Asthma control days (= asymptomatic day, undisturbed night and no reliever use) • FEV_1 (mean of all measurements during Rx) • AEs **Method of assessing outcomes:** • Daily patient diaries: – PEF (a.m. and p.m.) – symptoms, effects and use of medication • Spirometry [baseline; clinic visits 3–7 (frequency not specified)] • AEs reported spontaneously and assessed at clinic visits (including some biochemistry and ECGs) **Length of follow-up:** None beyond 1-year study period

[a] Delivered dose; metered dose = 400 μg.
[b] Delivered dose; metered dose = 12 μg.
[c] Delivered dose; metered dose = 0.5 mg.

continued

Results

Outcomes	Group A (n = 947)	Group B (n = 943)	Comparisons	p-Value
FEV_1, mean throughout study – litres	2.54	2.45	MD: 0.10 (0.071 to 0.130)[a]	<0.001
PEF:				
a.m. – l/minute (range)	372.1 (100–751)	348.5 (93–805)	MD: 20.3 (17 to 24)[a]	<0.001
p.m. – l/minute (range)	369.6 (99–720)	354.7 (91–808)	MD: 14 (10 to 18)[a]	<0.001
SFDs – % (range):	41.7 (0–100)	34 (0–100)	MD: 7.5 (5 to 10)[a]	<0.001
Nocturnal awakenings – % (range)	9.4 (0–100)	13.0 (0–100)	MD: –3.3 (–4.8 to –1.7)[a]	<0.001
Acute exacerbations:				
Patients with events – n (%):	170 (18%)	259 (27%)	HR (95% CI): 0.61 (0.50 to 0.74)	<0.001
Patients with events requiring Medical interventions – n (%):	137 (14%)	212 (22%)	HR (95% CI): 0.61 (0.49 to 0.75)	<0.001
Events – n:	331	546		
hospitalisation/ER – n	15	25		
systemic steroid courses – n	182	324		
PEF falls – n	134	197		
Events requiring medical Interventions – n:	197	349		
Use of systemic corticosteroids, treatment days – n	1776	3177		
Use of reliever medication, rescue-free days – % (range):	59.8% (0–100%)	47.2% (0–100%)	MD: 11.0% (8 to 14%)[a]	<0.001
Days with >2 puffs – %	12%	21%		
Days with >4 puffs – %	3%	6%		
Mortality				
QoL				
AEs – n (%):				
Any	526 (56%)	533 (57%)		0.677[b]
Serious	58 (6%)	55 (6%)		0.846[b]
Oral candidiasis	11 (1%)	13 (1%)		0.688[b]
Dysphonia	23 (2%)	17 (2%)		0.425[b]
Palpitation, tremor or tachycardia	16 (2%)	13 (1%)		0.709[b]
Discontinuation due to AEs	24 (3%)	38 (4%)		0.072[b]
Other:				
Asthma control days – % (range)	38.3% (0–100%)	29.3% (0–100%)	MD: 8.6% (6 to 11%)[a]	<0.001
Mean daily ICS dose – µg/day	466	640		

ER, emergency room; HR, hazard ratio; MD, mean difference.
[a] Mean differences calculated by ANOVA model, with 95% CIs.
[b] Two-tailed Fisher's exact test, *calculated by reviewer*.

Comments

- Time to first severe exacerbation was significantly prolonged in Group A vs Group B ($p < 0.001$)
- Of 331 exacerbations defined by PEF falls, only 30 (95) were noted by investigators
- The rate of severe exacerbations requiring medical intervention/patient was reduced by 45% in Group A vs Group B (95% CI 34 to 54%, $p < 0.001$)
- Number-needed-to-treat to avoid 1 exacerbation over 1 year, Group A vs Group B = 5
- No "clinically important differences" were observed between groups for any laboratory variables studied
- Mean morning cortisol concentration baseline:end-point ratio 15% higher in Group A vs Group B ($p = 0.06$)
- Mean maximum cortisol concentration following ACTH stimulation baseline:end-point ratio was 8% higher in Group A vs Group B ($p = 0.4$)

continued

Methodological comments

- **Allocation to treatment groups**: block randomisation according to schedule computer-generated by a third party
- **Blinding**: double-blind, double-dummy design, with each participant receiving three identical inhalers: a.m. (placebo or BUD); p.m. (BUD + FF or BUD); p.r.n. (BUD + FF or terbutaline)
- **Comparability of treatment groups**: the groups are reported to be comparable with regard to demographic and baseline disease characteristics; however, no measures of variability are reported for baseline variables (ranges only)
- **Method of data analysis**: differences in time to first severe exacerbation evaluated by log-rank test and a Cox proportional hazards model was used to compare treatments and calculate instantaneous risk. Total number of severe exacerbations requiring medical intervention and mild exacerbation days compared between groups using a Poisson regression model (CIs and *p*-values were adjusted for over-dispersion). Changes from baseline for diary card variables analysed by ANOVA with treatment and country as fixed factors and baseline value as a covariate
- **Sample size/power calculation**: designed to recruit 800 participants per group, to detect (with 80% power; $\alpha = 0.05$) a 19.2% reduction in the incidence of severe exacerbations, assuming the true incidence of exacerbations was 25% in one group
- **Attrition/drop-out**: all randomised patients included in efficacy and safety analyses. 15% of Group A, 18% of Group B. Withdrawals were due to unspecified ("other") reasons in 7% and 9% of Group A and B, respectively

General comments

- **Generalisability**: inapplicable to ICS-naïve populations and those well controlled on ICS alone
- **Outcome measures**: primary efficacy variable relies on definition of exacerbations that incorporates subjective judgements on the part of participants (e.g. hospital attendance) and investigators (e.g. need for systemic steroids)
- **Inter-centre variability**: not reported; unclear whether randomisation was stratified by centre; ANOVA accounts for country
- **Conflict of interests**: study support by and 2 authors from AstraZeneca (manufacturers of BUD + FF)

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the care provider blinded?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Reported
9. Were withdrawals and drop-outs completely described?	Partial

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 247 **Author:** Vogelmeier *et al*. **Year:** 2005 **Country:** 16 countries including Italy, France, Germany and UK **Study design:** RCT, open-label, parallel-group **Number of centres:** 246 **Funding:** AstraZeneca, Sweden	**Group A:** *n* = 1067 Drug(s): BUD/FF Dose: 160/4.5 μg 2 puffs b.d. – titrated up or down to improve control[a], plus additional inhalations for relief as needed Delivery: DPI Turbuhaler (Symbicort) Duration: 52 weeks **Group B:** *n* = 1076 Drug(s): FP/SAL Dose: 250/50 μg b.d. – titrated up or down to improve control[a], plus salbutamol for relief Delivery: DPI Diskus (Seretide) Duration: 52 weeks **Run-in period:** Duration: 2 weeks ICS: existing ICS (and LABA, if appropriate) Relief: as needed medication permitted **Additional treatment allowed:** • Relief: as above • Other: • Trial aim: to compare effectiveness of BUD/FF for maintenance plus as-needed medication, with FP/SAL plus salbutamol as rescue medication	**Number randomised:** 2143 **Sample attrition/drop-out:** 269 (13%) discontinued (Group A *n* = 119; Group B *n* = 150). • Eligibility criteria violation: 83 (Group A *n* = 37; Group B *n* = 46) • AEs: 34 (Group A *n* = 13; Group B *n* = 21) • Lost to follow-up 34 (Group A *n* = 15; Group B *n* = 19) • Miscellaneous reasons: *n* = 118 (Group A *n* = 54, Group B *n* = 64) **Sample crossovers:** None reported **Inclusion criteria:** • Outpatients aged ⩾12 years with a diagnosis of asthma (American Thoracic Society) for ⩾6 months • ⩾500 μg/day of BUD or FP (or ⩾1000 μg of another ICS, e.g. BDP) for at least 1 month before study entry • Pre-terbutaline FEV_1 40–90% predicted • At least 1 severe exacerbation >2 weeks but ⩽12 months before study entry • At randomisation: – use of as-needed medication on ⩾4 of the last 7 days of run-in **Exclusion criteria:** • Use of BUD/FF or FP/SAL during last 3 months **Baseline characteristics, mean (range) unless stated otherwise:** Male:female – 880:1263 Age (years) – 45 (range 12–84) Asthma duration – 12–13 years (range 0–75) across groups Pre-terbutaline FEV_1 % predicted – 73 (range 28–115 across groups) FEV_1 reversibility – 13 ICS dose (μg/day) at entry – 881–888 (range 50–3000) across groups Baseline ICS: BUD *n* = 1318 (62%); FP *n* = 525 (24%); BDP *n* = 300 (14%) Inhaled LABA use at study entry: *n* (%) 811 (38) Reliever use inhalations per 24 hours: 2.6–2.7 (range 0.2–33.7) across groups Overall ACQ-5 score[b]: 1.86–1.87 (range 0.00–5.20) across groups • Overall AQLQ(S)[c] score: 4.95–4.97 (range 1.19–7.00) across groups • Use ⩽4 puffs of as-needed medication per week % of patients: 5	**Primary measure:** Time to first severe exacerbation (defined as hospitalisation/emergency room treatment, oral steroids for ⩾3 days or an unscheduled visit leading to treatment change) **Secondary measures:** • Pre- and post-terbutaline FEV_1 • As-needed medication use • Symptoms (ACQ-5) • HRQoL [AQLQ(S)] • AEs • Severe exacerbations excluding unscheduled visits, not resulting in hospital admission/ emergency room, oral steroids • Severe exacerbations, number of days with exacerbations and days with oral steroids **Method of assessing outcomes:** • Patients attended clinic at beginning and end of run-in, and at 1, 3, 6 and 12 months (visits 1–6). • Additional patient-initiated contacts were permitted • At each visit spirometry was performed (best of three readings), and patient-reported maintenance and as needed medication use during preceding 2 weeks was recorded • AEs were recorded spontaneously and at visits 2–6 **Length of follow-up:** 12 months

[a] **Treatment (further details)**: From week 4 onwards treatment in both groups was titrated by physicians at scheduled or unscheduled visits. Maintenance treatment was titrated up or down to improve control or to attain the lowest dose at which effective symptom control was maintained. The maintenance dose for Group A could be down-titrated from 160/4.5 μg 4 inhalations per day to 2 inhalations per day. In Group B, downwards titration from 250/50 to 100/50 μg b.d. was allowed. In this group, physicians could step up to 500/50 μg b.d.

[b] Five questions scored on a scale of 0–6, where 0 = no symptoms.

[c] 32 scored on a scale of 1–7, where 7 represents least impairment. A change in ACQ-5 and AQLQ(S) overall scores of ⩾0.5 is considered clinically relevant.

continued

Results

Outcomes	Group A (n = 1067)[a]	Group B (n = 1076)[a]	p-Value
PEF:			
FEV_1 (pre-terbutaline) adjusted mean change from baseline	0.17	0.14	0.066
FEV_1 (post-terbutaline) adjusted mean change from baseline	0.07	0.04	0.045
SFDs			
SFNs			
Symptoms: mean adjusted change in overall ACQ-5 score from baseline	–0.64	–0.58	0.069
Severe exacerbations – patients with an event, *n* (%)	159 (15)	204 (19)	0.0076[b]
Severe exacerbations – total number of events[d]	255	330	<0.01
Severe exacerbations – rate events per patient – $year^{-1}$	0.24	0.31	0.0025[c]
Severe exacerbations excluding unscheduled clinic visit – patients with an event, *n* (%)	132 (12)	167 (16)	0.025[b]
Severe exacerbations excluding unscheduled clinic visit – rate events per patient-1 – $year^{-1}$	0.19	0.23	0.023[c]
Severe exacerbations – number of unscheduled visits[d]	40	60	
Severe exacerbations – number of hospitalisations/emergency room visits[d]	45	50	
Severe exacerbations due to ER visits/hospitalisations – patients with an event, *n* (%)	31 (3)	46 (4)	0.18[b]
Severe exacerbations due to ER visits/hospitalisations rate events per patient – $year^{-1}$	0.04	0.05	0.38[c]
Severe exacerbations – number of courses of oral corticosteroids[d]	170	220	
Use of rescue medication in last 2 weeks of study (maximum of 4 inhalations per week), %	76	66	
Use of rescue medication in last 2 weeks of study[d] (>4 inhalations per week), %[d]	24	34	
Mortality	0	2[e]	
QoL: mean adjusted change in overall AQLQ(S) score from baseline	0.60	0.57	0.51
Serious AEs – *n* (%):	80	88	

[a] 2143 patients were randomised and a total of 2135 patients were included in the efficacy and safety analysis. No data were available for 8 patients following randomisation, but it is not reported how they were distributed between the groups. Therefore, the numbers for the groups presented here are as randomised
[b] *p*-Value based on the instantaneous risk of experiencing at least one severe exacerbation (Cox proportional hazards model)
[c] *p*-Values based on relative rate analysis (Poisson regression)
[d] Estimated from graph by reviewer
[e] Not considered to be causally related to the investigational products

Comments

- The time to first severe exacerbation was prolonged in patients in Group A vs Group B ($p = 0.0051$)
- The total rate of severe exacerbations was 22% lower with Group A vs Group B (95% CI 9 to 44%, $p = 0.0025$)
- The risk of a severe exacerbation was 25% lower in Group A (95% CI 7 to 39%, $p = 0.0076$)
- The risk of a severe exacerbation excluding unscheduled visits was 23% lower in Group A (95% CI 3 to 39%, $p = 0.025$)
- A small between group difference in the total number of severe exacerbations emerged before the start of the dose-titration phase and continued to increase ($p = 0.0025$, Poisson regression analysis of rate of exacerbations)
- There was a 34% reduction in oral steroid days due to severe exacerbations (1980 vs 2978, respectively)
- Mean as-needed use inhalations per day was –0.93 in Group B and –0.58 in Group A $p < 0.001$
- The odds of using a maximum of four as-needed inhalations per week (defined as low use) was higher in Group A than Group B (OR 1.68; 95% CI 1.38 to 2.05, $p < 0.001$)
- Overall 1 patient in Group A and 2 in Group B had serious AEs that were considered by the investigator to be causally related to study medication
- Authors report that 55 patients discontinued the study due to AEs (27 in Group A vs 28 in Group B). This is discrepant with other figures reporting that 34 patients discontinued due to AEs (13 in Group A, and 21 in Group B)
- Average daily ICS dose (μg) was similar between the two groups over the treatment period, Group A = 562 μg (maintenance) + 91 μg (as-needed) vs Group B 583 μg (maintenance only). Corresponding values expressed as BDP doses were 1019 μg/day (Group A maintenance and as needed) vs 116 μg/day (Group B maintenance only)
- Approximately 40% of Group B patients received the maximum dose (100/1000 μg/day) at some time during the study and 27% completed the study on this dose. Overall, 32% of Group B patients had their dose stepped down at some point during the study (13% from the maximum dose), with 14% completing the study on the lowest dose
- 39% of Group A patients halved their maintenance dose from 640/18 to 320/9 μg/day (4 vs 2 maintenance inhalations per day) and 31% completed the study on this dose

continued

Methodological comments

- **Allocation to treatment groups**: patients were randomised in chronological order at each centre according to a computer-generated code, and treatment was communicated via an interactive voice response system
- **Blinding**: open-label, to allow the appropriate maintenance dose of the combinations to be titrated up or down
- **Comparability of treatment groups**: reports that baseline characteristics were comparable between groups. Groups appear comparable on demographic and prognostic variables
- **Method of data analysis**: states ITT but data from eight patients randomised unavailable. Time to first severe exacerbation compared between groups using a log rank test/Cox proportional hazards model. Rate of severe exacerbation per patient per year was compared between groups using a Poisson regression model. Mean use of as-needed medication was calculated from all patient estimates during treatment. Groups were compared using ANOVA with treatment and country as factors. A *post hoc* analysis was performed at the final visit to assess patients' as-needed use during last 2 weeks to define good symptom control. FEV_1 and overall ACQ-5 score were analysed as change from baseline using the average of all measurements during the treatment period. Overall AQLQ(S) was analysed as change from baseline to visit 6. Analyses were performed using ANOVA
- **Sample size/power calculation**: a total of 1000 patients per group was required to have a 90% chance of detecting a reduction from 15 to 10% in proportion of patients with severe exacerbations (at the two-sided 5% significance level)
- **Attrition/drop-out**: 269 (13%) discontinued: Group A $n = 119$ (11%); Group B $n = 150$ (14%). Reasons for drop-out are given above

General comments

- **Generalisability**: generalisable to patients with moderate chronic asthma requiring LABA in addition to maintenance ICS therapy
- **Outcome measures**: appropriate and generally comprehensive
- **Inter-centre variability**: not reported
- **Conflict of interests**: study funded by AstraZeneca, Sweden. One of the co-authors affiliated with AstraZeneca

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Inadequate
5. Was the care provider blinded?	Inadequate
6. Was the patient blinded?	Inadequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Study	Treatment	Participants	Outcomes
Ref.: 225 **Author:** Zhong *et al*. **Year** 2004 **Country:** China **Study design:** Multi-centre, randomised, open-label, parallel-group **Number of centres:** 21 **Funding:** No information provided	**Group A:** *n* = 199 (ITT); 179 (PP) Drug(s): FP + SAL Dose: 100 + 50 μg b.d. Delivery: DPI (Accuhaler) Duration: 6 weeks **Group B:** *n* = 187 (ITT); 175 (PP) Drug(s): BUD Dose: 400 μg b.d. Delivery: MDI (Turbuhaler) Duration: 6 weeks **Run-in period:** Duration: 2 weeks ICS: continued treatment with routine ICS Relief: salbutamol **Additional treatment allowed:** Relief: salbutamol Other: not reported	**Number randomised:** 398 **Sample attrition/drop-out:** • 6 patients failed to fulfil eligibility criteria • 38 patients not evaluable: – AEs: 9 – lost to follow-up: 13 – protocol deviation: 4 – non-adherence to therapy: 11 – problems with the device: 1 (Of these: 12 patients were excluded from efficacy and safety analysis as 9 had no evidence of administration of any dose of study drug and 3 had no post-treatment efficacy data records) • ITT population = 386 • PP population = 354 **Sample crossovers:** None reported **Inclusion criteria:** • At entry: – age 18–70 years – documented history of asthma, currently receiving BUD or BDP at a total daily dose ≤500 μg/day for previous ≥4 weeks • Symptom score (day and night) ≥2 on 4/last 7 days of run-in period • Reversibility: – ≥15% reversibility and 200 mL elevation in FEV_1 after inhalation of β_2-agonist (salbutamol 400 μg) during run-in; and/or – diurnal variation of ≥20% in PEF rate on ≥1/last 7 days of run-in; and/or – documented historical reversibility of 15% in FEV_1 after inhalation of a β_2-agonist in 6 months prior to visit 1 • 50% ≤FEV_1 ≤85% of predicted at visit 2/2a (bronchodilators withheld previous ≥4 hours) • Ability to understand and complete diary record card, use a mini-Wright peak flow meter and record PEF correctly **Exclusion criteria:** • Use of systemic corticosteroids within 4 weeks, antileukotriene agents within 2 weeks, inhaled LABAs or oral β_2-agonists within 1 week of visit 1 • Change of asthma medication within 2 weeks of study entry • Upper/lower respiratory tract infections, acute exacerbation of asthma necessitating hospitalisation • Having used any investigational drugs within 4 weeks of entry • FEV_1 ≤50% or ≥85% of predicted at visit 2/2a • Unduly troubling symptoms • Any serious uncontrolled disease (including serious psychological disorders) likely to interfere with study • Evidence of alcohol or drug abuse • Known/suspected hypersensitivity to inhaled corticosteroids, β_2-agonists or lactose • Pregnancy or inadequate contraception in women of child-bearing age	**Primary measure:** Mean a.m. PEF **Secondary measures:** • P.m. PEF • Use of rescue medication • Day- and night-time asthma symptoms scores • FEV_1 • AEs **Method of assessing outcomes:** • Daily patient diary: – a.m. and p.m. PEF (highest of 3) – use of rescue medication – symptom scores – AEs – concomitant medication use • Visit 1 (week –2): – medical history – physical and oropharyngeal examinations – vital signs – lung function (FEV_1) • Visit 2/2a[a] (week 0): – FEV_1 • Visits 3 and 4 (weeks 3 and 6): – "routine assessments" – FEV_1 – compliance evaluation • Visit 5 (week 6 + 1): – clinic assessment for safety purposes **Length of follow-up:** 6 weeks treatment period + follow-up at week 6 + 1 for safety purposes

continued

Study	Treatment	Participants	Outcomes
		Baseline characteristics (ITT population): **Group A (*n* = 199)** • Age [mean (range)] (years): 46 (44–47) • Male:female [*N* (%)]: 88:111 (45:56) • Inhaled corticosteroid therapy [N (%)]: 198 (99.5) • Theophylline therapy [*N* (%)]: 62 (31) • Oral β_2-agonist therapy [*N* (%)]: 6 (3.0) • Mean FEV_1 (litres): 1.91 • Mean morning PEF (l/minute): 272 • Mean evening PEF (l/minute): 278 • Mean daytime symptom score (0–5): 1.62 • Mean night-time symptom score (0–5): 1.20 • SFDs (%): 13.39 • SFNs (%): 25.68 • SFDs (24-hour periods) (%): 7.0% • Rescue medication (mean no. of puffs/day): 1.34 • Rescue medication-free days [*N* (%)]: 22 (31) • % Rescue medication-free daytime period (%): 28.7% • % Rescue medication-free night-time period (%): 34.6% **Group B (*n* = 187)** • Age [mean (range)] (years): 46 (44–47) • Male:female [*N* (%)]: 83:104 (44:56) • Inhaled corticosteroid therapy [*N* (%)]: 187 (100) • Theophylline therapy [*N* (%)]: 61 (33) • Oral β_2-agonist therapy [*N* (%)]: 6 (3.2) • Mean FEV_1 (litres): 1.90 • Mean morning PEF (l/minute): 273 • Mean evening PEF (l/minute): 275 • Mean daytime symptom score (0–5): 1.65 • Mean night-time symptom score (0–5): 1.25 • SFDs (%): 13.48 • SFNs (%): 21.29 • SFDs (24-hour periods) (%): 9.0% • Rescue medication (mean no. of puffs/day): 1.34 • Rescue medication-free days [*N* (%)]: 20 (28) • Rescue medication-free days [*N* (%)]: 20 (28) • % Rescue medication-free daytime period (%): 26.9% • % Rescue medication-free night-time period (%): 32.2%	

[a] Visit 2a = re-evaluation 3 days after visit 2 for participants who did not initially meet randomisation criteria.

continued

Results

Outcomes (ITT population)	Group A (*n* = 199)	Group B (*n* = 187)	*p*-Value
FEV_1 mean change from baseline at 6 weeks (ml)	310[a]	280[a]	0.2614
PEF, a.m.:			
Mean[b] at endpoint – l/minute (95% CI)	326 (318 to 334)	303 (295 to 311)	
Mean change from baseline – l/minute (95% CI)			
Week 1; *n* = 198 (A), *n* = 187 (B)	25.6[c] (20.7 to 30.4)	7.2[c] (1.8 to 12.6)	<0.0001
Week 2; *n* = 198 (A), *n* = 186 (B)	33.4[c] (27.4 to 39.3)	14.1[c] (8.2 to 20.0)	<0.0001
Week 3; *n* = 198 (A), *n* = 186 (B)	38.1[c] (31.6 to 44.6)	21.6[c] (15.1 to 28.1)	<0.0001
Week 4; *n* = 192 (A), *n* = 181 (B)	46.1[c] (39.1 to 53.2)	23.9[c] (16.8 to 31.0)	<0.0001
Week 5; *n* = 190 (A), *n* = 180 (B)	50.9[c] (43.4 to 58.4)	26.5[c] (18.8 to 34.3)	<0.0001
Week 6; *n* = 189 (A), *n* = 180 (B)	52.4[c] (44.2 to 60.6)	29.9[c] (22.2 to 37.6)	<0.0001
SFDs after 6 weeks treatment – %	57.2[c] (43.8)	41.0[c] (27.5)	<0.001
SFNs after 6 weeks treatment – %	65.9[c] (40.2)	47.7[c] (26.4)	<0.001
Symptom-free 24-hour periods after 6 weeks treatment – %	66.5%[c]	46.6%[c]	<0.001
Nocturnal awakenings[d] – % at end-point	34.1%	52.3%	<0.001
Acute exacerbations			
Use of systemic corticosteroids			
Rescue medication-free days (24 hours) during 6 weeks treatment [mean % (95% CI)]			
Week 1; *n* = 98 (A), *n* = 186 (B)	43.9[c] (37.8 to 49.9)	31.3[c] (25.2 to 37.3)	<0.0001
Week 2; *n* = 198 (A), *n* = 185 (B)	47.8[c] (41.7 to 53.9)	34.4[c] (28.3 to 40.6)	<0.0001
Week 3; *n* = 198 (A), *n* = 186 (B)	51.7[c] (45.6 to 57.8)	39.2[c] (32.9 to 45.5)	<0.0001
Week 4; *n* = 192 (A), *n* = 180 (B)	61.4[c] (55.3 to 67.5)	39.9[c] (33.4 to 46.4)	<0.0001
Week 5; *n* = 190 (A), *n* = 180 (B)	62.2[c] (55.9 to 68.4)	42.5[c] (35.8 to 49.1)	<0.0001
Week 6; *n* = 189 (A), *n* = 180 (B)	63.2[c] (56.9 to 69.4)	44.4[c] (37.7 to 51.1)	<0.0001
Rescue medication-free daytime period (week 6) – %	67.8%[a]	49.1%[a]	<0.0002
Rescue medication-free night-time period (week 6) – %	71.7%[a]	53.6%[a]	<0.01
Mortality	0	0	
QoL			
Overall incidence of AEs – *n* (%)	47 (23%)[e]	45 (24%)[f]	
Serious AEs[g] (*n*)	1 (biliary colic)	1 (acute pancreatitis)	
Drug-related/possibly drug-related AEs – %	8%	5%	
Patients withdrawing due to AEs (*n*)	3 (headache, palpitations or ankle oedema)	2 (rash or chest pain)	
P.m. PEF, mean change from baseline – l/minute			
Week 1	20.8[e]	10.5[e]	0.0012
Week 6	45.6[e]	32.1[e]	0.0066

[a] Significance of difference from baseline not reported.
[b] Least-squares adjusted mean.
[c] Significantly different from baseline ($p < 0.05$).
[d] 1 – symptom-free nights.
[e] Most commonly reported AEs: pharyngitis, oedema, rash, palpitations, headache.
[f] Most commonly reported AEs: pharyngitis, ECG abnormalities, voice alterations, cough.
[g] Authors did not consider either to be related to study medication.

Comments

- Compliance not reported for treatment groups
- Efficacy conclusions were based on the results from the ITT population, with support from the results of the PP population [*n* = 179 (A), *n* = 175 (B)]

continued

Methodological comments

- **Allocation to treatment groups**: central randomisation according to computer-generated randomisation codes that were presented to investigators in sealed envelopes
- **Blinding**: open-label
- **Comparability of treatment groups**: demographic and baseline characteristics of the 2 treatment groups are reported to be "similar". From table the groups appear comparable although no statistical tests are reported
- **Method of data analysis**:
  - Mean PEF compared between groups using ANCOVA, allowing for effects as a result of baseline PEF, centre, gender, age and treatment group. For secondary efficacy variables, time was substituted for baseline value
  - % SFDs and SFNs compared between groups using the van Elteren extension to the Wilcoxon rank sum test, with centre as the stratifying variable
  - FEV_1 values compared using ANCOVA
  - No last observation carried forward (LOCF) performed for missing diary record card data as actual no. of days with non-missing data for each patient was used as denominator for calculation of % values. However, if patients withdrew prematurely, LOCF used for ITT analysis of mean PEF values
- **Sample size/power calculation**: estimated total of 300 evaluable patients (150 per group) required to ensure power of 90% to demonstrate a difference of 15 l/minute with 95% confidence (treatment with SAL/FP was defined as superior to treatment with BUD if the lower limit of the 95% CI for the treatment difference was >0 l/minute, and assuming a maximum SD of 40 l/minute)
- **Attrition/drop-out**: reported

General comments

- **Generalisability**: relatively inclusive eligibility criteria; population all Chinese with poorly controlled asthma on low-dose inhaled corticosteroids
- **Outcome measures**: appropriate and relatively objective
- **Inter-centre variability**: effects of 'centre' included in ANCOVA analyses, but results not reported
- **Conflict of interests**: none declared

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Inadequate (open-label)
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were outcome assessors blinded to the treatment allocation?	Inadequate
5. Was the care provider blinded?	Inadequate
6. Was the patient blinded?	Inadequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an ITT analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

From: NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: guidance for those carrying out or commissioning reviews* (Report 4). URL: http://www.york.ac.uk/inst/crd/report4.htm.

Appendix 5

Systematic review of clinical effectiveness: list of studies from updated literature search to be included in any future update of the assessment report

RCTs

Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. *J Allergy Clin Immunol* 2006;**117**:563–70.

Dahl R, Chuchalin A, Gor D, Yoxall S, Sharma R. EXCEL: a randomised trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. *Respir Med* 2006;**100**:1152–62.

Horiguchi T, Hayashi N, Ohira D, Torigoe H, Ito T, Hirose M, *et al*. Usefulness of HFA–BDP for adult patients with bronchial asthma: randomized crossover study with fluticasone. *J Asthma* 2006;**43**:509–12.

Jarjour NN, Wilson SJ, Koenig SM, Laviolette M, Moore WC, Davis WB, *et al*. Control of airway inflammation maintained at a lower steroid dose with 100/50 µg of fluticasone propionate/salmeterol. *J Allergy Clin Immunol* 2006;**118**:44–52.

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.

Nathan RA, Rooklin A, Schoaf L, Scott C, Ellsworth A, House K, *et al*. Efficacy and tolerability of fluticasone propionate/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescent and adult patients with persistent asthma: a randomized, double-blind, placebo-controlled, 12-week study. *Clin Ther* 2006;**28**:73–85.

Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T, *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**:246–56.

Zietkowski Z, Bodzenta-Lukaszyk A, Tomasiak MM, Szymanski W, Skiepko R. Effect of ciclesonide and fluticasone on exhaled nitric oxide in patients with mild allergic asthma. *Respir Med* 2006;**100**:1651–6.

Systematic review

Kaliner MA. Pharmacologic characteristics and adrenal suppression with newer inhaled corticosteroids: a comparison of ciclesonide and fluticasone propionate. *Clin Ther* 2006;**28**:319–31.

Appendix 6

Systematic review of clinical effectiveness: conference abstracts identified in the clinical effectiveness review

Bateman ED, Palmqvist M, Juniper EF, Zhu Y, Ekstrom T. Single inhaler therapy with budesonside/formoterol has superior efficacy to fixed-dose budesonide/formoterol or a higher dose of budesonide alone [Abstract]. American Thoracic Society 100th International Conference, 21–26 May 2004, Orlando, FL, A37. Poster J75.

Boonsawat W, Goryachkina L, Millns H, Balsara S. The efficacy and safety of seretide/advair once daily (50/100 µg) compared with fluticasone propionate (100 µg) once daily and placebos initial maintainence therapy in mild asthma [Abstract]. American Thoracic Society 100th International Conference, 21–26 May 2004, Orlando, FL, A37. Poster J82.

Buhi R, Wolf S, Tiesler C, Escher A, Weber HJ. Once-daily ciclesonide is as effective as twice-daily fluticasone propionate in improving lung function in patients with mild-to-moderate persistent asthma [Abstract]. American Thoracic Society 2005 International Conference, 20–25 May 2005, San Diego, CA, B35. Poster G19.

Busse W, Kaliner M, Bernstein D, Nayak A, Kundu S, Williams J, *et al*. The novel inhaled corticosteroid ciclesonide is effacious and has a favourable safety profile in adults and adolescents with severe persistent asthma [Abstract]. *J Allergy Clin Immunol* 2005; **115**:S213.

D'Urzo A, Vogeimeier C, Jaspal M, Merino JM, Boulet S. Symbicort (budesonide/formeterol) for both maintenance and relief reduces the exacerbation burden compared with titration of seretide (salmeterol/fluticasone) in patients with asthma, a real life study [Abstract]. American Thoracic Society 2005 International Conference, 20–25 May 2005, San Diego, CA, B35. Poster G24.

Keonig S, Waitkus-Edwards K, Yancey S, Prillman B, Dorinsky P. Loss of asthma control when patients receiving fluticasone propionate/salmeterol 100/50 µg Diskus are "stepped-down" to fluticasone propionate, salmeterol or montelukast alone [Abstract]. *J Allergy Clin Immunol* 2004;**113**:S94.

Pauwels R, Smiltena I, Bagdonas A, Eliraz E, Firth R. Seretide 50/100 µg once daily is more effective than budesonide 400 µg once daily in mild asthma [Abstract]. American Thoracic Society 100th International Conference, 21–26 May 2004, Orlando FL, A37. Poster J81.

Rojas RA, Paluga I, Goldfrad CH, Duggan MT. Fluticasone propionate/salmeterol 250/50 µg BD is significantly superior to fluticasone propionate 250 µg BD as initial maintenance therapy in moderate asthma [Abstract]. American Thoracic Society 2005 International Conference, 20–25 May 2005, San Diego, CA, B35. Poster G14.

Syamsi L, Yunus F, Wiyono WH, Mangunnegord H, Jusuf A, Prasetyo S. Effectivity of combination inhaled salmeterol/flutikason 2 times 50/250 µg/day compared flutikason 2 times 500 µg/day in moderate asthma persistent [Abstract]. *Respirology* 2004;**9**:A91.

Weinstein S, Friedman B, Kundu S, Banerji D. Ciclesonide is effective and well tolerated in adults/adolescents with severe persistent asthma [Abstract]. American Thoracic Society 2005 International Conference, 20–25 May 2005, San Diego, CA, B35. Poster G26.

Appendix 7

Systematic review of economic evaluations: additional tables

Additional information is given in *Tables 98–100*.

TABLE 98 *Relevant published economic evaluations of corticosteroids for asthma in adults: study designs*[a]

Study	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Andersson *et al.*, 2001[252]	CEA/trial (FACET, Pauwels *et al.*, 1997[280])	UK, Spain, etc. 9 countries (without Sweden). Setting NR	Moderate, persistent symptoms. Age 17–80 years	• BUD + FF 200 + 24 (separate inhalers) vs BUD 200 • BUD + FF 800 + 24 (separate inhalers) vs BUD 800	Society (Sweden, UK and Spain)	12 months No discounting	1. Direct medical costs: drugs, physician visits, emergency visits, hospitalisation, etc., in connection with a mild and a severe exacerbation 2. From expert opinion survey	1. Mild/severe exacerbations 2. Episode-free days 3. Symptom-free days	One-way and 2-way threshold analysis
Booth *et al.*, 1995[253]	CEA/trial (Langdon and Capsey, 1994[193])	UK, conducted in 57 general practices	Asthma patients. Age 18–70 years (oral steroids naïve during the previous 6 weeks)	• FP 400 • BUD 800	Not reported (but implicit: NHS)	8 weeks. No discounting	1. Study medication 2. Relief medication 3. Medication used to treat "causally related AEs"	Cost per successfully treated week (successful treatment: an increase of ⩾5% of predicted PEF)	One-way, varying the level of improvement in PEF
Briggs *et al.*, 2006[254b]	CEA and CUA/ trial and model	44 countries. Patients were from general practice and hospital clinics[c]	Uncontrolled asthma. Age ⩾12 years and <80 years	**For strata 1 and 2:** • FP/SAL: 200/100, 500/100 or 1000/100 • FP 200, 500 or 1000; **For stratum 3:** • FP/SAL: 500/100 or 1000/100 • FP 500 or 1000	UK NHS	52 weeks. No discounting	1. Secondary care visits (visits to EDs, length of time/no. of days in ICU, outpatient visits, and inpatient days) 2. Primary care visits (GP home visits, primary care clinic visits, and telephone calls to primary care clinic) 3. Medication (daily cost for each dosage level of study drugs, and per occasion cost of rescue medication use)	Control status (totally, well or not well controlled) QALYs	Not clear

continued

TABLE 98 *Relevant published economic evaluations of corticosteroids for asthma in adults: study designs[a] (cont'd)*

Study	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Ericsson *et al.*, 2006[281]	CEA/trial (Bateman *et al.*, 2003[228])	37 centres in 6 countries (4 in Europe). Setting NR	Persistent asthma. Age ⩾18 years	• BUD/FF: 400/12 • FP 500	Healthcare payer, society and drug budget holder, respectively. (NB. German and Dutch unit costs used)	12 weeks. No discounting	Pooled across countries 1. Study, rescue, and other asthma medication 2. Health care: Hospitalisation (general medicine and ICU) ER visits Physician visits Nurse visits House call Telephone calls Pharmacy contacts 3. Work days lost	Episode-free days	One-way (only for 2 variables)
Johansson *et al.*, 2006[256]	CEA/trial (Vogelmeier *et al.*, 2005[247])	16 (6 Asian, 10 European, countries including UK). Setting NR	Adults and adolescents ⩾12 years previously used ICS	• BUD/FF: 800/24, plus additional inhalations as needed • PF + SAL: 500/100, plus additional inhalations as needed	European societal perspective	12 months. No discounting	1. Direct costs: study drug and other asthma medication use, and the number of ER visits, specialist or primary care physician visits and the number of other healthcare provider contacts 2. Indirect costs: time taken off work by patients and their carers	Number of severe exacerbations per patient per year	No sensitivity analysis (but 'bootstrap' CIs estimated for base case ICER)

continued

TABLE 98 *Relevant published economic evaluations of corticosteroids for asthma in adults: study designs[a] (cont'd)*

Study	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Johansson *et al.*, 1999[282] (NB. dual publication of 1 of 3 comparisons in Lundbäck, 1999[259])	CEA/trial (Edwards *et al.*,1998,[283] and Nathan *et al.*, 1999[284])	North American effectiveness and resource use data. Setting NR	Adults and adolescents with asthma	• FP/SAL: 200/100 • FP 200	Swedish healthcare system	12 weeks. No discounting	1. Hospital contacts: ER visits, inpatient days 2. GP contacts: clinic visits 3. Medication: study drug, relief medications and concurrent drugs	1. Successfully treated weeks (%) 2. Episode-free days (%) 3. SFDs (%)	One-way and two-way
Jönsson *et al.*, 2004[285d]	CEA/trial (OPTIMA, O'Byrne *et al.*, 2004[286])	17 countries (15 in Europe). Setting NR	Mild-to-moderate persistent asthma. Aged ⩾12 years	• BUD 200 • BUD/FF: 200/12 • BUD 400 • BUD/FF: 400/12	Swedish healthcare payer and society	12 months. No discounting	1. Healthcare: days in hospital, visits to health professionals 2. Medication use (study, reliever, and other) 3. Days off work due to asthma	1. SFDs 2. Severe exacerbations	Applying unit cost (prices) from the UK and Spain to entire patient population
Lundbäck, 1999[259]	CEA/3 trials (Edwards *et al.*, 1998,[283] Nathan *et al.*, 1999,[284] Pieters *et al.*, 1998,[287] and White *et al.*, 1999[288])	North American (FP = 200 or 500), and European (FP = 1000). Setting NR	Adult and adolescent patients with asthma	• FP/SAL 200/100 vs FP 200 • FP/SAL 500/100 vs FP 500 • FP+SAL 1000+100 separate inhalers vs FP 1000	Swedish healthcare system	12 weeks. No discounting	1. Concurrent therapy 2. Relief mediation 3. Study drug 4. Primary care 5. Hospitalisation	1. Successfully treated weeks (%) 2. Episode-free days (%) 3. SFDs (%)	One-way and two-way. For successfully treated weeks: redefining the percentage improvement in PER from 1 to 10% in 1% increments. For the other efficacy parameters, using best/worst case scenario

continued

TABLE 98 *Relevant published economic evaluations of corticosteroids for asthma in adults: study designs[a] (cont'd)*

Study	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Lundbäck *et al.*, 2000[289]	CEA/trial (Jenkins *et al.*, 2000[223])	44 centres in 10 countries including 8 in Europe.[e] Setting NR	Age ⩾12 years; moderate to severe asthma, symptomatic on current doses of inhaled CIS (BDP or BUD 800–1200, or FP 400–800)	• FP/SAL: 500/100 • BUD 1600	Swedish healthcare system	24 weeks. No discounting	1. Direct healthcare cost (hospital contacts and GP contacts) 2. Drug costs	1. Successfully treated weeks (%) 2. Episode-free days (%) 3. SFDs (%)	One-way and two-way. Varied the criterion for successfully treated week in 1% increments. Best/worst case scenario for symptom- and episode-free days
Marchetti *et al.*, 2004[260]	CUA/model	Italy. Setting NR	Adults with moderate or severe persistent asthma	*For moderate:* • BDP 1000 • BDP-extra fine 400 • FP 400 • BUD 800 *For severe:* • BDP 1500 • BDP-extra fine 800 • FP 1000 • BUD 1600	Both the Italian healthcare system and society	2 months, discounting at 0.03 for utility; not stated for cost	1. Healthcare services: • GP visit • Hospital Day hospital ED visit including hospitalisation, complicated diagnosis diagnostic related group (DRG), and discharged from ED Pneumologist 2. Increased asthma 3. Related medication	QALE	By varying the unit cost for ICS, and transition rates

continued

TABLE 98 *Relevant published economic evaluations of corticosteroids for asthma in adults: study designs[a] (cont'd)*

Study	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Palmqvist *et al.*, 1999[261] (NB. dual publication of 1 of 3 comparisons in Lundbäck, 1999[259])	CEA/trial (White *et al.*, 1999[288])	North America. Setting NR	Adults and adolescents with moderate-to-severe asthma	• FP/SAL: 500/100 • FP 500	Swedish healthcare system	12 weeks. No discounting	1. Hospital contacts: ER visits, inpatient days 2. GP contacts: clinic visits 3. Medication costs: study drug, relief medications and concurrent drugs	1. Successfully treated weeks (%) 2. Episode-free days (%) 3. SFDs (%)	One-way and two-way
Pieters *et al.*, 1999[262] (NB. dual publication of 1 of 3 comparisons in Lundbäck, 1999[259])	CEA/trial (Pieters *et al.*, 1998[287])	Patients were from centres in France, Germany and The Netherlands. Setting NR	Corticosteroid-dependent asthma. Age not reported	• FP+SAL: 1000 + 100, separate inhalers • FP 1000	Swedish healthcare system	12 weeks. No discounting	1. Hospital contacts: accident and emergency visits, ICU days, inpatient days and outpatient visits 2. GP contacts: daytime home visits, night-time home visits, office/practice visits and telephone calls 3. Study drugs, study relief medication and concurrent drugs	1. Successfully treated weeks (%) 2. Episode-free days (%) 3. SFDs (%)	One-way
Price and Briggs, 2002[263]	CEA/trial (Kavuru *et al.*, 2000[235]) and model	42 centres in the USA.[f] Setting NR	Adults and adolescents (⩾12 years) with symptomatic asthma	• FP/SAL: 200/100 • FP 200	Implicitly, UK healthcare system	12 weeks. No discounting	Costs associated with primary and secondary exacerbation health states: medication usage, physician time and hospital costs	Proportion of successfully controlled weeks	PSA

continued

TABLE 98 *Relevant published economic evaluations of corticosteroids for asthma in adults: study designs[a] (cont'd)*

Study	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Steinmetz *et al.*, 1998[264]	CEA/trial (Steinmetz and Trautmann, 1996[290])	45 ambulatory or outpatient centres in Germany	Corticosteroid-naïve patients with moderate asthma. Age 17–70 years	• FP 500 • BUD 1200	German third-party payer	6 weeks. No discounting	Study medication, additional asthma-related medication (e.g. rescue medication), any medications used to treat an AE related to asthma or its treatment, office-based physician visits and hospitalisations	1. Number of successfully treated patients (with ⩾10% improvement in PEF) 2. % SFDs (24-hour period without day- or night-time asthma symptoms)	One-way
Venables *et al.*, 1996[265]	CMA/trial (Venables *et al.*, 1996[291])	UK in general practice	Symptomatic asthmatics; age 18–70 years inclusive (steroid-free or receiving ⩽200 μg/day ICS)	• BUD 400 q.d. • BUD 200 b.d. • FP 400 q.d.	Implicit NHS perspective	8 weeks. No discounting	Drug cost: study medication, relief medication, medication for causally related AEs	Cost-effectiveness ratio of: 1. % SFDs 2. % days on which patients achieved a ⩾5% improvement from baseline in predicted a.m. PEF	Two-way and one-way

ED, emergency department; ICU, intensive care unit; QALE, quality-adjusted life expectancy.

[a] Dosages are in μg/day. LABA added to ICS are in combination inhalers unless specified otherwise.

[b] The study had two phases. Phase I: dose escalation in a case they filed to achieve total control in at least 7 weeks of an 8-week assessment period. Phase II: maintenance at the dose they reached at the end of phase I. Patients were stratified into 3 strata according to their use of ICS 6 months prior to screening for study entry and then they were randomised from the 3 strata to receive either FS or FF – Stratum 1: no ICS; Stratum 2: ⩽500 μg BDP daily or equivalent; Stratum 3: from 500 to ⩽1000 μg BDP daily or equivalent.

[c] Information from the GOAL study by Bateman *et al.*[234]

[d] All BUD + FF combinations were delivered by separate inhalers.

[e] Data from the supplement of the trial by Jenkins *et al.*, 2000;94:715–23.[223]

[f] Data from supplement of the trial by Kavuru *et al.*[235]

TABLE 99 *Relevant model-based economic evaluations of corticosteroids for asthma in adults: decision model design and key assumptions*

Study	Model structure	Sources of probabilities	Sources of utilities	Sources of costs	Model validation
Marchetti *et al.*, 2004[260]	Markov model	• Transition probabilities from six published RCTs: Price *et al.*, 2002; Fireman *et al.*, 2001;[317] Worth *et al.*, 2001;[318] Aubier *et al.*, 2001; Reichel *et al.*, 2001;[319] and Fairfax *et al.*, 2001[320] • Exacerbations: Hoskins *et al.*, 2000 • Local AEs of ICS: assumed	Asthma Symptom Utility Index (ASUI) scores reported in each trial (implicitly, the same trials as those used for transition probabilities)	• Healthcare resource consumption in different health states: interview with 9 doctors • Unit costs: Prontuario Farmaceutico Sistema Sanitario Nazionale and Intercontinental Medial Statistics • Hospital stays: Decreto Ministeriale 30 Giugno 1997 • GP service: Tarricone *et al.*, 2001 • ED for an exacerbation: assumed • Retail prices: www.sanita.it (accessed September 2004) • Working days lost: Ungar, 2000 • Time off paid work: Banca d'Italia, 2000 • Overall number of unproductive days: assumed	None described
Price and Briggs, 2002[263]	Markov model	The trial by Kavuru *et al.*, 2000[235]	The trial by Kavuru *et al.*, 2000[235]	• Medication costs: the Monthly Index of Medical Specialities, November 2000 • Costs associated with the primary and secondary exacerbation health states: Hoskins *et al.*, 1998 • The Hospital and Community Health Service (HCHS) inflation index (Netten *et al.*, 1998)	None described

TABLE 100 *Relevant published economic evaluations of corticosteroids for asthma in adults: results*[a]

Study	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Andersson *et al.*, 2001[252]	BUD 200	BUD + FF: 200 + 24, separate inhalers	Total direct costs: • UK: €191 • Sweden: €–549 • Spain: €–28	Average per-patient-year Number of SFDs: 38, $p < 0.01$ Number of episode-free days: 34, $p < 0.01$ Number of mild exacerbations: 7.9, $p < 0.001$ Number of severe exacerbations: 0.5, $p < 0.01$	ICER of SFDs • UK: €4.67 • Sweden: not relevant (dominate) • Spain: not relevant (dominate)
	BUD 800	BUD + FF: 800 + 24, separate inhalers	Total direct costs: • UK: €271, $p < 0.001$ • Sweden: €–286 • Spain: €103	Average per-patient-year: Number of SFDs: 41, $p < 0.01$ Number of episode-free days: 33, $p < 0.05$ Number of mild exacerbations: 5.7, $p < 0.01$ Number of severe exacerbations: 0.4, $p < 0.01$	ICER of SFDs • UK: €6.60 • Sweden: not relevant (dominate) • Spain: €2.51
Booth *et al.*, 1995[253]	BUD 800	FP 400	*Total average cost per patient per week: £0.97*	*Proportion of successfully treated weeks: +11.9%*	*ICER = £8.15*
Briggs *et al.*, 2006[254]	• FP 200 • FP 500 • FP 1000	• FP/SAL: 200/100 • FP/SAL: 500/100 • FP/SAL: 1000/100	Stratum 1: treatment cost £3.31, other healthcare cost –£0.18 Stratum 2: treatment cost £2.77, other healthcare cost –£0.22	Stratum 1: weighted average HRQoL/QALYs 0.012 Stratum 2: weighted average HRQoL/QALYs 0.012	Stratum 1: cost-per-QALY gained £13,700 (95% CI 11,000 to 18300) Stratum 2: cost-per QALY gained £11,000 (95% CI 8600 to 14,600)
	• FP 500 • FP 1000	• FP/SAL: 500/100 • FP/SAL: 1000/100	Stratum 3: treatment cost £2.04, other healthcare cost –£0.31	Stratum 3: weighted average HRQoL/QALYs 0.012	Stratum 3: cost-per QALY gained £7600 (95% CI 4800 to 10,700)

continued

TABLE 100 *Relevant published economic evaluations of corticosteroids for asthma in adults: results[a] (cont'd)*

Study	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Ericsson *et al.*, 2006[281]	FP 400	BUD/FF: 400/12	*Mean cost (€) per patient over 12 weeks:* • *Total medication: German –40, Dutch 35* • *Total healthcare including medication: German –79, $p = 0.0043$; Dutch –2, $p > 0.05$* • *Productivity: German –70, $p > 0.05$; Dutch –55, $p > 0.05$* • *Total: German –149, $p = 0.0254$; Dutch –58, $p > 0.05$*	• Change in morning PEF (l/min): 19.7 (95% CI 13.6 to 25.9), $p < 0.001$ • Change in evening PEF (l/min): 17.2 (95% CI 11.2 to 23.2), $p < 0.001$ • % change in FEV_1 (l): 4.7 (95% CI 2.0 to 7.4), $p < 0.001$ • Change in reliever medication (inhalations/day): 0.18 (95% CI –0.35 to –0.01), $p = 0.04$ • Patients with one or more mild exacerbations (%): –12.3 (95% CI –22.2 to –2.17), $p = 0.017$ • Patients with one or more severe exacerbations (%): not statistically significant	BUD/FF was dominant
Johansson *et al.*, 2006[256]	BUD/FF: 800/24, + as needed	PF + SAL: 500/100, + as needed	*Total cost: £72, $p = 0.13$*	Severe exacerbations per patient per year (ITT): 0.07	*Cost per severe exacerbation per patient per year: £1028*
Johansson *et al.*, 1999[282]	FP 200	FP/SAL: 200/100	*Total direct costs per patient per day: SEK 6.4 (US$0.78)*	• *Mean proportion of successfully treated weeks: 32%, $p < 0.00001$* • *Mean proportion of episode-free days: 7.6%, $p = 0.134$* • *Mean proportion of symptom-free days: 9.2%, $p = 0.096$*	• Cost per successfully treated week: SEK 133.4 (95% CI 89.4 to 215.6) • Cost per SFD: SEK 44.5 • Cost per episode-free day: SEK 46.9
Jönsson *et al.*, 2004[285]	BUD 200	BUD 400	*Total healthcare costs per patient per year: 594* *Total costs per patient per year: 1313*[b]	*SFDs %: +3.59* *Number of SFDs per year: +13* *Severe exacerbations avoided per year: –0.03*	*Healthcare cost/SFD: £46* *Exacerbations avoided: BUD 400 is dominated by BUD 200*
	BUD 200	BUD + FF: 200 + 12, separate inhalers	*Total healthcare costs per patient per year: 1747* *Total costs per patient per year: 1538*[b]	*SFDs %: +5.09* *Number of SFDs per year: 18* *Severe exacerbations avoided per year: –0.25*	*SFDs: dominated (extended dominance)* *Exacerbations: dominated (extended dominance)*

continued

TABLE 100 *Relevant published economic evaluations of corticosteroids for asthma in adults: results[a] (cont'd)*

Study	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
	BUD 200	BUD + FF: 400 + 12, separate inhalers	*Total healthcare costs per patient per year: 2186* *Total costs per patient per year: 1513[b]*	*SFDs %: 6.24* *Number of SFDs per year: 23* *Severe exacerbations avoided per year: 0.54*	*SFDs: dominated (extended dominance)* *Healthcare cost/exacerbation avoided: £4048*
	BUD 400	BUD + FF: 200 + 12, separate inhalers	*Total healthcare costs per patient per year: 1153, p = 0.045* *Total costs per patient per year: 225[b]*	*SFDs %: 1.5, p = 0.55* *Number of SFDs per year: 5* *Severe exacerbations avoided per year: 0.28, p = 0.021*	*SFDs: dominated (extended dominance)* *Exacerbations: BUD 400 is dominated by BUD 200*
	BUD 400	BUD + FF: 400 + 12, separate inhalers	*Total healthcare costs per patient/year: 1592, p = 0.006* *Total costs per patient per year: 200[b]*	*SFDs %: 2.65, p = 0.28* *Number of SFDs per year: 10* *Severe exacerbations avoided per year: 0.57, p = 0.002*	*Healthcare cost/SFD: £159* *Exacerbations: BUD 400 is dominated by BUD 200*
	BUD + FF: 200 + 12	BUD + FF: 400 + 12, separate inhalers	*Total healthcare costs per patient per year: 439* *Total costs per patient per year: –25[b]*	*SFDs (%): 1.15* *Number of SFDs per year: 5* *Severe exacerbations avoided per year: 0.29*	*SFDs: dominated (extended dominance)* *Exacerbations: dominated (extended dominance)*
Lundbäck *et al.*, 1999[259]	FP 200[c]	FP/SAL: 200/100[c]	*SEK 6 (read from Fig. 4)*	Change in percentage of successfully treated weeks: +32% Change in percentage of SFDs: +9% Change in percentage of episode-free days: +8%	Cost per successfully treated week: SEK 133.4 (95% CI 89.4 to 215.6) Cost per SFD: SEK 44.5 Cost per episode-free day: SEK 46.9
	FP 500[d]	FP/SAL: 500/100[d]	SEK 0.7	Change in percentage of successfully treated weeks: +38% Change in percentage of SFDs: +18% Change in percentage of episode-free days: +19%	Cost per successfully treated week: SEK 12.6 (95% CI –82.2 to 93.1) Cost per SFD: SEK 3.9 (95% CI –27.8 to 37.2) Cost per episode-free day: SEK 3.9 (–25.4 to 35.9)
	FP 1000[e]	FP + SAL: 1000 + 100, separate inhalers[e]	SEK 6.6	Change in percentage of successfully treated weeks: +25% Change in percentage of SFDs: +10% Change in percentage of episode-free days: +5%	Cost per successfully treated week: 192.1 (95% CI 58.3 to 436.7) Cost per SFD: SEK 66.8 (95% CI 17.5 to 318.2) Cost per episode-free day: SEK 120

continued

TABLE 100 *Relevant published economic evaluations of corticosteroids for asthma in adults: results[a] (cont'd)*

Study	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Lundbäck *et al.*, 2000[289]	BUD 1600	FP/SAL: 500/100	SEK 1.1 per patient per day (= SEK 184 over 24 weeks of the trial)	Change in percentage of successfully treated weeks: +24% Change in percentage of SFDs: +11% Change in percentage of episode-free days: +12%	Cost per successfully-treated week: SEK 31.6 Cost per episode-free day: SEK 7.7 Cost per SFD: SEK 9.2
Marchetti *et al.*, 2004[260]	**Societal perspective**				
	Moderate				
	FP 400	BDP 1000	4.00	Quality-adjusted life expectancy (QALE): 0.59	Cost per QALE: €6.77
	BUD 800	BDP 1000	–15.00	QALE: 1.10	BDP dominant
	FP 400	BDP 400	47.00	QALE: –1.74	BDP is dominated
	BUD 800	BDP 400	28.00	QALE: –1.23	BDP is dominated
	BUD 800	*FP 400*	*–19.00*	*QALE: 0.50*	*FP dominant*
	Severe				
	FP 1000	BDP 1500	15.00	QALE: 1.04	Cost per QALE: €14.42
	BUD 1600	BDP 1500	26.00	QALE: 0.56	Cost per QALE: €46.43
	FP 1000	BDP 800	56.00	QALE: –0.50	BDP is dominated
	BUD 1600	BDP 800	67.00	QALE: –0.98	BDP is dominated
	BUD 1600	*FP 1000*	*11.00*	*QALE: –0.48*	*FP is dominated*
	NHS perspective				
	Moderate				
	FP 400	BDP 1000	13.00	QALE: 0.59	Cost per QALE: €22.03
	BUD 800	BDP 1000	–1.00	QALE: 1.10	BDP dominant
	FP 400	BDP 400	34.00	QALE: –1.74	BDP is dominated
	BUD 800	BDP 400	20.00	QALE: –1.23	BDP is dominated
	BUD 800	*FP 400*	*–14.00*	*QALE: 0.50*	*FP dominant*
	Severe				
	FP 1000	BDP 1500	36.00	QALE: 1.04	Cost per QALE: €34.61
	BUD 1600	BDP 1500	40.00	QALE: 0.56	Cost per QALE: €71.43
	FP 1000	BDP 800	48.00	QALE: –0.50	BDP is dominated
	BUD 1600	BDP 800	52.00	QALE: –0.98	BDP is dominated
	BUD 1600	*FP 1000*	*4.00*	*QALE: –0.48*	*FP is dominated*

continued

TABLE 100 *Relevant published economic evaluations of corticosteroids for asthma in adults: results[a] (cont'd)*

Study	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Palmqvist *et al.*, 1999[261]	FP 500	FP/SAL: 500/100	Total direct costs: SEK 0.7 per patient per day	• *Change in percentage of successfully treated weeks: +39.4%, $p < 0.00001$* • *Change in percentage of SFDs: +18.2%, $p = 0.0004$* • *Change in percentage of episode-free days: +18.1%, $p = 0.0017$*	• Cost per successfully treated week: SEK 12.6 (95% CI –82.2 to 93.1) • Cost per episode-fee day: SEK 3.9 (95% CI –25.4 to 35.9) • Cost per symptom free day: SEK 3.9 (95% CI –27.8 to 37.2)
Pieters *et al.*, 1999[262]	FP 1000	FP + SAL: 1000 + 100, separate inhalers	*Total non-drug resource costs: 2.4 SEK* *Total direct costs/patient/day: SEK 6.6 (US$0.8)*	(Read from Figure 1 in the paper) • *Proportion of successfully treated weeks: 23.9%, $p = 0.001$* • *Proportions of SFDs: 9.8%, $p = 0.012$* • *Proportions of episode-free days: 5.4%, $p = 0.068$*	• Cost per successfully treated week: SEK 192.1 (95% CI 58.3 to 436.7) • Cost per SFD: SEK 66.8 (95% CI 17.5 to 318.2) • Cost per episode-free day: SEK 120 (no significant difference)
Price and Briggs, 2002[263]	FP 200	FP/SAL: 200/100	*Mean weekly direct asthma management costs: £3.94*	*% successfully controlled weeks/patient: 19*	• Average incremental cost per successfully controlled week with FP/SAL: £20.83 (95% CI –£65 (FP/SAL dominant) to £113)
Steinmetz *et al.*, 1998[264]	BUD 1200	FP 500	*Average treatment costs (DM 1997) per patient/day:* • *Study drug: –0.61* • *Additional medication: –0.09* • *Secondary care costs: –0.26* *Total treatment costs: –0.96*	• *Proportion of successfully treated patients (with 10% increase in morning PEF, l/minute) = +5%* • *SFDs (%): +6%*	FP is dominant (cheaper and more effective than BUD)

continued

TABLE 100 *Relevant published economic evaluations of corticosteroids for asthma in adults: results[a] (cont'd)*

Study	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Venables *et al.*, 1996[265]	BUD 400 q.d.	FP 200 b.d.	*£0.46*/day ($P < 0.001$)	• *Percentage SFDs: 5%* (not significant) • *Percentage days with ⩾5% PEF improvement: 3%* (not significant)	• Cost per SFD: *£9.2* • Cost per successfully treated day: *£15.33*
	BUD 200 b.d.	FP 200 b.d.	*£0.44*/day ($p < 0.001$)	• *Percentage SFDs: 9%* (not significant) • *Percentage days with ⩾5% PEF improvement: 9%* (not significant)	• Cost per SFD: *£4.89* • Cost/successfully treated day: *£4.89*

[a] Dosages are in μg/day, the LABA adding to ICS are in combination inhalers and the ICERs are not discounted or not applicable, unless specified otherwise. *Results in Italic were calculated by the reviewer.*
[b] From the societal perspective there were no statistically significant differences in total costs between three of the treatment groups. The ICER was from healthcare payer perspective (taking into account healthcare costs only). The costs are in SEK (Swedish Krone).
[c] This comparison also published separately as Johansson *et al.*, 1999.[282]
[d] This comparison also published separately as Palmqvist *et al.*, 1999.[261]
[e] This comparison also published separately as Pieters *et al.*, 1999.[262]

Appendix 8

Review of existing economic models of asthma

Despite the large number of clinical trials identified in the current review (Chapter 3), there are very few studies reporting methods for the modelling of asthma and its treatment for the purposes of CEA. A systematic literature search, undertaken as part of the current review (see Appendix 3), identified only four studies presenting a modelling approach to the assessment of cost-effectiveness of treatments for asthma.[260,263,292,293] A short summary of each of the four identified studies is presented here.

The Asthma Policy Model[292]

Paltiel and colleagues[292] present the Asthma Policy Model (APM) and results from its use to assess the cost-effectiveness of ICS therapy in mild-to-moderate adult asthma. The application of the model compared short-acting β-agonists alone versus short-acting β-agonists plus ICS therapy. This application is not relevant for the current discussion, and detail on intervention specific model inputs and model results are not referred to here.

The APM is a mathematical model estimating the clinical outcomes, HRQoL (utility impact) and costs over time in adults with asthma. It is a Markov state-transition model, comprising a large number of health states stratified by disease status, lung function impairment, prior hospitalisation history and two age groups (*Table 101*). The model also has a health state for death. The model is presented with a time horizon of 10 years, and a monthly model cycle. Patients transit between health states over time (at each cycle). Transition probabilities are mainly determined using a logistic regression approach, predicting acute events (e.g. emergency department visits) as a function of the FEV_1 % predicted for patients (patient groups). The model is based almost entirely around lung function, using FEV_1 % predicted, and it assumes that the impact of therapy on acute events can be captured using data on FEV_1 % predicted. Treatment effect (clinical differences between compared strategies) is based on the differences in FEV_1 % predicted reported in published clinical trials. The model does not use treatment effects independent of FEV_1 % predicted.

TABLE 101 *Dimensions defining health states used in the APM*

Dimensions	Categories
Disease status	Chronic/stable, acute/hospital, dead
Lung function impairment	Mild or moderate; based on FEV_1 % predicted, where >80% = mild, 60–80% = moderate
Prior hospitalisation	None, one, more than one
Age[a]	18–35 years, over 35 years
Death (cause)	Asthma-related, other

[a] Asthma-related mortality rates were stratified by age groups.

Functional relationships are presented for the percentage of symptom days and FEV_1 % predicted, and for rate of emergency department (ED) visits and FEV_1 % predicted. These regression functions are presented as

$$\%\ \text{symptom days} = 1/[1 + \exp(-12.5 + 0.1550 \times FEV_1\ \%\ \text{predicted})] \times 100$$

$$\text{ED rate} = 1/[1 + \exp(-2.1872 + 0.0560 \times FEV_1\ \%\ \text{predicted})]$$

These logistic regression equations are used in combination with other observational data on exacerbation events.

The model considers a cohort of patients, with the initial distribution of patients distributed according to published data on lung function, prior hospitalisations and age. The APM incorporates utility values using a stated functional relationship between FEV_1 % predicted and preference (utility) scores. The model draws this relationship from a companion study, a cross-sectional study of 100 adults (USA) with asthma, and health state values elicited from these subjects via a range of valuation techniques. The APM is presented using time trade-off (TTO) values, applying the following functional relationship:

$$TTO = 0.521 + 0.003958 \times FEV_1\ \%\ \text{predicted}$$

The utility study referred to by Paltiel and colleagues was published in abstract format only (by Neumann and colleagues[294]) with no substantive information provided to support the derivation of the functional relationship presented.

In the model presented costs are estimated (1998 US$) from published data (two USA studies) on resource use. Healthcare management costs are based on medications, consultations and laboratory tests. Acute event costs were estimated for non-ED urgent care visits ($63), ED visits ($242) and hospitalisations ($3200).

The model presents results comprising estimates of cost and of quality-adjusted life-months. Virtually all deaths were attributable to non-asthma-related causes. The model predicted a mean of 36.7% symptom days and 4.5 acute episodes per person (over 10 years). Cost-effectiveness summary measures are presented for cost per QALY and cost per additional SFD. The study reported by Paltiel and colleagues acknowledges financial support from AstraZeneca.

12-week patient level model presented by Price and Briggs[263]

Price and Briggs[263] present a Markov model based on individual patient-level data from one 12-week RCT, comparing alternative ICS therapies in adults and adolescents with symptomatic asthma.[268] The model presents a UK analysis. The model uses a composite measure of asthma control (based on GINA guidelines), estimating cost per successfully controlled week. In the model, the occurrence of exacerbation events is a central consideration. The model uses five health states: successful control, sub-optimal control, treatment failure (absorbing state for patients not continuing treatment), hospital-managed exacerbation and primary care-managed exacerbation. The model uses a time horizon of 12 weeks and a 1-week cycle length (12 × 1-week cycles). Transition probabilities between each state are informed by individual patient-level data from the 12-week RCT, with patient location at each week counted and transformed into a transition probability. Where events were very rare (i.e. no hospital exacerbations were recorded in the trial) and the resulting probabilities were judged to lack face validity, a Bayesian approach, with prior probabilities, was used to inform the model inputs.

A cost estimate is presented for each weekly cycle, comprising study medication costs, rescue medication costs, costs for acute events and costs associated with treatment failure. Cost estimates for exacerbation events are based on a published UK study.[295] Event costs (2000 UK£) per week were reported as £1815–1821 for hospital-managed exacerbations and £95–100 for primary care-managed exacerbations.

The model presents results (over 12 weeks) according to the proportion of successfully controlled weeks per patient and the cost per successfully controlled week. The study presents detailed sensitivity analysis using probabilistic methods. The development of the model was funded by GlaxoSmithKline (support acknowledged by the authors).

Asthma utility model by Marchetti and colleagues[260]

This model is based on a range of utility states corresponding to asthma status. The model is built around the Asthma Symptom Utility Index (ASUI), a health status measure for asthma stated to be capable of estimating the utility of patients with asthma.[293] It is a Markov-type model with seven utility states (U1–U7), each of which is described according to the ASUI scores drawn from clinical trials. The presentation of the model by Marchetti and colleagues compares different ICS therapy in terms of CUA, from the perspective of the Italian NHS and the Italian societal perspective.

The time horizon for the model was 2 months (baseline analysis). Transition probabilities between the seven health states were derived using data on percentage of SFDs/SFNs from published RCTs. Data on percentage of SFDs/SFNs were converted into an ASUI score and transition probabilities derived. The frequency of exacerbation events was informed by published studies. Resource use and cost estimates were informed by expert opinion (nine clinical experts). Affiliation of the authorship included pharmaceutical company representation (Chiesi Farmacutici, Italy).

Model for severe asthma by DeWilde and colleagues[310]

This model was developed to estimate the cost-effectiveness of omalizumab plus optimised

standardised therapy (ST) versus optimised ST alone in patients with severe persistent IgE-mediated asthma. The model presents an analysis for Sweden, comparing lifelong ST with a treatment period of omalizumab add-on therapy followed by ST. The model is based on a 28-week RCT (INNOVATE trial) and additional Swedish data on life expectancy and treatment cost. This model was developed for a patient group with severe asthma (uncontrolled despite GINA step 4 therapy), and is not relevant to the patient group considered in the current review. Briefly, the model comprised five health states: daily symptoms, clinically significant non-severe exacerbations, clinically significant severe exacerbations, severe exacerbation-related death and death from all causes. The RCT used to inform the model reported a statistically significant reduction in clinically significant exacerbations and severe clinically significant exacerbations. The model is a lifetime horizon model with 2-week cycles. Transitions between health states are based on exacerbation rates, with exacerbation data taken from the INNOVATE RCT. Utility estimates used in the model are discussed in Appendix 9 of the present report. Results are presented as differences in costs and consequences and as cost per QALY estimates. The majority (85%) of the QALY gains estimated are due to extended life expectancy. The study was funded by Novartis.

Summary of the published literature on models for asthma

The published literature on modelling asthma and asthma treatment is sparse, and is not relevant to the development of a model to consider the cost-effectiveness of ICS therapy in a UK context using secondary data.

The studies identified are all based on different approaches. Two of the studies are based on specific clinical trial data. One of these studies uses individual patient level data,[254] whereas the other uses specific trial data for a severe patient treatment group. One of the models is dependent on the validity of a specific asthma utility measure (ASUI),[293] which involves specific trial data for that measure of asthma control. The APM is a general generic model, but it is based on the use of lung impairment alone, and is dependent on the regression equations estimated to link utility, symptom days and acute events with specific measures of FEV_1 % predicted. The APM is also presented with data specific to US patients for exacerbation events.

Appendix 9

Review of studies reporting health state utility values

A literature search was undertaken to identify studies reporting health state utility values associated with defined asthma health states using the strategy outlined in Appendix 3. The search, together with information from experts and the industry submissions, identified 19 studies potentially to provide health state values for specific asthma health states.[30,294,296–310]

The majority of the identified studies did not provide estimates of health state values by different levels of asthma control (e.g. well-controlled asthma, poorly-controlled asthma). Most commonly, studies presented an estimate of the mean health state value for the sample used in the study or trial. Only four studies were identified that presented estimates by either level of asthma control[254,310] level of FEV_1 % predicted[294] or used a multi-attribute system to characterise symptoms and control measures.[306] These four studies and the health state values presented are outlined in the following section.

Neumann and colleagues[294] presented health state values for asthma by level of FEV_1 % predicted. This was available as a published abstract only. The study was undertaken to inform the asthma model presented by Paltiel and colleagues;[292] however, the full details of the utility study remain unpublished and there is an absence of detail on the methods used. The study undertaken used a convenience sample of 100 adults who had drug therapy indicative of asthma and self-reported asthma. Health state values from a range of valuation techniques are reported by FEV_1 % predicted strata (<60, 60–80, >80), and for the total sample, as in *Table 102*.

TABLE 102 *Health state values for asthma presented by Neumann and colleagues[294]*

FEV_1 %	SG	TTO	RS	HUI3	ASUI
<60 (*n* = 26)	0.86	0.66	0.55	0.49	0.49
60–80 (*n* = 33)	0.93	0.82	0.65	0.58	0.69
>80 (*n* = 41)	0.92	0.90	0.72	0.61	0.66
Total (*n* = 100)	0.91	0.81	0.65	0.57	0.63

ASUI, Asthma Symptom Utility Index; HUI3, Health Utility Index Mark 3; RS, rating scale; SG, standard gamble; TTO, time trade-off.

The limited methodological information provided in the abstract indicates that regression modelling between FEV_1 % predicted and health state value was undertaken. This resulted in an equation (functional relationship), cited in Paltiel and colleagues,[292] where TTO (health state value) = $0.521 + (0.003958 \times FEV_1$ % predicted). This equation provides estimates of 0.838, 0.798 and 0.758 for FEV_1 % predicted of 80, 70 and 60%, respectively. However, it is not possible to consider the methodological robustness of this study, given the lack of transparency in the methods employed.

Chiou and colleagues[306] developed a multi-attribute outcome measure for children with asthma [the Pediatric Asthma Health Outcome Measure (PAHOM)], and present health state values for states defined by the multi-attribute matrix of symptoms (three levels), emotion (two levels) and activity (two levels). The study presents values elicited using the VAS and the standard gamble (SG) valuation techniques from a sample of adults in the USA (n = 114). The published study does not provide detail on the selection of the sample, therefore it is assumed to be a convenience sample. The health states that were used for valuation purposes were derived from a review of the literature and consultation with experts. The adult respondents were asked to respond for children.

The matrix developed comprised 12 health states. However, two of these states were removed for the preference weight survey as they were deemed implausible (unnecessary), and the remainder were used in the VAS survey. Only five health states were valued using the SG technique, and therefore a power function was used to transform the VAS values to an SG utility value. The values presented in the study for VAS, SG and transformed SG utility (SG power function) may be interpreted in the context of level of asthma control (e.g. using the level of symptoms). For example, where the symptom domain is at level 2, "the child has tightness in the chest, shortness of breath, coughing, and wheezing, …", this may reflect a state of poor asthma control, and it is valued at 0.79 using the VAS and 0.93 using the SG approach. At level 3 on the symptom score, "the child has a severe breathing problem and must go to the hospital or visit a doctor", and this state

(combined with emotional problems and problems with activities) is valued at 0.03 using VAS and 0.65 using the SG approach. This latter state is classed as the worst state in the multi-attribute matrix. However, this study may have limitations due to the design of the health state classification system or the way in which the preferences were elicited (e.g. context and framing effects, proxy values), but does present some indication of values for the health states presented.

Briggs and colleagues[263] present CEA relevant to an economic evaluation undertaken alongside the GOAL trial.[234] The RCT did not include a utility measure as part of its design, but did include assessment using the AQLQ over time. The study by Briggs and colleagues uses the AQLQ data from the trial and translates these data into a utility score via a mapping algorithm (which converts the AQLQ health status data into a single index utility score). Briggs and colleagues do not provide information on the mapping algorithm used (which remains unpublished), with the only explanation of methods being cited as a personal communication with the research team responsible for the algorithm. Briggs and colleagues used the data mapped to utility scores to undertake regression analysis that allowed utility scores to be associated with the asthma control status observed in the trial. The analysis used a utility value of 0.902 for total asthma control (with the states defined according to GINA guidelines).[2] Utility decrements were then applied for the state of "well-controlled" asthma (–0.045), "not well-controlled" asthma (–0.104) and for an exacerbation event (defined as deterioration in asthma requiring treatment with an oral corticosteroid, an ED visit or hospitalisation) (–0.216). For UK analysis the study suggests that each health state is subject to an additional utility value of 0.044 (based on regression results).

DeWilde and Turk[310] present a modelling study that estimates the cost-effectiveness of omalizumab, a new monoclonal antibody therapy for severe persistent asthma. In their study they use health states of daily asthma symptoms ("day to day asthma"), two exacerbation related states and death states. The exacerbation health states were "clinically significant" asthma exacerbations (CS) and "clinically significant severe" asthma exacerbations (CSS). The CS state is defined as worsening of asthma symptoms requiring treatment with systemic corticosteroids. The CSS state is defined as CS but also with patients PEF or FEV_1 less than 60% of personal best. The health state utilities used for these exacerbation states were 0.572 for CS and 0.326 for CSS. These exacerbation utilities were based on EQ-5D data from UK patients; however, the patient numbers were small (very small for CSS): for CS $n = 21$ and for CSS $n = 5$. Dewilde and Turk discuss a range of possible utility values for the "day to day asthma" state. The health state values for this state following treatment (ST) were (1) a mean of 0.669 ($n = 169$) when data were mapped indirectly from AQLQ values and (2) 0.784 ($n = 166$) when using data from a direct utility study (Yang and colleagues, 2006; unpublished discussion paper).

Overall, the general literature on health state values (utilities) for asthma health states is sparse and undeveloped. Many of the studies identified suggest that when asthma is well controlled it has only a small impact on HRQoL (i.e. values are only marginally different from full health). However, the studies outlined generally use techniques (e.g. VAS, TTO, SG) that provide values on an interval scale, and these should not be interpreted as being derived from a ratio scale. Therefore, it can be suggested that the prime interest is the interval (increment) between health states values, and not the absolute values themselves. From the three studies identified in the present review, Briggs and colleagues[254] report a difference (increment) of 0.104 between asthma health states of "total control" and "not well controlled". Neumann and colleagues[294] indicate an increment/decrement of 0.14–0.17 between well-controlled (80 FEV_1 % predicted) and poorly controlled (<60 FEV_1 % predicted), based on the valuation techniques of either SG, TTO or rating scale. This difference is much smaller when comparing those with FEV_1 % predicted of >80 with those in a range 60–80. DeWilde and Turk[310] present estimates that suggest a difference of around 0.10–0.22 for the health states of "daily symptoms" and "clinically significant non-severe exacerbation"; however, the latter state may not map directly to a definition of poor control. Values presented by Chiou and colleagues[306] indicate a decrement of between 0.07 and 0.13 for health states that may reflect poor control, compared with no problems on symptom, emotion and activities scales. Further findings presented also indicate a decrement of between 0.22 and 0.28 when comparing states that could be interpreted as "poor control" and states that require a hospital visit (possible severe exacerbation state). Briggs and colleagues[254] also report a comparable decrement of 0.216 for an exacerbation (defined as deterioration in asthma requiring treatment with an oral corticosteroid, an ED visit or hospitalisation). DeWilde and Turk[310] use utility data that reflect a difference of 0.246 between non-severe exacerbation and severe exacerbation.

Appendix 10

The PenTAG asthma model

Methods

Model structure

A Markov state transition model for asthma treatment was developed in Microsoft Excel (Microsoft, Redmond, WA, USA). *Figure 32* presents an influence diagram of the model structure showing the five represented states as described below.

1. **Controlled asthma**: patients who are undergoing the prescribed treatment regimen who do not experience any exacerbations during the modelled cycle.
2. **GP/self-managed exacerbations**: patients who experience at least one exacerbation during the model cycle and whose management of this is achieved either through treatment or advice in general practice or through application of self-care and self-administered medication. Exacerbations are defined as a worsening of asthma control such that at least one course of oral steroids is required.
3. **Hospital exacerbations**: a cycle in which a patient experiences an exacerbation which requires either attendance at an A&E Department or inpatient admission and care within a hospital. Exacerbations are defined as a worsening of asthma control such that at least one course of oral steroids is required.
4. **Treatment failure**: a change in the treatment regimen due to treatment failure within the defined treatment context of the model. For example, this could entail stepping up from Step 2 to Step 3 treatment as defined by the BTS/SIGN Guideline. A separate stratum of the model is used (using a replica of the generic framework) to assess the likely dynamics of treatment after change and hence derive cost and utility estimates for patients entering this state.
5. **Step down**: a change in the treatment regimen due to sustained control within the defined treatment context of the model leading to a reduction in the potency of the treatment used. For example, this could entail stepping down from Step 3 to Step 2 treatment as defined by the BTS/SIGN Guideline. This is an 'absorbing state' in the model and is assigned an aggregate value for cost and utility.

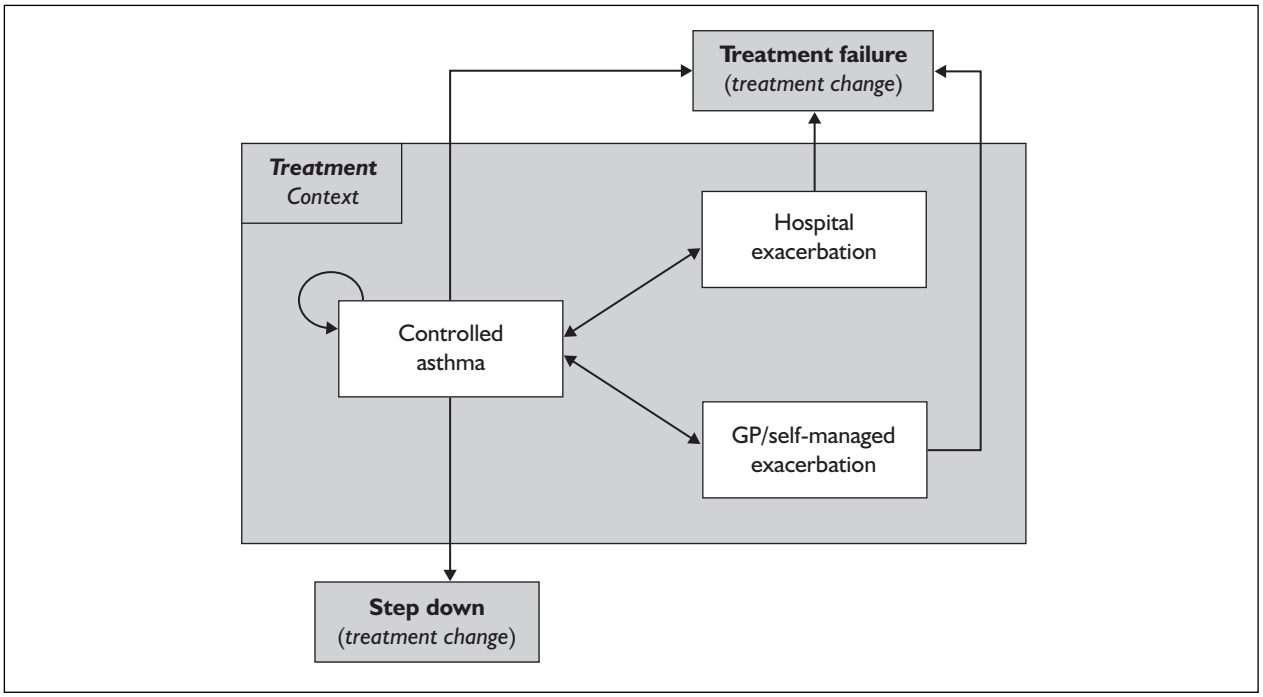

FIGURE 32 *Influence diagram showing the generic model framework*

Model outputs

The primary outputs of the model were the incremental costs and benefits between the compared arms. Costs and benefits are discounted at 3.5% per year in accordance with current UK Treasury advice. All costs were assessed from the perspective of the UK NHS and PSS. Half-cycle correction was not applied to the outputs at each cycle since it is not relevant for such a short cycle length.

Given the uncertainty in model parameters, PSA provides the most meaningful outputs. Summary findings from the PSA are reported below for each investigated research question using scatter plots of ICERs and cost-effectiveness acceptability curves (CEACs).

Results

Research question 3a(i) – BUD/FF versus ICS only

Model inputs

Resource use and costs for the controlled asthma state only comprised maintenance medication costs, calculated using the specific mix of ICS or BUD/FF products and doses used in the trials from which the effectiveness transition probabilities were obtained (*Table 103*). The cost for the GP/self-managed exacerbations included some patients (20% in base case) who self-administered a short course of oral steroids, and the remainder who had oral steroids plus an unplanned primary care attendance [either in-hours (80%) or out-of-hours (20%)]. The cost of a hospital-managed exacerbation included both admitted inpatient and A&E only use of hospital services, and at least a long course of oral steroids. The inpatient cost was separately estimated for those who were admitted via GP or A&E and who had a stay in an intensive care ward. Services prior to (ambulance/paramedic) and following (GP or outpatient) the hospitalisation or A&E attendance were also factored in. Many of these assumptions drew on patient administration data from the Royal Devon and Exeter Hospital and the Southampton University Hospital supplemented by expert advice where no other data were available.

Probabilistic sampling for costs in the PSA used triangular distributions using the lower and upper limits as specified in *Table 103*.

Utility values for the defined health states were obtained from the 2006 study by DeWilde and Turk,[310] since they more closely matched our defined health states than other studies containing utility estimates by health state or lung function (e.g. by Paltiel and colleagues[292] or Briggs and colleagues[254]) (*Table 104*). While it is acknowledged that these utility values for exacerbation states are lower than in some other studies (probably because the source study involved patients with severe persistent asthma), the utility decrement between the controlled and the exacerbation states should still be appropriate for patients with milder disease.

Probabilistic sampling for utilities in the PSA used beta distributions using the standard errors in

TABLE 103 *Model inputs (BUD/FF versus higher dose ICS): costs (£/cycle)*

	Central estimates		Lower limit		Upper limit	
State	**ICS only**	**BUD/FF**	**ICS only**	**BUD/FF**	**ICS only**	**BUD/FF**
Step down	1.00	1.00	0.00	0.00	2.00	2.00
Controlled asthma state	3.69	4.04	2.59	3.85	5.18	4.43
GP/self-managed exacerbation	22.93	23.28	18.25	18.68	27.62	27.89
Hospital exacerbation	1130.14	1130.49	369.66	370.01	1890.62	1890.97

TABLE 104 *Model inputs (BUD/FF versus higher dose ICS): utility values*

State	ICS only and BUD/FF	Standard error
Step down	0.78	0.00877
Controlled asthma state	0.78	0.00877
GP/self-managed exacerbation	0.57	0.07753
Hospital exacerbation	0.33	0.14579

Table 104. Beta distributions constrain sampled utility values between 0 and 1 during the simulation.

Transition probabilities from the controlled to the two exacerbation states were based on the exacerbation rates reported in three trials of BUD/FF versus higher dose BUD, by O'Byrne and colleagues,[231] Rabe and colleagues[311] and Scicchitano and colleagues[232] (*Table 105*). For the central estimate we used a weighted average of all identified values, using patient-weeks (to reflect both study duration and cohort size) as the weighting factor. The decision to use exacerbation rates as the sole basis for the main transition probabilities in the model was made after considerable analysis of trial data to assess the feasibility of using other asthma outcomes to 'drive' the model (notably, FEV % predicted). Transition probabilities to treatment failure were based on reported rates of discontinuation due to lack of efficacy or worsening asthma, in five trials[228–231,311] (again using weighted averages based on patient-weeks).

Probabilistic sampling for transition probabilities in the PSA used beta distributions using the standard errors in *Table 105*. Beta distributions constrain sampled utility values between 0 and 1 during the simulation.

Simulation outputs

The summary results of the PSA analysis are shown in a cost-effectiveness plane scatter plot in *Figure 33*. Each point shows the output from each trial of the Monte Carlo simulation.

The plot reveals the wide spread of outputs caused by the parameter uncertainty in the model. The mean value reflects the base case output of a very small QALY gain associated with the BUD/FF arm against its ICS-only comparator. The output shows very little cost differential between arms.

The CEAC is plotted in *Figure 34* and shows the probability that BUD/FF is cost-effective for a range of willingness to pay (WTP) thresholds. This shows that there is a >50% probability that BUD/FF is cost-effective at a WTP threshold less than £30,000 per QALY. However, a great deal of uncertainty is apparent in these outputs. Even at relatively high WTP thresholds, the confidence that BUD/FF represents the more cost-effective option does not exceed 70%. This uncertainty in these results is reflected in a different way in the variable results of the previously presented trial-specific cost–consequence analyses.

Probabilistic analysis of utility in the controlled asthma state

A further simulation analysis was performed to examine the effect of changes to the key variable of utility in the controlled asthma state for BUD/FF. An extra stochastic term was added to the model, allowing randomly sampled inter-arm variability in the utility of the controlled asthma state. The possible range of variation was gradually increased over a series of nine Monte Carlo simulations (each of 1000 trials). The resulting CEACs are presented in a three-dimensional array in *Figure 35* (the base case CEAC – no inter-arm variation – is given by the central curve).

This analysis shows the extreme sensitivity of model outputs to any differential utility between the arms in the controlled asthma state. The importance of this variable in determining the cost-effectiveness of an intervention in this context

TABLE 105 *Model inputs (BUD/FF versus higher dose ICS): transition probabilities*

	Central estimates		Standard error	
Description	**ICS only**	**BUD/FF**	**ICS only**	**BUD/FF**
Control to step down	0.00203	0.00203	0.001287	0.001287
Control to GP/self-managed exacerbation	0.00590	0.00419	0.000131	0.001397
Control to hospital exacerbation	0.00061	0.00050	0.000184	0.000162
GP/self-managed exacerbation to treatment change	0.4	0.2	0.114798	0.102043
Hospital exacerbation to treatment change	0.75	0.3	0.127553	0.076532
Controlled state to treatment change	0.00044	0.00027	0.000088	0.000052
Proportional change on failure of BUD/FF to ICS only[a]	–	0.15	–	0.063777

[a] Patients who have treatment failure in the BUD/FF arm of the model are either changed to a regimen based on the ICS-only treatment or to a regimen based on a higher dose of BUD/FF. This data parameter therefore determines the proportion who follow the first of these alternative pathways (the remainder receive higher dose BUB + FF). All patients who fail in the ICS only arm are 'stepped-up' to treatment with BUD/FF.

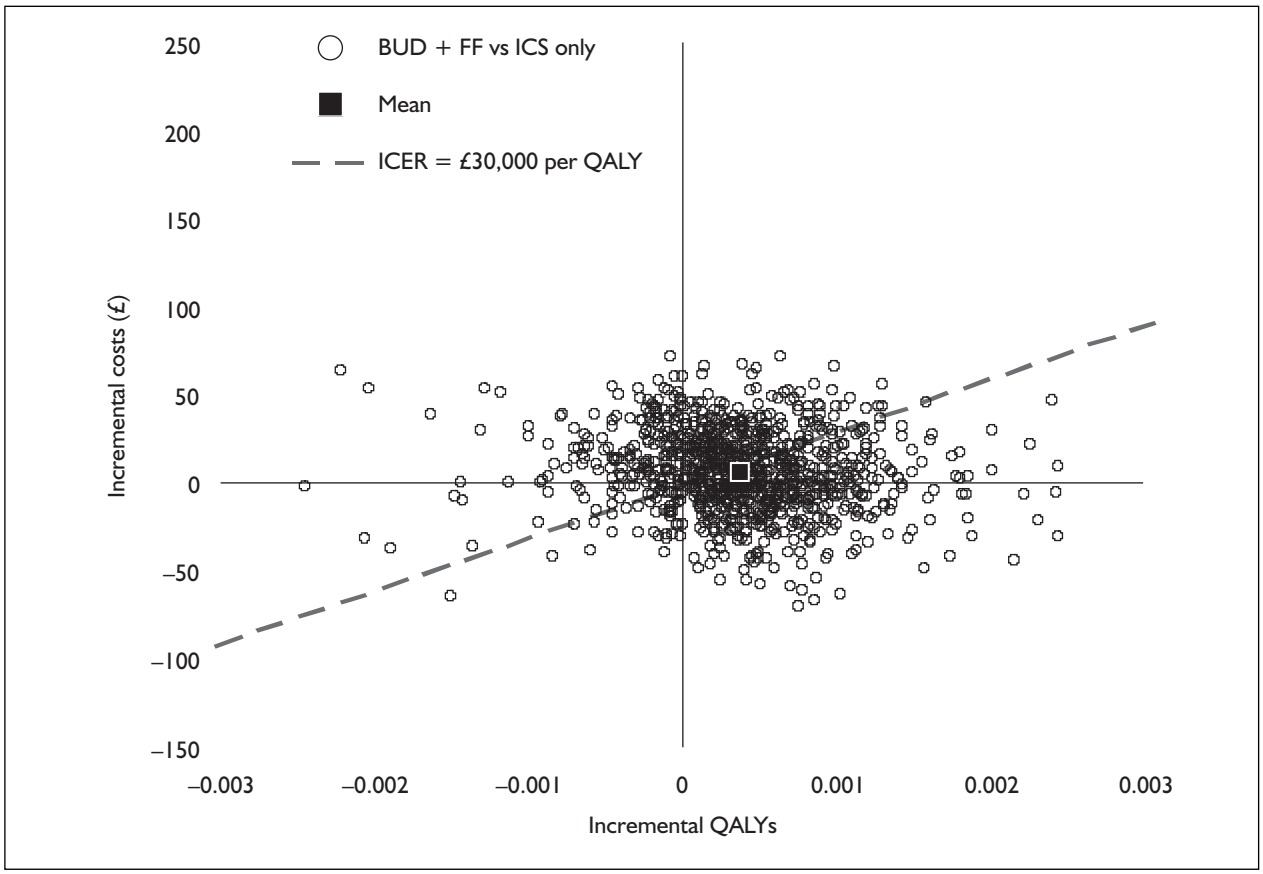

FIGURE 33 *BUD/FF versus higher dose ICS: probabilistic cost-effectiveness plane scatter plot, showing incremental cost-effectiveness of BUD/FF versus higher dose ICS in 1000 Monte Carlo simulations*

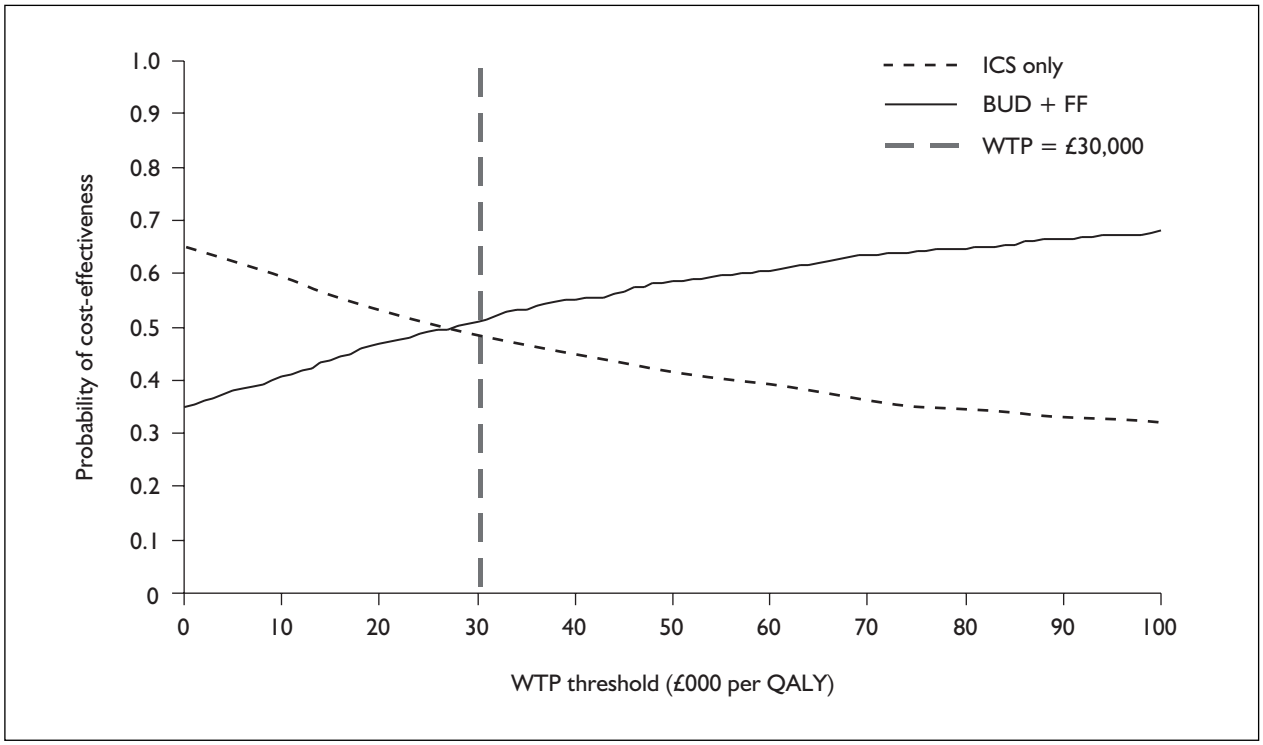

FIGURE 34 *BUD/FF versus higher dose ICS: CEAC, showing the probability that BUD/FF is cost-effective when compared with higher dose ICS at WTP thresholds of up to £100,000 per QALY gained; based on simulation output for 1000 Monte Carlo simulations*

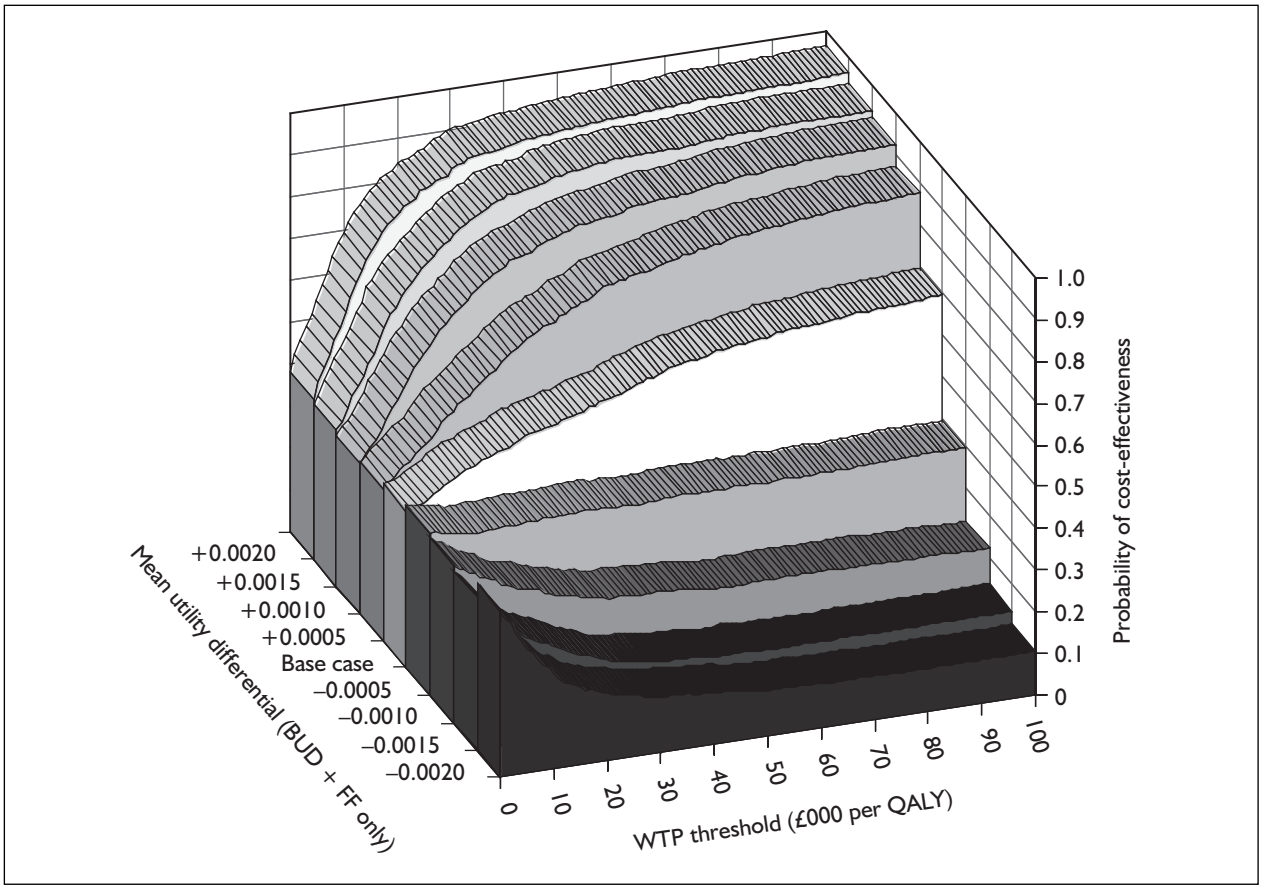

FIGURE 35 *BUD/FF versus higher dose ICS: cost-effectiveness acceptability array (utility differential), showing the impact of utility differential on the probability of cost-effectiveness (maximum utility differential gives upper bound of range from which inter-arm differential was sampled in each simulation); based on 1000 Monte Carlo simulations per curve*

illustrates the potentially major impact of quality of life improvements for asthma patients in periods without exacerbations.

Probabilistic analysis of costs in the controlled asthma state

The effect of changes to costs in the controlled asthma state for FP/SAL was examined using a differential factor applied as a fixed multiplier for the sampled cost value for each simulation. This analysis generated the array of CEACs shown in *Figure 36*.

Research question 3a(ii) – FP/SAL versus ICS only

Model inputs

Resource use and costs for the different states are calculated in the same way as described for the comparison between BUD/FF and higher dose FF, except that the medication costs are calculated using the specific mix of ICS or FP/SAL products and doses used in the trials from which the effectiveness transition probabilities were obtained (*Table 106*).

Probabilistic sampling for costs in the PSA used triangular distributions using the lower and upper limits as specified in *Table 106*.

Utility values for health states in this comparison were obtained from the cost-effectiveness study by DeWilde and Turk[310] (as for BUD/FF versus higher dose ICS) (*Table 107*).

Probabilistic sampling for utilities in the PSA used beta distributions using the standard errors in *Table 107*. Beta distributions constrain sampled utility values between 0 and 1 during the simulation.

Transition probabilities were difficult to estimate because none of the seven relevant trials that were identified reported exacerbation rates.[221–225,312,313] Transition probabilities from the controlled to the two exacerbation states therefore had to be based on the AE data reported by GlaxoSmithKline in four trials of FP/SAL versus higher dose BUD or FP (study summaries in the GSK online trial register for: Bateman and colleagues,[312]

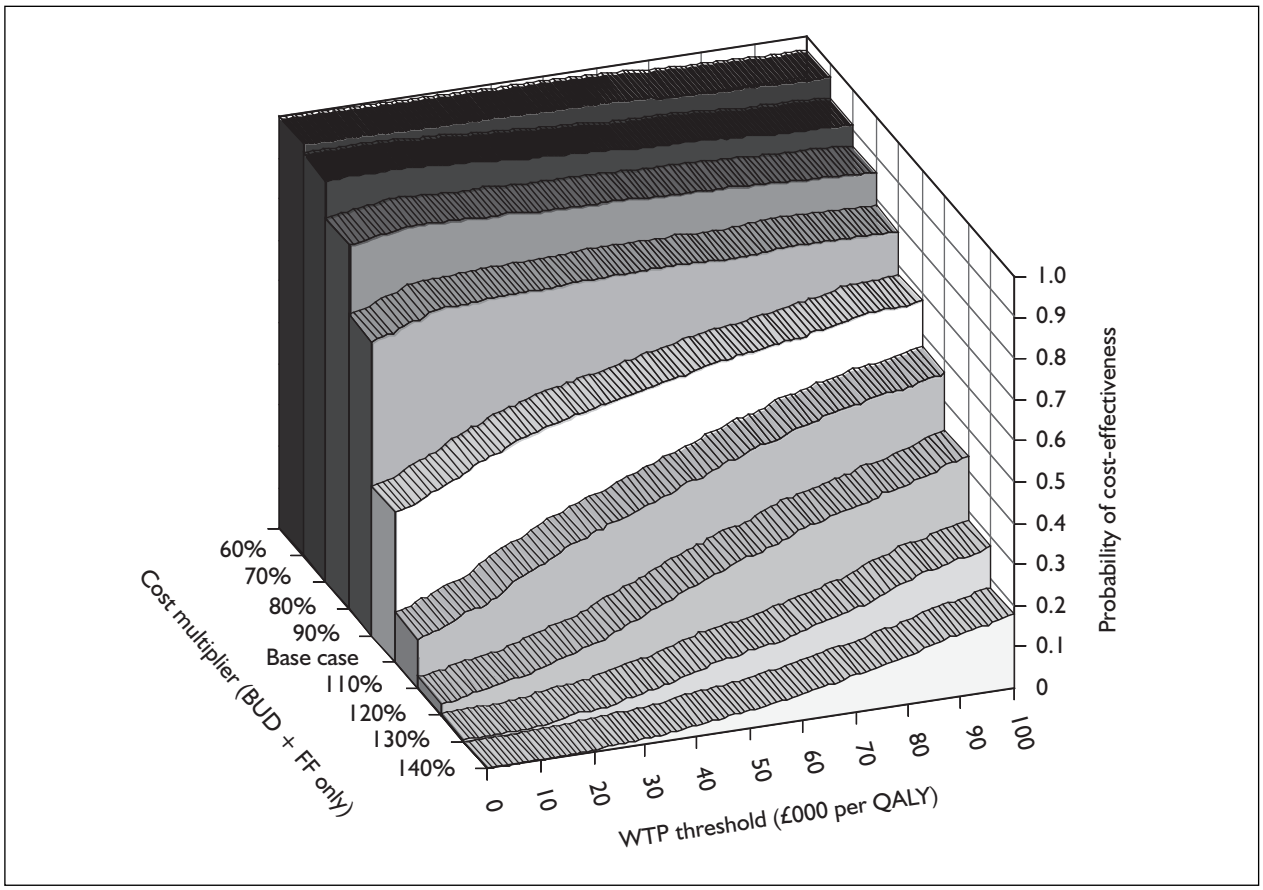

FIGURE 36 *BUD/FF versus higher dose ICS: cost-effectiveness acceptability array (cost differential), showing the impact of cost differential on probability of cost-effectiveness; based on 1000 Monte Carlo simulations per curve*

TABLE 106 *Model inputs (FP/SAL versus higher dose ICS): costs (£/cycle)*

	Central estimates		Lower limit		Upper limit	
State	**ICS only**	**FP/SAL**	**ICS only**	**FP/SAL**	**ICS only**	**FP/SAL**
Step down	1.00	1.00	0.00	0.00	2	2.00
Controlled asthma state	7.66	7.99	4.96	7.28	10.36	8.55
GP/self-managed exacerbation	26.91	27.23	21.65	22.61	32.16	31.86
Hospital-managed exacerbation	1134.11	1134.44	373.63	373.96	1894.59	1894.92

TABLE 107 *Model inputs (FP/SAL versus higher dose ICS): utility values*

State	ICS only and FP/SAL	Standard error
Step down	0.78	0.00877
Controlled asthma state	0.78	0.00877
GP/self-managed exacerbation	0.57	0.07753
Hospital-managed exacerbation	0.33	0.14579

Bergmann and colleagues,[222] Jenkins and colleagues[223] and Johannson and colleagues[224]), supplemented by data presented in an analysis by Matz and colleagues[314,315] (*Table 108*). As before, for the central estimate we used a weighted average of all identified values using patient-weeks as the weighting factor. Transition probabilities to treatment failure were based on reported rates of discontinuation due to lack of efficacy or worsening asthma, in three trials[221,223,225]

TABLE 108 *Model inputs (FP/SAL versus higher dose ICS): transition probabilities*

Description	Central estimates		Standard error	
	ICS only	FP/SAL	ICS only	FP/SAL
Control to step down	0.00203	0.002026	0.001287	0.001287
Control to GP/self-managed exacerbation	0.00713	0.003786	0.000858	0.000616
Control to hospital exacerbation	0.000196	0.000555	0.000174	0.000256
GP/self-managed exacerbation to treatment change	0.4	0.2	0.114798	0.102043
Hospital exacerbation to treatment change	0.75	0.3	0.127553	0.076532
Controlled state to treatment change	0.00191	0.00112	0.000405	0.000312
Proportional change on failure of FP/SAL to ICS only[a]	–	0.15000	–	0.063777

[a] Patients who have treatment failure in the FP/SAL arm of the model are either changed to a regimen based on the ICS-only treatment or to a regimen based on a higher dose of FP/SAL. This data parameter therefore determines the proportion who follow the first of these alternative pathways (the remainder receive higher dose BUB + FF). All patients who fail in the ICS only arm are 'stepped-up' to treatment with FP/SAL.

(again using weighted averages based on patient-weeks).

Probabilistic sampling for transition probabilities in the PSA used beta distributions using the standard errors in *Table 108*. Beta distributions constrain sampled utility values between 0 and 1 during the simulation.

Simulation outputs

The summary results of the PSA analysis are shown in the cost-effectiveness plane scatter plot in *Figure 37*. Each point shows the output from each trial of the Monte Carlo simulation.

The scatter plot reveals the wide spread of outputs caused by the parameter uncertainty in the model, spanning all four quadrants of the cost-effectiveness plane. The mean value shows a very small utility gain associated with the FP/SAL arm against its ICS-only comparator, but also a small extra annual cost of FP/SAL.

The CEAC in *Figure 38* charts the probability that FP/SAL will be found to be cost-effective for a range of WTP thresholds. This shows that at a WTP of £20,000 per QALY the probability that BUD/FF is cost-effective is less than one-third, at £30,000 it is about 38% and the probability does not exceed 50% until the WTP value is over 65%. However, a great deal of uncertainty is apparent in these outputs, and the results should be viewed alongside the previously presented trial-specific cost–consequence analyses.

Probabilistic analysis of utility in the controlled asthma state

A further probabilistic simulation analysis was performed to examine the effect on the CEAC of changes to the key variable of utility in the controlled asthma state for FP/SAL. This analysis generated the array of CEACs shown in *Figure 39*.

This analysis shows that relatively small alterations to utility values in one arm of the model will affect cost-effectiveness outputs dramatically. In the CEAC representing a maximum utility differential of 0.002 (mean 0.001), the probability that FP/SAL provides the better value for money, when compared with ICS only, exceeds 50% at a WTP of £30,000 per QALY. A utility increment sampled in the range 0–0.004 for FP/SAL increases the same probability to around 68%. This means that, if FP/SAL could be shown to provide a day-to-day utility gain of 0.73 quality-adjusted days per year or more, we would expect it to appear cost-effective in our model.

Probabilistic analysis of costs in the controlled asthma state

In this comparison, an additional simulation analysis was performed to examine the effect of changes to costs in the controlled asthma state for FP/SAL. In this instance, the differential factor was applied as a fixed multiplier for the sampled cost value for each simulation. This analysis generated the array of CEACs shown in *Figure 40*.

Research question 5 – FP/SAL versus BUD/FF

Model inputs

Model inputs for this question are given in *Tables 109–111*.

Probabilistic sampling for costs in the PSA used triangular distributions using the lower and upper limits as specified in *Table 109*.

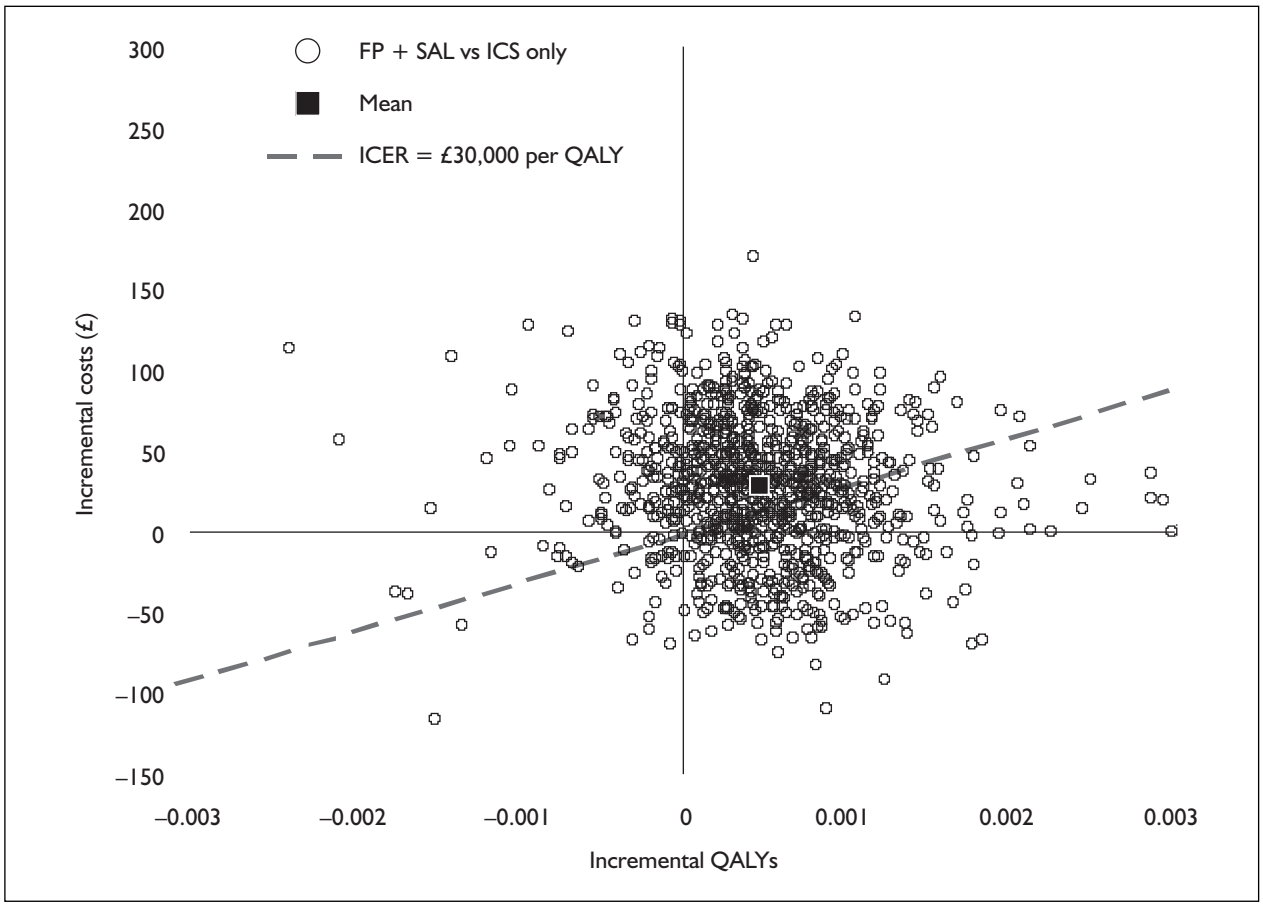

FIGURE 37 *FP/SAL versus higher dose ICS: probabilistic cost-effectiveness plane scatter plot, showing incremental cost-effectiveness of FP/SAL versus higher dose ICS in 1000 Monte Carlo simulations*

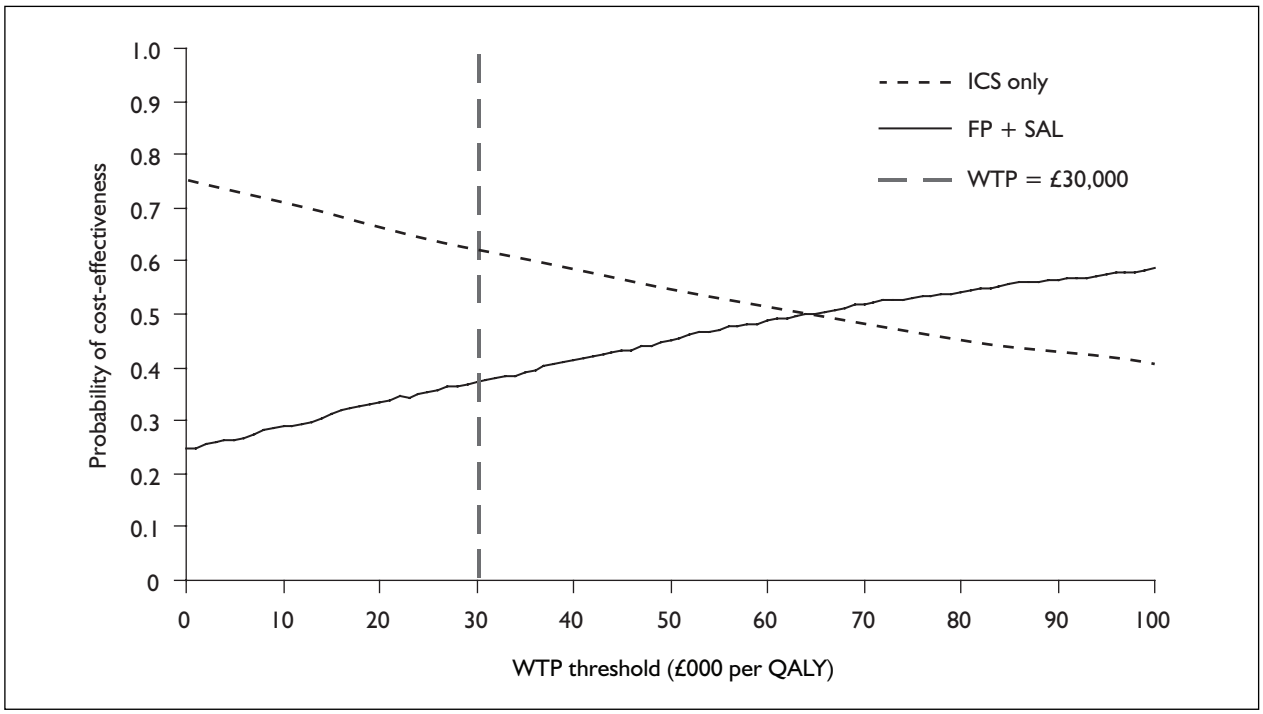

FIGURE 38 *FP/SAL versus higher dose ICS: CEAC, showing the probability that FP/SAL is cost-effective, when compared with higher dose ICS, at WTP thresholds of up to £100,000 per QALY gained; based on simulation output for 1000 Monte Carlo simulations*

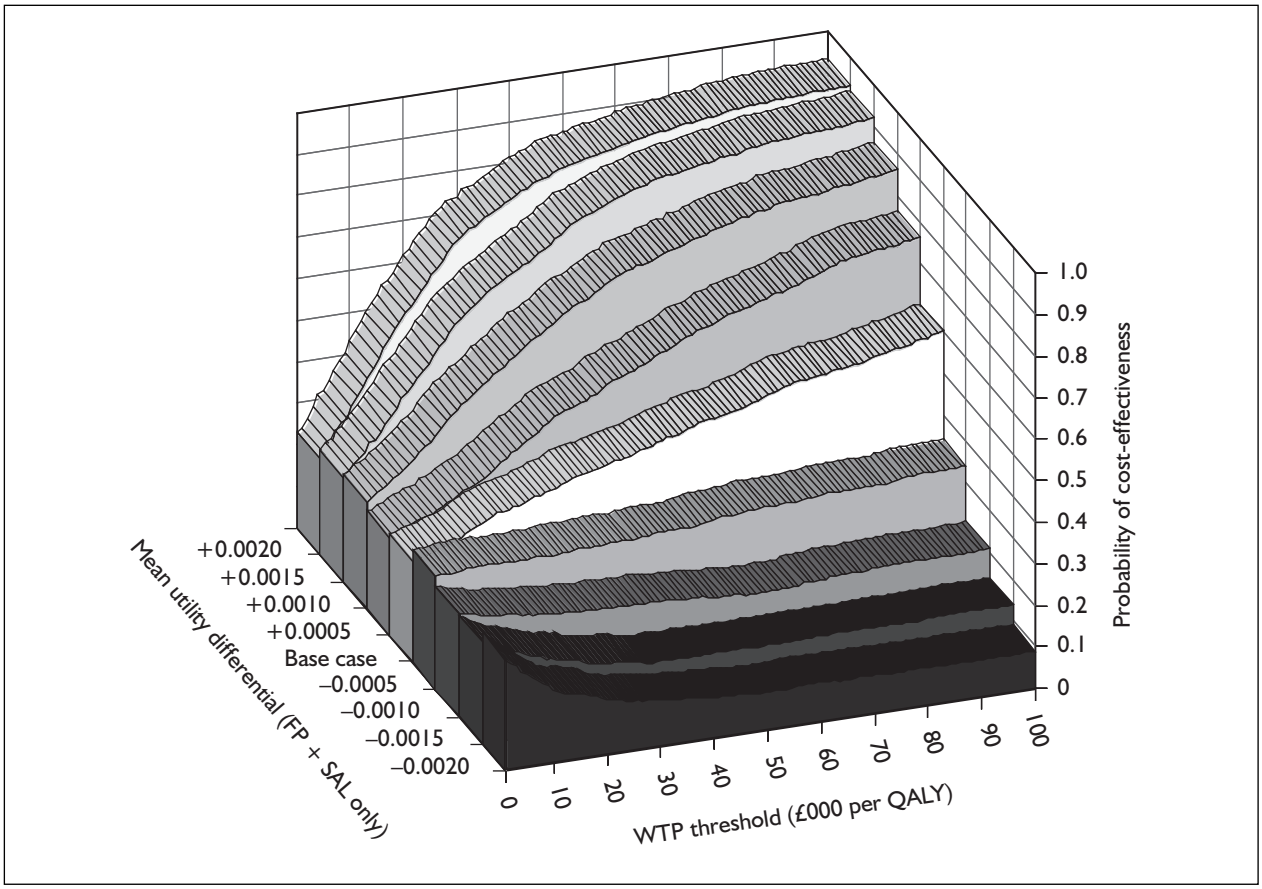

FIGURE 39 *FP/SAL versus higher dose ICS: cost-effectiveness acceptability array (utility differential), showing the impact of utility differential on probability of cost-effectiveness (maximum utility differential gives upper bound of range from which inter-arm differential was sampled in each simulation); based on 1000 Monte Carlo simulations per curve*

Probabilistic sampling for utilities in the PSA used beta distributions using the standard errors in *Table 110*. Beta distributions constrain sampled utility values between 0 and 1 during the simulation.

Probabilistic sampling for transition probabilities in the PSA used beta distributions using the standard errors in *Table 111*. Beta distributions constrain sampled utility values between 0 and 1 during the simulation.

Simulation outputs

The results of this analysis are shown in the cost-effectiveness plane scatter plot in *Figures 41*, where each point shows the output from each trial of the Monte Carlo simulation.

The ICER scatter plot reveals the wide spread of outputs caused by the parameter uncertainty in the model. The mean value reflects the deterministic output of very little differential between arms in terms of effectiveness, coupled with an apparent cost advantage in favour of BUD/FF. The cost parameters are therefore key to determining overall cost-effectiveness.

The CEAC is plotted in *Figure 42*. This charts the probability that FP/SAL will be found to be cost-effective for a range of WTP thresholds.

Probabilistic analysis of utility in the controlled asthma state

A further simulation analysis was performed to examine the effect of changes to the key variable of utility in the controlled asthma state for FP/SAL. This analysis generated the array of CEACs shown in *Figure 43*. This analysis confirms the importance of this variable in determining the cost-effectiveness of an intervention in this context.

Probabilistic analysis of costs in the controlled asthma state

In this comparison, an additional simulation analysis was performed to examine the effect of changes to costs in the controlled asthma state for

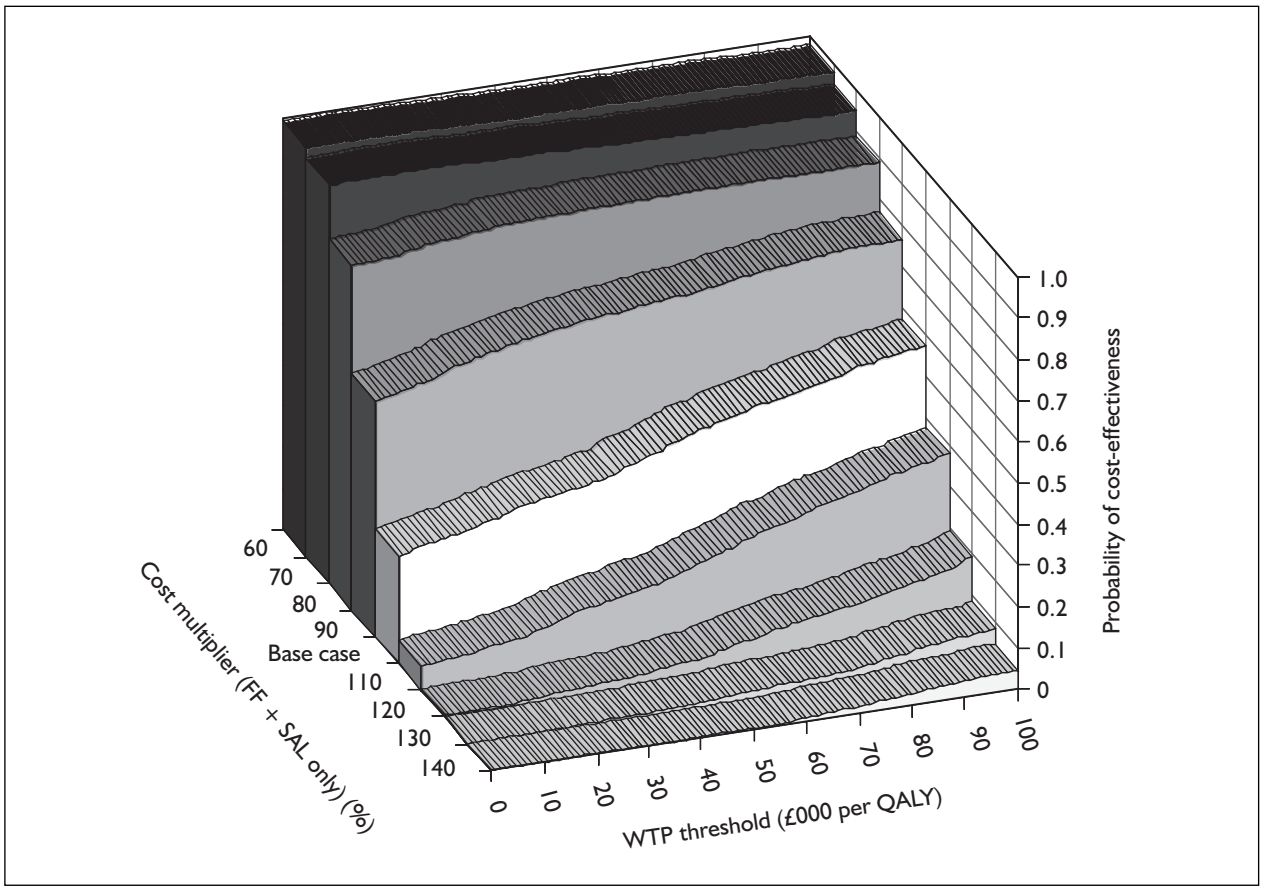

FIGURE 40 *FP/SAL versus higher dose ICS: cost-effectiveness acceptability array (cost differential), showing the impact of cost differential on probability of cost-effectiveness; based on 1000 Monte Carlo simulations per curve*

TABLE 109 *Model inputs (FP/SAL versus BUD/FF): costs (£/cycle)*

	Central estimates		Lower limit		Upper limit	
State	**BUD/FF**	**FP/SAL**	**BUD/FF**	**FP/SAL**	**BUD/FF**	**FP/SAL**
Step down	1.00	1.00	0.00	0.00	2.00	2.00
Controlled asthma state	7.43	8.62	4.43	7.28	8.87	9.55
GP/self-managed exacerbation	26.67	27.87	21.72	23.17	31.63	32.58
Hospital exacerbation	1133.88	1135.08	373.4	374.6	1894.36	1895.56

TABLE 110 *Model inputs (FP/SAL versus BUD/FF): utility values*

State	BUD/FF and FP/SAL	Standard error
Step down	0.78	0.00877
Controlled asthma state	0.78	0.00877
GP/self-managed exacerbation	0.57	0.07753
Hospital exacerbation	0.33	0.14579

FP/SAL. In this instance, the differential factor was applied as a fixed multiplier for the sampled cost value for each simulation. This analysis generated the array of CEACs shown in *Figure 44*.

This analysis confirms, in line with the ambiguity of the findings of the clinical effectiveness review, that differences in costs will always be crucial in determining the apparent cost-

TABLE 111 *Model inputs (FP/SAL versus BUD/FF): transition probabilities*

Description	Central estimates		Standard error	
	BUD/FF	FP/SAL	BUD/FF	FP/SAL
Control to step down	0.000986	0.000986	0.000418	0.000418
Control to GP/self-managed exacerbation	0.00458	0.00455	0.000131	0.001397
Control to hospital exacerbation	0.00054	0.00066	0.000184	0.000162
GP/self-managed exacerbation to treatment change	0.2	0.2	0.102	0.102
Hospital exacerbation to treatment change	0.3	0.3	0.0765	0.0765
Controlled state to treatment change	0.0001	0.00021	0.00004	0.00005

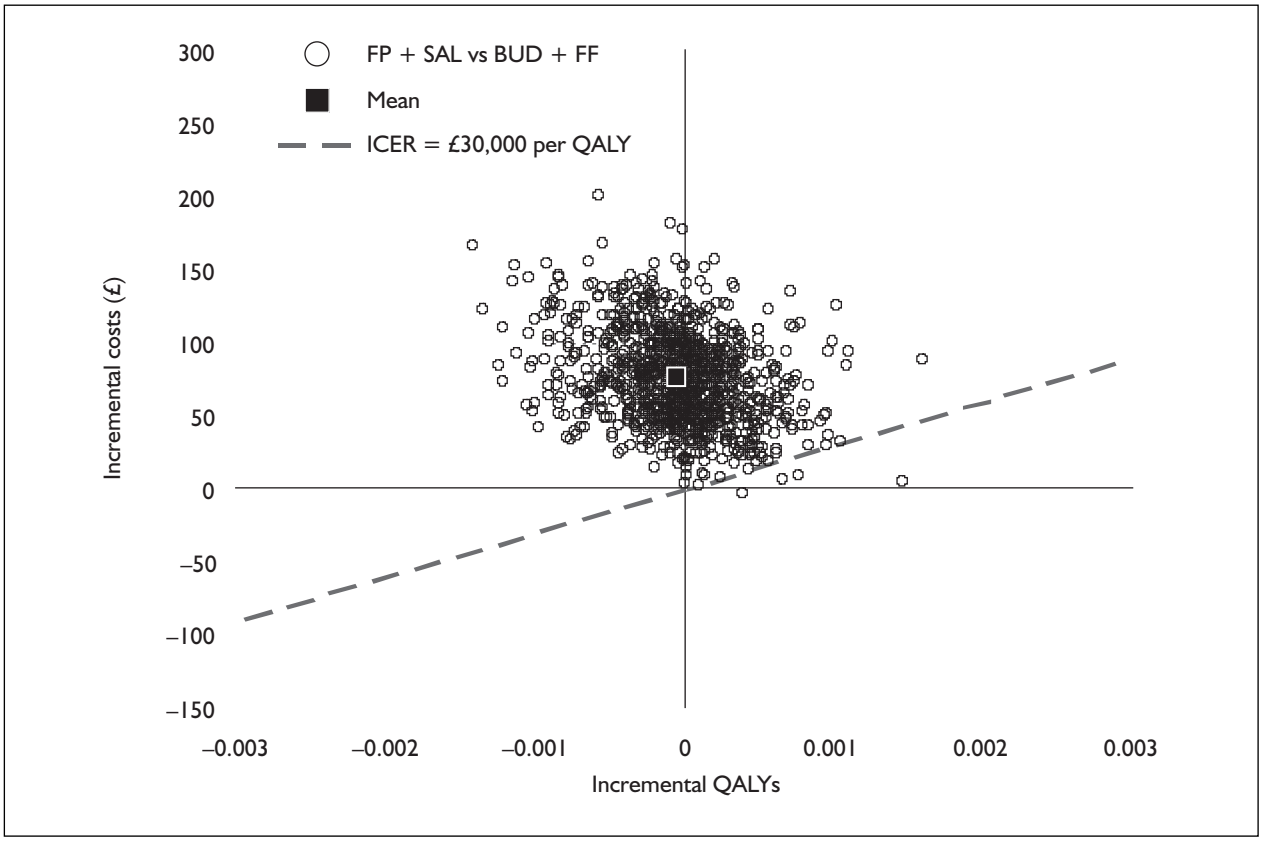

FIGURE 41 *FP/SAL versus BUD/FF: probabilistic cost-effectiveness plane scatter plot, showing incremental cost-effectiveness of FP/SAL versus BUD/FF in 1000 Monte Carlo simulations*

effectiveness of these two interventions. The very flat nature of each of the curves reflects the minimal effectiveness differential between the two treatments: given that there is so little to choose between them, on this count, the intervention that is simulated to be cheaper will dominate outputs regardless of WTP.

Discussion of model outputs

The following points summarise some of the main observations arising from the asthma model outputs for the comparisons as described above:

Context

In general, the model shows very little difference between the arms for all the comparisons investigated. Utility differences are particularly small. Cost differences between the arms rely on the cost assumptions used to derive central estimates. In all instances the uncertainty associated with the input parameters needs to be held paramount.

Model dynamics

The parameters of the controlled asthma state, where approximately 90% of population state occupancy resides during the 1-year model time

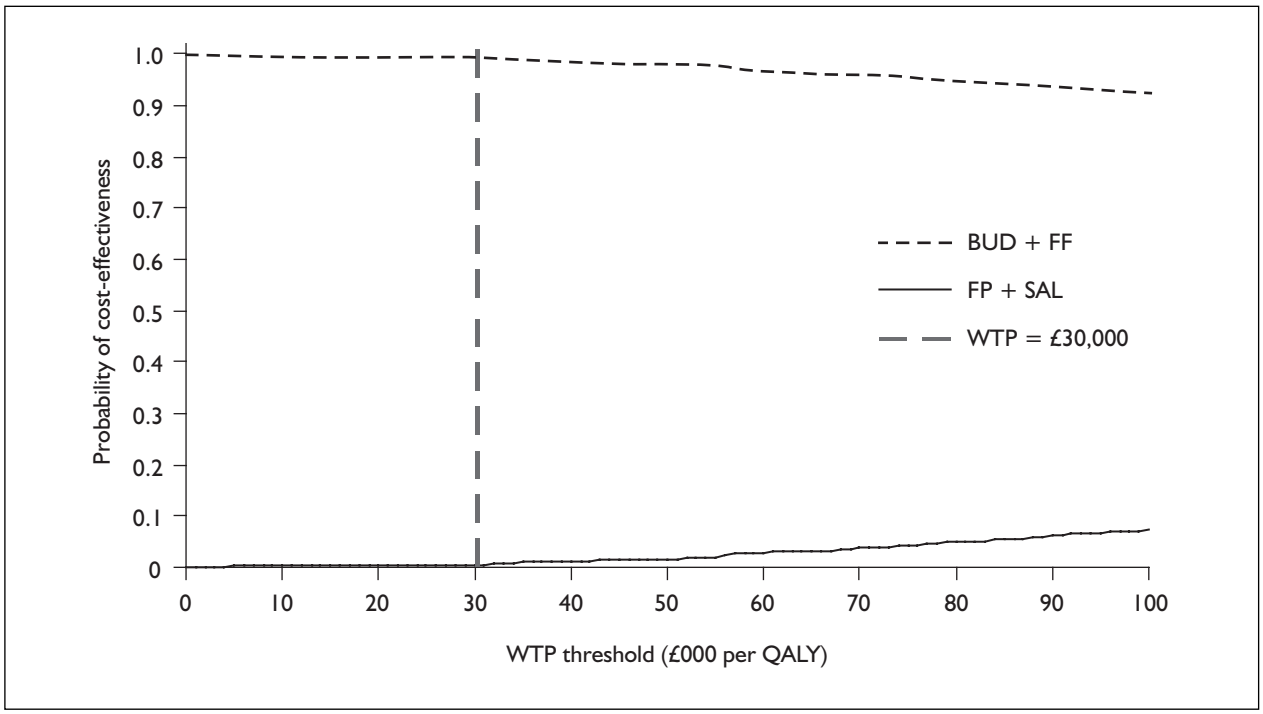

FIGURE 42 *FP/SAL versus BUD/FF: CEAC, showing the probability that FP/SAL is cost-effective, when compared with BUD/FF, at WTP thresholds of up to £100,000 per QALY gained; based on simulation output for 1000 Monte Carlo simulations*

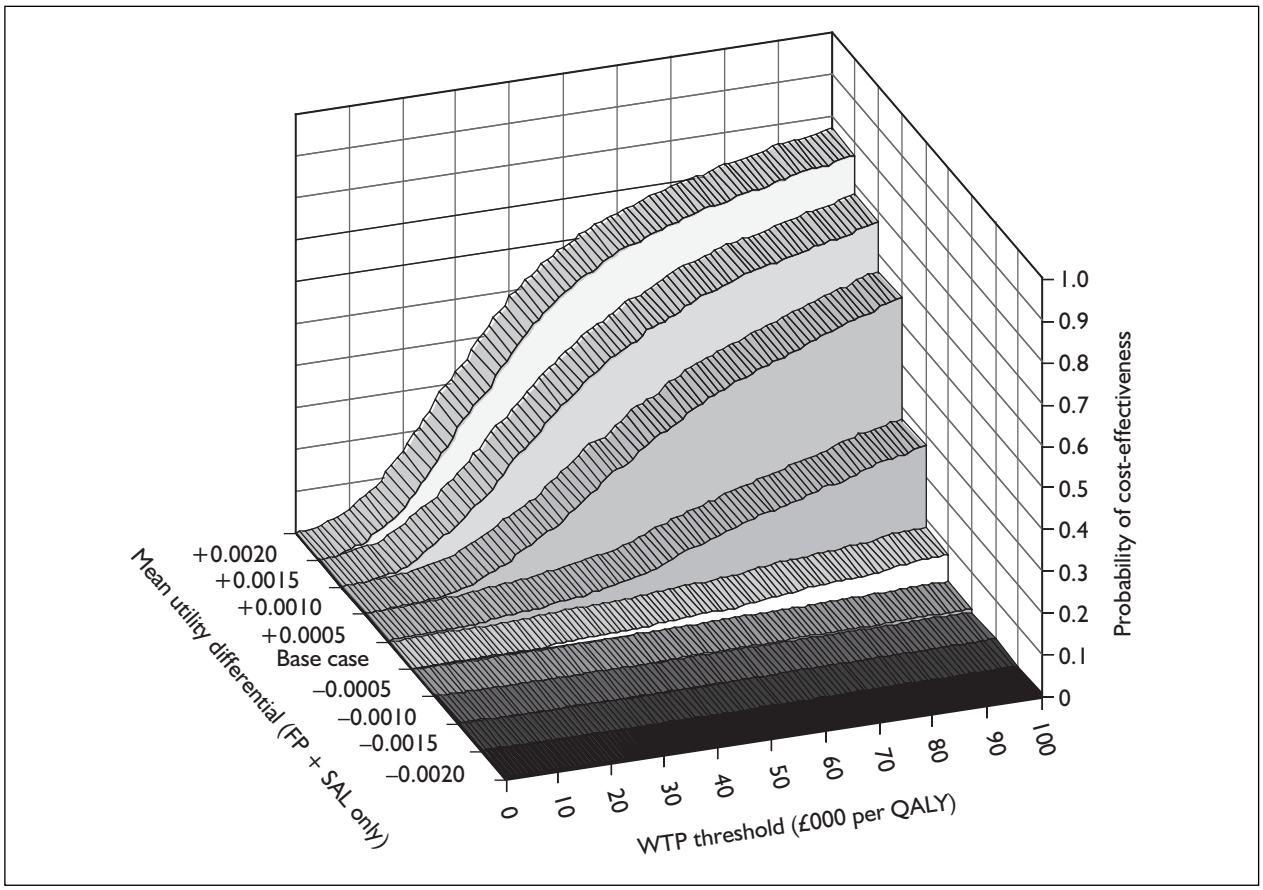

FIGURE 43 *FP/SAL versus BUD/FF: cost-effectiveness acceptability array (utility differential), showing the impact of utility differential on probability of cost-effectiveness (maximum utility differential gives upper bound of range from which inter-arm differential was sampled in each simulation); based on 1000 Monte Carlo simulations per curve*

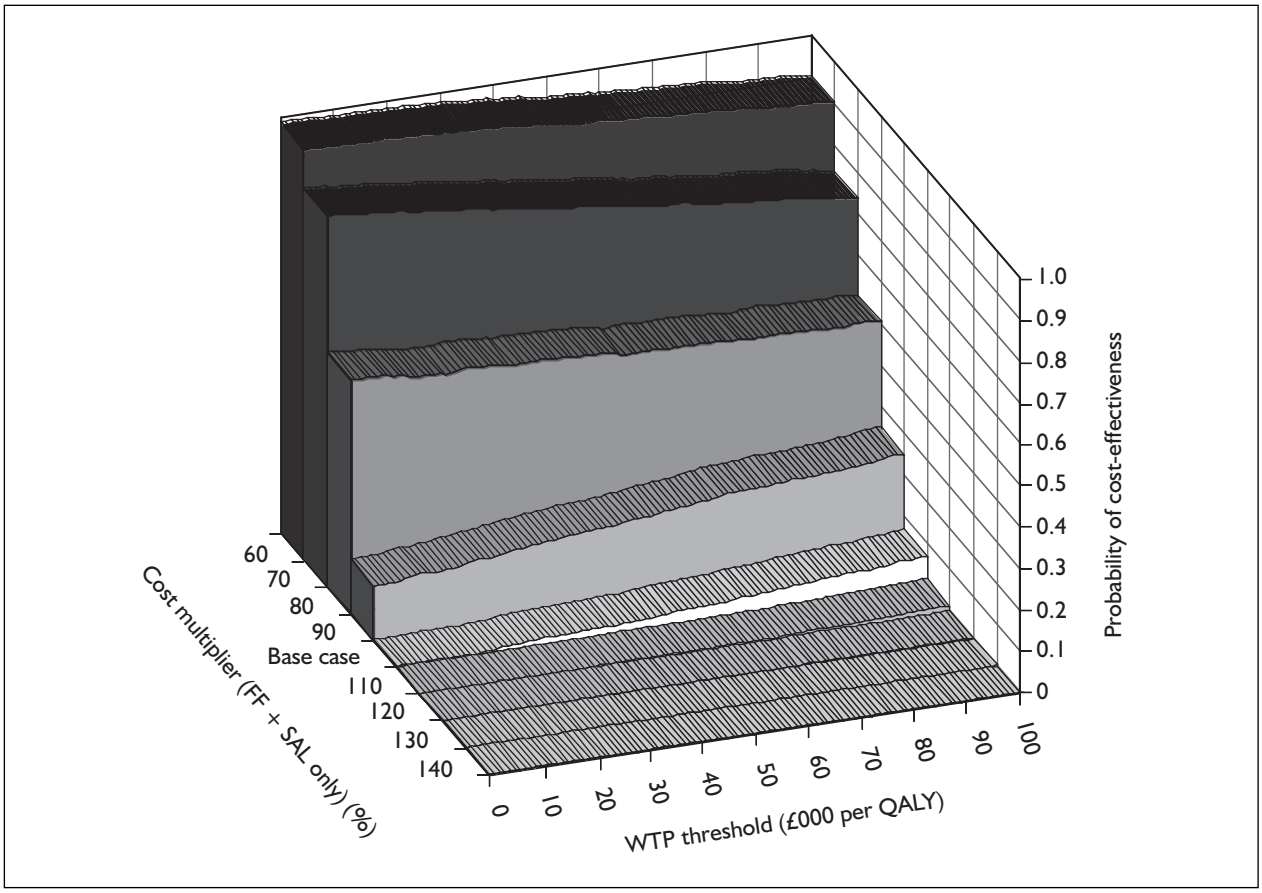

FIGURE 44 *FP/SAL versus BUD/FF: cost-effectiveness acceptability array (utility differential), showing the impact of utility differential on probability of cost-effectiveness (maximum utility differential gives upper bound of range from which inter-arm differential was sampled in each simulation); based on 1000 Monte Carlo simulations per curve*

horizon, are predominant in determining outputs.

Sensitivity to differences – especially in the controlled asthma state

For all comparisons, the model is highly sensitive to changes both in cost inputs and utility inputs affecting the controlled asthma state.

Utility sensitivities

The model is highly sensitive to any differential in utility in the controlled asthma state between the arms. Extremely small differences in utility levels between arms for this state radically alter the cost-effectiveness output. The implications of this finding suggest that if there is any evidence that a particular treatment provides a significant utility advantage over its comparator for controlled asthma, then that treatment is almost certain to be cost-effective.

Cost sensitivities

In all comparisons the model outputs are highly sensitive to changes in cost in the controlled asthma state, that is, the cost of the preventer medications themselves. This finding should be viewed in the context of the assumptions needed to derive cost estimates for each of the comparator treatments and the general uncertainty surrounding these estimates. A different set of assumptions resulting in different cost estimates would change the outputs of the model, in some cases radically.

Transition sensitivities

Differential rates of exacerbation and the rate of treatment failure after exacerbation do impact on the model outputs although these effects tend to be smaller than changes to the cost and utility of controlled asthma.

Exacerbation rates

Levels of exacerbation are important in determining cost-effectiveness, although their impact is less acute than changes made to the utility and cost parameters of the controlled asthma state. Given their substantially greater cost, it is unsurprising that hospital-managed

exacerbation rates have more of an influence on cost-effectiveness than the rate of GP/self-managed exacerbations. These findings generally should be considered in the wider clinical context of exacerbation avoidance and the need to prevent potentially severe outcomes in the treatment of asthma. The influence of exacerbations on model outputs depends critically on the general level of exacerbations in the model. For the modelled population in the studied comparisons this is fairly low. However, for more populations with more severe asthma, where the general exacerbation rate is likely to be higher, the sensitivity of the model to exacerbation rate will also be greater.

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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