ICS and LABAs for the treatment of chronic asthma in adults and children aged 12 years and over: Systematic review and economic analysis

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Southampton Health Technology Assessments Centre (SHTAC), Wessex Institute for Health Research and Development (WIHRD), University of Southampton

AUTHORS: **Mr Jonathan Shepherd**, Principal Research Fellow, SHTAC
Mr Gabriel Rogers, Research Assistant, PenTAG
Dr Rob Anderson, Senior Lecturer in Health Economics, PenTAG
Ms Caroline Main, Research Fellow, PenTAG
Dr Jo Thompson Coon, Research Fellow, PenTAG
Dr Debbie Hartwell, Research Fellow, SHTAC
Ms Zulian Liu, Research Assistant, PenTAG
Dr Emma Loveman, Senior Research Fellow, SHTAC
Mr Colin Green, Senior Lecturer in Health Economics, PenTAG (formerly SHTAC)
Dr Martin Pitt, Research Fellow, PenTAG
Dr Ken Stein, Senior Lecturer in Public Health, PenTAG
Ms Petra Harris, Research Fellow, SHTAC
Dr Geoff Frampton, Research Fellow, SHTAC
Dr Matthew Smith, Specialist Registrar in Public Health, SHTAC
Dr Andrea Takeda, Senior Research Fellow, SHTAC
Mrs Alison Price, Information Scientist, SHTAC
Ms Karen Welch, Information Officer, SHTAC
Dr Margaret Somerville, Senior Lecturer and Consultant in Public Health, PenTAG

CORRESPONDENCE TO:

Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC),
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton. SO16 7PX.

jps@soton.ac.uk

Caroline Main
Peninsula Technology Assessment Group (PenTAG),
Noy Scott House,
Barrack Road,
Exeter. EX2 5DW.

Caroline.Main@PenTAG.nhs.uk

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ABOUT SHTAC

The Southampton Health Technology Assessments Centre (SHTAC) was established in 2000. It was formed from the research group that supported the South and West and South East (formerly Wessex) Regional Development and Evaluation Committee from 1991 to 2000. SHTAC is part of the Wessex Institute for Health Research and Development (WIHRD), based in the School of Medicine at the University of Southampton. Collaborative links with the Southampton General Hospital Trust and other health providers nationally provide support for SHTAC's research programme.

SHTAC has a multidisciplinary research team encompassing a wide range of skills developed from a variety of academic and clinical backgrounds. There are currently 17 full and part-time staff, including health economists, economic and statistical modellers, systematic reviewers, and public health consultants. The SHTAC team work closely with experienced information scientists from the WIHRD Information Resource Centre.

ABOUT PENTAG

The Peninsula Technology Assessment Group is part of the Institute of Health and Social Care Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme and other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health and Social Care Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

CONTRIBUTIONS OF AUTHORS

For PenTAG:

Dr Rob Anderson	Economic evaluation and interpretation of results, contributed to model design, identification of inputs for models, analysis and interpretation of results, and report preparation
Mr Colin Green	Economic evaluation and interpretation of results, contributed to model design and report preparation
Ms Zulian Liu	Project support, data extraction and checking, contributed to economic evaluation and report preparation
Ms Caroline Main	Project management, report preparation, data extraction and checking, contributed to model design, identification of inputs for models, interpretation of results
Dr Martin Pitt	Developed and executed the model, analysis and interpretation of results
Mr Gabriel Rogers	Project support, data extraction and checking, contributed to model design, identification of inputs for models, analysis and interpretation of results, report preparation
Dr Margaret Somerville	Project direction, report preparation, contributed to model design, analysis and interpretation of results
Dr Ken Stein	Study design, report preparation, methodological advice
Dr Jo Thompson-Coon	Initial project management, contributed to model design, identification of inputs for model, interpretation of results, report preparation

For SHTAC:

Dr Geoff Frampton	Data extraction and checking, clinical effectiveness synthesis, report preparation
Ms Petra Harris	Data extraction and checking, clinical effectiveness synthesis, report preparation
Dr Debbie Hartwell	Project support, inclusion screening, data extraction and checking, clinical effectiveness synthesis, report preparation
Dr Emma Loveman	Project support, inclusion screening, data extraction and checking, clinical effectiveness synthesis, report preparation
Ms Alison Price	Design and execution of the cost-effectiveness review literature search strategies
Mr Jonathan Shepherd	Project management, protocol development, inclusion screening, data extraction and checking, clinical effectiveness synthesis, report preparation
Dr Matthew Smith	Data extraction and checking, clinical effectiveness synthesis, report preparation
Dr Andrea Takeda	Data extraction and checking, clinical effectiveness synthesis, report preparation
Mrs Karen Welch	Design and execution of the clinical effectiveness review literature search strategies

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CONFLICTS OF INTEREST

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Declaration of authors' competing interests

none

NOTES

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1. Glossary and list of abbreviations

Term/abbreviation	Definition
ACQ-5	Asthma Control Questionnaire
ACTH	Adrenocorticotropic hormone
AE	Adverse Events
AMD	Adjustable maintenance dose
ANCOVA	Analysis of Co-Variance
AQLQ	Asthma Quality of Life Questionnaire
AZ	AstraZeneca
BDP	Beclometasone Dipropionate
b.i.d	Twice daily
BMD	Bone mineral density
BNF	British National Formulary
BTS	British Thoracic Society
BUD	Budesonide
COPD	Chronic obstructive pulmonary disorder
CFC	Chlorofluorocarbon, a propellant used in pressured metered dose inhalers. Currently being replaced by hydrofluoroalkanes (HFA) propellants.
Cortisol	Cortisol is a corticosteroid hormone that is involved in the response to stress; it increases blood pressure and blood sugar levels and suppresses the immune system.
CI	Confidence interval
CIC	Ciclesonide
CEA	Cost-Effectiveness Analysis
CMA	Cost Minimisation Analysis
CUA	Cost-Utility Analysis
CRD	Centre for Reviews and Dissemination
DPI	Dry powder inhaler
EMEA	European Agency for the Evaluation of Medicinal Products
Ex-actuator	Used in reference to drug delivery. The content per actuation which is reflected in the labelled strength of the drug. Ex-actuator means metered – the amount of drug that is delivered from the mouthpiece to the patient.

Term/abbreviation	Definition
Ex-valve	Used in reference to drug delivery. The content per actuation which is reflected in the labelled strength of the drug. Ex-valve means metered – the amount of drug delivered from the inhaler into the mouthpiece.
ER	Emergency Room
FD	Fixed dose
FP	Fluticasone Propionate
FEV_1	Forced expiratory volume. The volume of air exhaled in the second of forced blowing into a spirometer.
$FEF_{25-75\%}$	Forced expiratory flow
FORM / FF / F	Fomoterol fumarate
FVC	Forced vital capacity. The total amount of air that a person can forcibly blow out after full inspiration, measured in litres.
GOAL	Gaining Optimal Asthma Control
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
Hypothalamic-pituitary-adrenal axis (HPA axis)	The hypothalamic-pituitary-adrenal axis (HPA axis) is a major part of the neuroendocrine system that controls reactions to stress and has important functions in regulating various body processes such as digestion, the immune system and energy usage.
HFA	Hydrofluoroalkane, a propellant used in pressured metered dose inhalers. Replacement for chlorofluorocarbon (CFC) propellant.
HRQOL	Health-related quality of life
I^2	A measure used to quantify heterogeneity in a meta-analysis It describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to represent substantial heterogeneity.
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled Corticosteroid (e.g. budesonide)
IQR	Inter quartile range
ITT	Intention-to-treat
L	Litre
LABA	Long-Acting $Beta_2$-Agonist (e.g. salmeterol or formoterol)
LOCF	Last Observation Carried Forward
LS	Least squares
MF	Mometasone Furoate
µg	Micrograms
mg	Milligrams

Term/abbreviation	Definition
ml	Millilitres
MHRA	Medicines and Health Care Products Regulatory Agency
NICE	National Institute for health and clinical Excellence
NSD / NS	No statistically significant differences
NW	Nocturnal wakenings
OCS	Oral corticosteroids
OR	Odds ratio
PEFR	Peak expiratory flow rate. The maximum rate at which air is expired from the lungs when blowing into a peak flow meter or spirometer.
PC	Plasma cortisol
PCA	Prescribing cost analysis
PC20	The provocative concentration of methacholine to induce a 20% decline in FEV_1
PD20	A value obtained in methacholine challenge testing to indicate severity of asthma.
pMDI	Pressured metered dose inhaler
PP	Per protocol
QALY	Quality Adjusted Life Year
QCT	Quantitative computed tomography
q.d.	Once daily
q.i.d.	Four times daily
RCT	Randomised Controlled Trial
SABA	Short-acting $beta_2$-agonist (e.g. salbutamol, or terbutaline)
SAL	Salmeterol
SD	Standard Deviation
SE / SEM	Standard Error of the Mean
SFD	Symptom-free Day
SFN	Symptom-free Night
SIGN	Scottish Intercollegiate Guidelines Network (SIGN)
SMART	Symbicort Maintenance and Reliever Therapy
SMD	Standardised Mean Difference
Spacer	Device attached to an inhaler to maximise the delivery of the drug to the lungs. A spacer consists of a container, usually in two halves that fit together. One end fits to a mouth- piece or a face- mask (e.g. for young children). The other end fits to the inhaler.
Spirometry	A pulmonary function test, measuring lung function

Term/abbreviation	Definition
SS	Symptom scores
t.i.d.	Three times a day
tx	Treatment
wk	Week
WMD	Weighted Mean Difference
µg	Microgram

2. Executive summary

2.1 Background to asthma

Asthma is a chronic inflammatory disorder of the airways leading to airway narrowing from both inflammatory processes and constriction of the smooth muscle in airway walls. Symptoms include recurring episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. Common risk factors include viral respiratory infections, allergens such as pollens, moulds, animal fur and house dust mite, cold and exercise. It is estimated that there are around 5.2 million people in the UK with asthma.

The aims of asthma management are the control of symptoms, including nocturnal symptoms and exercise-induced asthma, prevention of exacerbations and the achievement of the best possible lung function, with minimal side effects. A variety of strategies are used in the prevention and management of the condition. Pharmacological management includes, amongst other drugs, inhaled corticosteroids (ICS), and short- and long-acting beta$_2$-agonists (SABAs / LABAs).

Five ICS are available as licensed preparations in this population: beclometasone dipropionate (BDP), budesonide (BUD), fluticasone propionate (FP), mometasone furoate (MF) and ciclesonide (CIC). Two of the ICS are available as licensed preparations in combination with LABA: FP used in combination with salmeterol (FP/SAL), and BUD used in combination with formoterol fumarate (BUD/FF).

2.2 Objectives

The aim of this health technology assessment is to assess the clinical and cost-effectiveness of ICS alone and ICS used in combination with a LABA in the treatment of chronic asthma in adults and children over 12 years.

The objectives are:

- To identify, appraise and synthesise, where appropriate, the current evidence base which addresses the specific research questions on clinical effectiveness listed below.

- To identify the costs associated with the different treatments.
- To identify, appraise and synthesise, where appropriate, the current evidence base which addresses the specific research questions on cost-effectiveness listed below.
- To provide estimates of cost-effectiveness, where possible, of the different treatment options.

An accompanying health technology assessment has been conducted in children aged under 12 years.

2.3 Methods

The assessment comprises a systematic review of clinical and cost-effectiveness studies and some economic analyses.

The assessment was conducted within the context of the British Thoracic Society (BTS) / Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the management of asthma. Using the steps in the guidelines, the following review questions were identified:

Q1. Which is the most clinically and cost-effective of the three ICS when used in low doses (400 – 800µg BDP per day or equivalent) at Step 2 of the guidelines?

Q2. Which is the most clinically and cost-effective of the three ICS when used in high doses (800-2000µg BDP per day or equivalent), at Step 4 of the guidelines?

Q3. Which is the more clinically and cost-effective approach to introducing a LABA into a treatment regimen at steps 2-3 of the guidelines:

a. To increase the dose of ICS alone or to add a LABA to treatment with ICS?

b. To continue with an ICS alone or to add a LABA to treatment with a similar dose of ICS using a combination inhaler?

Q4. Which is the more clinically and cost-effective treatment:

FP and SAL in a combination inhaler or given in separate inhalers?

BUD and FF in a combination inhaler or given in separate inhalers?

Q5. Which is the more clinically and cost-effective treatment: FP/SAL in a combination inhaler or BUD/FF in a combination inhaler, when used at Step 3 of the guidelines?

For the assessment of clinical effectiveness a literature search was conducted on a number of electronic databases, up to February/March 2006 (and updated again in October 2006). Systematic reviews and Randomised Controlled Trials (RCTs) were included. Trials testing different drugs by different inhalers or propellants, and trials testing the same drug by different inhalers were not included. The following outcomes were relevant: objective measures of lung function (e.g. FEV_1, PEFR); symptoms (e.g. symptom-free days and nights); incidence of mild and severe acute exacerbations; use of rescue medication; adverse effects of treatment; health-related quality of life; adverse effects; mortality. Titles and abstracts of studies identified by the searches were screened according to inclusion criteria. Full papers for studies that appeared relevant were retrieved and screened in detail. All trials, except those included in relevant Cochrane reviews, were fully data extracted and quality assessed. Results of the included trials were synthesised narratively with quantitative meta-analysis where appropriate and feasible.

Economic analyses methods

A flexible framework was used to allow different types of analyses for each of the five identified questions. For each question a cost comparison or a cost-consequence comparison was conducted. These two different methods of analysis were used in light of the findings from the accompanying clinical effectiveness review. Cost comparisons between the different ICS or ICS plus LABA regimens were undertaken where the clinical effectiveness review showed no consistent evidence of differential treatment effects between the comparators. A cost consequence comparison was undertaken where the clinical effectiveness review indicated that there were some significant differences in effects between the comparators. Here the overall pattern of effectiveness differences identified in the systematic review were presented along-side the estimated medication costs for each of the comparators in the trials.

2.4 Results

2.4.1 Clinical effectiveness review

Of 5175 reports identified through systematic literature searching, 113 reports describing 84 studies were included. Of these,

- 67 were fully published RCTs (of which 38 had been included in the Cochrane reviews)
- 7 were systematic reviews (of which 5 were Cochrane reviews)
- 10 were post-2004 conference abstracts

The assessment of clinical effectiveness is based on the 67 RCTs. They varied considerably in patient characteristics, duration, regimens, outcomes and methodological quality, as would be expected given the breadth of this assessment. There is a comparatively large evidence base for the more established ICS (BDP, BUD, FP) compared to the newer ICS (MF and CIC). It was not possible to perform all of the comparisons due to a lack of RCTs. In many cases quantitative meta-analysis was not appropriate or feasible.

The most frequently reported relevant outcomes in the 67 RCTs were lung function, symptoms, use of rescue medication, and adverse events. Exacerbations and health related quality of life were reported less frequently.

ICS versus ICS

Twenty-two RCTs were identified that compared the five ICS at low doses according to Step 2 of the guidelines and twenty-four comparing them at high doses according to Step 4 of the guidelines. In general, all of the ICS were associated with favourable changes from baseline to end-point across efficacy and safety outcomes. When evaluated in pair-wise comparisons at the accepted clinically equivalent doses no consistent significant differences or patterns among the outcomes were evident. Where any one of the outcome measures was significantly different between the comparators in any of the trials, this was generally not reflected across the other outcomes assessed. Notably, where any significant differences were observed this tended to be in trials of MF, FP or CIC versus either BUD or BDP, and the comparisons were not made between the accepted clinically equivalent doses. The occurrence of adverse events appeared similar between the ICS.

ICS versus ICS/LABA

A total of ten RCTs evaluated the effectiveness of combination ICS/LABA therapy (FP/SAL or BUD/FF) versus a higher dose of ICS alone. The general findings indicated a significant treatment benefit for combination therapy across a range of outcomes compared to ICS alone, when that ICS was double the accepted clinically equivalent dose of the ICS in the combination inhaler. This applied to both of the combination inhalers. In addition, nine further trials assessed the effects of the adding a LABA to a similar dose of ICS in each of the trial arms. Six evaluated FP/SAL combination and three BUD/FF combination. In all the trials the same ICS and dose was used in both comparator arms. The results showed that ICS/LABA combination therapy was statistically superior to ICS alone across most of the outcomes.

ICS/LABA versus ICS/LABA

FP/SAL combination inhaler and BUD/FF combination inhaler each compared with their constituent drugs delivered in separate inhalers was assessed in three RCTs and two RCTs respectively. An additional trial compared FP/SAL combination inhaler against BUD+FF in separate inhalers. There were very few statistically significant differences between the treatments across the various efficacy outcomes. For some outcomes (e.g. lung function) non-inferiority was demonstrated. Meta-analysis of adverse events showed no statistically significant differences between combination versus separate inhaler therapy.

Three RCTs evaluated the combination inhalers versus each other. The results were mixed, with the FP/SAL combination significantly superior on some outcomes, and BUD/FF combination superior on others. Meta-analysis showed there were no significant differences between the two treatments in the rate of adverse events.

2.4.2 Economic analyses

ICS versus ICS

A cost comparison was undertaken to compare the costs of ICS at both low and high dose.

At daily doses of 400µg per day BDP-CFC propelled devices are currently the cheapest available, and remain so but at a higher annual cost if CFC-propelled products are excluded from the analyses.

At 800µg/day and 1500-1600µg/day BDP-CFC propelled products remain the cheapest available. At these doses if CFC-propelled products are excluded then FP products can be on average the cheapest ICS product available if the mean is weighted by market share). On the whole when only CFC-free products are considered the mean annual cost of both BUD and BDP increases. For FP, CIC and MF there are currently no CFC-propelled products available, therefore their costs remain constant. However, the use of weighted averages to represent the cost associated with each ICS tends to conceal the wide variations in costs between the individual preparations of each drug, and the wide overlap in costs between the drugs.

ICS versus ICS/LABA

A trial-based cost consequence analysis was used to examine the overall pattern of differential treatment effects alongside the estimated medication costs for each of the comparators.

Overall, based on the nine included trials, combination inhalers were more often cheaper than doubling the dose of ICS alone. However, the costs were highly variable and dependent upon both the dose required and the preparation used in the trials. The estimated mean annual cost of FP/SAL combination varied from being £94 cheaper to £109 more expensive than the alternative of BUD at a higher dose. For the combination of BUD/FF the combination varied from being of £163 cheaper to £66 more expensive than the higher dose of either BUD or FP.

ICS/LABA versus ICS/LABA

Cost comparisons were undertaken to compare the costs of ICS/LABA versus ICS/LABA delivered in either separate or combination inhalers.

Taking an ICS with a LABA as either of the two currently available combination products of FP/SAL, or BUD/FF, is cheaper than taking the relevant ingredient drugs in separate inhalers. In terms of the relative costs associated with both of the combination inhalers, there

were no consistent cost differences between the two inhalers, as the costs depend on the dose required and the preparation used. Therefore there is no combination inhaler which is cheapest in all circumstances.

2.5 Discussion

There is a vast evidence base on the clinical effectiveness of ICS used alone or in combination with a LABA for the treatment of chronic asthma in adults. Approximately two-thirds of the RCTs identified compared one ICS with another. Of these, the trials were predominantly of the older ICS, BUD, BDP and FP. There were fewer trials of the newer ICS drugs, MF and CIC. Methodological quality of the included RCTs varied, and there was variability in the way outcomes were measured and reported. In general there were few statistically significant differences between the five ICS when evaluated in pair-wise comparisons. The ICS could therefore be considered generally equivalent in clinical terms, although few studies explicitly aimed to assess clinical equivalence / non-inferiority. The differences in cost between the five comparators varied with the daily dose of ICS required. In general at a low starting dose of 400µg per day, CFC-propelled BDP is the cheapest ICS currently available. At the higher doses of 800µg/day and 1500-1600µg/day CFC-BDP remains the cheapest available. When CFC-propelled products are excluded from the analysis, FP is the cheapest ICS product available at these higher doses. With the exclusion of CFC-propelled products from the market the cost of ICS therapy is likely to increase, although the overall cost differences between the five ICS drugs may diminish.

The results of trials that have assessed the effects of ICS/LABA compared with an increased dose of ICS alone have tended to favour treatment with the combination therapy. Although significant differences in effects are not observed consistently across all outcome measures. Based on the costs only, the extra annual cost of combination therapy versus an increased dose of ICS alone varies greatly depending on the exact ICS preparation used. The more expensive ICS products used at higher dose are more expensive than combination inhaler products, whilst the use of cheaper ICS preparations compared to combination therapy will be cost saving.

Comparisons of ICS/LABA in a combination inhaler compared with separate inhalers have indicated there are very few statistically significant differences between the outcomes.

However use of a combination inhaler is nearly always cheaper than taking the same ingredient drugs in separate inhalers. There appear to be no consistent significant differences in effects between the two combination inhalers, with mixed results in terms of significant differences in outcomes being observed across the three trials in which the combination inhalers have been compared head-to-head. Likewise, the costs associated with both of the combination products are mixed. There are no consistent cost differences between the two inhalers, as the costs depend on the dose required and the preparation used. Therefore there is no combination inhaler which is cheapest in all circumstances.

2.6 Conclusion

The evidence reviewed indicates there are no consistent significant differences in effects between the five ICS licensed for use in adults and adolescents over the age of 12 years, at either low or high dose. On average, BDP products currently tend to be the cheapest ICS available at starting doses of Step 2 of the BTS/SIGN Guidelines. As the daily ICS dose required increases, BDP products tend to remain the cheapest. The exclusion of CFC-propelled products may increase the mean annual cost of both BDP and BUD, but should have no affect on the cost of MF, FP or CIC, as all products for these drugs are CFC-free. The higher cost of BUD and BDP may decrease the overall cost differences between the ICS comparators. However, it should be noted that whilst the use of weighted averages averages to calculate these costs can provide a useful way of representing the major differences between the drugs, they often conceal the wide variations in the cost of individual products containing each drug. These costs will also inevitably be sensitive to year-on-year shifts in the market share or price of individual products.

There is evidence that the addition of a LABA to an ICS is potentially more clinically effective compared to doubling the dose of ICS alone, although consistent significant differences between the two treatment strategies are not observed for all outcome measures. The cost differences between combination therapy compared with ICS monotherapy are highly variable and dependent upon the dose required and the particular preparations used. For the combination therapies of ICS/LABA there are potential cost savings to the NHS with the use of combination inhalers compared to separate inhalers with no differences between the two treatment strategies in terms of effects. The evidence regarding the relative effects of the two combination inhalers available is mixed. Neither of the two drug combinations

(FP/SAL or BUD/FF) is consistently superior in terms of treatment effect. A comparison of the costs associated with each combination therapy indicates there are no clear cost differences between the two inhalers, and neither is cheapest in all circumstances.

3. Background

SECTION CONTENTS

3.1 Natural history of asthma

3.1.1 Definition

Asthma is a chronic inflammatory disorder of the airways, leading to airway narrowing from both inflammatory processes and constriction of the smooth muscle in airway walls (bronchoconstriction). Remodelling is a characteristic part of the pathological process, consisting of mucus gland and smooth muscle hypertrophy and increased collagen deposition in the airway walls. It is characterised by widespread, variable airflow obstruction and increased responsiveness of the airways to various stimuli. Resulting symptoms include recurring episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. Common symptom triggers include respiratory infections, allergens such as pollens, moulds, animal fur and house dust mite, cold and exercise.[1;2]

3.1.2 Diagnosis

There is no confirmatory diagnostic test or investigation for asthma. It is usually diagnosed on the basis of symptoms (wheeze, shortness of breath, chest tightness and cough) together with objective tests of lung function such as peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV_1). Typical asthma symptoms tend to be variable, intermittent, worse at night and provoked by triggers (e.g. allergens or exercise). Variability of PEFR and FEV_1, either spontaneously over time or in response to therapy is a characteristic feature of asthma which is also often used in diagnosis.[1]

3.1.3 Asthma severity

Assessing asthma severity is difficult and depends on the level of treatment. In the UK, asthma severity is graded according to the amount of medication an individual needs to keep symptoms under control and is based on the BTS/SIGN Guidelines on the Management of Asthma described in more detail in section 3.3.1 below. The Global Initiative for Asthma (GINA) classifies asthma severity as intermittent or persistently mild, moderate or severe based on combined assessments of symptoms and lung function (*Table 1*). Severity varies amongst individuals, does not necessarily correlate with the frequency or persistence of symptoms, and can change in one individual over time. When an individual is already on treatment, the classification of severity is based on the clinical features present and the step

of the daily medication regimen that the individual is currently on. Under this classification, the presence of one of the features of severity is sufficient to place an individual in that category. Individuals at any level of severity can have severe exacerbations.[2]

TABLE 1 *GINA classification of asthma severity*

	Symptoms/day	**Symptoms/night**	**PEFR or FEV1 variability**
STEP 1 **Intermittent**	< once a week Asymptomatic and normal PEFR between exacerbations	< 2 times a month	> 80% < 20%
STEP 2 **Mild persistent**	> once a week but < once a day Exacerbations may affect activity	> 2 times a month	> 80% 20-30%
STEP 3 **Moderate persistent**	Daily Exacerbations affect activity	> once a week	60-80% > 30%
STEP 4 **Severe persistent**	Continuous Limited physical activity	Frequent	< 60% > 30%

Source: Pocket Guide for Asthma Management and Prevention[2]

A cross-sectional study of 12,203 patients from 393 general practices in the UK, performed by Neville and colleagues in 1994/5 reported that the majority of individuals with asthma in the UK are treated at steps one and two of the BTS/SIGN Guidelines (*Figure 1*).[3] This is particularly so for people between the ages of 16 and 45, with more patients treated at Step 3 in the younger and older populations.

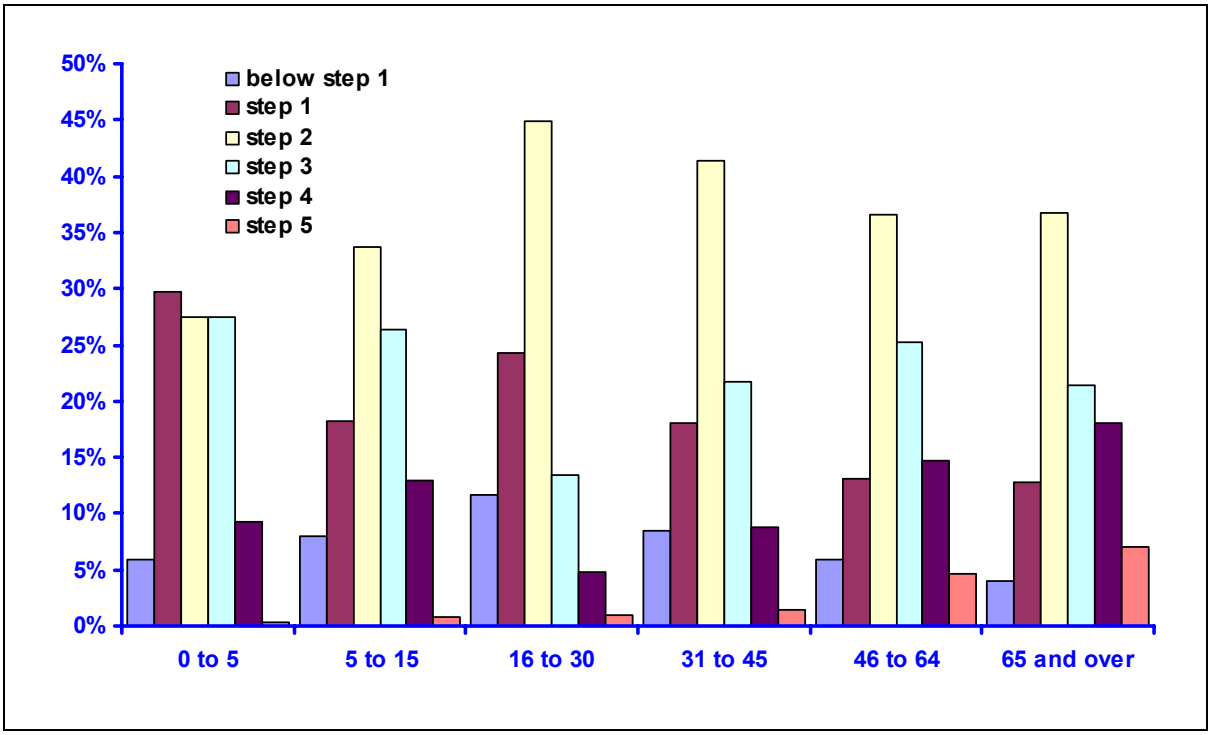


FIGURE 1 *Percentage of individuals at each step of the BTS/SIGN Guidelines by age-group from a cross-sectional study performed by Neville and colleagues in 1994/95*[3]

3.1.4 Asthma exacerbations

Asthma exacerbations are acute episodes of a progressive increase in shortness of breath, cough, wheezing or chest tightness or a combination of these symptoms, usually triggered by a variety of stimuli, most commonly a viral respiratory infection. Severe exacerbations can be life threatening. Most exacerbations can be treated with high doses of inhaled SABAs (SABAs), although sometimes a short course of oral corticosteroids is also needed.[1]

3.1.5 Asthma control

The aims of the pharmacological management of asthma are the control of symptoms, including nocturnal symptoms and exercise-induced asthma, prevention of exacerbations and the achievement of the best possible lung function, with minimal side effects.[1] A fixed level of lung function or symptom control is not normally defined as individuals may have different treatment goals and may wish to balance these against potential side effects.

3.1.6 Prognosis

Asthma usually develops in childhood but may occur for the first time at any age. There is no cure for asthma, although people may experience long periods of 'remission' during which symptoms are less evident or absent.

Epidemiological studies of the natural history of lifetime lung function in healthy subjects suggest that FEV_1 increases during normal growth in childhood, followed by a stable phase in adolescence and early adulthood and a slow decline in FEV_1 after the age of 32 years. The maximum level of FEV_1 achieved and the rate of decline determine the severity of lung function impairment later in life in symptomatic adults. Risk factors associated with smaller increases in lung function and lower maximally attained levels of lung function in children and adolescents include lower respiratory tract infections and passive and active smoking.[4-6] The rate of decline is generally greater in people with asthma than in the general population,[7] possibly as a result of deterioration in potentially reversible disease or the development of persistent obstruction following airway remodelling.[8] The normal between subject variation in maximally achievable FEV_1 is reflected in reference values used to calculate lung function as a percentage of that predicted for a person of similar height, sex, age and race (weight is also sometimes considered) without a diagnosis of asthma (e.g. FEV_1 % predicted).

3.2 Epidemiology of asthma

3.2.1 Incidence and prevalence in the UK

Asthma UK estimate that there are 5.2 million people with asthma in the UK; this includes 700,000 people over the age of 65 years and 590,000 teenagers, approximately 2.9 million women and girls and 2.3 million men and boys.[9] The Health Survey for England commissioned by the Department of Health in 2001 included data on respiratory symptoms obtained from interviews with 15,647 adults aged 16 years or over. The prevalence of lifetime-doctor-diagnosed asthma was 13% in men and 16% in women (*Figure 2*). Approximately 1% of men and women reported a diagnosis within the preceding 12 months.[10]

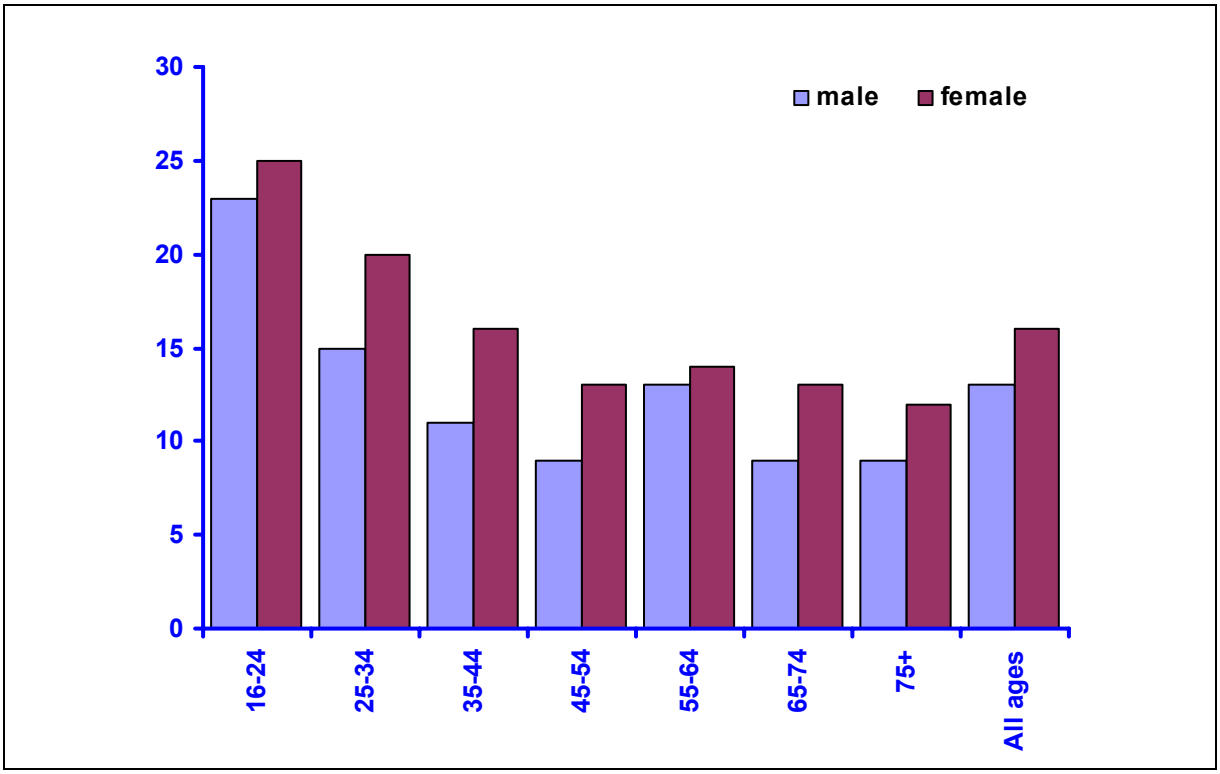


FIGURE 2 *Percentage of men and women with a lifetime-doctor-diagnosis of asthma, 2001*
Source: Health Survey for England 2001[10]

The 1998 figures from the General Practice Research Database with a sampling frame of 211 General Practice's in England and Wales indicated that the prevalence of treated asthma in men aged 15 years and over ranged from 44.5 – 89.4 per 1000 patients, with an age standardised rate of 73.2 per 1000. For women the rate of treated asthma was slightly higher, with a range of 52.2 – 88.0 per 1000 patients, with an age standardised rate of 76.5 per 1000.[11] As treatment in the UK is strongly influenced by the BTS/SIGN Guidelines (see section 3.3.1) it may also be useful to consider asthma prevalence in terms of the treatment steps in the guidelines.

3.2.2 Mortality

Asthma deaths are rare; there were 1,266 reported deaths due to asthma in 2004 (*Figure 3*). Most of these (70%) were in people over the age of 65; asthma deaths were more common in women than in men (64% versus 36%). Several audits and case-control studies of asthma deaths in the UK have been conducted and suggest that risk factors fall into four categories i) disease severity, ii) medical care factors both prior to and during the fatal episode, iii) health

behaviour such as reduced concordance with prescribed medication, poor inhaler technique and reduced contact with primary care services and iv) adverse psychosocial factors and therefore a proportion of deaths due to asthma are preventable, especially in those under the age of 65 years.[12-16]

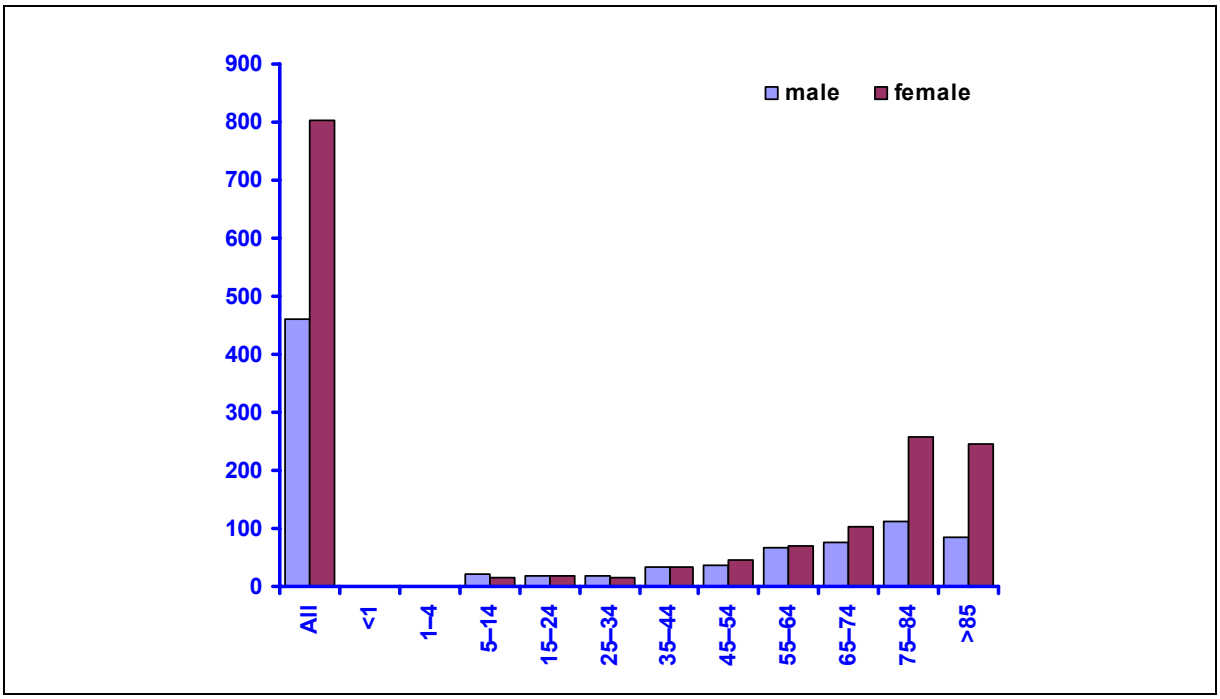


FIGURE 3 *Asthma deaths by age and sex, registrations in 2004*
Source: Office of National Statistics[17]

3.2.3 Impact of asthma on health related quality of life (HRQL)

Health related quality-of-life (HRQL) refers to the impact of disease and treatment on daily life. In contrast to the physiological outcome measures used to define control, the aim of HRQL measurement is to assess the impact asthma has on a person's daily functioning and emotional well-being.[18] Studies indicate that patients with asthma have impaired HRQL, and that morbidity as expressed by HRQL in patients with asthma is substantial.[19]

When considering the impact of asthma it is important to acknowledge the differences that may exist between control of disease, as defined by clinical measures, and its impact on HRQL. It should not be assumed that meeting clinical treatment goals will necessarily be meaningful to patients, in terms of improvements in HRQL.[20]

There are a wide range of disease specific health status measures available to assess quality of life in individuals with asthma. These include the Asthma Quality-of-Life Questionnaire (AQLQ),[21] the Mini Asthma Quality-of-Life Questionnaire (Mini AQLQ,[22] the Living With Asthma Questionnaire (LWAQ),[23] the St George's Respiratory Questionnaire (SGRQ),[24] and the Asthma Bother Profile (ABP).[25] The most commonly used instrument in adults is the AQLQ which was developed by Juniper and colleagues in the early 1990s.[21] The AQLQ is a well accepted, reliable, valid and responsive 32-item questionnaire divided into four domains (symptoms, emotional function, activity limitation and environmental stimuli). Each item is assessed on a 7-point scale (higher score indicates less impairment) based on an individuals' recall of their condition over the previous two weeks. Individual domain scores and overall scores (mean of all 32 questions) are calculated in the AQLQ assessment. A within-group change of 0.5 points from baseline is regarded as the minimum meaningful clinically relevant change for each domain. A change of one point for each domain is considered a moderate change in HRQL.[26]

The advantage of using disease specific measures of HRQL is the clear relevance of the instruments to the affected population. However, the instruments do not make it easy to compare outcomes across different diseases (e.g. for purposes of resource allocation), therefore generic instruments such as the short-form 36, (SF-36)[27] the Nottingham Health Profile (NHP),[28] the Sickness Impact Profile (SIP),[29] and the EuroQol (EQ-5D),[30] have also been used to assess the impact of asthma on quality of life.

There is some evidence of a weak to moderate correlation between individual clinical measures (e.g. lung function) and HRQL.[31;32] Moy and colleagues retrospectively examined data from two completed clinical trials, which included individuals with mild asthma and moderate to severe asthma.[31] Using the Asthma Quality of Life Questionnaire (AQLQ) they reported that lung function alone was not an independent predictor of HRQL. Asthma severity, defined by the combination of lung function, symptoms, and reliever medication use was correlated with HRQL, although these parameters accounted for less than half of the variation in HRQL.[31] Carranza Rosenzweig and colleagues performed a retrospective analysis of data from randomised clinical trials (RCTs) in individuals with persistent asthma, suggesting that the impact of asthma on HRQL is not fully accounted for by objective measures such as lung function.[32]

It is not surprising that objective and subjective measures of the impact of asthma differ. This is a common finding in the general literature on health state valuation.[33] Individuals differ in the value they place on the many disturbances of daily life and well-being that result from asthma, resulting in differences across HRQL scores. For example, there may be variation in the perception of asthma symptoms (regardless of clinical status) and adaptation to the condition over time.

Bateman and colleagues, whilst recognising that individual measures such as lung function may be poor predictors of HRQL, present findings from empirical analyses that suggest that individuals with well-controlled asthma can achieve near-maximal AQLQ scores, representing little or no impact of asthma on their lives.[20] The study suggests that if individuals achieve guideline based composite control they will achieve larger improvements in HRQL than if success in only a single measure is achieved. Conversely, failure to achieve control in a single parameter does not necessarily predict failure in terms of HRQL improvements. Nishiyama and colleagues have also reported a significant relationship between lung function and HRQL in individuals with well-controlled asthma.[34] In this study, although correlations between physiological measures and HRQL were weak to moderate, maintaining PEFR above 80% of the predicted value was significantly associated with better HRQL.

For economic evaluations aiming to provide summary measures of cost-effectiveness e.g. cost per quality adjusted life year (QALY), health state values associated with the different scenarios of asthma health status (e.g. by severity, or by level of control) are necessary. The literature on studies reporting health state values for individuals with asthma is discussed in section 6.3.1.

3.3 Current Service Provision

3.3.1 Asthma management in the UK

As previously stated, the management of asthma in the UK is largely based on the BTS/SIGN Guidelines developed by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guideline Network (SIGN).[1] The Guideline is evidence-based and was developed in collaboration with Asthma UK, the Royal College of Physicians of London, the Royal College of Paediatrics and Child Health, General Practice Airways Group, and the

British Association of Accident & Emergency Medicine using SIGN methodology adapted for UK-wide utilisation. The Guideline recommends strategies for both non-pharmacological management of chronic and acute asthma. Only the pharmacological management of chronic asthma is relevant to this appraisal and is described in more detail below.

The Guideline advocates a stepwise approach to pharmacological management, which aims to achieve early control and to maintain control by stepping up treatment when control is poor and stepping down treatment when control is good (*Figure 4*). At all levels, there is an emphasis on checking inhaler technique, concordance with existing therapy and avoidance of trigger factors before the level of therapy is increased. Regular review of treatment level and asthma control is also recommended at all levels, so that individuals are maintained at the lowest possible step of the Guideline.

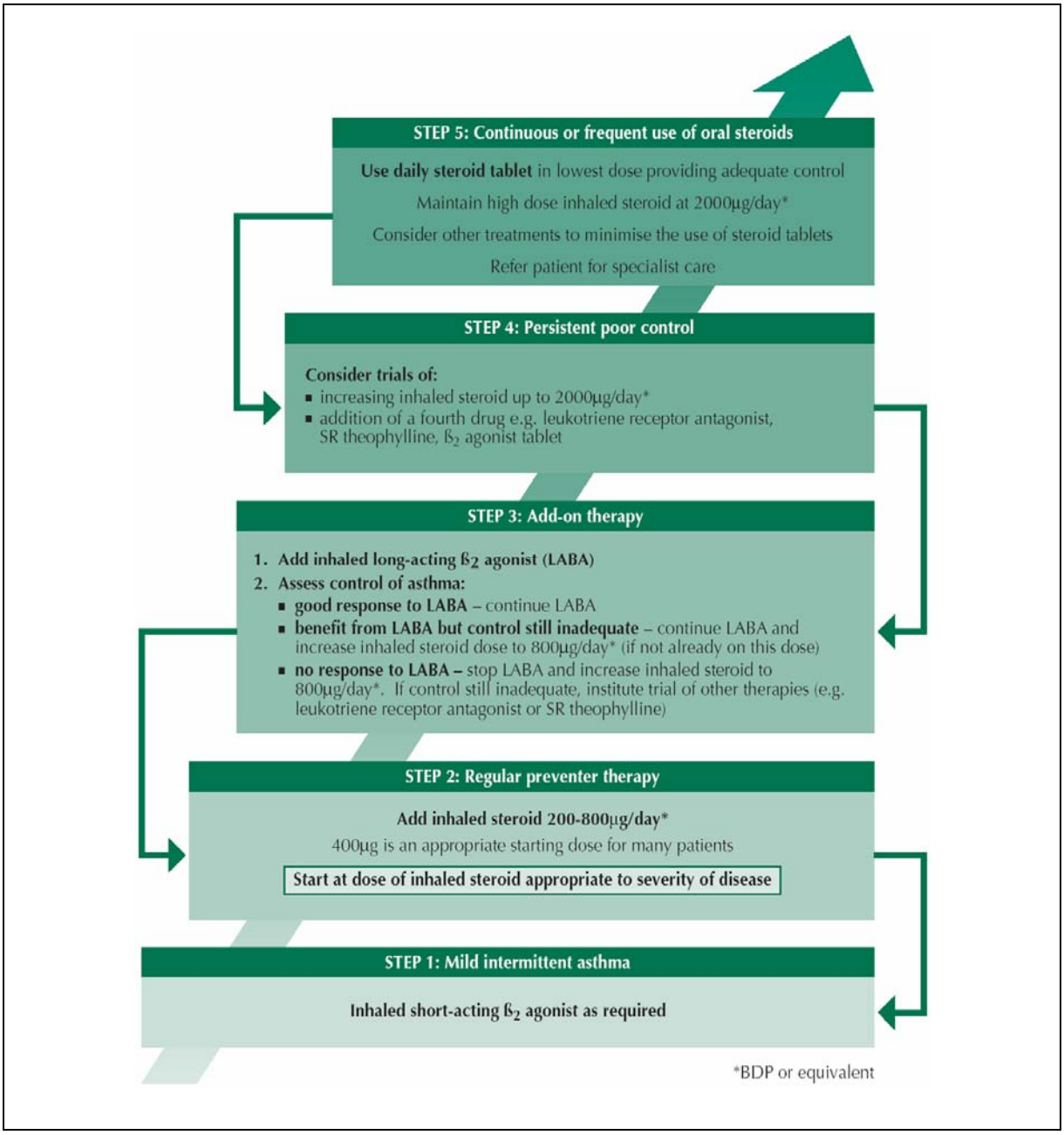


FIGURE 4 *Summary of step-wise asthma management in adults*
Source: *BTS/SIGN Guidelines*[1]

At *Step one* (mild intermittent asthma), inhaled SABAs are recommended as the agent of choice, to be prescribed as needed. A review of asthma management with possible movement to *Step two* (introduction of regular preventer therapy) is indicated if an individual has had exacerbations of asthma in the last two years, is using inhaled SABAs three times a

week or more or is symptomatic three times a week or more, or waking on one occasion a week. There is no exact threshold at which movement to step two should be considered as it varies between individuals. The recommended preventer therapy at step two is an ICS at a starting dose of 400µg per day (BDP [*BDP*] equivalent; given as 200µg twice daily). This dose can then be titrated to the lowest dose at which effective control of asthma is maintained. *Step three* involves the introduction of an additional therapy. Again the exact threshold at which this should be considered has not been established. The first choice of add-on therapy is a LABA, although other agents can be used such as leukotriene receptor antagonists, theophyllines and slow release beta$_2$-agonist tablets. If asthma control remains sub-optimal after the addition of a LABA, the dose of ICS may be increased to 800µg per day (BDP equivalent) with or without the LABA. If asthma control still remains sub-optimal, despite treatment with 800µg per day of ICS, other agents should be trialled before moving to Step four. In *Step four*, if control remains inadequate on 800µg per day of an ICS plus a LABA (or following an unsuccessful trial of a LABA) the following further interventions may be considered: increasing the dose of ICS to 2000µg per day, adding in a leukotriene antagonist, adding in a theophylline preparation, adding in a slow release beta$_2$-agonist tablet. In *Step five* continuous or frequent courses of oral corticosteroids can be introduced. The aim of treatment at this level is to control asthma symptoms using the lowest possible dose of oral corticosteroids or, if possible, to step back down to step four (i.e. eliminate oral corticosteroids altogether).

Once control of asthma is achieved, it is recommended that treatment be stepped down to the lowest possible level.

A large proportion of individuals with asthma are managed within primary care, often within nurse-led asthma clinics. As part of the new General Medical Services contract and Quality Outcomes Framework in England/UK, general practitioners are encouraged to perform annual reviews on all registered individuals with asthma within their practice.[35] Figures for England for 2004-2005 suggest that most practices are achieving the targets for asthma set out within the framework (91% of the total points achievable were awarded).[36]

Discussions with clinicians both locally and nationally suggest that whilst the Guideline forms the basis of most pharmacological treatment of asthma in the UK, there is some variation from these recommendations in practice. Examples of this include the introduction of combination inhalers at an earlier stage (possibly eliminating the need for Step 2) and a

greater preference for combination inhalers above separate inhalers (for the concomitant administration of a LABA and an ICS) in some patient groups (children, those more at risk of severe exacerbation) than others.

3.3.2 Asthma management plans (action plans)

The use of written plans to aid individuals in the self-management of their asthma symptoms has been shown to lead to reduced utilisation of health care resources, days off work or school and improvements in nocturnal asthma symptoms[37] and to protect against death from asthma.[38] The use of action plans is advocated in the BTS/SIGN Guidelines.[1] The evidence for their efficacy in people with moderate to severe asthma, treated primarily within the secondary care setting is particularly good.[39-41] Plans based on both symptom scores and measurements of PEFR have both been found to be effective.[42] The aim of such plans is to provide individuals with information that allows them to respond to changes in their asthma control either by changing their level of treatment or by seeking advice from a health professional at the first signs of an asthma exacerbation. Despite this evidence of effectiveness, there is some indication in the literature that asthma management plans are not very popular with health professionals or with individuals.[43] Action plans that incorporate an individuals' personal experience of their disease are likely to be more successful.[44]

3.3.3 Concordance

Improving concordance with ICS therapy is recognised as an important aim for education and management. Since the effects of ICS can take several days or maybe even weeks both to manifest themselves following initiation of therapy and to decline following cessation of therapy, there may appear to be little incentive for individuals to take these medications, as prescribed, for long periods of time. Anxiety surrounding the risk of adverse events with ICS may also affect concordance. A systematic review conducted in 2000 by Cochrane and colleagues identified ten studies that reported concordance with ICS measured using electronic devices contained within the inhaler device.[45] All but one of these studies was conducted in adults. Overall, patients took the recommended doses of medication on 20 to 73% of days. Average concordance, measured as the ratio of doses taken to doses prescribed ranged from 63 to 92%.[45] Concordance measured in these studies is likely to be better than that seen in the community since patients were aware that their condordance with

prescribed treatment regimens was under scrutiny. A study that used records from the General Practice Research Database in the UK and included 284,733 individuals prescribed ICS over a ten-year study period found that only 42% of individuals obtained a repeat prescription for ICS within the expected timeframe of the preceding prescription.[46] A further UK study, conducted in a general practice in Nottinghamshire reported that 39% of patients on regular corticosteroids had requested less than 80% of the expected dose. The authors comment that this may be due to non-concordance or due to individuals adjusting their ICS dose as a result of improvements in asthma control.[47] Some education programmes have been shown to improve concordance in adults and may also play a role in improving concordance within families.[48]

3.4 Description of technology under assessment

3.4.1 ICS

3.4.1.1 Products available

There are currently five ICS licensed for use in adults in England and Wales.

- *Beclometasone dipropionate* (*BDP*) was the first ICS available in the UK, introduced in 1972. It is available in MDIs with CFC-propellants and in breath activated MDIs in both proprietary (Becloforte [Allen and Hanburys] and Becotide [Allen and Hanburys] and non-proprietary formulations (AeroBec [3M], AeroBec Forte [3M], Beclazone Easi-Breathe [IVAX], Filair [3M], Filair Forte [3M], Pulvinal BDP [Trinity]), MDIs with non-CFC propellants (Qvar [IVAX]), DPIs (Asmabec Clickhaler [Celltech], Becodisks [Allen & Hanburys], Easyhaler [Ranbaxy]) and hard capsule powder inhalers (BDP Cyclocaps [APS]).
- *Budesonide* (*BUD*) is available in MDIs with CFC-propellants in both proprietary (Pulmicort [AstraZeneca] and non-proprietary formulations (Novolizer [Meda]), DPIs (Pulmicort Turbohaler [AstraZeneca) and hard capsule powder inhalers (BUD Cyclocaps [APS]).
- *Fluticasone propionate* (*FP*) is available in MDIs with non-CFC propellants (Flixotide Evohaler [Allen & Hanburys] and in DPIs (Flixotide Accuhaler, Flixotide Diskhaler [Allen & Hanburys]).

- *Ciclesonide* (*CIC*) is available in MDIs with non-CFC propellants (Alvesco [Altana]).
- *Mometasone furoate* (*MF*) is available in DPIs (Asmanex Twisthaler [Schering-Plough]).

3.4.1.2 Devices

Several types of inhaler device have been developed in order to deliver drugs directly to the airways, rather than rely on absorption of oral preparations.

Metered dose inhalers (MDI) are pressurised inhalers, some of which are breath activated. They contain the drug either as a suspension in a carrier liquid or as a solution which is delivered through a chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) propellant. HFA propellants were phased in to replace CFC propellants when it was realised that the latter have ozone depleting properties. Studies show that HFA propellants deliver a greater proportion of fine particles than CFC propellants in the same device resulting in a greater proportion of the drug being deposited in the small airways.[49] Use of a spacer device in conjunction with an MDI can also alter patterns of lung deposition[50] and increase the total proportion of actuator dose delivered to the lower airways.

Dry powder inhalers (DPIs) require less co-ordination by an individual in order to achieve correct inhaler technique. However, lung deposition is flow-dependent requiring a forceful, deep inhalation to correctly trigger the device. The higher the flow rate, the smaller the particle size and the better the lung deposition.[51]

There is a wide variety of available delivery systems based on these three types of inhaler device. Inhaler technique, individual preference and cost are all factors that may guide health care providers in their choice of inhaler device.

Although potentially important in the decision as to which ICS might be best suited to an individual, the comparison of inhaler devices is beyond the scope of this appraisal.

3.4.1.3 Inhaler technique

The ability to correctly use an inhaler is essential if the anticipated dose of an agent is to be successfully delivered to the correct area within the lungs. The method of assessment of inhaler technique in clinical trials has varied and includes a physician rating of correct technique and an evaluation of the percentage of patients not complying with the individual

tasks necessary for successful inhalation e.g. expiration prior to inhaling, inhaling deeply and breath-holding at the end of the inhalation. A systematic review of the assessment of correct inhaler technique identified 15 studies that evaluated inhaler technique using a variety of inhaler devices (including MDIs and DPIs).[45] Physicians assessed inhaler technique as 'good' in between 5% and 86% of patients. Co-ordination of MDI activation with onset of inspiration was cited as a particular task which individuals found difficult (17 to 68% of individuals were unable to do this in this set of studies).[45] In several studies, education greatly improved technique, but the amount of improvement was variable (from 6 to 46% in one study).[52]).

3.4.1.4 Mechanism of action

ICS suppress inflammation in the lungs and are therefore the mainstay in the prophylactic treatment of chronic asthma. Regular treatment with ICS reduces inflammation, swelling and mucus production in the lungs resulting in better airflow in and out of the airways, fewer exacerbations, better control of symptoms and lung function and ultimately a reduction in hospital admissions and deaths from asthma.[53-55] The anti-inflammatory effects may take between one to three weeks to become apparent[56] and it may take up to 12 weeks of regular daily treatment before maximum benefit is seen. However, the length of time taken to achieve maximal treatment benefit is dependent upon both asthma severity at baseline and the outcome meaure used to assess treatment effect.[56;57] Those with severe asthma when ICS treatment is started may take longer to achieve maximal treatment effect compared to those with mild asthma.[56] The efficacy of ICS therapy for asthma depends on the agent being delivered in the correct dose (see section 3.3.3) to the correct site within the airways (see section 3.4.1.3). ICS are often referred to by individuals with asthma as 'preventers'.

3.4.1.5 Pharmacology

The mechanism of action of corticosteroids in asthma has not been fully elucidated. However, corticosteroids are known to exert their effects by binding to a glucocorticoid receptor located in the cytoplasm of target cells. Once activated the drug-receptor complex moves into the nucleus of the cell and binds to the deoxyribonucleic acid (DNA) and directly or indirectly regulates the transcription of target genes. Control of inflammation is believed to be a result of an increase in the transcription of anti-inflammatory genes and a decrease in

the transcription of inflammatory genes.[58] Potency of a given corticosteroid is governed by the affinity of the drug to bind to the glucocorticoid receptor. Receptor affinity is usually measured relative to dexamethasone. Of the currently available compounds MF has the highest relative receptor affinity, followed by FP and the active metabolites of BDP (17- BDP monopropionate) and CIC (des-CIC) (*Table 2*).

Two of the currently available ICS (BDP and CIC) are prodrugs i.e. a pharmacologically inactive compound which is activated by esterases found only in the lungs.[58]

Due to the ubiquitous nature of the glucocorticoid receptor, corticosteroids act on a wide range of cell types and are therefore capable of producing unwanted systemic effects in addition to their anti-inflammatory actions (see section 3.4.1.6). By administering corticosteroids directly to the airways via inhaler devices, smaller doses of the drug are required, drug concentrations at the site of action are higher and the likelihood of systemic side effects is reduced.

The bioavailability of ICS determines the extent of systemic side effects and is a measure of the rate and extent at which the drug reaches the target site and the systemic circulation. After inhalation, a large proportion of the dose may be swallowed, the proportion depending on inhaler device and technique. Oral bioavailability depends on absorption characteristics from the gastrointestinal tract, lipophilicity of the compound and the extent of first pass metabolism. It ranges from 1% (FP) to 26% (active metabolite of BDP) for currently available compounds (*Table 2*). Pulmonary bioavailability depends on the amount deposited in the lungs, will differ for different delivery devices and ranges from 11% for MF delivered via a DPI to 52% for the active metabolite of CIC[59-65] (*Table 2*).

Once it reaches the circulation, most of the absorbed drug binds to plasma proteins; less than 1% remains unbound for CIC increasing to 13% unbound for BDP.[59-65] Only the unbound fraction is pharmacologically active. All currently available ICS are cleared by the liver.

TABLE 2 *Pharmacodynamic and pharmacokinetic characteristics of currently available ICS*

	RRA	Oral bioavailability (%)	Pulmonary bioavailability (device) [%]	Comments	Refs
BDP	53	15-20	55-60 (HFA-MDI)		59
17-BMP	1,345	26	36 (CFC-MDI)	Active metabolite of BDP	59
BUD	935	11	18 (CFC-MDI)		60;61
FP	1,800	<1	17 (DPI) 26 (CFC-MDI) 29 (HFA-MDI)		62;63
CIC	12	<1	-		64
DES-CIC	1,200	<1	52 (HFA-MDI)	Active metabolite of CIC	64
MF	2,300	<1	11 (DPI)		63;65

Key: RRA – relative receptor affinity; BDP – BDP; 17-BMP – 17-BDP monopropionate; BUD – BUD; FP – FP; CIC – CIC; DES-CIC – DES-CIC; MF – MF; HFA-MDI – metered dose inhaler with HFA propellants; CFC-MDI – metered dose inhaler with CFC propellants; DPI – dry powder inhaler

3.4.1.6 Adverse events

Adverse events associated with ICS use can be categorised into local or systemic events. There appears to be a wide spectrum of level of concern amongst clinicians about the occurrence of adverse events a result of therapy with ICS. Anecdotally, some clinicians appear to be very aware of the risk of systemic adverse events, whilst others are reassured by the low frequency at which they are encountered in practice.

Local adverse events are the most commonly observed and whilst they do not cause significant morbidity, they may lead to diminished concordance. The most frequently occurring local adverse events are dysphonia, oropharyngeal candidiasis, cough, throat irritation and reflex bronchoconstriction.

- *Dysphonia* is reasonably common in individuals using ICS.[66] Although the exact mechanism of dysphonia is unknown, it is thought to be related to vocal cord inflammation.[67] Measures that reduce deposition of the drug around the larynx therefore help to alleviate symptoms. These can include the use of a spacer device or alternative inhaler device, slowing the speed of inhalation, holding post-inspiratory breath for a longer period of time, and decreasing the dose and frequency, although in some cases temporary withdrawal of medication may be necessary.
- *Oral candidiasis* occurs less commonly than dysphonia, being reported in approximately 4% to 13% of adult ICS users, and 1% of children.[68;69] Its prevalence is positively

correlated with total daily dose and with dosing frequency.[70;71] Other risk factors include concomitant antibiotic therapy, concomitant nasal or systemic corticosteroids, and immunosuppression. *Candida* overgrowth is usually the direct result of local corticosteroid inhibition of the normal host defence functions of neutrophils, macrophages, and T lymphocytes at the oral mucosal surface. Therefore overgrowth can be reduced by use of a spacer device, decreasing the dosing frequency and rinsing the mouth after drug administration.

- The adverse events of *cough, throat irritation and bronchoconstriction* are thought to be caused primarily by upper airway irritation by the propellants or surfactants present in the aerosol. This reaction, which may be most marked after upper respiratory tract infections, can prevent adequate deposition of the ICS in the lungs, and thereby cause a worsening of asthma symptoms. These post inhalation symptoms can be reduced by pre-treatment with a bronchodilator, use of a spacer device, use of a slow inhalation technique or a change to a dry powder formulation.[66]

Systemic adverse events occur as a result of the amount of drug that reaches systemic circulation by absorption through the lungs or the gastro-intestinal system. As previously outlined, this is influenced by the pharmacokinetics of the ICS, the site of deposition, as well as inter-individual characteristics that may influence the risk of systemic adverse events. Accurate assessment of systemic adverse events associated with ICS use is often confounded by the concomitant use of other steroid preparations, such as oral or nasal ICS.[70;72;73] The most commonly occurring systemic adverse events potentially associated with long term ICS use are adrenal suppression, growth retardation in infants, children and adolescents, osteoporosis, skin thinning and easy bruising, cataract formation and glaucoma.

The effects of ICS on *suppression of hypothalamic-pituitary-adrenal (HPA) function* have been well documented.[73-75] In general, studies have indicated that HPA axis suppression is associated with the use of doses exceeding the equivalent of 1,500µg per day of BDP or BUD in adults (the equivalent of 400µg of BDP or BUD per day in children). The effect appears to be more marked with BDP than with BUD.[76-80] Dose-ranging studies in adults and children indicate that single doses of FP exhibit threefold greater adrenal suppression than BUD, on a microgram equivalent basis.[81] One randomised controlled trial compared the effects of FP 1,500µg per day and BUD 1,600µg per day with placebo in both healthy participants and participants with moderately severe asthma over a seven day duration.[82]

The trial used the outcomes of urinary levels of total cortisol metabolites (TCM), morning serum cortisol levels and osteocalcin levels as markers of corticosteroid absorption. Results indicated that FP had a greater effect on the two markers of the HPA axis (TCM and morning serum cortisol levels) than BUD, although neither difference was significant. Conversely, BUD was associated with a significant difference in reduced osteocalcin concentration levels in both healthy and asthmatic participants relative to FP.

There have also been cases of adrenal crisis associated with ICS use documented in the literature.[83;84] A survey of the frequency of adrenal crisis associated with ICS use[83] showed that from an initial 2912 questionnaires, 33 cases of adrenal crisis were identified. Twenty-eight of the cases were identified in children and five in adults. Of these 33 patients who had received ICS in the range of 500-2000µg per day, 30 (1%) had received FP, one (3%) FP and BUD, and two (6%) BDP. In all these patients except one, the duration of oral corticosteroid therapy in the previous 12 months was estimated to be less than 21 days.

Overall, although the biochemical changes in markers of HPA axis suppression are unequivocal, their clinical importance remains unclear, and even at high doses of ICS there remains significant inter-individual variability with many patients demonstrating little or no evidence of adrenal suppression.[76;77]

Although these biochemical changes are unequivocal, their clinical importance remains unclear, and even at high doses of ICS there remains significant inter-individual variability with many patients demonstrating little or no evidence of adrenal suppression.[76;77]

One of the major concerns of long-term ICS use is the potential for adverse effects on bone turnover, resulting in an increased risk for *osteoporosis and fracture*. This is mediated through the inhibition of osteoblast function (bone formation) and by increasing osteoclast function (leading to increased bone resorption). These act indirectly by inhibiting intestinal calcium absorption and renal calcium re-absorption, causing secondary hyperparathyroidism. A number of studies have assessed the effects of high dose ICS use on markers of serum osteoclastin and urinary hydroxyproline.[85;86] These studies have shown mixed results with some demonstrating decreased bone formation and increased bone re-absorption in a dose dependent manner,[85;86] whilst others have shown no effects on plasma osteoclastin concentrations at doses of BDP and BUD as high as 2000µg per day.[87] Similarly, high doses of both BDP and BUD have also not shown any effect on urinary calcium excretion, intestinal

calcium absorption, serum calcium, phosphate or parathyroid hormone levels.[88;89] In relation to bone density, there is limited evidence from two studies that high dose ICS use for a duration of three years was associated with an 18% reduction in lumbar spine density[89]and a reduction in both lumbar spine and femoral neck density.[90] However, in both of these studies all patients had previously received treatment with oral corticosteroids. Additional evidence from a cross-sectional study of patients treated with ICS at a median cumulative dose of 876µg/day over a six-year period, indicated that there was a negative association between cumulative steroid dose and bone-mineral density at the lumbar spine, femoral neck, Ward's triangle, and trochanter, both before and after the adjustment for the effects of age and sex.[91] A doubling of the dose of ICS was associated with a decrease in bone-mineral density at the lumbar spine of 0.16 SD (95% CI: 0.04; 0.28). Decreases of a similar magnitude were observed at the femoral neck, Ward's triangle, and trochanter. The majority of the study participants were from a primary-care population with relatively mild asthma, so that potentially neither the underlying disease itself not a substantial use of oral corticosteroids were probable confounders. Additionally, the study participants were between 20 and 40 years of age, so that the confounding effects of age and menopausal status were minimised. However, the exact implications of the findings of an association between cumulative dose of ICS and reductions in bone mineral density from the study would need to be verified in a longitudinal study, particularly since bone loss with oral corticosteroid therapy is time dependent and most rapid in the first 12-24 months of treatment duration.[92]

Three further studies conducted in children, have shown that doses of BDP and BUD up to 800µg per day did not affect bone density,[93;94] and the lumbar spine density of children receiving BDP 300 to 400µg per day for six months was not different from that of the control group.[95] Overall, the long term consequences of administering ICS for many decades from early childhood are not known.

There is evidence that the use of high dose ICS is associated with *skin thinning and easy bruising*.[96;97] One study showed that skin thickness measured by an ultrasound scan was significantly reduced by 15% to 19% in patients on BDP 1,000 to 2,250µg per day compared to controls.[96] In addition the prevalence of bruising was significantly higher at 48% in this patient population compared to 12% in the control population.[96] The results of a further survey also indicated that easy bruising was the commonest reported symptom with the use of ICS occurring in almost half of the patients.[97] The relative risk of easy bruising was more than double that of a population of a similar age and sex distribution not taking ICS. This risk

also increased with age, dose, and duration of therapy.[97] The presence of skin bruising can be considered a visible marker of the adverse effects of ICS therapy on collagen turnover in connective tissue. However, it is unclear whether early susceptibility to skin bruising relates to effects on collagen in other systemic tissues such as bone.[98] Therefore the absence of skin bruising cannot necessarily be taken as a guide to the safety of a given dose of ICS.

- *Posterior subcapsular cataract* (PSC) is a well recognised complication of treatment with oral corticosteroids with the incidence increasing with both dose and duration of treatment.[99;100] The incidence also depends on the individual's age (particularly in children) and ethnic origin, with Hispanic people being more susceptible to development of PSCs.[99] However, the evidence of an association between ICS use and development of a PSC is equivocal and often confounded by previous exposure to oral corticosteroid therapy. Three studies have reported no association between long-term low and high dose ICS therapy in adults and the prevalence of PSCs.[101-103] A further population based survey, reported that after adjustment for age and sex, the relative prevalence ratio for corticosteroid versus no corticosteroid exposure was 1.9 (95% CI: 1.3, 1.9) for posterior subcapsular, 1.5 (95% CI: 1.2, 1.9) for nuclear, and 1.1 (95% CI: 0.9, 1.3) for cortical cataracts.[104] The relative prevalence ratio of posterior subcapsular cataracts for a lifetime dose of BDP greater than 2000µg per day was 5.5 (95% CI: 2.3, 13.0).[104]
- There have also been case reports suggesting that ICS use may be associated with the development of *ocular hypertension or open-angle glaucoma*.[105;106] The results of one case-control study showed that after adjustment for age, sex, diabetes, systemic hypertension, and the use of ophthalmic or oral corticosteroids, there was no association between current use of inhaled or intranasal corticosteroids and an increased risk for ocular hypertension or open-angle glaucoma. However, those patients who were using high doses of corticosteroid on a regular basis for three or more months were at a small, significantly increased risk; odds ratio of 1.44 (95% CI: 1.10, 2.06).[107]

3.4.2 LABAs

3.4.2.1 Products available

There are currently two long-acting beta$_2$-agonists (LABAs) licensed for use in adults in England and Wales.

- *Salmeterol* (SAL) is available in MDIs with CFC-propellants (Serevent® [Allen & Hanburys]) and in DPIs (Accuhaler® [Allen & Hanburys] and Diskhaler® [Allen & Hanburys].
- *Formoterol fumarate* (FF; previously known as *eformoterol*) is available in MDIs with non-CFC propellants (Altimos Modulite® [Trinity-Chiesi]) and in DPIs (Oxis® Turbohaler [AstraZeneca] and Foradil® [Novartis]).

Combination products available

There are currently two combination products containing an ICS and a LABA licensed for use in adults in England and Wales.

- *BUD* combined with *FF* (BUD/FF) is available in DPIs (Symbicort® Turbohaler [Astrazeneca]).
- *FP* combined with *SAL* (FP/SAL) is available in MDIs with non-CFC propellants (Seretide® Evohaler [Allen & Hanburys]) and DPIs (Seretide® Accuhaler [Allen & Hanburys]).

3.4.2.2 Mechanism of action of LABAs

LABAs produce sustained bronchodilation (relaxation of the airways), improving airflow in and out of the lungs. In contrast to SABA (e.g. salbutamol, terbutaline), which are used for quick relief of symptoms, these compounds are administered on a regular basis for the long-term control of symptoms.

3.4.2.3 Pharmacology

The two currently available LABAs (SAL and FF) are highly selective beta$_2$ adrenoceptor agonists which produce a bronchodilator effect lasting for at least 12 hours after a single inhalation. They act principally on smooth muscle beta$_2$-adrenoceptors which are widely distributed throughout the bronchial tree; the highest density of beta$_2$ -adrenoceptors is found in the alveoli.[108] Both agents are highly potent (i.e. they are effective at low concentrations). Comparative studies suggest that the potency ratio is approximately 5:1 (FF:SAL) both for systemic side effects seen in healthy volunteers[109;110] and bronchodilator effects seen in people with asthma.[111] Onset of bronchodilation with FF is within 2-3 minutes whereas the

onset of bronchodilation with SAL takes approximately 10 minutes and the maximal effect may not be apparent for several hours.[112] FF is more lipophilic than SAL and has a much higher degree of intrinsic agonist activity.[113] In addition to bronchodilator effects, LABAs also provide protection from a number of stimuli causing bronchial hyperresponsiveness e.g. methacholine, cold air, exercise, hyperventilation and histamine.[114] Despite some indication of anti-inflammatory activity in laboratory experiments, neither SAL nor FF have been shown to have anti-inflammatory effects in patients with asthma,[115;116] although preliminary evidence suggests that LABAs might have some mild anti-inflammatory effects when given in combination with ICS (see section 3.4.3) as a result of inadvertent potentiation of the effects of the ICS.[117] The main adverse effects of LABAs relate to their systemic activity (see section 3.4.2.4). Both drugs are relatively well tolerated at recommended doses but their therapeutic window is fairly narrow.[109]

3.4.2.4 Adverse events

Most adverse events related to the use of LABAs are a result of systemic absorption (due to stimulation of $beta_2$-adrenoceptors in the heart, peripheral vasculature and skeletal muscle) and are dose-related. At standard doses, adverse events such as tachycardia, increase in the QTc interval, hypokalemia, hyperglycaemia and tremor are minimal in most individuals.[114] At higher doses (which may be relevant during an acute asthma attack), both SAL and FF produce dose-related effects on heart rate, diastolic and systolic blood pressure, QTc interval and plasma potassium levels.[109]

3.4.2.5 Tolerance

Tolerance to the effects of regular LABA exposure, as a result of down-regulation of $beta_2$-adrenoceptors, may result in a diminution of response and associated worsening of disease control. This has been the subject of much basic and clinical research.[118-123] Whilst down-regulation of $beta_2$-adrenoceptors has been demonstrated in laboratory studies, most large clinical trials of LABAs have shown that tolerance to the bronchodilator effects of LABAs is not a significant clinical problem.[113] Tolerance to the bronchoprotective effects of LABAs against bronchoconstrictor stimuli such as methacholine challenge or exercise has been demonstrated in clinical studies.[124-127] Although bronchoconstrictor challenges are considered to be a surrogate for conditions during an asthma exacerbation, whether these

laboratory-conducted studies are relevant to the every-day treatment of asthma with LABAs is unclear. There is also some evidence to suggest that during regular LABA therapy there might be a reduced response to SABA, although some of the studies in this area are difficult to interpret.[113;128]

3.4.2.6 Effect of LABAs on life threatening asthma attacks and asthma-related deaths

Concerns have been raised in the literature regarding the association between treatment with a LABA and an increased risk of death due to asthma. This association however, has remained uncertain, since it can be suggested that a high level of beta$_2$-agonist use is probably correlated with severity of asthma, and that those with more severe asthma are at greater risk of death.[129] Two post marketing surveillance studies have therefore assessed the safety of SAL and salbutamol either versus each other or placebo,[130;131] and the US Food and Drug Administration (FDA) have assessed data from three clinical trials[132;133] submitted in support of the approval of Foradil Aerolizer for marketing in the United States for reports of serious asthma exacerbations.[134]

Salmeterol Nationwide Surveillance study (SNS)

The SNS study conducted in the United Kingdom in 1990-1991, randomised 25,180 patients with asthma who were considered to require regular bronchodilator treatment.[130] Patients were randomised to receive either SAL 50µg twice daily (n=16,787) or salbutamol, 200µg four times daily (n=8,393) in combination with their previously prescribed asthma drugs for 16 weeks. Approximately three quarters of the patients were taking either an oral or ICS. The incidence of drug-related serious adverse events was similar in both groups (1.19% versus 1.15% respectively), but a significantly lower rate of severe, non-fatal asthma-related adverse events was observed in the SAL group compared with the salbutamol group (9.9% versus 1.6% respectively). The incidence of the combined trial endpoint of respiratory and asthma-related deaths was not significantly different between the SAL treatment group and the salbutamol treatment group (0.07% versus 0.02% respectively).[130]

Salmeterol Multicentre Asthma Research Trial (SMART)

The SAL Multicentre Asthma Research Trial (SMART) was a randomised, placebo controlled study that compared the effects of adding SAL or placebo to usual asthma therapy.[131] Patients were randomised to receive either SAL, 42µg twice daily via a metered-dose-inhaler (MDI) or placebo twice daily for a duration of 28 weeks. The planned safety interim analysis was conducted after 26,355 patients had been randomised. At this point the trial was terminated as it was found that the overall rate of death was higher in patients treated with SAL compared with placebo. The interim analysis indicated that the occurrence of the primary outcome (combined respiratory-related deaths or life-threatening asthma attacks) was low and not significantly different between the groups. However, there was a small but significant increase in respiratory related deaths (24 versus 11) and asthma-related deaths (13 versus 3) in patients receiving SAL compared with placebo. Further post-hoc analysis showed that compared to placebo, a higher rate of asthma-related deaths occurred in the SAL group in both whites (0.01% versus 0.07%) and African Americans (0.04% versus 0.31%) respectively. However, the overall estimates of excess deaths attributable to SAL were greater in the African American trial patients due to a higher event rate. It was also observed that the occurrence of asthma-related deaths and life-threatening experiences were similar in both groups in those patients using ICS at baseline (16 versus 13 respectively). However, overall the trial was not designed or conducted in a manner that allowed for any conclusions to be drawn regarding whether or not ICS significantly modify the risk of death or risk of experiencing a life threatening episode purportively associated with the use of SAL.[131]

Combined FF trials

Data from three pivotal randomised, placebo controlled, double-blind trials submitted to the FDA by Novartis Pharmaceuticals Corporation in support of the approval of Foradil Aerolizer for marketing in the US have been assessed for reports of serious asthma exacerbations.[132;133] Two of the trials were conducted in adults and one in a paediatric population. The two 12-weeks trials that were conducted in adults compared the effects of FF 12µg twice daily or 24µg twice daily, with either albuterol 180µg four times daily or placebo. Both the 12µg and 24µg twice daily doses of FF were significantly more beneficial in terms of improvement in the primary endpoint of FEV_1 at 12 week follow-up. Neither of the trials showed a statistically significant benefit for FF, 24µg twice daily compared with FF 12µg

twice daily. However, the rate of serious asthma exacerbations was higher in the FF 24µg twice daily dose group compared with the groups receiving placebo or albuterol, or the group randomised to 12µg twice daily of FF. In the two 12-week trials in adults/adolescents, nine patients in the FF 24µg twice daily group experienced a serious asthma exacerbation, all of which required hospitalisation. One patient died due to a cardiorespiratory arrest. In comparison, two placebo group patients experienced a serious but non-fatal asthma exacerbation, both of which required hospitalisation. In the trial that was conducted in a paediatric population for the duration of one year, 11 patients in the FF 24µg twice daily group had a serious nonfatal asthma exacerbation, compared with 8 patients in the FF 12µg twice daily group, and no patients in the placebo group.

Summary of the risk of mortality or serious asthma exacerbation associated with LABA use

The results from trials and post marketing surveillance studies provide conflicting evidence on any increased risk of mortality or serious asthma exacerbations associated with the use of a LABA. The majority of prospective trials show a decrease in exacerbation rates with the use of a LABA either in addition to an ICS, or used alone. Additionally, there is no significant excess in mortality or the rate of severe exacerbations generally observed. However, the majority of these trials are relatively short term and are usually not powered to detect relatively rare adverse events. In contrast post marketing surveillance studies have showed mixed results regarding an increased risk of either severe adverse events or mortality with LABA use. The results of the SNS[130] indicated that there were fewer severe non-fatal adverse events with the use of SAL compared with salbutamol, whilst there were no significant differences in the mortality rates between the groups. In contrast the results of SMART[131] showed that there was a significantly higher rate of respiratory and asthma-related deaths in the SAL group compared to the placebo group. No difference in the primary composite outcome was observed between the groups. Likewise, the three trials that have assessed the use of FF have indicated that there is an excess risk of severe exacerbation associated with higher doses of FF (24µg twice daily,) compared with either lower doses of FF (12µg twice daily), albuterol or placebo.

Overall it is difficult to quantify the excess risk of severe exacerbation associated with the use of either SAL or FF, but it appears to be reasonably rare. However, the degree to which this

reflects the use of a LABA alone, and may be attenuated by the use of combination ICS plus LABA therapy warrants further investigation in future post marketing surveillance studies.

FDA actions on the use of LABAs

The FDA has recently asked for a 'black box' warning to appear on the labels of products containing SAL. The labelling includes a warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths with the use of SAL. A similar warning has also been included in the prescribing information. The labelling for FF remains unchanged.

3.4.3 Combination inhalers

3.4.3.1 Pharmacology

LABA and ICS affect different aspects of asthma control and many studies have demonstrated the superiority of the combination of agents over increasing the dose of ICS.[135-137] Whether the combined effect is additive or synergistic (i.e. the combined effect is greater than the sum of the effects due to the individual agents) has been the subject of much research, both basic and clinical, and remains controversial.[138-140]

There are no apparent differences in systemic pharmacodynamics or pharmacokinetics when inhaled FP and SAL are given separately or in combination.[141]

3.5 Economic aspects of asthma

The research literature on economic aspects of asthma is large and diverse. While it is dominated by economic evaluations comparing the cost-effectiveness of alternative treatments for asthma, it also comprises: cost-of-illness studies; cost analyses of particular treatments; longitudinal studies; regression analyses of claims databases; and other studies to elicit patient preferences about different types of treatment and care provision.

Our aim in the following sections is to (i) give a broad overview of those economic aspects of asthma that have been identified in the research literature, focussing especially on studies conducted in the UK and/or focussing on asthma in adults, and (ii) attempt to identify the key

causal relationships and trade-offs that seem to exist between resource use and the nature of chronic and acute asthma in adults, in order to best characterise the decision problem and model structure. It is not, therefore, intended to be totally comprehensive either in terms of the economic issues covered or the research literature included on each issue.

3.5.1 NHS cost impacts of asthma

People with asthma place various demands on the NHS budget, ranging from the cost of prescribed asthma medications, to various levels of planned and unplanned health service use (e.g. GP and nurse consultations, secondary care outpatient visits, accident & emergency department visits, and hospital admissions). There is some evidence that adults with asthma place relatively smaller demands on health services than children with asthma.

Cost-of-illness studies of asthma consistently show relatively high "indirect costs" (including for example, the estimated cost of lost days of work or school) compared with the direct health care costs of service use.[142] They sometimes also show the dominant role of people with severe asthma in generating the bulk of asthma-related heath care costs.

Gupta and colleagues have published the most recent well-conducted cost-of-illness study of asthma in the UK.[143] Overall, they estimated that the cost to the NHS of asthma in 2000 was £754 million, of which almost 78.9% (£594 million) was due to community-dispensed prescriptions, 12.7% (£96 million) was due to GP consultations, and 8.4% (£63 million) was due to hospital admissions. This contrasts with most international studies, in which hospital costs account for a higher proportion of the costs associated with health care use.[142] Of the costs associated with hospital admissions over 86% (£54.7 million) were due to non-elective admissions (i.e. probably to treat asthma exacerbations). More recent estimates by the UK's *Lung and Asthma Information Agency* (and cited in the *Asthma UK Cymru* report on "Asthma in Wales today") suggest this cost to the NHS has increased to £889 million annually.[144] In a different study, cited in the same Asthma UK report, difficult-to-control asthma was estimated to cost the NHS £680 million a year.

Other data in the study by Gupta and colleagues suggests that, compared to children, adults (aged 15 and over) contribute proportionately less to both the primary care and secondary care NHS costs (*Table 3*). This data also suggests that amongst adults there is one hospital

admission for asthma for every 13 to 15 GP consultations (for asthma), whereas amongst children there is an asthma-related hospital admission for every eight GP consultations.

TABLE 3 *GP consultations and hospital admissions for asthma in the UK*

Age-group	Weekly number of GP consultations (per 100,000 in age-group) in 2002	Annual number of hospital admissions (per 100,000 in age-group) in 2000/2001
0 – 14 years	46	292
15 – 44 years	25	84
45+ years	21	83

Source: Gupta and colleagues[143]

The Prescriptions Cost Analysis database[145] details the number and cost of all prescriptions dispensed in the community in England. Listing of drug classes (by 317 BNF sub-paragraphs) shows that expenditure in 2005 on corticosteroids for respiratory conditions cost the NHS £436 million. Although only 15th in terms of the number of prescriptions, this is the third largest component of the total cost of community-dispensed drugs in England (after lipid-regulating drugs £625 million, and proton pump inhibitors £446 million). Corticosteroids for respiratory conditions cost the NHS more than double the amount spent on many other major drug classes, such as ACE inhibitors, anti-psychotic drugs and intermediate and long-term insulins.

Of the £436 million spent on respiratory corticosteroids, £276 million was spent on combination inhalers (Symbicort® and Seretide®) (*Figure 5*).

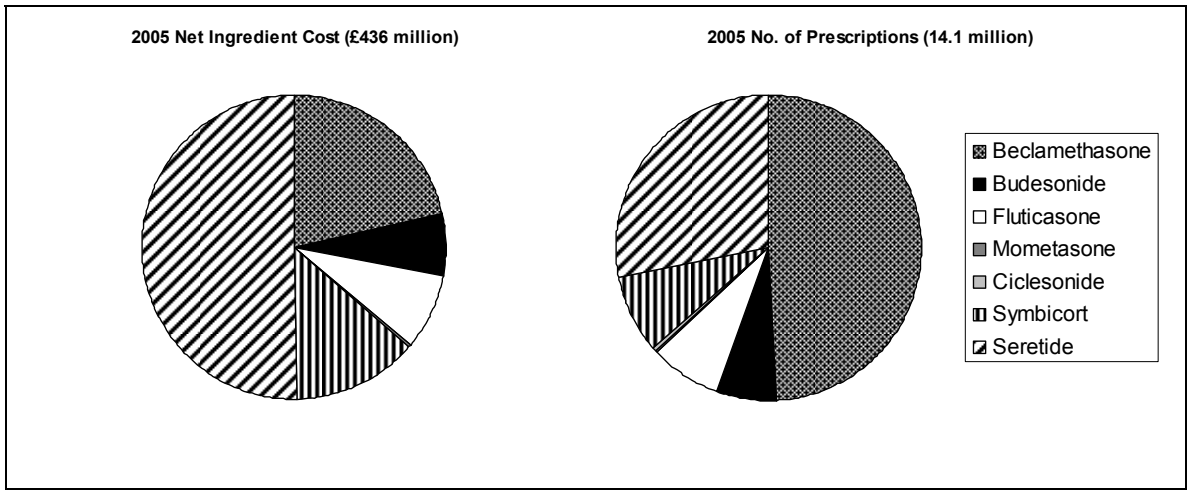


FIGURE 5 *Number and cost of community-dispensed prescriptions for ICS in England 2005*
Source: NHS Health & Social Care Information Centre[145]

Effective drug treatment for asthma relies upon the correct use of various inhaler devices. It is therefore conspicuous that the extra cost of related education and support to encourage correct inhaler technique has usually not been included in economic analyses comparing drug treatments (for example, respiratory nurse education on the correct use of pressurised MDIs). This omission may be particularly important in younger age groups.

3.5.2 Cost to individuals with asthma, their carers and society

3.5.2.1 Financial cost of medicines

In most countries people have to pay all or a part of the cost of their asthma medications. In the UK, NHS prescriptions are subsidised for most adults (by a fixed fee per prescription), and are free of charge for children (aged 16 and under), pregnant mothers (until a year after birth), those aged 60 years or over, and those who meet certain income-related criteria. In addition, people with certain chronic conditions – such as insulin-dependant diabetes or epilepsy – are exempt from all NHS prescription charges, but asthma is not one of these exempt conditions.[146] Across the UK, approximately 50% of individuals are eligible to pay prescription charges, but only 13% of prescriptions dispensed actually incur a charge.[146]

Patient charges for medicines may also play a part in non-concordance with recommended treatment. While in the short-term this might be a cost saving, the longer term health consequences of not taking prescribed medications may generate considerable cost impacts. People are known to employ a variety of strategies to reduce or avoid prescription charges: they do not have their medicines dispensed in full; they substitute cheaper over-the-counter medicines; or they sometimes skip doses to make the prescription last longer. For example, a survey of Citizens Advice clients showed that 28% did not have their medicines dispensed in full, and over a third of these people had long-term conditions.[146](168) In comparison with other countries however, a recent large survey of adults in a number of countries showed that only 4% of people in the UK report not collecting a prescription or skipping medication doses because of cost (compared with 9%, 11%, 12% and 21% in Canada, New Zealand, Australia and the United States).[147]

3.5.2.2 Other financial costs

Economic evaluations and cost-of-illness studies have not usually measured the use of resources such as medical equipment and consumables to support asthma self-medication and self-monitoring. Such equipment and consumable includes nebulisers, inhalers and peak flow meters.[148] Also, families may incur costs as part of asthma allergen avoidance strategies (such as dust-mite-proof bedding, or house renovations to reduce carpeting or damp and mould).

People with asthma also inevitably have to pay more of the various costs of attending more frequent primary care or hospital consultations, for example for travel, car parking, and child care.[149]

3.5.2.3 Indirect costs to individuals with asthma, carers and society

Cost-of-illness studies in a number of countries suggest that a significant proportion – usually 50% or more – of all costs due to asthma are due to the "indirect costs" of lost days at work (or school), which may be estimated by asthma morbidity and treatment, and/or by premature deaths due to asthma.[142] Adults may lose work days as a result of either their own asthma, or due to looking after children or other dependents with asthma. Two early studies estimated the annual number of working days lost due to asthma in the UK to be 5.7 million or 7 million, corresponding to an estimated 50% and 90% of all asthma costs.[150;151]

Other time costs to individuals and carers include healthy time lost (either work or leisure); the time individuals put into the process of receiving health care; and the time carers put into caring for friends and relatives with asthma.[152] These costs are in principle measurable, but much harder to value – including the thorny issue of whether some "time costs", such as lost leisure time, should be counted as a reduction in quality of life (i.e. outcome) rather than counted as a monetary input to the process of producing better health.

3.5.3 Health care resource use and asthma severity

Some published studies have specifically examined the relationship between asthma severity and resource use and costs. Few of these are UK-based studies. Nevertheless, the positive association between asthma severity, whether defined using the GINA classification or other methods, and health care costs seems strong in a range of health systems.[153;154]

A Spanish study, using an internationally recognised system for classifying people's asthma as mild, moderate or severe, found that the average annual asthma-related cost was US$1,336, US$2,407 and US$6,393 respectively.[155] A minority of people with severe asthma incurred 41% of the total costs. Also, both indirect and direct costs increased with higher levels of asthma severity.

Jakeways and colleagues analysed data from a 1991 cross-sectional survey of 2,633 adults (general population) in Nottingham, UK, and calculated the odds ratios for experiencing a range of asthma symptoms - including an "attack of shortness of breath" following strenuous activity, in the past year (25.7% of those surveyed). The relationship between the risk of an asthma attack and FEV_1 % predicted was strongest for values of FEV_1 % predicted below 75%.[156] Since asthma exacerbations are known to be a key driver of asthma-related health care costs (see below), this can be regarded as further evidence of a relationship between asthma severity and costs. However, a US-based study of 2,378 people with severe and difficult-to-treat asthma, found no association between FEV_1 and the level of health care use.[157]

3.5.4 Health care resource use and level of symptom control

Although much asthma medication is prescribed as prophylactic therapy, and some asthma-related health care consultations are for routine clinical reviews, a sizeable proportion of medication use and many consultations occur in response to worsening symptoms. It is therefore possible that there might be a strong relationship between degree of asthma (symptom) control and resource use. As a result, the level of use of healthcare resources is sometimes suggested as a possible measure of effectiveness of asthma treatments.[148]

Vollmer and colleagues, in a prospective US-based study, found that those with three to four control problems experienced rates of acute care episodes that were 3.5 times higher (95% CI: = 2.9, 4.3) than those for people with no reported control problems at the beginning of the study year.[158] Interestingly, they also noted that poor asthma control predicted higher levels of both acute and routine health care use.

A key indicator of poor symptom control is a greater frequency of use of reliever medication (e.g. inhaled salbutamol), which has implications for medication costs. Also, anecdotally, poor asthma symptom control may prompt better adherence to maintenance medication.

The key driver of the higher costs of having poor symptom control appears to be the resource consequences of asthma exacerbations.

3.5.5 Exacerbations and health care resource use

Asthma exacerbations (or asthma "attacks") are one of the key acute events which lead to the consumption of additional medications, or to patient-initiated health care consultations. They are also the likely cause of the more expensive types of asthma-related health care use, such as A & E attendances and hospital admissions.

For example, in a UK-wide cohort study of 12,203 people with asthma followed for one year, those who experienced an attack incurred over three times as much health care costs as those who did not (£381 vs. £108, 1997 NHS costs).[159] Further breakdown of these costs showed that most of this difference was due to hospital stays (£169 vs. £7, over the year) and medication costs (£129 vs. £75). *Figure 6*, below, shows how the proportion of people with asthma admitted to hospital in each age-group is broadly related to the proportion experiencing asthma attacks.

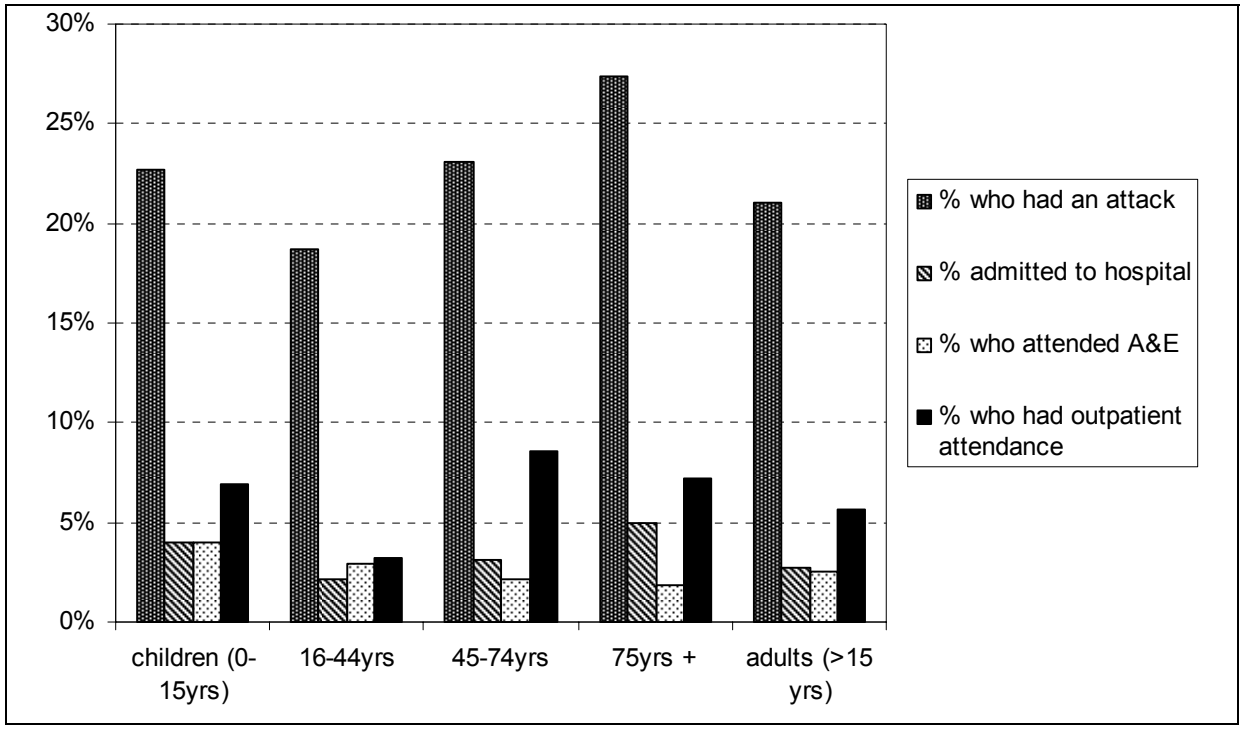


FIGURE 6 *Annual incidence of asthma attacks and usage of secondary care in the UK, by age group*

Source: Hoskins and colleagues[159]

A recent international comparative study has examined whether changes in hospital admissions for asthma (between 1990 and 2000) might be related to changes in the national level of consumption of ICS and other asthma drugs.[160] Overall, they found a negative relationship between falling admissions and increased use of respiratory drugs in 9 of 11 developed countries. The UK was one of three countries where this negative regression coefficient between hospital admissions and asthma drug sales volumes was statistically significant. The relationship was stronger for temporal changes in ICS drug use (using a pooled estimate from a random effects model). Although these findings will potentially reflect a number of factors that may have changed over time – such as the prevalence and severity of asthma, and proportion of people with asthma being treated – the pattern of decline in asthma-related hospital admissions in many countries, including the UK, is consistent with a beneficial effect of the corresponding increasing use of asthma drugs.

There is also a documented relationship between the cost of treating an exacerbation, especially secondary care costs, and the severity of the exacerbation.[161]

It should be noted that many of these published studies predate the existence of NHS Direct, NHS Walk-in Centres and GP out-of-hours cooperatives. In the UK these services now provide either a new pathway to some of the more long-standing providers of acute care (e.g. GPs, Accident & Emergency departments), or provide emergency care and advice in their own right. It is quite possible that these services, by being better publicised and more accessible than traditional models of healthcare delivery, have made it easier for people with asthma to obtain care or advice when they experience symptoms or have other asthma-related queries.

3.5.6 Health care resource use and other factors

In addition to asthma severity and level of asthma symptom control, there are other published studies which have documented a relationship between asthma-related resource use and:

- Co-morbidities (such as allergic rhinitis, diabetes)[162;163]
- Age of adults (with older age-groups incurring higher costs).[163]
- Sex (females being more likely to use care for asthma)
- Self-management programmes
- Health service organisation and accessibility (e.g. balance of primary care provided by nurses vs GPs, availability and use of telephone advice lines).[163;164]
- Health-related quality of life[158;163;165]

3.5.7 Summary points of the economic impact of asthma

Asthma has considerable economic impacts beyond the resources used in providing health care. These impacts comprise lost days of work of asthma sufferers and their families, and lost days of school amongst children.

Of the costs incurred for providing health care for people with asthma, a high proportion is associated with the use of hospital services. Asthma exacerbations, both their frequency and their severity, appear to be the major driver of the cost of using health services.

As asthma severity increases and level of asthma control decreases, the costs to the health system increase. There may be interaction effects, but we are not aware that they have

been explicitly studied (e.g. poorly controlled severe asthma may lead to more consumption of health care resources than the separate effects added). People with difficult-to-control asthma may be another sub-group which generate more health care costs, but they have been less studied.

While there has been a great deal of research to examine the cost-effectiveness of switching to alternative treatments for people with poorly controlled asthma, there do not appear to have been any economic evaluations of stepping down treatment in individuals whose asthma is well-controlled.

In the last ten years there have been considerable changes in the range of available NHS services for people with asthma, especially those for urgent care and advice – such as NHS Direct, Walk-in centres and GP After-Hours Cooperatives. These may have changed the pathways by which people access health care, and perhaps also altered the balance of self-care and formal care. In addition, the cost or cost-effectiveness of allergen avoidance strategies to reduce asthma symptoms have not been studied.

There are some dynamic interrelationships between resource use (costs) and the level of actual or perceived symptom control. For example, patient charges for medication may be a factor in poor concordance with prophylactic therapy, and therefore symptom deterioration (and ultimately higher health care costs). Also, the lack of perceived symptoms may encourage a gradual reduction in the use of prophylactic therapies resulting in a costly exacerbation of asthma symptoms.

4. Decision problems

SECTION CONTENTS

4.1 Aims and Objectives

Assessment aim

To aim of this health technology assessment is to assess the clinical and cost-effectiveness of ICS, used alone or in combination with a LABA, for the treatment of chronic asthma in adults and children aged 12 years and over and to provide guidance to the NHS in England and Wales.

Objectives

- To identify, appraise and synthesise, where appropriate, the current evidence base which addresses the specific research questions on clinical effectiveness listed above
- To identify the costs associated with the different treatments
- To identify, appraise and synthesise, where appropriate, the current evidence base which addresses the specific research questions on cost-effectiveness listed above
- To provide estimates of cost-effectiveness, where possible, of the different treatment options

4.2 Definition of the decision problems

There are five ICS available as licensed preparations in this population: BDP, BUD, FP, MF and CIC. The drugs may all be administered via different devices, including pMDIs, with or without a spacer, and DPIs. Assessment of the effect of device on the dose of corticosteroid delivered to the airways, and, by extension, the effect of device on the clinical effectiveness of ICS, is not included in this report. Similarly, the effect of the propellant (CFC versus HFA) used in the MDIs is not considered.

In addition, two corticosteroids under consideration are available as licensed preparations in combination with LABA: FP/SAL (Seretide) and BUD/FF (Symbicort).

For each ICS, the appropriate comparators are the other ICS. For each combination inhaler, the appropriate comparators are the other combination inhaler and ICS alone.

The BTS/SIGN Guidelines[1] are the context in which the decision problem is set. These are outlined in section 3.3.1. Using the steps in the guidelines, the following specific research questions were identified:

Q1. At low doses (200 – 800µg BDP per day or equivalent), which is the most clinically and cost-effective of the five ICS? (Step 2 of the guidelines)

The relevant population for which this intervention should be considered is asthmatics who have been treated at Step 1 or Step 2 of the guidelines [(i.e. they have either not been treated with corticosteroids previously or have received low doses (as defined above) of ICS)].

Q2. At high doses (800-2000µg BDP per day or equivalent), which is the most clinically and cost-effective of the five ICS? (Step 4 of the guidelines)

The relevant population for which this intervention should be considered is asthmatics who have been treated at Step 2-3 of the guidelines (i.e. they have been treated with ICS previously in conjunction with other treatments such as LABA). They should not be steroid-naïve.

Q3. Which is the more clinically and cost-effective approach to introducing a LABA in to a treatment regimen:

a. To increase the dose of ICS alone or to add a LABA to treatment with an ICS? (steps 2-3 of the guidelines).

b. To continue with an ICS alone or to add a LABA to treatment with a similar dose of ICS using a combination inhaler? (steps 2-3 of the guidelines).

The relevant population for which this intervention should be considered is asthmatics who have been treated at Step 2 of the guidelines (i.e. they have been treated with low dose ICS previously). They should not be steroid-naïve.

Question 3a is viewed as the more clinically relevant of the two sub-questions, because if patients remain uncontrolled on lower dose ICS alone, treatment protocols in line with the BTS/SIGN Guidelines would indicate that either the ICS dose is increased, or a LABA is added to the lower dose of ICS. However, the literature searches conducted for the present assessment also identified trials in which a LABA was added to the ICS treatment regimen without the dose of ICS alone being increased. Whilst this treatment strategy is not in line with that advocated in the BTS/SIGN Guidelines for completeness these studies are included in the clinical effectiveness review as a separate sub-question. This sub-question is not addressed in the cost-effectiveness evaluation.

Q4. Which is the more clinically and cost-effective treatment:

FP and SAL in a combination inhaler or given in separate inhalers?

BUD and FF in a combination inhaler or given in separate inhalers?

Q5. Which is the more clinically and cost-effective treatment: FP and SAL in a combination inhaler or BUD/FF in a combination inhaler? (Step 3 of the guidelines)

The relevant population for which this intervention should be considered is asthmatics who have been treated at Step 2 of the guidelines (i.e. they have been treated with low dose ICS previously). They should not be steroid-naïve.

Within the context of the BTS/SIGN Guidelines, it is generally accepted that the following are clinically equivalent doses: BDP 400µg, BUD 400µg, FP 200µg, CIC 200µg and MF 200µg. Studies which compare these drugs at these drug ratios, delivered through the same device, are thus the most appropriate method for testing this hypothesis.

The clinical effectiveness of treatments for asthma can be assessed against a wide variety of outcome measures, which can be broadly divided into the following categories:

- Objective measures of lung function (e.g) FEV_1, PEFR
- Symptoms (e.g.) Nocturnal waking, morning cough, symptom-free days and nights, symptom scores
- Use of rescue medication (e.g.) SABA, short courses of oral corticosteroids
- Acute exacerbations, defined in a number of ways (e.g.) increase in symptoms or medication or contact with health services
- Adverse events
- Health-related quality of life (HRQoL)
- Mortality

Whilst there is some evidence of the minimally perceived change in PEFR considered to be clinically relevant by patients, for the majority of the above outcome measures it is unclear for which, if any, there is a generally accepted definition of the minimum level of change that is clinically significant.

5. Assessment of clinical effectiveness

SECTION CONTENTS

5.1 Methods for reviewing effectiveness

A peer-reviewed protocol was published during in May 2006 on NICE's website and circulated amongst the Consultees, outlining the agreed scope and methodology for this assessment.[166] This was based upon the scope of the appraisal as published by NICE.[167]

The scope proposed that the assessment be conducted within the context of the stepwise approach as advocated by the BTS/SIGN Guidelines on the management of chronic asthma.[1] As far as possible these guidelines have been taken into account in the assessment of clinical effectiveness.

An over-arching philosophy of the assessment of clinical effectiveness was the need to capitalise, where possible, on existing evidence syntheses of the effectiveness of ICS and LABAs for chronic asthma. The rationale was to reduce duplication and to ensure the assessment was manageable.

A number of systematic reviews of pharmacotherapy for chronic asthma have been published in The Cochrane Database of Systematic Reviews. Some of these are relevant to the scope of this assessment,[54;168-171] although in places their aims and inclusion criteria vary to those of the current assessment. Where possible we have adopted the rigorous methods employed in these reviews, and added to the data presented in them.

5.1.1 Identification of studies

A search strategy for electronic bibliographic databases was devised and tested by an experienced information scientist (*Appendix 3*). Once finalised it was applied to a number of databases including: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; Database of Abstracts of Reviews of Effectiveness (DARE); the NHS Economic Evaluation Database (NHS EED); Medline (Ovid); Embase (Ovid); National Research Register; Current Controlled Trials; ISI Proceedings (Web of Knowledge); Science Citation Index (Web of Knowledge); and BIOSIS.

Searches were run up to February/March 2006, and were restricted to studies published in English. An update search was conducted in October 2006.

The drug manufacturers' submissions to NICE, which we received in August 2006, were also searched for potentially relevant trials.

Additional searches of MEDLINE, EMBASE, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) Database and Cochrane Database of Systematic Reviews were conducted to identify systematic reviews of the long-term adverse events associated with either ICS use alone or in combination with a LABA. For a copy of the full search strategy and search dates refer to *Appendix 3*.

All identified studies were downloaded into a Reference Manager database for storage and retrieval as necessary. A keywording system was devised to enable each reference to be categorised according to pre-specified inclusion and exclusion criteria (See section 5.1.2).

5.1.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria were specified *a priori* based on the scope issued by NICE,[167] as agreed in the published protocol.[166]

5.1.2.1 Intervention

Trials reporting evaluations of the following ICS were included:

- BDP
- BUD
- CIC
- FP
- MF

Trials reporting evaluations of the following ICS combined with LABAs in the same inhaler (i.e. combination inhalers) were included:

- BUD/FF
- FP/SAL

Trials reporting ICS delivered by pMDIs (CFC and HFA excipients), and by DPIs were included, however, those using nebulisers were excluded.

To be included the treatment had to last for greater than four weeks.

5.1.2.2 Comparators

- The ICS were compared with each other.
- The combination inhalers were compared with: each other; and with ICS only. They were also compared with ICS and LABAs administered in separate inhalers.
- Trials testing only different doses of the same agent were not included as these were outside the scope of the assessment. (NB. Cochrane systematic reviews of different doses of BUD,[172] BDP[173] and FP[174] are available). However, trials which compared more than one dose of an ICS against a different ICS were included.
- Trials testing different ICS by different inhalers or propellants were not included (e.g. DPI vs pMDI, or HFA pMDI vs CFC pMDI). The role of delivery device has been assessed by a published systematic review.[175;176] The review found that there was no evidence for differences in effectiveness between different types of hand-held inhaler. However, some clinical trials of different ICS identified in our literature search were specifically designed to demonstrate superiority of one device over another, or in some cases that one inhaler device can be used to achieve comparable asthma control at a lower ICS dose than an alternative device. For this reason we chose to limit the review to comparisons of different ICS via the same type of inhaler or propellant in order to reduce any potential confounding associated with devices.
- NB. Trials reporting comparisons between ICS and placebo were sought and included in order to potentially support economic modelling (e.g. model parameters). Details of these studies are not reported in the assessment of clinical effectiveness.

5.1.2.3 Types of studies

- Fully published randomised controlled trials (RCTs) or systematic reviews of RCTs. Double blinding was not a pre-requisite for inclusion, although blinding was assessed as part of critical appraisal (see Section 5.1.4). Indicators of a 'systematic' review include: explicit search strategy, inclusion criteria, data extraction and assessment of quality.
- Trials reported in abstracts or conference presentations from 2004 onwards were retrieved, however their details were not extracted, critically appraised or analysed (NB.

the exception to this was where an abstract was available which provided data supplementary to a fully published trial report of a particular study. This occurred in a handful of cases).

- Where unpublished full trial reports were available (e.g. as supplied by the drug manufacturers in their submissions to NICE) these were included.

5.1.2.4 Population

- Adults and children aged 12 years and over diagnosed with chronic asthma. Studies in which the patient group were asthmatics with a specific related co-morbidity (e.g. bronchitis; cystic fibrosis) were not included, except for chronic obstructive pulmonary disease (COPD) as requested in the NICE Scope.
- Studies reporting the treatment of acute exacerbations of asthma were not included.
- Trials reporting the effectiveness of ICS with LABAs were only included if the patients had been previously treated with an ICS. Trials assessing the effectiveness of initiating treatment with ICS in combination with LABAs in steroid naïve patients are not within the context of the BTS/SIGN Guidelines (see Section 3.3.1).

5.1.2.5 Outcomes

At the inclusion/exclusion screening stage studies reporting one or more of the following outcomes were included:

- objective measures of lung function (e.g. FEV_1, PEFR)
- symptoms (e.g. symptom-free days and nights)
- incidence of mild and severe acute exacerbations (e.g. mild – requiring unscheduled contact with healthcare professional; severe – requiring hospitalisation, systemic corticosteroids or visit to accident and emergency department).
- use of systemic corticosteroids (e.g. prednisolone)
- adverse effects of treatment
- health-related quality of life
- mortality

NB. A list of specific measures for each of these outcomes was devised for the data analysis (see 5.1.5.1).

Titles and abstracts of studies identified by the searches were screened by one reviewer based on the above inclusion/exclusion criteria. A second reviewer checked a random 10% of these. Any discrepancies were resolved through discussion and involvement of a third reviewer where necessary.

Full papers of studies included on title or abstract were requested for further assessment. All full papers were screened independently by one reviewer and checked by a second. Any discrepancies were resolved by discussion with involvement of a third reviewer where necessary.

All included papers were keyworded in the Reference Manager database as to their intervention and comparator, and were coded for the synthesis framework (see Section 5.1.5) to enable efficient retrieval of sub-sets of studies for analysis.

As far as possible all included papers describing a particular trial were linked together to form a 'set' of studies. One of the papers (usually the seminal journal article reporting the key efficacy and safety results) was designated as the primary publication, with the remaining papers classed as secondary publications.

All included trials were cross-referenced with the relevant Cochrane reviews to ascertain whether or not they had already been included in the reviews.[54;168-171] Those that were included were keyworded in our Reference Manager database accordingly. Conversely, the bibliography of included studies in the relevant Cochrane reviews were cross-referenced with our list of included studies and our inclusion criteria to ascertain whether there were any relevant studies in those reviews that had not been identified by our search.

5.1.3 Data extraction strategy

All trials, except those included in the relevant Cochrane reviews, were fully data extracted. Data were entered into a structured template by one reviewer and checked by a second. Any discrepancies between the data extracted and the original trial report were resolved and the data extraction was finalised (see *Appendix 4*). Data on the studies that met our

inclusion criteria which were also included in the Cochrane reviews are available from the Cochrane reviews themselves.[54;168-171]

5.1.4 Critical appraisal strategy

The methodological quality of the trials supplemental to the Cochrane reviews was assessed according to criteria specified by the Centre for Reviews and Dissemination (CRD)[177] (see *Appendix 4*). Quality was assessed by one reviewer and their judgements were checked by a second. Where there was disagreement a third reviewer was consulted and a final judgement agreed. Judgements about the quality of the trials included in the Cochrane reviews can be found by consulting the relevant review.[54;168-171]

5.1.5 Methods of data synthesis

Results of the included trials were synthesised narratively (see Section 5.1.5.1) with use of meta-analyses where possible and where appropriate (see Section 5.1.5.2). A framework was devised for the analysis and presentation of results, based on the step wise approach recommended in the BTS/SIGN Guidelines for the management of asthma.[1]

The review questions were:

1. Which ICS is the most-effective at low doses (200 – 800µg per day BDP/BUD equivalent[*]) (Step 2 of the guidelines)
2. Which ICS is the most-effective at high doses (800 - 2000µg per day BDP/BUD equivalent[†]) (Step 4 of the guidelines)
3. Which is the more clinically effective approach to introducing a LABA into a treatment regimen:

   a. To increase the dose of ICS alone or to add a LABA to treatment with ICS using a combination inhaler? (Steps 2-3 of the guidelines)

[*] For FP, CIC and MF the equivalent doses are 100 to 400 µg per day.

[†] For FP, CIC and MF high dose is greater than 400 µg per day.

b. To continue with an ICS alone or to add a LABA to treatment with a similar dose of ICS using a combination inhaler? (Steps 2-3 of the guidelines)

4. Which is the more clinically effective treatment:

   FP and SAL in a combination inhaler or given in separate inhalers?

   BUD and FF in a combination inhaler or given in separate inhalers?

5. Which is the most-effective – a combination inhaler containing BUD/FF, or a combination inhaler containing FP/SAL? (Step 3 of the guidelines)

Each included trial was coded according to which of the review questions it was relevant to. For example, a trial comparing 200µg per day of BDP with 200µg per day of BUD was assigned to review question 1, as it evaluated low dose ICS. Some trials were relevant to more than one review question as they tested multiple doses of inhaled steroids, some of which were relevant to review question 1 (i.e. low dose), and some which were relevant to question 2 (i.e. high dose). In a minority of cases a pair-wise comparison of ICS fell into both the high and low dose categories. For example, in a trial of 400µg per day of BUD compared to 500µg per day of FP, the FP arm falls into the high dose category by an additional 100µg. In cases such as these, where one arm of the trial marginally crossed the high dose threshold, the study was classified as being relevant to review question 1 (low dose), with a caveat for the analysis and interpretation of the results.

Each review question was stratified according to a number of pair-wise comparisons of the inhaled steroids and, where relevant, LABAs (where evidence allows). In addition, some trials were included in more than one pair-wise comparison as they evaluated two or more ICS (e.g. a three arm trial comparing FP with BUD and BDP).

Trials were also divided according to whether or not a parallel-group or cross-over design was used. It is generally considered inappropriate to pool these designs together within a meta-analyses.[178] Where necessary trials were then further divided according to the nominal dose ratio employed, following the approach used in the Cochrane review of FP compared to BUD or BDP.[168] Some trials aimed to test the equipotency of newer steroids such as FP using half the dose of older steroids such as BDP and BUD. Therefore, corresponding dose

ratios of 1:2 are common in the literature. Separate analyses of the ratios were necessary to reduce the risk of confounding associated with comparing trials with differing doses.

In summary, the framework comprised sets of trials grouped according to which review question, pair-wise comparison, study design and dose ratio they related to. For example:

- Review question1 - low dose ICS
  - Pair-wise comparison: FP vs BDP
    - Parallel-group trial 1:1 ratio
    - Parallel-group trial 1:2 ratio
    - Cross-over trial 1:1 ratio
    - Cross-over trial 1:2 ratio

It was anticipated that this framework would result in generally smaller sets of studies in each analysis, as opposed to a larger set with potentially more statistical power to identify effects. However, a framework such as this was essential in order to embed the review within the context of the BTS/SIGN Guidelines[1] (as stipulated in the scope for the appraisal issued by NICE) and to reduce the likelihood of confounding due to differences in trial design and dose ratio.

5.1.5.1 Narrative synthesis

As described above, the narrative synthesis comprises a framework whereby trials are summarised according to which review question, pair-wise comparison, study design and dose ratio they were relevant to. The results sections are organised according to this framework.

Within each pair-wise comparison all included trials were tabulated for their key characteristics, and described in the text (e.g. trial duration, patient profile, outcome measures, methodological quality). In addition, more detailed data on the trials are available in *Appendix 4*, for those trials which were supplemental to the Cochrane reviews (and which underwent full data extraction). For further details of the remaining studies please refer to the relevant Cochrane reviews. Each outcome measure is presented in turn and the key results are reported in the text.

There are numerous ways of measuring and reporting outcomes from asthma trials. For brevity we only report the following measures:

- Lung function - FEV_1 litres; FEV % predicted; morning/evening PEFR (Litres per minute).
- Symptoms - Days/nights without symptoms; symptom scores (total day-time; night-time; daily)
- Health related quality of life - Total HRQoL scores
- Use of rescue medication - Mean number of puffs per day of SABA
- Exacerbations: Rate of mild or severe exacerbations (where author's definition of exacerbations is not covered by one of our existing outcomes).
- Adverse events - Rate of adverse events; rate of serious adverse events; rate of withdrawals due to adverse events; urinary/serum cortisol; bone mineral density; growth.

5.1.5.2 Meta-analysis

The feasibility and appropriateness of meta-analysis was considered once narrative syntheses had been completed. The decision to pool was mediated by the likelihood that the trials were clinically homogenous, and that the necessary data were available. Potential clinical heterogeneity was assumed if there were differences between trials in:

- Dose
- Disease severity
- Treatment duration

To some extent the potential for clinical heterogeneity was reduced by virtue of the framework used for the review, whereby studies were grouped into sets according to whether or not a high or a low dose of ICS was used. Nonetheless, even within the low and high dose review questions the dose ranges are relatively wide (e.g. 800 to 2000µg per day). It could also be argued that dose is a proxy for severity, with less severe asthmatics treated with lower doses, and vice versa, although this is a generalisation. It was therefore important to consider severity as a potential source of heterogeneity. Furthermore, the influence of trial duration cannot be discounted. Whilst trials lasting around three months are common, some are designed to evaluate longer term effects on asthma control and adverse effects. Such

trials are likely to have differing aims and consequently if they appeared to be diverse in terms of the above factors they were not pooled.

If pooling was considered appropriate the data in each trial were examined to ascertain whether or not sufficient details were reported to facilitate meta-analysis. The Cochrane Airways Group kindly supplied us with their Review Manager software files containing extracted and analysed data. These files were edited to correspond to our review questions and framework (i.e. they were assembled into smaller sets of studies based on dose, design and pair-wise comparisons). Data from trials included in the Cochrane reviews which did not meet the inclusion criteria for this review were removed. Data from trials supplemental to the Cochrane reviews were added, based on the data extracted to our standardised template (as described in Section 5.1.3).

For continuous outcome measures (e.g. lung function, symptoms) mean values and standard deviations were required in order to calculate mean differences. These were entered where available from the trial reports. Where standard deviations were not reported we converted them from standard errors, p values or confidence intervals provided in the trial reports (where available), using standard formulae within a spreadsheet. Authors were not contacted to supply missing data.

Where trials report multiple comparisons there is potential for 'double counting' if all comparisons are included in the same meta-analysis. Where outcomes are dichotomous (e.g. rate of adverse events) the rate and the number of patients in the common comparator can be halved. Where outcomes are continuous (e.g. lung function) the effect estimate can be halved, but a corresponding measure of variance around the halved estimate has to be imputed. In this assessment where there were multiple comparisons within a meta-analysis and the data were dichotomous, the event rate and number of patients in the common comparator were halved. There were no instances where there were multiple comparisons within a meta-analysis and data were continuous.

Cross-over trials were only pooled where data were reported to facilitate appropriate analysis. Many cross-over trials report results as if the trial used a parallel-group design and pooling is not advised as this results in a unit of analysis error.[178] In such cases cross-over trials were described narratively, with appropriate caveats.

Pooled data were expressed separately in terms of change from baseline to end-point, and as end-point values. Trials were pooled within a meta-analysis as either one of these, but not both. We chose not to impute change values where not reported by authors as it requires estimations of the variance around mean differences, which involves assumptions about within-patient differences.[178] Data were not available to allow within-patient differences to be estimated (e.g. from an appropriate correlation co-efficient).

As mentioned, much of the data were continuous and where it was apparent that the same measurement scale had been used across studies a weighted mean difference (WMD) was used to summarise treatment effects. If it appeared that different measurement scales were employed a standardised mean difference (SMD) was used. Dichotomous data (e.g. rate of adverse events) were pooled using odds ratios. 95% confidence intervals were used for all measures of effect. A fixed-effects model was used, with random-effects model used if statistical heterogeneity was apparent. Statistical heterogeneity was measured using a chi-squared test with $p<0.10$ as the level of significance. The I^2 statistic was also used, whereby a value in excess of 50% indicates substantial heterogeneity.[178]

5.2 Results

5.2.1 Quantity and quality of research available

A total of 5,175 publications were identified through literature searching. Of these, 4,365 were excluded on title and abstract. Full reports for the remaining 807 were requested for more in-depth screening (NB. searches for this report were combined with the accompanying report on ICS in children under the age of 12 years. Consequently, a proportion of the 807 papers screened were included in that report.[179] Of these, 113 records describing 84 studies were included.

Of the 84 studies:

- 10 were conference abstracts published from 2004 onwards (*Appendix 6*)
- 7 were systematic reviews (of which 5 were Cochrane reviews) (see Section 5.2.8)
- 67 were RCTs (of which 38 had been included in the Cochrane reviews)

Literature searches were updated in October 2006. A further 245 publications were identified of which 26 full papers were retrieved for further inspection. Of these 26, nine appear relevant and would be eligible for inclusion in any future update and their bibliographic details are listed in *Appendix 5*) (eight RCTs, and one systematic review).

Table 4 to **TABLE 9** provide a breakdown of the number of RCTs for each pair-wise comparison by review question. (NB. numbers do not add up to 67 as some trials had multiple arms and were common to more than one comparison).

TABLE 4 *Breakdown of studies for Review Question 1 – low dose ICS*

Pair-wise comparison	**Number of RCTs included**
BDP and BUD	5
FP and BDP	6
HFA BDP and HFA FP	0
FP and BUD	5
CIC and BDP	0
MF and BDP	0
CIC and BUD	1
MF and BUD	2
CIC and FP	2
MF and FP	1
MF and CIC	0
Total	22

TABLE 5 *Breakdown of studies for Review Question 2 – high dose ICS*

Pair-wise comparison	Number of RCTs included
BDP and BUD	2
FP and BDP	10
HFA BDP and HFA FP	1
FP and BUD	6
CIC and BDP	0
MF and BDP	0
CIC and BUD	0
MF and BUD	1
CIC and FP	3
MF and FP	1
MF and CIC	0
Total	24

TABLE 6 *Breakdown of studies for Review Question 3a – ICS vs ICS+LABA (ICS dose higher when used alone)*

Pair-wise comparison	Number of RCTs included
FP vs FP/SAL	2
BUD vs FP/SAL	3
BUD vs BUD/FF	4
FP vs BUD/FF	1
Total	10

TABLE 7 *Breakdown of studies for Review Question 3b – ICS vs ICS+LABA (ICS dose similar in both treatments)*

Pair-wise comparison	Number of RCTs included
FP vs FP/SAL	6
BUD vs BUD/FF	3
Total	9

TABLE 8 *Breakdown of studies for Review Question 4 – combination inhaler vs separate inhalers*

Pair-wise comparison	**Number of RCTs included**
FP/SAL (combination) vs BUD+FF (separate)	1
FP/SAL (combination) vs FP+SAL (separate)	3
BUD/FF (combination) vs BUD+FF (separate)	2
Total	6

TABLE 9 *Breakdown of studies for Review Question 5 – combination inhaler vs combination inhaler*

Pair-wise comparison	**Number of RCTs included**
FP/SAL (combination) vs BUD/FF (combination)	3
Total	3

The 67 RCTs are described in the following sections, in terms of their characteristics and their results

5.2.2 Review question 1 – Effectiveness of low dose ICS

(Low dose corticosteroids are defined as 200 – 800µg per day of BDP/ BUD or their equivalent*. This is comparable to Step 2 of the clinical guidelines.)

To re-cap, 22 RCTs evaluated low dose ICS (**TABLE 10**). The following sub-sections describe the characteristics and results of these trials.

* For FP, CIC and MF the equivalent doses are 100 to 400 µg per day.

TABLE 10 *Breakdown of studies for Review Question 1 – low dose ICS*

Pair-wise comparison	Number of RCTs included
BDP and BUD	5
FP and BDP	6
HFA BDP and HFA FP	0
FP and BUD	5
CIC and BDP	0
MF and BDP	0
CIC and BUD	1
MF and BUD	2
CIC and FP	2
MF and FP	1
MF and CIC	0
Total	22

5.2.2.1 BDP and BUD (review Q1 – low dose ICS)

5.2.2.1.1 Study characteristics

Five RCTs evaluated the effectiveness of BUD compared to BDP, published between 1985 and 2004 (*Table 11*). Two were parallel designs,[180;181] the remaining three were cross-over studies.[182-184] The trials were all small studies, containing less than 100 patients.

The majority of studies contained two relevant arms, however in one study there was more than one comparison. Rafferty and colleagues[182] compared a daily dose of 800µg per day of BDP with two different regimens of BUD. The total daily dose in both BUD regimens was 800µg per day, but one group took two puffs daily whilst the other took four.

There were five comparisons at the same nominal daily dose ratio of 1:1, from five trials. One trial was a comparison of total daily doses of 400µg per day,[183] and four were comparisons of a total daily dose of 800µg per day.[180-182;184]

The five studies used the same delivery device for both inhaled steroids. Rafferty and colleagues[182] (BDP – brand not specified, GlaxoSmithKline; BUD - Pulmicort, AstraZeneca), Dal Negro and colleagues[180] (BDP - Pulvinal, Chiesi Famaceutici; BUD - Pulmicort Turbuhaler, AstraZeneca), Tjwa and colleagues[183] (BDP - Becotide Rotacap Rotahaler,

GlaxoSmithKline; BUD -Pulmicort Trubuhaler, AstraZeneca) together with Jäger and colleagues[184] (BDP - Beclomet Easyhaler, Ranbaxy; BUD - Pulmicort Turbuhaler, AstraZeneca) all used DPIs for delivery. Parakh and colleagues[181] used MDIs but did not provide any further details on the devices.

In terms of treatment duration the trials were relatively similar in length, ranging from eight to 12 weeks. Three trials lasted for eight weeks,[180;183;184] and one for 12 weeks.[181] In the final study the length of treatment was described as 'variable'.[182] For the first month of each treatment period patients received their normal maintenance dose of oral prednisolone plus either BDP or BUD. During the second and subsequent months prednisolone was reduced by 1mg until treatment with this drug was withdrawn or asthmatic symptoms 'broke through', or when prednisolone was withdrawn was taken as the end-point of each treatment period.

The age range of patients included in the RCTs, where reported, varied from 15 to 72 years. Two studies reported mean ages of approximately 40 to 50 years,[180;184] and one trial simply recorded that patients were aged 18 years or over.[183] One of the trials included patients described as having 'mild to moderate' asthma,[184] one study included patients with severe asthma taking oral corticosteroids,[182] and another study included patients with 'moderately severe' asthma.[183] The other two studies did not comment on severity,[180;181] although one reported a baseline FEV_1 % predicted of around 70%.[180] In general it appears that the trials were similar in terms of the severity of the constituent patients.

The studies varied in terms of their aims, and hence the way in which they assessed effectiveness. Two studies aimed specifically to compare the effectiveness of different DPI devices.[183;184] One of these aimed to test the hypothesis that there would be no statistically significant differences between the two inhalers,[184] although it does not appear to be an equivalence / non-inferiority trial. In the other study it is not explicitly stated whether the intention was to assess equivalence or superiority. Rafferty and colleagues[182] aimed to assess the relative efficacy of the same dose of BUD and BDP in reducing the need for oral steroids. The purpose of the study by Dal Negro and colleagues[180] was to compare the two steroids in order to correlate measures of lung function with serum eosinophil cationic protein. Parakh and colleagues[181] aimed to compare the relative effectiveness of BUD, BDP and FP in an Indian patient population. (NB. the comparison of FP and BDP from this study is reported in Section 5.2.2.2, and the comparison between FP and BUD is reported in Section 5.2.2.3).

Reported methodological quality was poor. Details of randomisation methods, whether or not this was concealed and whether or not ITT analysis had been performed were lacking. Only one of the two cross-over studies reported a wash-out period.[183] In the other no details were given on any attempts to eliminate carry-over effects.[182]

TABLE 11 *Characteristics of studies (BDP and BUD)*

Study ID	Design	Intervention	Patients	Outcomes
Dal Negro *et al.* (1999)[180]	RCT Parallel-group	1. BDP 200µg q.i.d. (daily total 800µg) 2. BUD 200µg q.i.d. (daily total 800µg) *Delivery device:* 1. DPI (Pulvinal, Chiesi Farmaceutici) 2. DPI (Turbuhaler, AstraZeneca) *Duration:* 8 wks *Run in period:* 2 wks	*Number randomised* 32 *Mean age* 1. 42.3 2. 41.6 *Baseline FEV_1% predicted* 1. 68.7 ± 14.1 2. 70.6 ± 9.1 *Previous ICS treatment (drug and dose)* BDP MDI at a constant dose 1,000 µg for previous 8 wks	FEV_1 PEFR $FEF_{25-75\%}$ MEF_{50} Symptom scores Daily rescue medication use Adverse events
Parakh *et al.* (2004)[181]	RCT Parallel-group Single-blind	1. FP 50µg 4 puffs b.i.d. (daily total 400µg) 2. BUD 200µg 2 puffs b.i.d. (daily total 800µg) 3. BDP 200µg 2 puffs b.i.d. (daily total 800µg) *Delivery device:* MDI (no further details on devices reported) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 42 *Age range* 15-45 *Baseline FEV_1% predicted* Not reported *Previous ICS treatment (drug and dose)* Not reported	Symptom scores FVC FEV_1 FEV_1/FVC PEFR Withdrawals

Study ID	Design	Intervention	Patients	Outcomes
Jäger *et al*. (2000)[184]	RCT Multi-centre Cross-over Open-label	1. BDP 400µg b.i.d. (daily total 800 µg) 2. BUD 400µg b.i.d. (daily total 800 µg) *Delivery device:* 1. DPI (Beclomet Easyhaler, Ranbaxy) 2. DPI (Pulmicort Turbuhaler®, AstraZeneca) *Duration:* 8 wks *Run in period:* 2 wks before randomisation	*Number randomised* 79 *Mean age* 1. 51 ±16 2. 50 ±14 *Baseline FEV_1 % predicted* 1. 75 ±18 2. 78 ±18 *Previous ICS treatment (drug and dose)* continued treatment with either BDP or BUD 800-1000 µg/day	*Primary outcome* AM PEFR *Secondary outcome* FEV_1 (L) PM PEFR FVC Diurnal variation in PEFR Asthma symptom scores day and night Patient-rated treatment efficacy scores Patient-rated acceptability of device Salbutamol inhalations per day Serum cortisol levels adverse events

Study ID	Design	Intervention	Patients	Outcomes
Rafferty *et al.* (1985)[182]	RCT Cross-over Double-blind	1. BDP 200µg 1 puff q.i.d. (daily total 800µg) + placebo 2. BUD 200µg 2 puffs b.i.d. (daily total 800µg) + placebo 3. BUD 200µg 4 puffs q.d. (daily total 800µg) + placebo *Delivery device:* 1. CFC-pMDI (GlaxoSmithKline*) 2. + 3. CFC-pMDI + Inhalet spacer (Pulmicort, AstraZeneca*) *Duration:* variable *Run in period:* Not reported	*Number randomised* 40 *Age range* 23-72 *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* 5 mg oral prednisolone/d and inhaled BDP 400 µg daily for at least 9 months.	*Outcomes* Reduction in daily prednisolone (mg/d)
Tjwa *et al* (1995)[183]	RCT Cross-over	1. BDP 200µg 1 actuation b.i.d. (daily total 400µg) 2. BUD 200µg 1 actuation b.i.d. (daily total 400µg) *Delivery device:* 1. DPI (Becotide Rotacap, Rotahaler. GlaxoSmithKline) 2. DPI (Pulmicort Turbuhaler, AstraZeneca) *Duration:* 8 wks *Run in period:* Not reported	*Number randomised* 16 *Age* >18 *Baseline FEV_1 % predicted* 40-85 *Previous ICS treatment (drug and dose)* Inhaled steroid 150-800 µg/d	*Outcomes* FEV_1 FVC Morning PEFR Evening PEFR Daytime wheeze score/ daytime breathlessness score Daytime cough score Night-time wheeze score Night-time breathlessness score Night-time cough score Daytime SABA use (puffs/day) Night-time SABA use (puffs/day) Bronchial responsiveness to histamine (PC20 FEV_1)

* not stated explicitly, but deduced from the text

5.2.2.1.2 Results

Due to limitations in the data reported by the trials, and differences in study design meta-analysis was rarely possible. The results of this comparison are mostly presented narratively.

Lung function

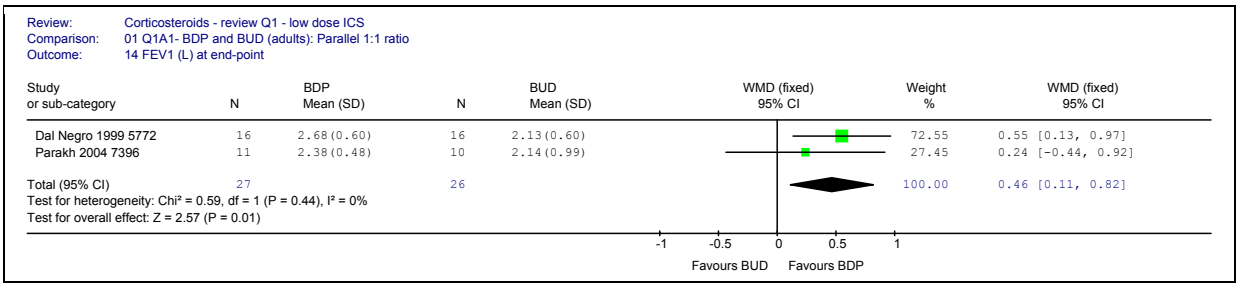
Four of the RCTs reported measures of lung function, however variability in methods of measurement and reporting meant that meta-analysis was not always possible.

Parallel 1:1 dose ratio studies

The two parallel 1:1 ratio trials, both comparing 800µg per day, reported $FEV_{1,}$ (L). In the trial by Parakh and colleagues[181] there was an increase of 0.51 L for the BDP group and 0.66 L for the BUD group between baseline and end-point (p>0.05 at end-point). In the trial by Dal Negro and colleagues[180] there was an increase of 0.48 L for BDP and 0.22 L for BUD between baseline and end-point. The difference between groups at end-point was reported as not being statistically significant but the results in the meta-analysis in *Figure 7* do not confirm this (mean difference 0.55 L, 95% CI 0.13 to 0.97, p=0.015).

The end-point values for the two trials were pooled in a fixed-effects meta-analysis. At end-point there was a statistically significant difference in favour of BDP (WMD 0.46, 95% CI 0.11, 0.82) (**FIGURE 7**).

FIGURE 7 *FEV_1 (L) at end-point (parallel 1:1 dose ratio studies)*



Dal Negro and colleagues[180] reported FEV_1 percent predicted normal. There was an increase of 13.7% in the BDP group, and 8% in the BUD group between baseline and end-point (no statistical significance value reported).

Morning and evening PEFR was reported by Dal Negro and colleagues.[180] Data have been estimated from a graph. There was an increase of 70 L/min for the BDP group and 40 L/min for the BUD group in morning PEFR. The difference at end-point between the groups was not statistically significant (p value not reported). There was an increase of 65 L/min for the BDP group and 35 L/min for the BUD group in evening PEFR. The difference at end-point between the groups was not statistically significant (p value not reported).

Cross-over 1:1 dose ratio studies

Jäger and colleagues[184] reported no significant differences between treatments in FEV_1 (L), and morning/evening PEFR.

Tjwa and colleagues[183] report changes in FEV_1 % predicted during the course of treatment. Increases were observed in both groups but the difference was not statistically significant (p=0.86). Also reported are mean values for PEFR during the second month of treatment. The mean between group difference in morning PEFR was 17 L/min (95% CI 2, 32 L/min, p<0.05), in favour of BUD. For evening PEFR the mean difference was 13 L/min (95% CI -0.3, 27 L/min, p=0.054), in favour of BUD.

Rafferty and colleagues[182] report that there were no significant differences between treatments for mean morning or evening PEFR during the last month of adequate control (no p values given). For morning PEFR end-point values were 215.7 (SD 110.0) L/min and

203.7 (SD 107) L/min for BDP and BUD, respectively. For evening PEFR corresponding values were 238.2 (SD 109.26) L/min and 232.7 (SD 108.3) L/min.

Symptoms

Parallel 1:1 dose ratio studies

Both of the parallel 1:1 ratio studies reported symptom scores, albeit using different scoring methods. Dal Negro and colleagues[180] measured five different symptoms on a four point rating scale (where 0=none, 3= severe, no reference supplied) and produced an overall summary score. There was a reduction of 3.1 points in the BDP group, compared to a reduction of 2 points in the BUD group. There was no significant difference between groups in scores at end-point (no statistical significance value reported).

Parakh and colleagues[181] measured symptoms but do not provide details of the scoring system used. Reductions in scores were 34.8 and 34.1 in the BDP and BUD groups respectively (the between group difference was not statistically significant, p>0.05).

Cross-over 1:1 dose ratio studies

Jäger and colleagues[184] measured day and night time symptoms using a four point rating scale (0=no symptoms; 3= severe symptoms, no reference supplied). Scores for individual items were summed and were presented as mean percentage of maximum symptom scores. Scores decreased for both treatments, but with no significant difference between them (p value reported).

Tjwa and colleagues[183] measured symptoms using a scoring system that appears similar to that used by Jäger and colleagues.[184] Scores are presented for individual symptoms, but an overall summary score is not presented.

Rafferty and colleagues[182] report that there were no significant differences between treatments for symptom scores during the last month of adequate control (no p values given). End-point scores were 9.66 (SD 10.44) and 11.48 (SD 11.1) in the BDP and BUD groups, respectively. No details are provided on the scoring system used other than patients used a visual analogue scale labelled ‘no symptoms’ at one end and ‘severe symptoms’ at the other.

Health related quality of life

None of the trials reported this outcome.

Use of rescue medication

Parallel 1:1 dose ratio studies

Dal Negro and colleagues[180] reported changes in use of salbutamol, which reviewers have estimated from a graph. There was a reduction of 1.6 puffs per day and 0.7 puffs per day in the BDP and BUD groups respectively, between baseline and end-point. The difference between groups at end-point was not statistically significant (no p value reported).

Cross-over 1:1 dose ratio studies

The mean number of daily salbutamol inhalations per day was described as 'comparable' between the two treatments in the study by Jäger and colleagues.[184] No statistically significant differences in day time or night time use of SABAs were reported in the study by Tjwa and colleagues.[183]

Exacerbations

Dal Negro and colleagues[180] reported a reduction in 24 hour bronchospasm attacks of 0.8 and 0.3 in the BDP and BUD groups respectively from baseline to end-point. Differences between groups at end-point were not statistically significant. None of the other studies reported exacerbations.

Adverse events

Parallel 1:1 dose ratio studies

No 'adverse reactions' were reported by Dal Negro and colleagues.[180] Negligible increases in morning serum cortisol were reported in both groups: 0.5 (µg /100ml) and 1 (µg /100ml) in the BDP and BUD groups respectively. Parakh and colleagues[181] did not report safety as an outcome.

Cross-over 1:1 dose ratio studies

Jäger and colleagues[184] reported three adverse events (4%), two with BDP and one with BUD. Treatment was reported to have no effect on morning serum cortisol levels. Safety was not reported in the trials by Tjwa and colleagues[183] or Rafferty and colleagues.[182]

5.2.2.1.3 Summary

Five RCTs of varying size and design have compared BDP with BUD at 'low' doses in patients predominantly with mild to moderate asthma. They compared similar doses of the two drugs, ranging from 400µg/day to 800µg/day. There were few statistically significant differences between the drugs across the outcome measures.

5.2.2.2 FP and BDP (review Q1 – low dose ICS)

5.2.2.2.1 Study characteristics

Six RCTs, published between 1999 and 2004, have evaluated the effectiveness of BDP compared to FP (*Table 12*). All six studies were parallel designs, and ranged in size from a single-centre study with 20 patients to a multi-centre trial with 399 patients.

Three of the studies contained two arms,[185-187] in which one regimen of BDP was compared with one regimen of FP. One study contained three arms, in which FP was compared with BDP and BUD[181] (this study is also referred to in Section 5.2.2.1 and 5.2.2.3). The remaining two studies each contained four arms.[188;189] However, in one of these (Medici and colleagues[189]), only two of the arms are relevant to this particular section as they evaluated low doses of BDP and FP (the other two arms evaluated high doses and are reported in review question 2 – high dose ICS, see Section 5.2.3.2). The remaining study (Raphael and colleagues[188]) can be divided into two separate two-arm comparisons of BDP against FP, each with a dose ratio approximating 1:2 (*Table 12*).

In all six of the studies, comparisons of FP against BDP were at, or approximated, a nominal daily dose ratio of 1:2. The total daily doses of FP:BDP that were compared were 200:400µg (two studies[185;188]), 250:400µg (one study[186]), 400:800µg (three studies[181;188;189]), 500:800µg (one study[188]) and 750-1500µg (one study[189]). A study by Szefler and colleagues[187] did not compare a single daily dose of each drug but instead compared sequentially increasing

doses of FP with sequentially increasing doses of BDP, at a 1:2 dose ratio, over an 18-week period (100:200µg in weeks 1-6; 400:800µg in weeks 6-12; and 800:1600µg in weeks 12-18).

All studies employed the same delivery device for both the inhaled steroids. This was an MDI (Raphael and colleagues: FP - Flovent Inhalation aerosol, BDP - Flovent Inhalation Aerosol, & Beclovent Inhalation Aerosol all GlaxoSmithKline;[188] Szefler and colleagues: FP - Flovent CFC, GlaxoSmithKline and BDP - Vanceril CFD, Schering-Plough;[187] Ige and colleagues: FP – Fluvent, BDP – Becotide both GlaxoSmithKline;[186] no further details for devices from Parakh and colleagues[181] or Prasad colleagues[185]) or an MDI with spacer (no details about devices reported Medici and colleagues[189]) (*Table 12*).

The duration of the treatments in most of the studies was relatively short, being six weeks (the low-dose comparison of Szefler and colleagues[187]), eight weeks (Ige and colleagues[186]) or 12 weeks (Parakh and colleagues;[181] Prasad and colleagues;[185] Raphael and colleagues[188]). An exception is the 12-month study by Medici and colleagues.[189]

The age of patients included in the RCTs ranged from 12-83 years. The mean age was reported in five of the studies, and ranged between 28 and 40. Two studies mentioned that baseline asthma severity was mild to moderate.[186;189] The severity of asthma was not mentioned in the remaining studies, but in two of the studies can be inferred from the reported baseline % of predicted FEV_1 as being moderate[187] or moderate to severe.[188]

In four of the studies the primary aim was to compare the efficacy of FP against that of BDP[181;185;186;188] at a dose ratio of (or approximating) 1:2. One study was described by the authors as "a feasibility study rather than a comparative trial" (Szefler and colleagues, page 411[187]), with the objective of comparing the relative beneficial and systematic effects for two ICS in a dose-response relationship. The remaining study[189] aimed primarily to investigate effects of FP and BDP on bone mass and metabolism. None of the efficacy studies specified a null hypothesis in terms of equivalence or superiority. Reasons for carrying out the efficacy studies included an identified need to simultaneously compare FP, BUD and BDP in the same trial,[181] extending knowledge of effects of FP in Nigeria[186] and India,[185] and a need for simultaneous testing of FP and BDP at a range of doses commonly used to treat asthma.[188]

Reported methodological quality was generally inadequate. Details of randomisation and allocation concealment procedures were not always reported.

TABLE 12 *Characteristics of studies (FP and BDP)*

Study ID	Design	Intervention	Patients	Outcomes
Parakh et al (2004)[181]	RCT Parallel-group Single-blind	*Drug(s):* 1. FP 50µg 4 puffs b.i.d. (daily total 400µg) 2. BUD 200µg 2 puffs b.i.d. (daily total 800µg) 3. BDP 200µg 2 puffs b.i.d. (daily total 800µg) *Delivery device:* 1, 2, 3. MDI (no further details on devices reported) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 42 *Age range (years)* 15-45 (stated that age did not differ significantly between treatment groups) *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* Not reported	*Outcomes* Symptoms FEV_1 PEFR FVC Withdrawals
Prasad et al (2004)[185]	RCT Parallel-group Double-blind	*Drug(s):* 1. FP 50µg 2 puffs b.i.d. (daily total 200µg) 2. BDP 100µg 2 puffs b.i.d. (daily total 400µg) *Delivery device:* 1, 2. MDI (no further details about devices reported) *Duration:* 12 wks *Run in period:* Not reported	*Number randomised* 74 *Mean age (year) + range* 1, 2. 28 (12-60) *Baseline FEV_1 % predicted* <80 *Previous ICS treatment (drug and dose)* Not reported directly but inferred from symptom scores that patients would have needed 400 µg /day BDP at time of enrolment	*Outcomes* FEV_1 PEFR FEV_1/FVC Symptoms

Study ID	Design	Intervention	Patients	Outcomes
Raphael et al (1999)[188]	RCT Multi-centre Parallel-group Double-blind	*Drug(s):* 1. FP 44µg 2 puffs b.i.d. (daily total 200µg ex valve) 2. FP 110µg 2 puffs b.i.d. (daily total 500µg ex valve) 3. BDP 42µg 4 puffs b.i.d. (daily total 400µg ex valve) 4. BDP 42µg 8 puffs b.i.d. (daily total 800µg ex valve) *Delivery device:* 1, 2. MDI (Flovent Inhalation Aerosol, GSK) 3. MDI (Inhalation Aerosol, GSK) 4. MDI (Beclovent Inhalation Aerosol, GSK) GSK = GlaxoSmithKline *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 399 *Mean (years)age (±sd, range))* *1. 38.4 (± 1.4, 13-70)* 2. 37.8 (± 1.3, 13-72) 3. 41.5 (± 1.5, 13-83) 4. 39.8 (± 1.7, 12-72) *Baseline FEV_1 % predicted* 46-65 *Previous ICS treatment (drug and dose)* 8-12 puffs/day of BDP or triamcinolone acetomide for at least 1mth prior to enrolment	*Outcomes* FEV_1 FEF_{25-75} FVC PEFR am and pm SABA use Daily asthma symptom score % days with no rescue SABA use % days with no symptoms Asthma exacerbations Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Szefler et al (2002)[187]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP serially increased doses: 88 → 704µg q.d. (daily total 100 → 800µg ex valve) 2. BDP serially increased doses: 168 → 1344µg q.d. (daily total 200 → 1600µg ex valve) *Delivery device:* 1. MDI + spacer (Flovent CFC, GlaxoSmithKline) 2. MDI + spacer (Vanceril CFC, Schering-Plough) *Duration:* 21 wks (dose escalation every 6 wks) *Run in period:* 3 wks	*Number randomised* 30 *Mean (years)age(±sd)* 1. 29.58 (± 7.21) 2. 30.27 (± 7.64) (range 18-55) *Mean baseline FEV_1 % predicted (±sd)* 1. 75.07 (± 11.16) 2. 73.33 (± 11.08) *Previous ICS treatment (drug and dose)* No use of ICS within 6 months before enrolment	*Outcomes* Cortisol FEV_1 Methacholine PC20 Exhaled nitric oxide Exercise max absolute fall in FEV_1 Exercise fall in area under curve (explanation not given) Sputum eosinophilis +0.2 (%) Neutrophilis (%) Eosinophilic cationic protein Symptoms Rescue medication usage

Study ID	Design	Intervention	Patients	Outcomes
Ige et al (2002)[186]	RCT Single-centre Parallel-group Open-label	*Drug(s):* 1. FP 220 µg /day (daily total 250 µg ex valve) 2. BDP 400 µg /day *Delivery device:* 1. pMDI (Fluvent, GlaxoSmithKline*) 2. pMDI (Becotide, GlaxoSmithKline) *Duration:* 8 wks *Run in period:* 1 wk	*Number randomised* 20 *Mean (years) age (±sd, range)* 1. 36.00 (± 15.46,16-56) 2. 29.30 (± 15.20, 16-61) *Baseline FEV_1 % predicted* 1. 83.5 (SD 13.37) 2. 76.8 (SD 8.55) *Previous ICS treatment (drug and dose)* 400 µg SABA for 1 wk screening	*Outcomes* FEV_1 PEFR Symptoms Rescue medication usage

Study ID	Design	Intervention	Patients	Outcomes
Medici et al. (2000)[189]	RCT Parallel-group Double-blind	*Drug(s):* 1. FP 200µg b.i.d. (daily total 400µg) 2. BDP 400µg b.i.d. (daily total 800µg) 3. FP 375µg b.i.d. (daily total 750µg) 4. BDP750µg b.i.d. (daily total 1,500µg) Only groups 1 and 2 reported in this section *Delivery device:* 1, 2, 3, 4. MDI + spacer (no other details about devices reported) *Duration:* 12 mths *Run in period:* 4 wks	*Number randomised* 69 *Mean (years)age (±sd)* 1. 39 (± 8) 2. 38 (± 8) 3. 38 (± 10) 4. 40 (± 10) (range 20-55 across all groups) *Baseline FEV_1 % predicted* mean baseline % predicted PEFR: 78.4 to 97.8 across groups *Previous ICS treatment (drug and dose)* BDP 800µg q.d. or 1,500µg q.d. depending on the dose of ICS use prior to entry	*Primary outcome* Bone mineral density (BMD) of the distal radius *Secondary outcomes* Cortisol Biochemical markers of bone metabolism Lung function: PEFR and FEV_1 Adverse events

* not stated explicitly, but deduced from the text

5.2.2.2.2 Results

Parallel 1:2 dose ratio studies

All outcomes reported here for comparisons between FP and BDP refer to parallel 1:2 dose ratio studies. The study by Szefler and colleagues involved three periods with incrementally increasing doses (six weeks each of 100:200µg, 400:800µg and 800:1600µg FP:BDP). However, only the 100:200µg comparison of Szefler and colleagues is reported here because the later comparisons (7-12 and 13-18 weeks) are not independent of the drug use in the preceding weeks.

Lung function

Five of the studies provided quantitative data on lung function. However, these data are not appropriate for meta-analysis because either there is only one study per outcome (e.g. for FEV_1 % predicted[185]), or the doses are not strictly comparable across the studies. For example, although three studies reported the change in FEV_1 at a nominal dose ratio of (approximately) 1:2 (FP:BDP), each study involved different actual doses (100:200µg,[187] 250:400µg,[186] or 400:800µg[181]).

FEV_1 at end-point

In the three comparisons of FEV_1 at end-point for FP and BDP, FEV_1 was consistently higher in FP-treated than in BDP-treated patients, with the difference decreasing with increasing dose (*Table 13*). However, these differences were either not tested statistically, ,[187] or were reported in the primary studies as not statistically significant.[181;186]

TABLE 13 *FEV_1 at end-point for FP and BDP at a nominal dose ratio approximating 1:2*

FP: BDP doses (µg/day)	Mean ± SD FEV_1 for FP (L)	Mean ± SD FEV_1 for BDP (L)	Study
100 : 200	3.40 ± 0.61	3.28 ± 0.68	187
250 : 400	3.06 ± 0.35	2.10 ± 0.41	186
400 : 800	2.395 ± 0.771	2.389 ± 0.488	181

Change in FEV_1 from baseline to end-point

The change in FEV_1 from baseline to end-point was compared for FP and BDP in five cases. The increase in FEV_1 was consistently larger for patients in the FP group (*Table 14*). However, statistical significance cannot be ascertained for the individual comparisons because standard deviations are reported only for the start (baseline) and end-point in three of comparisons.[181;186;187] In the remaining two comparisons, an overall test of the difference between the drugs was carried out for two dose regimes combined (200:400µg/day and 500:800µg/day, FP:BDP)[188] (*Table 14*). For the combined comparison, the difference between drugs was statistically significant (p=0.006).[188]

TABLE 14 *Change from baseline in FEV_1 at end-point for FP and BDP at a nominal dose ratio approximating 1:2*

FP: BDP doses (µg/day)	Mean ± SD change in FEV_1 for FP (L)	Mean ± SD change in FEV_1 for BDP (L)	Study
100 : 200	0.36 (n=15)	0.27 (n=15)	187
200 : 400	0.31 ± 0.50 (n=99)	0.18 ± 0.41 (n=104)	188
250 : 400	0.85 (n=10)	-0.13 (n=10)	186
400 : 800	0.53 (n=11)	0.52 (n=11)	181
500 : 800	0.36 ± 0.50 (n=101)	0.21 ± 0.49 (n=95)	188

Change in FEV_1 % predicted

Only one study, by Prasad and colleagues,[185] reported a quantitative comparison between FP and BDP of the change in the FEV_1 % predicted from baseline to end-point. The FEV_1 % predicted increased in both patient groups by approximately 35%, and the difference was not significant (mean ± SD FP 34.70 ± 4.15; BDP 36.94 ± 6.31; unpaired *t*-test p>0.05).

Change in morning PEFR

Only one study, by Raphael and colleagues,[188] quantitatively reported the change in morning PEFR from baseline to end-point. As mentioned above, Raphael and colleagues[188] compared effects of two doses each of FP and BDP in a two-arm study (200:400µg/day and 500:800µg/day FP:BDP). The mean ± SD of the change in morning PEFR (L/min) for these dose regimens were, respectively, 15.8 ± 50.0 L/min : 0.7 ± 42.0 L/min and 22.8 ± 42.2 L/min : 7.2 ± 41.0 L/min. For both dose regimens the change in morning PEFR is clearly higher in

patients treated with FP. The primary study reports a significant overall difference in effects between the drugs (ANOVA excluding dose as a factor $p \leq 0.001$); a separate analysis of treatment effects for each dose regimen is not reported.

Change in evening PEFR

As with the change in morning PEFR, the study by Raphael and colleagues[188] was the only one that quantitatively evaluated effects of FP and BDP on the change in evening PEFR. The mean ± SD of the change in evening PEFR (L/min) is FP 7.8 ± 44.0 L/min : BDP 2.10 ± 47.0 L/min for the lower dose regimen and FP 14.2 ± 38.0 L/min : BDP 9.7 ± 36.0 L/min for the higher dose regimen. For both dose regimens the change in evening PEFR is higher in patients treated with FP. Overall, this difference between treatments (excluding the effects of dose) is significant (ANOVA excluding dose as a factor p=0.06).

Symptoms

Change in % symptom-free days

The change from baseline to end-point in the % of symptom-free days was reported quantitatively only by Raphael and colleagues.[188] As with the morning and evening PEFR, comparisons are available for two dose regimens of each treatment (the details of these are given above). The mean ± SD change in % symptom-free days is 14.0 ± 32.0 FP and 4.9 ± 33.0 BDP for the lower-dose regimen; and 8.7 ± 28.0 FP and 4.4 ± 29.0 BDP for the higher-dose regimen. For both dose regimens the largest improvement of symptom scores was in FP-treated patients. The overall treatment effect (excluding the effects of dose) was significant (ANOVA excluding dose as a factor p=0.027).

Change in symptom scores

The change from baseline to end-point in symptom scores was reported at two dose regimens of each inhaled steroid (referred to as relatively 'low' and 'high', as described above) by Raphael and colleagues.[188] In another study with a single dose regimen, Parakh and colleagues[181] provided baseline and final symptom scores but did not include a relevant estimate of the variance (*Table 15*). In the study by Raphael and colleagues[188] the decrease in symptom scores was largest for FP-treated patients whereas in the study by Parakh and

colleagues[181] the largest decrease in symptom scores was for BDP-treated patients (*Table 15*). Overall, for both dose regimens combined, the change in symptom scores reported by Raphael and colleagues was statistically significant (p=0.024).[188] However, in the study by Parakh and colleagues the difference between drugs cannot be tested statistically.[181]

TABLE 15 *Change in symptom scores for FP and BDP at a nominal dose ratio approximating 1:2*

FP: BDP doses (µg/day)	Mean ± SD change in symptom score for FP	Mean ± SD change in symptom score for BDP	Study
200 : 400	-0.24 ± 0.70 (n=99)	-0.05 ± 0.61 (n=104)	188
400 : 800	-30.2 (n=11)	-38.4 (n=11)	181
500 : 800	-0.26 ± 0.60 (n=101)	-0.15 ± 0.58 (n=95)	188

Nocturnal awakening

Three studies provide quantitative data on the effects of FP and BDP on nocturnal awakening. However, meta-analysis is not possible for these studies as the time units were either not stated (Raphael and colleagues[188]) or differed between studies (Ige and colleagues[186] reported sleep disturbances per month, whereas Prasad and colleagues[185] reported night-time awakening per week).

Raphael and colleagues[188] reported that there was no significant difference between the FP and BDP patient groups in the change in nocturnal awakenings from baseline to end-point (12 weeks) (p = 0.458). These data are for overall comparisons of FP to BDP; they do not distinguish the separate lower and higher dose comparisons that were included within the study (200 to 400µg/day and 500 to 800µg/day; details above).

Ige and colleagues[186] reported that the percentage reduction in the frequency of weekly night-time awakening was significantly higher for FP than BDP, although it is not clear to which time periods the statistics presented by Ige and colleagues refer. The mean ± SD of the weekly frequency of night-time awakening at end-point (8 weeks) was 0.1 ± 0.32 for FP and 3.5 ± 1.27 for BDP.

Data reported by Prasad and colleagues[185] on the change in frequency of sleep disturbance per month for FP and BDP patient groups are difficult to interpret due to ambiguity of the data description (the tabulated data appear to show an increase in awakening frequency from baseline whereas the text describes a decrease). However, Prasad and colleagues report

that the change in sleep disturbance per month did not differ significantly between FP and BDP patient groups ($p > 0.05$).

Use of rescue medication

Change in use of rescue medication

One study, by Raphael and colleagues,[188] quantitatively reported the change from baseline to the end of the study in the use of rescue medication. As described above, Raphael and colleagues[188] compared two dose regimens each of FP and BDP. The mean ± SD change in use of rescue medication (puffs per day) is -0.9 ± 2.0 FP and 0.0 ± 2.0 BDP for the lower-dose regimen; and -0.5 ± 2.0 FP and -0.3 ± 2.0 BDP for the higher-dose regimen. For both dose regimens the largest improvement (reduction in use of rescue medication) was in FP-treated patients. The overall treatment effect (excluding the effects of dose) was significant (ANOVA excluding dose as a factor p=0.004).

Exacerbations

Of the six studies, four did not comment on asthma exacerbations. In the study by Prasad and colleagues,[185] the mean number of exacerbations per month did not differ significantly between the drug treatments ($p > 0.05$). The mean ± SD reduction in number of exacerbations per month was 18.13 ± 1.85 for FP and 17.35 ± 2.00 for BDP. These numbers appear high, probably reflecting a broad definition of exacerbations (no definition is provided in the paper). Medici and colleagues[189] also reported that the rate of exacerbations did not differ significantly between the FP and BDP treatments; they noted that one patient receiving the BDP 800µg/day treatment required a short course of corticosteroids due to an asthma exacerbation. However, Medici and colleagues[189] did not define the rate of exacerbations or provide statistics for the comparison.

Adverse events

Three of the six studies reported the presence or lack of adverse events due to one or both of the drug treatments. Of these, Szefler and colleagues[187] provided plasma cortisol estimates for FP and BDP and commented that overnight plasma cortisol was suppressed in a dose-dependent manner for all patients. Szefler and colleagues also provide quantitative

data on plasma cortisol but these are difficult to interpret as the outcome units are not specified and the measures of variance (SD or CV) are not clearly identifiable.

Raphael and colleagues[188] reported that three patients from each treatment group were withdrawn due to symptoms possibly related to the use of study medication (headache, insomnia, jitters, tachycardia, edema, muscle pain, fatigue, light-headedness, rash, or hoarseness). They also reported that, overall (combining both the relatively low and high dose comparisons; details above), there were no significant differences between FP and BDP in the incidence of adverse events potentially related to the study treatment (range 9% to 15%, p=0.664).

In the remaining study, Medici and colleagues[189] noted that adverse events were reported by a similar number of patients in the FP and BDP groups, with no withdrawals having been due to adverse events. The geometric mean of the morning serum cortisol concentration (in nmol/L) estimated by Medici and colleagues[189] remained within the normal range for both FP and BDP-treated patients throughout the 12-month study period.

The authors also provided a detailed evaluation of the impact of FP and BDP on bone mineral density (in g/cm^3) and other bone metabolism markers. They reported median changes from baseline in trabecular, integral and compact bone mineral density measurements for both the radius and tibia (i.e. six outcomes). Changes in these six outcomes at either six or 12 months from baseline did not differ significantly between FP and BDP-treated patients (p > 0.05 in all cases; Wilcoxon rank-sum test). Changes from baseline in the bone mineral density of the lumbar spine also did not differ between FP and BDP at six months (p > 0.05). However, changes in lumbar bone mineral density at 12 months were significantly different, with a net increase in FP-treated patients (median 0.020 with quartile range -0.005 to 0.033 g/cm^3) but a decrease in BDP-treated patients (median -0.003 with quartile range -0.016 to 0.009 g/cm^3).

Medici and colleagues[189] also reported a statistically significant change from baseline at 12 months in another bone metabolism marker, osteocalcin concentration (units not stated), indicative that bone formation activity is lower in patients taking 800µg/day BDP than in patients taking 400µg/day FP (p=0.047). However, absolute concentrations and percentage changes from baseline suggest that the difference would not be clinically significant.[189]

5.2.2.2.3 Summary

Six RCTs of varying size and design have compared low dose FP with BDP. In almost all cases, the measured outcomes for lung function either favour treatment with FP over treatment with BDP, or indicate no difference between the drugs. In most cases the differences cannot be tested statistically but where differences were statistically significant the change in morning PEFR, evening PEFR and the change in FEV_1 from baseline to end-point each favour FP.

Changes in symptom scores and symptom-free days generally favour the use of FP over BDP. An exception is that Parakh and colleagues[181] found a greater improvement in symptom scores under treatment with BDP; however, the results are not analysable statistically. The incidence of nocturnal awakening was either reduced more by FP than by BDP, or showed no difference between the drugs. The use of rescue medication was reduced to the largest extent in FP-treated patients.

In the cases where exacerbations were recorded, the incidence did not differ between FP and BDP patient groups. In general, there were no differences in adverse events between patients treated with FP and those treated with BDP. However, an exception is for the baseline to end-point change in lumbar bone mineral density, which at 12 weeks had increased in the FP patient group but decreased in the BDP patient group.

5.2.2.3 FP and BUD (review Q1 – low dose ICS)

5.2.2.3.1 Study Characteristics

Five parallel group RCTs[181;190-193] evaluated the effectiveness of BUD compared to FP, published between 1994 and 2004 (*Table 16*). Four studies were multi-centre studies where study sample sizes ranged between 157 and 281 participants, while the fifth study was a single centre study where the sample size was 42.[181] No power calculation was undertaken for this latter study, however, adequate power calculations were made for the other four studies.

All five included studies had two-arm comparisons of BUD versus FP although one study[181] also had a third intervention arm of BDP and this arm is therefore not reported here.

One trial[190] stratified patients into two groups to compare BUD and FP (low-dose 400µg/day, high dose 800µg/day) to ensure there were equal numbers of high and low dose patients in each of the two treatment groups details (not stated explicitly, but deduced from the text: FP – Flixotide Diskhaler®, no further details reported; BUD – Pulmicort Turbohaler®; AstraZeneca). But the dose ratio between the two randomised groups was reported to be equal.

Four trials compared FP and BUD at a dose ratio of 1:2. Two trials compared 200µg per day of FP with 400µg per day of BUD (no further details on devices reported by Landgdon and colleagues;[192] whilst only the details for FP - Becodisks Diskhaler, Allen and Hanburys, could be deduced from the text of Connolly and colleagues[193]) and two trials compared 400µg per day of FP with 800µg per day of BUD[181;191] (no further details reported about devices reported by either study).

The devices used in three studies were DPIs (Diskhaler for the FP groups and Turbohaler for BUD respectively),[190;191;193] whereas the devices were MDIs for both intervention groups in the other two trials.[181;192]

The treatment duration was similar between the included trials ranging between 8 weeks in four studies and 12 weeks in one study.

The aims of the trials were largely similar. The one trial using equal doses of the two comparator drugs used an alternative methodology of reducing the standing doses in symptomatic patients to compare efficacy. The study argued that dose reduction will result in a decrease in lung function unless the steroid which is used has greater potency. The trials using a 1:2 ratio of FP to BUD were aiming to compare efficacy to see if a potency ratio exists, and in the case of the two trials using DPIs to see if this exists using these devices. None of these studies described themselves as equivalence trials and in those where a power analysis was undertaken this was to detect a difference between groups. However, these trials did report that they were assuming similar efficacy between the higher dose BUD and lower dose FP. The Parakh and colleagues trial also aimed to simultaneously compare three corticosteroids in an adult Indian population.[181]

The ages of participants in four trials are likely to be similar. Three trials report age ranges that lie between 18-70 years[190;191;193] and one trial reports a mean age of approximately 47

years.[192] The other trial[181] included a slightly younger group of patients (range 18-45 years). The severity of asthma was similarly mild to moderate across the included trials and four trials explicitly required patients to be symptomatic/inadequately controlled. In the Basran and colleagues[190] trial all patients were already on higher doses of ICS, whereas in the remaining trials some of the patients were steroid-naïve whilst others were taking ICS. Baseline FEV_1 % predicted was reported in four of the included trials to be either greater than 40 or greater than 50. The fifth trial[181] did not report baseline FEV_1 % predicted.

Quality of the included trials was generally adequate. The method of randomisation was described and appropriate in all trials except the Parakh and colleagues study[181] which did not report the method used. In two trials the allocation concealment used a central coding of randomisation schedules,[190;192] but in the remainder the method of allocation was unclear. Intention-to-treat analysis was reported to be undertaken in all but two trials.[181;191] These factors reduce the possibility of selection biases and measurement biases respectively.

TABLE 16 *Characteristics of studies (FP and BUD)*

Study ID	Design	Intervention	Patients	Outcomes
Basran et al (1997)[190]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP 100 or 200µg b.i.d. (daily total 200 or 400µg) 2. BUD 100 or 200µg b.i.d. (daily total 200 or 400µg) *Delivery device:* 1. DPI Diskhaler® (Flixotide, no manufacturer reported*) 2. DPI (Pulmicort Turbuhaler, AstraZeneca) *Duration:* 8 wks *Run in period:* 2 wks	*Number randomised* 176 *Age range (years)* 18-60 *Baseline FEV_1 % predicted* > 40 *Previous ICS treatment* Either BUD or FP at either 400 or 800µg	FEV_1 FVC PEFR am and pm Diurnal variation in PEFR Day and night-time asthma symptom score Day and night-time SABA use
Langdon et al (1994)[191]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP 200µg b.i.d. (daily total 400µg) 2. BUD 400µg b.i.d. (daily total 800µg) *Delivery device:* 1. DPI Diskhaler® (Flixotide GlaxoSmithKline*) 2. Reservoir DPI (no further details about device reported) *Duration:* 8 wks *Run in period:* 2 wks	*Number randomised* 281 *Mean (range) age (years)* 1. 39 (18-68) 2. 41 (18-68) *Baseline FEV_1 % predicted* >50 *Previous ICS treatment* No previous ICS treatment or either BUD or BDP up to 600µg.	PEFR am and pm Diurnal variation in PEFR Daily asthma symptom score Day and night-time rescue SABA use Patient assessed degree of asthma control Physician assessed success of treatment Morning plasma cortisol

Study ID	Design	Intervention	Patients	Outcomes
Langdon et al (1994)[192]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP 50µg 2 puffs b.i.d. (daily total 200µg) 2. BUD 200 b.i.d. (daily total 400µg) *Delivery device:* 1, 2. MDI (no further details about devices reported) *Duration:* 8 wks *Run in period:* 2 wks	*Number randomised* 157 *Mean (±sd) age (years)* 1. 47.6 (±15.2) 2. 46.2 (±17.4) *Baseline FEV_1 % predicted* >50 *Previous ICS treatment* Mild to moderate asthma - BDP or BUD no dose reported.	FEV_1 FVC Clinic PEFR Morning PEFR Evening PEFR Daily asthma symptom score Daytime rescue SABA use Night-time rescue SABA use Morning plasma control Patient assessed degree of asthma control Physician assessed success of treatment
Connolly et al (1995)[193]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP 100µg b.i.d. (daily total 200µg) 2. BUD 200µg b.i.d. (daily total 400µg) *Delivery device:* 1. DPI Diskhaler® (Becodisks Diskhaler, Allen & Hanburys*) 2. Reservoir DPI (no further details about devices reported) *Duration:* 8 wks *Run in period:* 2 wks	*Number randomised* 190 *Age range (years)* 18-70 *Baseline FEV_1 % predicted* > 50 *Previous ICS treatment* BDP or BUD with a range of doses.	*Outcomes* Change in morning PEFR Change in diurnal variation in PEFR % symptom-free days % symptom-free nights % rescue SABA free days % rescue SABA free nights Physician assessed level of overall asthma control Patient assessed level of overall asthma control Morning plasma cortisol

Study ID	Design	Intervention	Patients	Outcomes
Parakh et al (2004)[181]	RCT Single-centre Parallel-group Single-blind	*Drug(s):* 1. FP 50µg 4 puffs b.i.d. (daily total 400µg) 2. BUD 200µg 2 puffs b.i.d. (daily total 800µg) 3. BDP 200µg 2 puffs b.i.d. (daily total 800µg) *Delivery device:* 1, 2, 3. MDI (no details about devices reported) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 42 *Age range (years)* 15-45 *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* Not reported	Symptoms FEV_1 PEFR FVC Withdrawals

* not stated explicitly, but deduced from the text

5.2.2.3.2 Results

Lung function

Parallel design, 1:1 dose ratio

Basran and colleagues[190] report values for baseline and end-point FEV_1 (litres) for BUD and FP groups respectively but do not present a change value. These values are not presented with an estimate of variance and therefore don't allow change from baseline results to be estimated. They do however report a p-value of the difference between the treatment groups in the change from baseline and this was not statistically significant (p=0.22).

For morning and evening PEFR (l/min) Basran and colleagues[190] again only report values at baseline and at end-point for the two comparison groups, but the p-value is of the difference between the treatment groups in the change from baseline. There was no statistically significant difference in the change from baseline scores for the two groups for either morning or evening PEFR (p=0.35 and p=0.69, respectively).

Parallel design, 1:2 dose ratio

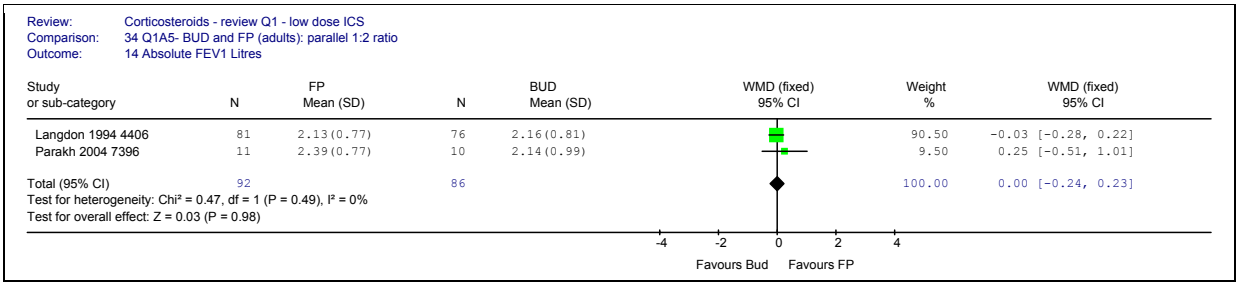
In the two trials reporting a dose ratio of 1:2 with FP at 200µg and BUD 400µg per day only Langdon and colleagues[192] report data on FEV_1 (litres). Change from baseline in the FP group was 0.07 (SD 0.34) and in the BUD group was 0.81 (SD 0.44) but this was reported not to be statistically significantly different between the two groups (no p value given). The difference in the mean change in morning PEFR to the last four weeks of treatment between the FP and BUD groups of the Connolly and colleagues trial[193] was 39.70 (SD 50.0) for FP versus 26.10 (SD 48.0) BUD. No statistical significance test was reported. Change from baseline in morning PEFR in the FP group versus the BUD group of the Langdon and colleagues[192] trial was 32.70 (SD 55.1) versus 24.70 (SD 44.5) respectively (not statistically significantly different, p=0.36). Similarly there was no statistically significant difference in the change from baseline evening PEFR between the two groups (FP 18 (SD 35.6); BUD 18 (SD 36.3)) although no p value was reported.

In the two trials reporting higher doses (FP 400µg and BUD 800µg) Langdon and colleagues[191] looking at the use of DPI inhalers report mean morning PEFR values between

the two groups but only present data on the change from baseline morning and evening PEFR in a figure. At week eight an adjusted mean morning PEFR in the BUD group was 404.0 and in the FP group was 423.6 (difference 19.6, 95% CI 5.1, 34.2, p=0.009) in favour of FP. The adjustment was made due to differences in baseline values and this should be considered when interpreting the results. Estimating the change from baseline results for morning PEFR from figures presented in the publication would suggest a change of 23 litres per minute for BUD and 35 litres per minute for FP at the eighth week (p<0.05). Estimating the change from baseline results for evening PEFR from figures presented in the publication would suggest a change of 16 litres per minute for BUD and 22 litres per minute for FP at the eighth week (p=0.057). No data were reported for mean evening PEFR at week eight. Similarly in the trial by Parakh and colleagues[181] no change from baseline results were presented. At the 12-week end-point mean FEV_1 values were 2.40 (SD 0.78) in the FP group and 2.15 (SD 1.00) in the BUD groups respectively. These figures were not statistically significantly different but as analysis also included a third comparison group (BUD) was unlikely to have been a pairwise comparison between the BUD and FP groups. No data on morning or evening PEFR were presented.

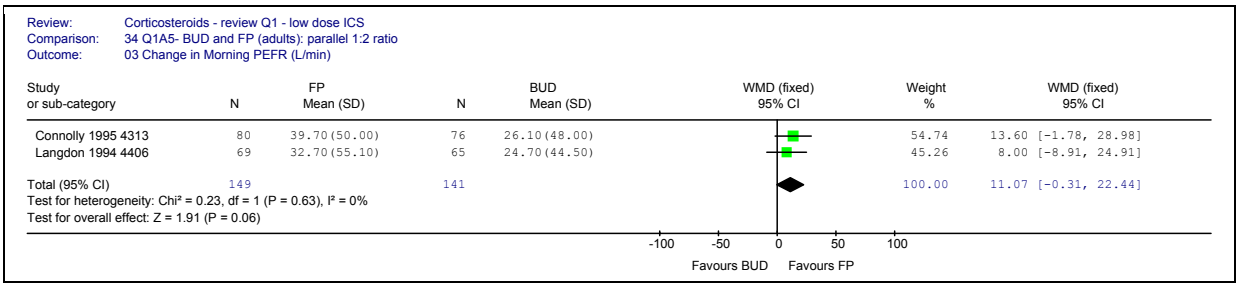
Two of the four studies provided data (mean and standard deviation) on end-point FEV_1 that allowed them to be combined in a meta-analysis (*Figure 8*). Pooling the data using a fixed-effects model showed no difference between the two groups (WMD 0.00 (95% CI -0.21, 0.23). The test for heterogeneity was not significant (p=0.49, I^2=0%).

FIGURE 8 *End-point FEV_1 (litres) FP versus BUD, parallel 1:2 nominal dose ratio*



Two of the four studies provided data (mean change and standard deviation) on morning PEFR that allowed them to be combined in a meta-analysis (*Figure 9*). Pooling the data using a fixed-effect model showed a trend towards greater improvement with FP but this was not statistically significant (WMD 11.07 [95% CI: -0.31, 22.44], p=0.06). Heterogeneity was not statistically significant at p=0.63, I^2 =0%.

FIGURE 9 *Change in morning PEFR, FP versus BUD, parallel 1:2 nominal dose ratio*



Symptoms / health related quality of life

Parallel design, 1:1 dose ratio

Asthma symptom scores were recorded on a 4-point scale where 0= none and 3 = severe, in the Basran and colleagues trial.[190] In both arms there was an observed improvement in symptom scores (no data provided of the change score) but the difference in the change in scores for symptoms during the day or during the night were not statistically significantly different between the two arms (p=0.50 daytime score, p=0.42 night-time score).

Parallel design, 1:2 dose ratio

Of the two studies of lower dose FP (200µg) and BUD (400µg) Langdon and colleagues[192] noted that mean symptom scores (on a 10-point scale where 0=none and 9=severe) fell during both treatments (FP 3.1 at baseline versus 2.4 at end-point, BUD 3.2 at baseline versus 2.9 at end-point) but that this was reported to be statistically significantly greater in the FP group (p=0.08). In the Connolly and colleagues trial[193] a statistically significant difference was observed in the change in number of symptom-free days in favour of FP (24% FP versus 0% BUD, p=0.05). The proportion of symptom-free nights increased during treatment in both groups but this was again reported to be greater in the FP group than the BUD group (FP 29% versus 17% p=0.05).

Symptom scores were undertaken in the Parakh and colleagues.[181] No details of the type of measurement scale were reported. The publication reports that changes were not statistically significantly different between study groups, although this is likely to be based on a comparison of the three arms of the trial as discussed earlier.

Use of rescue medication

Parallel design, 1:1 dose ratio

Basran and colleagues[190] show no statistically significant differences in the change from baseline in SABA use between the BUD and FP arms respectively (p=0.31 daytime use, p=0.25 night-time use). While values for these outcomes are presented for baseline and end-point, no data are presented of the change from baseline SABA use.

Parallel design, 1:2 dose ratio

No data on use of rescue medication in terms of puffs per day were reported in the included trials in this category.

Exacerbations

Parallel design, 1:1 dose ratio

No data on exacerbation rates was reported in the Basran and colleagues[190] trial.

Parallel design, 1:2 dose ratio

No data on exacerbation rates were reported in the included trials in this category.

Adverse events

Parallel design, 1:1 dose ratio

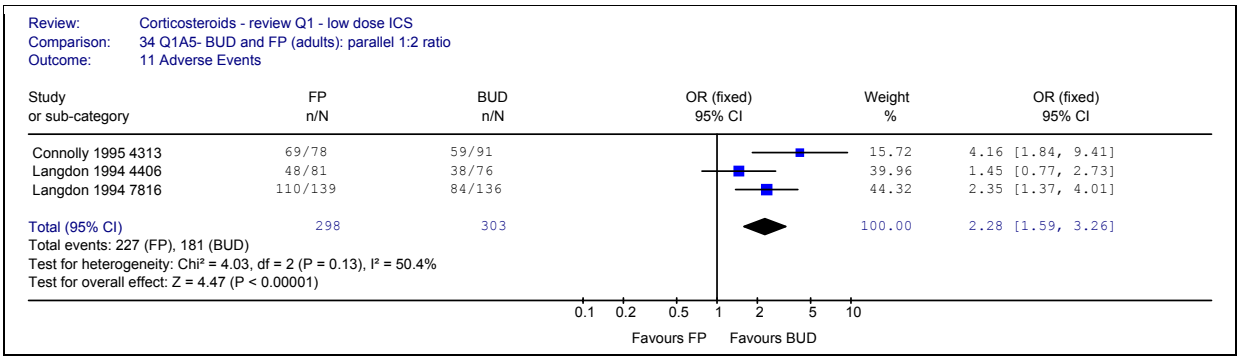
The overall incidence of adverse events was similar in both treatment groups in the Basran and colleagues[190] trial (43/83 BUD versus 56/93 FP) although no statistical significance testing was undertaken. Two adverse events in the BUD group and three in the FP group were classified as serious.

Parallel design, 1:2 dose ratio

Proportions of patients with adverse events was generally higher in the FP arms of the included studies than in the BUD arms (as can be seen in *Figure 10* below). No statistical significance testing was undertaken in any of these studies.

Three of the four studies provided data that allowed them to be combined in a meta-analysis (*Figure 10*). Pooling the data using a fixed-effect model showed a statistically significantly more favourable adverse event profile with BUD (OR 2.28 [95% CI: 1.59, 3.26]; p<0.00001). Heterogeneity was not significant at p=0.13, I^2 = 50.4%. It is important to note that whilst these three trials had a dose ratio of 1:2 they did not all have the same dose of FP and BUD.

FIGURE 10 *Adverse events, FP versus BUD, parallel nominal 1:2 ratio*



Four patients in the FP arm of the Langdon and colleagues trial[192] discontinued due to adverse events. Two due to serious adverse events, although this is reported to be unlikely to be related to therapy in one and during the run-in period in the other and two due to less severe adverse events. Six patients discontinued due to adverse events from the BUD arm, four were reported to be asthma related, one low cortisol and one due to pregnancy. One patient in each arm of the Connolly and colleagues[193] trial discontinued due to adverse events.

Summary

Parallel design, 1:1 dose ratio

On measures of lung function no differences were observed between those treated with BUD and those treated with FP. There were also no differences between the two treatments on symptoms, use of rescue medication or adverse events.

Parallel design, 1:2 dose ratio

No differences on measures of lung function were reported between BUD and FP, for the lower dose studies or the higher dose studies. Reports of symptoms were favourable for FP compared to BUD. Adverse event profiles, however, were statistically significantly more favourable for BUD.

5.2.2.4 CIC and BUD (review Q1 – low dose ICS)

5.2.2.4.1 Study Characteristics

One RCT,[194] published in 2005, evaluated the effectiveness of CIC compared to BUD (*Table 17*). An unpublished report containing more extensive results for this trial was made available to us by the manufacturer.[195] The trial was a parallel-group, multi-centre RCT which randomised 405 patients. There were three treatment groups comparing the two drugs in a 1:2 dose ratio: 400µg BUD; 200µg CIC given in the morning; and 200µg CIC given in the evening. CIC was delivered by HFA-MDI (not specifically stated - Alvesco®, made by Atlana*) and BUD by MDI (BUD-100, Cipla Ltd), and treatment continued for 12 weeks.

Patients' ages ranged from 18-69, with median ages for the treatment groups of 29-32 years. Patients had been managed on low to medium doses of ICS, with daily ICS doses of ≤500µg/d of BDP or equivalent four weeks before baseline. The mean FEV_1 % predicted across the trial's arms was 92.94%.

The method of randomisation (a computer generated randomisation list with coded labelling) reported by the trial was adequate, but the method used to conceal the allocation to treatment arms was unclear. Patients in the CIC groups were blinded to treatment by use of an identical placebo MDI device, but patients in the BUD group were reported to have

received the drug on an open-label basis. All patients received two puffs from a white-labelled device in the morning and two puffs from a blue-labelled device in the evening. Intention-to-treat analysis was assessed to be partially adequate, including all patients who received at least one dose of study medication.

The rationale of the study was to test the non-inferiority of CIC compared to BUD in terms of efficacy as measured by change in the primary outcome measure, FEV_1(L). A 2-sided 95% CI for differences between the treatment groups was used to test the primary hypothesis for non-inferiority. A sample size of 100 patients per treatment group was calculated to ensure 90% power to establish the non-inferiority of 160µg/day CIC (evening dose) to 400µg/day BUD. The non-inferiority acceptance limit for FEV_1 was -0.20L.

TABLE 17 *Characteristics of studies (BUD and CIC)*

Study ID	Design	Intervention	Patients	Outcomes
Niphadkar et al. (2005)[194]	RCT Multi-centre Parallel group Double blind, Double-dummy (CIC) or Open-label (BUD)	1. CIC 160µg ex-actuator AM q.d. + placebo PM (daily total 200µg ex valve) 2. CIC 160µg ex-actuator PM q.d. + placebo AM (daily total 200µg ex valve) 3. BUD 200µg b.i.d. (daily total 400µg) *Delivery device:* 1, 2. HFA-MDI (CIC -Alvesco®, made by Atlana*) 3. MDI (BUD-100, Cipla Ltd) *Duration:* 12 wks *Run in period:* 2-2.5 wks	*Number randomised* 405 *Mean age (range)* 31 (18-65) 29 (18-63) 32 (18-69) *Baseline FEV_1 % predicted* 94 93 92 *Previous ICS treatment (drug and dose)* Constant dose of ICS (≤500µg/d BDP, 200-250µg/d FP, 400µg/d BUD, or equivalent)	*Primary outcome* Change in FEV_1 (L) *Secondary outcomes* Difference in FEV_1 (L) between randomisation and study visits FVC AM & PM PEFR Diurnal PEFR fluctuation Asthma symptom scores Rescue medication use Adverse events

* not specifically stated in text

5.2.2.4.2 Results

For some outcomes means are calculated using the least squares method, as indicated by (LS) in the text. Results presented are for intention-to-treat analysis, unless otherwise stated.

Lung function

FEV_1 L

Niphadkar and colleagues[194] did not report changes from baseline FEV_1 for the three treatment groups, but did report the LS mean difference between the groups' changes from baseline. The difference between patients who received 200µg CIC in the morning and patients in the 400µg/day BUD group was -0.036L (95% CI -0.120, 0.045). The difference between the change in those who received an evening dose of 200µg CIC and those who received 400µg/day BUD was 0.022L (95% CI -0.061, 0.105). These differences were not statistically significant, and superiority of morning or evening CIC vs. BUD was not demonstrated (p=0.383, p=0.598, respectively). The non-inferiority of CIC to BUD was demonstrated as the lower confidence limits exceeded the acceptance level of -0.2L. Altana report FK1-120[195] reported the mean changes from baseline for the three groups. The group which received 200µg CIC in the morning had a LS mean change from baseline of -0.104L (95% CI -0.166, -0.043; p=0.0010), compared with -0.046L (95% CI -0.109, 0.017; p=0.1509) in the evening 200µg CIC group and -0.068L (95% CI -0.132, -0.005; p=0353) in the BUD group.

Morning PEFR

As with FEV_1, Niphadkar and colleagues[194] reported the results of comparison between the two CIC groups and the BUD group's change from baseline, but did not report the actual mean changes from baseline. However, Altana report FK1120[195] reported that patients who received 200µg CIC in the morning had a LS mean change from baseline morning PEFR of -5.7L/min (95% CI -14.8, 3.3; p=0.2149), compared with 8.0 L/min (95% CI -1.3, 17.4; p=0.0923) in the evening 200µg CIC group and -1.3L/min (95% CI -10.4, 7.8; p=0.78) in the BUD group. Between-group comparisons for differences in change from baseline were -

4.4L/min (95% CI -16.4, 7.5; p=0.464) for morning CIC vs. BUD, and 9.3L/min (95% CI -2.8, 21.5; p=0.131) for evening CIC vs. BUD. Non-inferiority of CIC to BUD was demonstrated as the lower confidence limits exceeded the acceptance level of -25L/min.

Evening PEFR

For evening PEFR, Niphadkar and colleagues[194] reported between-group comparisons for change from baseline evening PEFR of -1.1L/min (95% CI -12.4, 10.3; p=0.855) for morning CIC vs. BUD, and 4.0L/min (95% CI -7.5, 15.5; p=0.490) for evening CIC vs. BUD. Altana report FK1120[195] reported the actual mean differences. Patients who received 200µg CIC in the morning had a LS mean change from baseline evening PEFR of -1.1L/min (95% CI -9.7, 7.6; p=0.8082), compared with 4.0 L/min (95% CI -4.8, 12.9; p=0.3728) in the evening 200µg CIC group and -0.0L/min (95% CI -8.7, 8.6; p=0.9971) in the BUD group. Non-inferiority of CIC to BUD was demonstrated as the lower confidence limits exceeded the acceptance level of -25L/min.

Symptoms

Niphadkar and colleagues[194] assessed asthma symptoms using a five-point scale (0= no symptoms, 4= awake most of the night or unable to perform daily activities, no reference given for scale). The percentages of symptom-free days were 89%, 91% and 93% for the morning CIC, evening CIC and BUD groups, respectively (p=NS for both comparisons with BUD). The percentage of days that were free of nocturnal awakenings was 100% in each group. Altana report FK1120[195] reported the change from baseline sum of asthma scores. The Hodges-Lehmann point estimate was reported to be 0.00 for all treatment groups, with a 95% CI of (0.00, 0.00) for the morning CIC and BUD groups (p=1.0 and =0.5253, respectively). However, for the evening CIC group, the point estimate's 95% CI is -0.07, 0.00, and a p-value of 0.0068 is presented in the report, suggesting a statistically significant change from baseline. The mean baseline score for this group was 0.27, compared with a score of 0.21 at the end of treatment. For between-group comparisons, the Hodges-Lehmann point estimate was reported to be 0.00 for both comparisons, with a 95% CI of (0.00, 0.00) for both comparisons. No statistically significant differences were reported for the comparison between morning CIC and BUD (p=0.6661) or between evening CIC and BUD (p=0.1045).

Health related quality of life

Niphadkar and colleagues[194] did not report this outcome.

Use of rescue medication

Niphadkar and colleagues[194] did not report this outcome.

Exacerbations

Niphadkar and colleagues[194] did not report this outcome. Altana report FK1120[195] reported that seven patients in the morning CIC group (5%), 12 patients (9%) in the evening CIC group and 12 patients (9%) in the BUD group experienced a minor exacerbation.

Adverse events

Adverse events were reported by 24 patients in the morning CIC group (17.1%), 32 (24.4%) in the evening CIC group and 28 (21.1%) in the BUD group. Comparisons between the two CIC groups and the BUD group were not statistically significant (p=0.443, p=0.558, respectively, calculated by reviewer). Severe adverse events were rare, occurring in seven patients (5.0%) in the morning CIC group, one patient (0.8%) in the evening CIC group and two patients (1.5%) in the BUD group. Differences between the groups were not statistically significant (p=0.174 for morning CIC vs. BUD, p=1.0 for evening CIC vs. BUD). One patient in each of the morning CIC and BUD groups withdrew due to adverse events (0.7% and 0.8%, respectively), but no patients in the evening CIC group withdrew for tis reason.

5.2.2.4.3 Summary

One parallel-group RCT[194] published evaluated the effectiveness of CIC compared to BUD. The study was of reasonable methodological quality, although open-label BUD was used. The trial demonstrated the non-inferiority of CIC to BUD for the primary outcome measure of change from baseline FEV_1, and also for morning and evening PEFR. There was no significant difference between the CIC groups and the BUD group in terms of symptom-free days, although there appeared to be a statistically significant difference between morning CIC and BUD in terms of change from baseline asthma symptom score. There was no

statistically significant difference between the two drugs in terms of adverse events, severe adverse events or discontinuations due to adverse events.

5.2.2.5 MF and BUD (review Q1 – low dose ICS)

5.2.2.5.1 Study Characteristics

Two multicentre, parallel-group RCTs compared BUD with MF (*Table 18*). The RCT by Corren and colleagues[196] included 262 patients and ran for eight weeks. The RCT by Bousquet and colleagues[197] lasted for 12 weeks, and randomised 730 patients.

Patients in the study by Corren and colleagues were randomised in an approximately 2:2:1 ratio to one of three treatment groups: placebo; once-daily 440µg MF (daily metered dose); once-daily 400µg BUD (daily metered dose). Every morning, patients in the placebo arm took two inhalations from two placebo DPIs, and patients in the active treatment arms took two inhalations from the treatment DPI plus two inhalations from a placebo DPI (no details about devices reported, MF made by Schering-Plough). The daily dose ratio was approximately 1:1 for the two active treatment arms.

The study by Bousquet and colleagues had four treatment arms; 100µg MF twice daily plus placebo; 200µg MF twice daily plus placebo; 400µg MF twice daily plus placebo, and 400µg BUD twice-daily. Daily dose ratios were therefore 1:4, 1:2 and 1:1, respectively. Patients in the MF arms took one inhalation from each of two DPIs (either one active and one placebo, or two active DPIs) in the morning and again in the evening (no details about devices reported, MF made by Schering-Plough). Patients randomised to BUD took one inhalation from each of two Turbohaler DPI devices, morning and evening (Pulmicort Turbuhaler®, AstraZeneca -not explicitly stated, but deduced from the text). No placebo Turbohaler was available, so only evaluators were blind to treatment group allocation.

Corren and colleagues aimed to compare the efficacy and safety of MF and BUD delivered via DPI. Bousquet and colleagues aimed to compare the efficacy and safety of the two drugs delivered DPI (MF) or Turbohaler DPI (BUD).

Patients in the two studies were of similar ages. Patients in the study by Corren and colleagues ranged in age from 12 to 82 years, with a mean age of 37.67 years. Those in the study by Bousquet and colleagues ranged from 12-76 years, with a mean age of 41. Corren

and colleagues did not describe the severity of patients' asthma, but reported that baseline mean percentage of predicted FEV_1 ranged from 71.6 to 75.1 for the three treatment groups. Bousquet and colleagues do not describe the severity of patients' asthma in their RCT. Baseline mean percentage of predicted FEV_1 ranged from 76.0% in the BUD group to 77.9% in the 400µg b.i.d. MF group.

All patients in both trials had used ICS before the studies started. FP was the most widely used ICS in the trial by Corren and colleagues, being taken by 37% of patients at a mean dose of 388µg/day. Just over a quarter (26%) of patients had taken BDP at a mean dose of 328µg/day, with a further 20% having used 696µg/day triamcinolone. The remaining patients had used BUD (8%) or flunisolide (8%) at daily doses of 664µg and 1136µg, respectively. In the trial by Bousquet and colleagues, patients had used the following mean doses of ICS: 699µg/day BDP; 662µg/day BUD; 659µg/day flunisolide; 438µg/day FP or 416µg/day triamcinolone.

FEV_1 (L) was used as the primary outcome by both studies (Bousquet and colleagues also reported FEV_1 percent of predicted value), although Corren and colleagues used both FEV_1 (L) and PEFR as primary outcomes. Neither study used a strictly ITT method of efficacy analysis. One patient in the study by Corren and colleagues, and ten patients in the study by Bousquet appear to have been excluded from analyses due to missing efficacy data. Both studies used an adequate method of randomisation, although it is not clear whether allocation to treatment groups was concealed in either study.

TABLE 18 *Characteristics of studies (MF and BUD)*

Study ID	Design	Intervention	Patients	Outcomes
Corren et al. (2003)[196]	RCT Multi-centre Parallel-group Double-blind, Double-dummy Placebo- and active-controlled	1. MF 200µg b.i.d. (≈ 440µg ex valve) 2. BUD 160 b.i.d. (≈ 400µg ex valve) 3. placebo *Delivery device:* 1, 2. MF-DPI (made by Schering-Plough) *Duration:* 8 wks *Run in period:* Not reported	*Number randomised* 262 *Mean age* 37.67 yrs *Baseline FEV_1 % predicted* 73.37 *Previous ICS treatment (drug and dose)* 200-2000 ug q.d. of FP, BUD, BDP, flunisolide or triamcinolone	*Primary outcome* FEV_1 (L) PEFR (am & pm) *Secondary outcomes* $FEF_{25\%-75\%}$ FCV Asthma symptoms Albuterol use Nocturnal awakenings Physician-evaluated response-to-therapy scores & compliance Percentage of asthma symptom-free days* Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Bousquet et al (2000)[197]	RCT Multi-centre Parallel-group evaluator-blind active-controlled	1. MF 100µg b.i.d. (daily total 200µg) + placebo 2. MF 200µg b.i.d. (daily total 400µg) + placebo 3. MF 400µg b.i.d. (daily total 800µg) + placebo 4. BUD 400µg b.i.d. (daily total 800µg) + placebo *Delivery device:* 1, 2, 3. MF-DPI (made by Schering-Plough) 4. DPI Turbuhaler® (Pulmicort, AstraZeneca*) *Duration:* 12 wks *Run in period:* Not defined	*Number randomised* 730 *Mean (years) age (range)* 41(12-76) *Baseline FEV_1 % predicted* 76.8 *Previous ICS treatment (drug and dose)* as previously prescribed inhaled ICS	*Primary outcome* Change from baseline to end-point in FEV_1 (L) *Secondary outcomes* FVC PEFR Symptom scores Nocturnal awakenings requiring salbutamol use as rescue medication Daily salbutamol use Physician evaluation of response to therapy Adverse event

* not stated explicitly, but deduced from the text

5.2.2.5.2 Results

NB. Results for the comparison between 400µg MF twice daily plus placebo, and 400µg BUD twice-daily (i.e. the 1:1 dose ratio) in the trial by Bousquet and colleagues[197] are reported in section 5.2.3.5, as this MF dose falls into the 'high dose' category (Review question 2).

Lung function

Parallel 1:1 dose ratio studies

Corren and colleagues reported a significant difference between the two active treatment arms in terms of FEV_1 change at end-point and percentage change at end-point. The mean FEV_1 value changed by 0.19L± 0.04 in the MF group and 0.03L± 0.04 in the BUD group ($p<0.01$). These represent percentage changes of 8.9% and 2.1% for the two groups, respectively ($p<0.01$).

Corren and colleagues reported that change from baseline morning PEFR was statistically significantly greater in the MF group (19.96L/min± 4.15) than in BUD group (0.54L/min ± 4.08; $p<0.01$). In terms of change from baseline in evening PEFR scores, MF patients had a mean change of 19.04L/min ± 4.19, compared with 4.93L/min ± 4.13 in the BUD group. MF was statistically significantly better than BUD ($p<0.05$). However, baseline mean PEFR values (both morning and evening) were lower in the MF group than in the BUD group. The difference between MF and BUD groups for evening PEFR was statistically significant ($p<0.05$). These unbalanced baseline values may have influenced the results at end-point.

Parallel 1:2 or 1:4 dose ratio studies

Change from baseline FEV_1 and percent of predicted FEV_1 value were presented by Bousquet and colleagues. The 200µg b.i.d. MF group reported a mean change from baseline FEV_1 that was statistically significantly greater than change in the BUD group (0.16L ± 0.03 vs. 0.06L± 0.03 in the BUD group, $p<0.05$). Similarly, the end-point percent of predicted FEV_1 was statistically significantly different between the 200µg b.i.d. MF group (81.6% ± 1.2) and BUD (77.9% ± 1.1; $p<0.05$). In the 100µg b.i.d. MF group, change from

baseline (0.10L ±0.03) and end-point percent of predicted FEV_1 (79.6% ± 1.1) were not statistically significantly different from the BUD group.

Bousquet and colleagues did not find a statistically significant difference between MF and BUD in terms of change in morning PEFR. Change from baseline to end-point was 24.75L/min ±5.3 in the BUD group, compared with 18.20L/min ± 5.3 in the 100µg b.i.d. MF group and 37.84L/min ± 5.4 in the 200µg b.i.d. MF group. Changes in evening PEFR were not presented, but were reported to be similar to changes in morning PEFR.

Symptoms

Parallel 1:1 dose ratio studies

Total morning and evening asthma symptom scores were reported by Corren and colleagues using the total score of three symptoms, each rated on a four point scale (0=none, no reference given). Mean morning scores decreased for the MF group (i.e. patients' symptoms improved) by 0.42 points ±0.12. Patients in the BUD group also showed an improvement in symptoms with a mean change in morning score of -0.12±0.11, but this was not statistically significantly different from the MF group. Evening asthma scores decreased in the BUD (-0.11±0.12) and MF groups (-0.46±0.12). The difference between the MF group and the BUD group was statistically significant ($p<0.05$). Corren and colleagues also reported a statistically significant difference in the percentage of asthma symptom-free days. In the MF group, the percentage of symptom-free days was 39.7% ± 3.4 compared with 26.8% ± 3.3 in the BUD group ($p<0.01$).

In the trial by Corren and colleagues, the percentages of patients with no nocturnal awakenings due to asthma were 60.8%, 78.8% and 81.1% for the placebo, MF and BUD groups, respectively (p=NS).

Parallel 1:2 or 1:4 dose ratio studies

Bousquet and colleagues did not report symptom-free days, but did report change from baseline to end-point in mean number of nocturnal awakenings requiring salbutamol rescue medication. Mean number of awakenings was 0.36 in the 100µg b.i.d. MF group, 0.33 in the

200µg b.i.d. MF group and 0.30 in the BUD group. Differences between the groups were not statistically significant.

Health related quality of life

Neither study reported measures of health related quality of life.

Use of rescue medication

Parallel 1:1 dose ratio studies

Corren and colleagues reported that the mean average decrease in use of albuterol for patients in the MF arm was 0.91± 0.23 puffs, compared with a mean decrease of 0.21± 0.23 puffs in the BUD group ($p<0.05$).

Parallel 1:2 or 1:4 dose ratio studies

Bousquet and colleagues did not report symptom relief in terms of puffs/day.

Exacerbations

Neither study reported rate of asthma exacerbations.

Adverse events

Corren and colleagues reported that there were no significant differences between the trial arms in overall incidence of adverse events. Treatment-related adverse events were experienced by 8% of the MF group and by 9% of the BUD group. One patient in the MF group and two patients in the BUD group discontinued due to adverse events, which were unrelated to treatment.

Bousquet and colleagues reported that the incidence of treatment-related adverse effects was similar for all treatment groups (17-20%). Reports of serious adverse events were also similar across treatment arms, and none of these were thought to be related to treatment. Withdrawals due to adverse events were reported for six patients in the 100µg b.i.d. MF

group, one person in the 200µg b.i.d. MF group, three patients in the 400µg b.i.d. MF group and seven patients in the BUD group.

5.2.2.5.3 Summary

Two multi-centre, parallel-group RCTs compared the efficacy and safety of BUD (delivered via a Turbohaler or a DPI) with MF, delivered via a DPI. Both studies used an adequate method of randomisation, although neither study used a strictly ITT method of efficacy analysis.

A statistically significant difference in FEV1 favouring MF was apparent when MF and BUD were compared at a nominal dose ratio of 1:1. Corren and colleagues also reported that change from baseline morning and evening PEFR values was statistically significantly greater in the MF group than in the BUD group. Results from 1:2 and 1:4 dose ratio comparisons indicated that a 200µg b.i.d. MF dose was also statistically significantly more effective than 400µg b.i.d. BUD in terms of FEV_1 changes from baseline and percent of predicted FEV_1 value.

MF does not appear to be statistically significantly better than BUD in relieving morning asthma symptoms, although one study found a statistically significant improvement in evening asthma scores with 400µg MF compared with BUD. The study also found a statistically significantly higher percentage of symptom-free days in the MF group.

On the basis of the two studies discussed here, 200µg b.i.d. or 400µg MF (q.d.) appears to improve lung function compared with 400µg BUD (b.i.d. or q.d.), and may have a slightly higher impact on asthma symptoms. There do not appear to be any statistically significant differences between the drugs in terms of adverse effects.

5.2.2.6 CIC and FP (review Q1 – low dose ICS)

5.2.2.6.1 Study Characteristics

Two RCTs were identified which compared CIC with FP[198;199] (*Table 19*). An unpublished report of one of the trials[199] was supplied by Altana Pharma, the manufacturer of CIC (Alveso), as part of their submission to NICE, and has been classed as commercial in confidence. The non-inferiority, parallel group study by Buhl and colleagues[198] was a multi-

national, multi-centre trial with 529 participants. [redacted]

The 12 week study by Buhl and colleagues[198] had two arms and compared CIC 200µg/day (as a single daily dose in the evening) with FP 200µg/day (as two daily doses of 100µg/day) – the dosing ratio was 1:1. Both drugs were delivered by HFA-MDIs (CIC -Alvesco®, made by Atlana - however this is not specifically stated, nor are any further details on the FP device reported).

The primary outcome was the change in FEV_1 from beginning to end of treatment.

[redacted]

In the study by Buhl and colleagues,[198] patients were described as had mild to moderate asthma. Their ages ranged from 12-74 years and $FEV_{1\%}$ predicted from 48 to 108%. Patients were eligible for the study if they had been taking up to 500µg/day of BDP or equivalent. Both groups were generally similar at baseline in terms demographics and other characteristics. [redacted]

Buhl and colleagues[198] did not describe the processes used to randomise patients, conceal allocation or blind the treatment. The power calculation was adequate. A full ITT analysis was not performed – although the majority of participants were included in the efficacy analysis (probably as an available case analysis). [redacted]

[redacted]

TABLE 19 *Characteristics of studies (CIC and FP)*

Study ID	Design	Intervention	Patients	Outcomes
Buhl et al. (2006)[198]	RCT Multi-centre Parallel Double-blind Double-dummy	1. CIC 200µg ex-valve PM q.d. (daily total 160µg ex-actuator) 2. FP 100µg ex-valve b.i.d. (daily total 176µg ex-actuator) *Delivery device:* 1, HFA-MDI (CIC -Alvesco®, made by Atlana*) 2.HFA-MDI (no further details about device reported) *Duration:* 12 wks *Run in period:* 1-4 wks: ICS was discontinued & salbutamol rescue medication only.	*Number randomised* 529 *Median (years) age (range)* 1. 41 (12-74) 2. 38 (12-74) *Baseline mean FEV_1 % predicted (range)* 1. 75 (51-108) 2. 75 (48-92) *Previous ICS treatment (drug and dose)* Up to 500µg q.d. of BDP or equivalent	*Primary outcome* Change in FEV_1 from beginning to end of treatment *Co primary outcomes* Change in FVC and morning PEFR *Secondary outcome* FVC $FEF_{25-75\%}$ Evening PEFR Asthma symptom scores (0 no symptoms, 4 bad) Rescue medication use/free days Number of days and nights without symptoms Asthma exacerbations Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed

* not specifically stated in text

5.2.2.6.2 Results

The study by Buhl and colleagues[198] was designed to show non-inferiority of CIC with FP. Both ITT and PP (per protocol) results are presented in the paper. ITT results are reported here.

[redacted]

[redacted]

Lung Function

Parallel 1:1 dose ratio studies

FEV_1 L

In the study by Buhl and colleagues,[198] least squares means were used for the analysis of FEV_1 (L). The within-treatment mean difference (SE) in the CIC group was 0.489 (0.029), p<0.0001, and in the FP group was 0.499 (0.029), p<0.0001. The between-treatment mean difference was not significant (-0.010, 95%CI -0.085 to 0.066, p=0.801). Non-inferiority of CIC to FP was demonstrated as the lower limit of the 95% CI was above the pre-defined non-inferiority acceptance limit of -0.2L in both the ITT and the PP analysis.

[redacted]

Confidential Information Removed

FEV_1 % predicted

Buhl and colleagues[198] did not report on FEV_1% predicted.

[redacted]

Morning and evening PEFR

Buhl and colleagues[198] used least square means for the analysis of morning and evening PEFR (L/min). The morning PEFR within-treatment mean difference (SE) L/min in the CIC group was 33 (4), p<0.0001, and in the FP group was 36 (4), p<0.0001. The between-treatment mean difference was not significant (-3, 95%CI -13 to 7, p=0.582). Non-inferiority of CIC to FP was demonstrated as the lower limit of the 95% CI was above the pre-defined non-inferiority acceptance limit of -0.25 L/min in both the ITT and the PP analysis. Evening PEFR values were reported to have significantly improved over the 12 weeks following treatment with CIC and FP but no further details were provided.

[redacted]

[redacted]

Confidential information removed

[redacted]

Morning and evening PEFR

[redacted]

[redacted]

Symptoms

Parallel 1:1 dose ratio studies

Buhl and colleagues[198] reported data on the median percentages of days and nights without symptoms. The median percentage of symptom-free days at 12 weeks in the CIC group was approximately 58% and in the FP group 65%. The respective median percentages for nights without symptoms was 100% in both groups. The figures have been estimated from graphs by the reviewers and no statistical tests of significance were presented by the authors. [redacted]

Buhl and colleagues[198] reported median symptom scores using a five point scale (0 no symptoms to 4 severe symptoms, not referenced) and Hodges-Lehmann point estimates are presented. The within-treatment difference for total asthma symptom score in the CIC group was -0.75, p<0.0001, and in the FP group -0.86, p<0.0001. The between-treatment difference was not significant (0.07, 95%CI -0.11 to 0.29, p=0.387). The within-treatment difference for daytime symptom scores was -0.43, p<0.0001, in the CIC group and -0.50, p<0.0001, for the FP group. The between-treatment group difference was not significant (0.00, 95%CI -0.00 to 0.14, p=0.317). The within-treatment difference for night time symptom scores was -0.29, p<0.0001, in the CIC group and -0.33, p<0.0001, for the FP

group. The between-treatment group difference was not significant (0.00, 95%CI 0.00 to 0.10, p=0.530). Confidence intervals for the within-treatment differences were not reported.

[redacted]

[redacted]

Health related quality of life

Buhl and colleagues[198] did not report on this outcome. [redacted]

Use of rescue medication

Parallel 1:1 dose ratio studies

Buhl and colleagues[198] used Hodges-Lehmann point estimates in the analysis. The within-treatment difference for the median number of puffs per day of rescue medication in the CIC group was -1.00, p<0.0001, and in the FP group -1.21, p<0.0001. The between-treatment difference was not significant (0.14, 95%CI -0.00 to 0.43, p=0.130). [redacted]

[redacted]

Exacerbations

Parallel 1:1 dose ratio studies

Buhl and colleagues[198] did not report on this outcome.

[redacted]

Parallel 1:2 dose ratio studies

[redacted]

Adverse events

Parallel 1:1 dose ratio studies

In the study by Buhl and colleagues,[198] 97 (36%) participants in the CIC group and 89 (34%) in the FP group experienced an adverse event. A total of 270 adverse events occurred during the study. One serious adverse event occurred in each group, both thought not to be related to the study medication. Six patients in the CIC group and three in the FP group withdrew because of adverse events.

[redacted]

[redacted]

Confidential Information removed

[redacted]

[redacted]

5.2.2.6.3 Summary

Two studies were identified which compared CIC with FP. One of these is currently commercial in confidence.

In the study by Buhl and colleagues,[198] which used a 1:1 dosing ratio(CIC 200µg/day versus FP 200µg/day), there were no statistically significant differences between groups on any outcomes. FP appeared to be more favourable for percentage of symptom-free days,

although no statistical tests were reported. Non-inferiority was demonstrated for FEV_1 and morning PEFR.

[redacted]

5.2.2.7 MF and FP (review Q1 – low dose ICS)

5.2.2.7.1 Study characteristics

One parallel-group RCT, published in 2001, investigated the effectiveness of MF compared to FP (*Table 20*). The study was a multi-centre parallel trial with 733 patients. The study, by O'Connor and colleagues,[200] comprised four arms in which three doses of MF (200, 400 and 800µg/day) were compared with one dose of FP (500µg/day). The comparisons are approximately equivalent to rounded nominal dose ratios (MF: FP) of 1:1 (400 : 500µg/day), 1:2 (200 : 500µg/day) and 2:1 (800 : 500µg/day). The 500µg/day dose of FP is slightly above the upper threshold for a low-dose classification, but 500µg/day FP is included in this section to permit comparison with low-dose MF (dose ratios of 1:1 and 1:2). The 2:1 dose ratio covers high-dose classifications for both drugs and accordingly is reported in the under review question 2 – high dose ICS (see Section 0).

O'Connor and colleagues[200] employed DPIs for both MF and FP, but these were of different types: a newly-developed inhaler (MF-DPI) was used for MF whereas FP was administered using a standard Diskhaler formulation (FP-Flixotide Diskhaler®, Glaxo Smith Kline).

The study was of relatively short duration, lasting 12 weeks.[200] The mean age of patients included in the study was 41, and ages ranged from 12 to 79 years. The enrolled patients had moderate persistent asthma.

O'Connor and colleagues[200] employed a large-scale international dose-ranging study (with 60 centres in 20 countries) to compare the efficacy and safety of several doses of MF administered with a newly-developed inhaler with a single dose of FP administered with a standard inhaler. The primary comparison was between 200µg/day MF vs 800µg/day MF. If there was no significant difference them, pair-wise comparisons between all three doses of MF against FP would be performed.

The methodological quality was generally adequate, with randomisation by computer-generated code, adequate ITT analysis, and a power calculation reported. However, details of allocation concealment were not reported.

TABLE 20 *Characteristics of studies (MF and FP)*

Study ID	Design	Intervention	Patients	Outcomes
O'Connor et al. (2001)[200]	RCT Parallel-group Double-blind (dosage) Evaluator-blind (medication)	*Drug(s):* 1. MF 100µg b.i.d. (daily total 200µg) 2. MF 200µg b.i.d. (daily total 400µg) 3. MF 400µg b.i.d. (daily total 800µg) 4. FP 250µg b.i.d. (daily total 500µg) *Delivery device:* 1, 2, 3. MF-DPI (Schering-Plough) 4. DPI (Flixotide Diskhaler®, GlaxoSmithKline) *Duration:* 12 wks *Run in period:* 1-2 wks	*Number randomised* 733 *Mean age (years)* 41 (12-79) *Baseline FEV_1 % predicted* 75 *Previous ICS treatment (drug and dose)* As previously prescribed	*Primary outcome* mean change in FEV_1 from baseline to end-point *Secondary outcomes* PEFR FEF25-75% FVC Asthma symptom scores Rescue medication use Nocturnal awakenings Physician evaluation Adverse events

5.2.2.7.2 Results

The dose ratio comparisons reported here are for rounded nominal dose ratios as described above.

Lung function

Parallel 1:1 dose ratio

The change from baseline FEV_1 value did not differ between patients treated with 400µg/day MF and 500µg/day FP. The change in FEV_1 (mean ± SD) reported by O'Connor and colleagues[200] was the same (0.16 ± 0.54 L) for MF (n=182) as for FP (n=184). The change in morning PEFR reported by O'Connor and colleagues[200] (mean ± SD) was 29 ± 80.9 L / min for MF and 32 ± 67.8 L / min for FP (no p-values reported). The change from baseline to end-point in the evening PEFR was not reported quantitatively. However, the authors commented that the changes in evening PEFR were similar to changes in morning PEFR. Changes in both morning and evening PEFR values therefore appear to be independent of whether MF or FP was used, although tests of statistical significance for the small difference between the two drugs were not reported.

Parallel 1:2 dose ratio

The change in FEV_1 (mean ± SD) was 0.07 ± 0.54 L for MF (20µg/day) and 0.16 ± 0.54 L for FP (500µg/day) (p=NS). The change in morning PEFR (mean ± SD) was 15 ± 67.5 L / min for MF (200µg/day) and 32 ± 67.8 L / min for FP (500µg/day). This difference was statistically significant ($p \leq 0.05$).

Symptoms

Parallel 1:1 dose

O'Connor and colleagues[200] reported the occurrence of specific symptoms (wheeze, difficulty in breathing, or cough), but did not report changes in overall symptom score. The change from baseline in the number of nocturnal awakenings reported by O'Connor and

colleagues[200] was 0.01 for MF and -0.14 for FP. This difference between the drugs was not statistically significant.

Parallel 1:2 dose ratio

The change from baseline in the number of nocturnal awakenings was 0.07 for MF-treated patients and -0.14 for FP-treated patients. This difference was statistically significant ($p \leq 0.05$).

Use of rescue medicine

Parallel 1:1 dose ratio

O'Connor and colleagues[200] expressed the use of rescue medication in µg of albuterol use per day. The change from baseline to end-point was -94.84µg/day for MF-treated patients and -52.06 µg/day for FP-treated patients. The difference in rescue medication use between the two drugs was not statistically significant.

Parallel 1:2 dose ratio

The change from baseline in the use of albuterol rescue medication was -13.23µg/day for MF-treated patients and -52.06µg/day for FP-treated patients; this difference between the treatments is not statistically significant.

Exacerbations

O'Connor and colleagues[200] noted that aggravated asthma was one of the most frequent adverse events leading to the discontinuation of treatment. However, the occurrence of asthma aggravation was not reported separately from other adverse events (summarised below).

Adverse events

Parallel 1:1 dose ratio

In the study by O'Connor and colleagues,[200] 47 out of 182 patients treated with MF (26%) and 53 out of 184 patients treated with FP (29%) experienced treatment-related adverse events. Six patients that received MF and eight patients that received FP did not complete their treatment because of adverse events. The most frequent adverse events leading to discontinuation were aggravated asthma, bronchitis, pharyngitis and upper respiratory tract infection.

Parallel 1:2 dose ratio

Of 182 patients that were treated with 200 µg/day MF, 36 (20%) experienced treatment-related adverse events. Of the patients treated with 500 µg/day FP, 53 out of 184 (29%) experienced treatment-related adverse events. Nine patients that received MF and eight patients that received FP did not complete their treatment because of adverse events. The most frequent adverse events leading to discontinuation were aggravated asthma, bronchitis, pharyngitis and upper respiratory tract infection.

5.2.2.7.3 Summary

Only one RCT compared MF and FP. The limited data suggest that the two drugs are very similar in terms of clinical effectiveness when used in a 1:1 dose ratio. Results for a 1:2 dose ratio comparison showed a degree of statistical significance for some outcomes.

At the nominal dose ratio of 1:2, the change from baseline in the morning PEFR was significantly larger for FP. The change in nocturnal awakening also differed significantly between the two drugs, being positive for MF and negative (i.e. an improvement) for FP. These findings favour the use of 500µg/day FP over 200µg/day MF, both in terms of clinical effectiveness and safety. An exception is that a higher frequency of adverse events occurred with FP (29%) compared with MF (20%), but these differences were not evaluated statistically.

5.2.2.8 Summary of Q1 – relative effectiveness of low dose ICS

According to Step 2 of the BTS/SIGN Guidelines, the following drugs at the following doses (excluding considerations of device) are equivalent:

BUD 200µg/BDP 200µg/FP 100µg. MF 100µg is considered the appropriate equivalent dose at this level, likewise CIC 100µg (by assumption). Similarly, BUD 400µg/BDP 400µg/FP 200µg are considered equivalent, alongside MF 200µg and CIC 200µg, and 800µg/ BDP 800µg/FP 400µg, alongside MF 400µg, and CIC 400µg.

In general, all of the ICS in this assessment were associated with favourable changes from baseline to end-point across efficacy and safety outcomes. However, when evaluated in pair-wise comparisons, there were few statistically significant differences between them in terms of the outcomes prioritised for this assessment (although it was not always possible to discern whether significance testing had been performed). From the head-to-head comparisons of these drugs there is little evidence to reject the hypothesis that there is no difference in clinical effectiveness between them, with the exception of FP demonstrating some greater effectiveness when compared to BDP. The results are not so consistently in favour of FP when compared to equivalent doses of BUD or MF. In some cases non-inferiority was assessed and demonstrated, such as the comparison of CIC to equivalent doses of FP or BUD.

By way of a brief summary,

- BDP vs BUD (5 RCTs, all 1:1 dose ratio) - statistically significant differences only for lung function, in favour of BUD.
- FP vs BDP (6 RCTs, all 1:2 dose ratio) - few statistically significant differences, except for 1 RCT which found significant differences in favour of FP across a range of outcomes
- FP vs BUD (5 RCTs, 4 at 1:2 dose ratio, 1 at 1:1 dose ratio) – mixed findings. Significant difference for symptoms in favour of FP from one trial, significant difference for adverse events in favour of BUD from meta-analysis of two trials
- CIC vs BUD (1 RCT, 1:2 dose ratio) – no significant differences. Non-inferiority demonstrated for lung function

- MF vs BUD (2 RCTs, 1 at 1:1 dose ratio, 1 at 1:2 dose ratio) – At 1:1 dose ratio significant differences in favour of MF for lung function, symptoms and rescue medication. At 1:2 dose ratio MF significantly favourable only for lung function.
- CIC vs FP (2 RCTs, 1 at 1:1 Dose ratio, 1 at 1:2 dose ratio) – No significant differences at 1:1 dose ratio. Non-inferiority demonstrated for lung function. [redacted]
- MF vs FP (1 RCT, 1 at 1:1 dose ratio, 1 at 1:2 dose ratio) – No significant differences at 1:1 dose ratio. At 1:2 dose ratio there were significant differences in favour of FP on lung function and nocturnal wakenings.

The following tables provide a visual illustration of the results of pair-wise comparisons.

BUD vs. BDP n=5 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
400µg vs. 400µg	Jäger 8w Cross-over, open label DPI; n=79	*BDP*	NSD	NSD	NSD				NSD		C		2.5%
		BUD											1.1%
	Tjwa 8 w Cross-over DPI; n=16	*BDP*	NSD								NSD		
		BUD		+	+								

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800µg vs. 800µg	Meta-analysis Parakh; Dal Negro	*BDP*	+										
		BUD											
	Parakh 12w Parallel group DPI; n=32	*BDP*							NSD				
		BUD											
	Dal Negro 8w Parallel group MDI; n=42	*BDP*		NSD	NSD				NSD				
		BUD											
	Rafferty variable, Cross over, MDI; n=40	*BDP*		NSD	NSD				NSD				
		BUD											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies); NSD = no significant difference between trial arms; + indicates results favour this trial arm; C use of rescue medication stated to be comparable between trial arms. F indicates that results favour this trial arm but no significance testing has been reported. Blank cells signify no data reported on that outcome.

FP vs. BDP n=6 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800µg BDP vs. 400µg FP	Parakh, parallel-group, single blind RCT, 12 wks, MDI, n=42	*BDP*	NSD						F				
		FP											
400µg BDP vs. 200µg FP	Prasad Parallel-group, double-blind RCT, 12 weeks, MDI, n=74	*BDP*	NSD			NSD						NSD	
		FP											

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
400µg BDP vs. 200µg FP 800µg BDP vs. 500µg FP	Raphael Parallel-group, double-blind RCT, 12 wks, MDI, n=42 *(combined analysis of both doses)*	*BDP*				NSD							range 9% to 15%
		FP	+	+	+		+		+		+		
200µg BDP vs. 100µg FP	Szefler Parallel-group, Open-label RCT, 21 wks, MDI+ spacer, 21 weeks, n=30	*BDP*											

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
		FP	F										
BDP 400 µg vs. 250 µg FP	Ige Parallel-group, open-label RCT, 8 wks, pMDI, n=20	*BDP*	NSD										
		FP				+							
800µg BDP vs. 400µg FP 1500µg BDP vs. 750µg FP	Medici Parallel-group, Double-blind RCT, 12 months, MDI + spacer, n=69	*BDP*										NSD	
		FP											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

FP vs BUD n=5 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
200 or 400µg FP vs. 200 or 400µg BUD	Basran, Parallel-group, Open-label RCT, 8 wks, DPI, n=176 *(results only reported for FP vs. BUD, not by dose groups)*	*FP*	NSD	NSD	NSD				NSD		NSD		60.2%
		BUD											51.8%

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
200µg FP vs. 400µg BUD	**Meta analysis** Langdon[192] Connolly	*FP*		NSD									
		BUD											
	Langdon[192] Parallel-group Open-label RCT, MDI, 8 weeks, n=157	*FP*			NSD		+	+	+				59.3%
		BUD											50%
	Connolly Parallel-group Open-label RCT, DPI Diskhaler or reservoir DPI, 8 weeks, n=190	*FP*											88.5%
		BUD											64.8%
400µg FP vs. 800µg BUD and 200µg FP vs. 400µg BUD	Meta analysis Langdon[192] Parakh	*FP*	NSD										
		BUD											

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
400µg FP vs. 800µg BUD	Langdon[191] Parallel-group Open-label RCT, DPI Diskhaler or reservoir DPI, 8 weeks, n=281	*FP*		+	NSD								79.1%
		BUD											61.8%
	Parakh Parallel-group Single-blind RCT, MDI, 12 weeks, n=42	*FP*							NSD				
		BUD											
200µg FP vs. 400µg BUD and 400µg FP vs. 800µg BUD	**Meta analysis** Langdon[192] Langdon[191] Connolly	*FP*											+
		BUD											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

BUD vs CIC n=1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
CIC 200µg ex-actuator am CIC 200µg ex-actuator BUD 400µg	Niphadkar Parallel group double blind RCT, 12 weeks, HFA-MDI or MDI, n=405 (extra data from Altana report FK1-120)	1. CIC AM	NSD 1 vs. 3 2 vs. 3 NID 1 vs. 3 2 vs. 3	NSD 1 vs. 3 2 vs. 3 NID 1 vs. 3 2 vs. 3	NSD 1 vs. 3 2 vs. 3 NID 1 vs. 3 2 vs. 3	C	NSD 1 vs. 3 2 vs. 3		NSD 1 vs. 3 2 vs. 3			F 1 vs. 3	
		2. CIC PM										C 2 vs. 3	
		3. FP											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported; NID=non-inferiority demonstrated. Blank cells signify no data reported on that outcome.

BUD vs. MF n=2 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results									
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
400µg MF vs. 320µg BUD	Corren, Parallel-group Double-blind, Double-dummy RCT, DPI, 8 weeks, n=262	*MF*	+	+	+	NSD	+				+		8%
		BUD											9%

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
200µg/ 400µg/ MF vs. 800µg BUD	Bousquet Parallel-group evaluator-blind active-controlled RCT, DPI, 12 weeks, n=730	*1.MF* 200µg	NSD 1 vs. 3	NSD 1 vs. 3 2 vs. 3	NSD 1 vs. 3 2 vs. 3	NSD 1 vs. 3 2 vs. 3							4.3%
		2. MF 400µg	+ 2 vs. 3										2.9%
		3. BUD											2.2%

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

FP vs. CIC n=2 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
	Confidential Information removed	Confidential Information removed	Confidential Information removed	Confidential Information removed									Confidential Information removed
		Confidential Information removed											
200µg CIC vs. 200µg FP	Buhl *et al* Parallel-group Double-blind, Double-dummy RCT, HFA-MDI, 12 weeks, n=529 Non-inferiority (1:1 dose ratio)	*CIC 200µg*						C	NSD		NSD		
		FP 200µg					F						

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed			Confidential information removed	Confidential information removed	Confidential information removed		Confidential information removed	Confidential information removed	Confidential information removed
		Confidential information removed			Confidential information removed		Confidential information removed	Confidential information removed	Confidential information removed		Confidential information removed	Confidential information removed	Confidential information removed
		Confidential information removed			Confidential information removed								Confidential information removed

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported; NID=non-inferiority demonstrated. Blank cells signify no data reported on that outcome.

FP vs. MF n=1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
200µg/ 400µg/ MF vs. 500µg FP	O'Connor, parallel-group, double-blind RCT	*1. 200µg MF*	NSD 1 vs. 3 2 vs. 3								NSD 1 vs. 3 2 vs. 3		20%
		2. 400µg MF		C 2 vs. 3	C 2 vs. 3	NSD 2 vs. 3							26%
		3. FP		+ 3 vs. 1		+ 3 vs. 1							29%

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

5.2.3 Review question 2 – Effectiveness of high dose ICS

(high dose defined as 800 - 2000µg per day BDP/BUD equivalent*) (Step 4 of the guidelines)

To re-cap, 24 RCTs evaluated high dose ICS (*Table 21*). The following sub-sections describe the characteristics and results of these trials.

TABLE 21 *Breakdown of studies for Review Question 2 – high dose ICS*

Pair-wise comparison	Number of RCTs included
BDP and BUD	2
FP and BDP	10
HFA BDP and HFA FP	1
FP and BUD	6
CIC and BDP	0
MF and BDP	0
CIC and BUD	0
MF and BUD	1
CIC and FP	3
MF and FP	1
MF and CIC	0
Total	24

5.2.3.1 BDP and BUD (review Q2 – high dose ICS)

5.2.3.1.1 Study characteristics

Two double-blind, cross-over RCTs evaluated the effectiveness of BDP compared with BUD (*Table 22*).[79;201] The two studies were small, with 28 patients in the single centre study by Ebden and colleagues[79] and 15 patients in the multi-centre study by Kaur and colleagues.[201]

* For FP, CIC and MF high dose is greater than 400 µg per day.

Both of the RCTs contained two trial arms with nominal 1:1 daily dose ratios, but the doses were different. The study by Ebden and colleagues[79] had two treatment periods, each of six weeks. Treatment A consisted of three puffs of 250µg BDP and four puffs of placebo BUD twice daily (total daily dose 1500µg BDP). Treatment B consisted of four puffs of 200µg BUD and three puffs of placebo BDP twice daily (total daily dose 1600µg BUD). The crossover trial by Kaur and colleagues[201] compared 1000µg twice daily of each drug (total daily doses 2000µg), with a six-week treatment period for each. Treatment drugs in the two RCTs were delivered via MDIs (no details reported for Ebden and colleagues;[79] BDP – Beclate and BUD –Budecort – both by Cipla Ltd for Kaur and colleagues[201]), with or without spacers.

Kaur and colleagues[201] aimed to assess whether the same doses of the two drugs produced clinically important differences in side effects, and Ebden and colleagues[79] aimed to compare the efficacy of similar doses of the drugs. Neither of the trials clearly stated what the primary outcome measure was.

Patients in the study by Ebden and colleagues[79] had a mean age of 54 years (ranging from 19-72). However, those in the study by Kaur and colleagues[201] were considerably younger, having a mean age of 28.6 years (no range reported). Neither of the two RCTs provided any details of the severity of asthma in the trial populations or reported baseline FEV_1 % predicted values. The mean daily dose of BDP before entry to the cross-over study by Ebden and colleagues was 887.5µg. Kaur and colleagues did not report prior treatment for their RCT population.

The cross-over study by Kaur and colleagues[201] used computer-generated random numbers to assign patients to treatment groups, but the other RCT[79] did not describe the randomisation procedure. Concealment of allocation was not reported. The two studies were reported to have been double blind, but few details were provided in the publications. Ebden and colleagues[79] did not report a wash-out period between treatments, so it is possible that the effects of the first treatment influenced results in the second half of the trial. No power calculations were reported, and it is possible that the study may be too small to be statistically powered (n=27). Results were not analysed on an ITT basis. Kaur and colleagues[201] included a one week washout period prior to cross-over, to reduce the likelihood of any effects from the first treatment distorting results during the second treatment. Analysis of trial data was not ITT, and was based on only 13 of the 15 patients who completed the trial.

TABLE 22 *Characteristics of studies comparing BDP and BUD*

Study ID	Design	Intervention	Patients	Outcomes
Ebden et al. (1986)[79]	RCT Cross-over (no washout Double-blind	1. BDP 250µg 3 puffs b.i.d. (daily total 1500µg) + placebo 4 puffs b.i.d. 2. BUD 200µg 4 puffs b.i.d. (daily total 1600µg) + placebo 3 puffs b.i.d. *Delivery device:* 1. pMDI + placebo plus spacer * 2. pMDI + spacer plus placebo * * no further details about devices provided *Duration:* 6 wks *Run in period:* Not reported	*Number randomised* 28 *Mean age (years)* 54 *Baseline FEV_1 (L)* 1.85 *Previous ICS treatment (drug and dose)* Not reported	*Outcomes* FEV_1 FVC PEFR (am & pm) Daily SABA (puffs/day) Daytime wheeze score Morning serum cortisol Serum cortisol 30 minutes post 250 µg tetracosactrin
Kaur et al. (2005)[201]	RCT Multi-centre Cross-over Double-blind	1. BDP 1000µg b.i.d. (daily total 2000µg) 2. BUD 1000µg b.i.d. (daily total 2000µg) *Delivery device:* 1. MDI + spacer (Beclate, Cipla Ltd) 2. MDI + spacer (Budecort, Cipla Ltd) *Duration:* 6 wks *Run in period:* 1 wk	*Number randomised* 15 *Mean (years) age (±sd)* 28.6 (± 8.0) *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* Not reported	*Outcomes* Serum cortisol (9am) µg/100ml Serum cortisol (4pm) µg/100ml 24h urinary steroids mg/24h FVC (L) FEV_1 (L)

5.2.3.1.2 Results

It was not appropriate to pool the results of the two BDP vs. BUD RCTs in a meta-analysis due to differences in doses. A narrative summary of the key results is presented below.

Lung function

Mean change from baseline FEV_1 value in the cross-over study by Ebden and colleagues[79] was 0.02L in the BUD group and -0.09L in the BDP group (p=NS). Mean morning PEFR for the last three weeks of treatment was similar in the two groups. The mean was 314.1 (SEM 4.0) L/min during BUD treatment and 311.2 (SEM 4.1) L/min during BDP treatment. The mean evening PEFR during the last three weeks of treatment was also very similar for the two treatments. The mean scores were 335.9 (SEM 3.9) L/min during BUD treatment and 334.0 (SEM 3.7) L/min during BDP treatment. Significance values were not reported for PEFR scores. Ebden and colleagues[79] also compared lung function during high dose treatment with function during existing treatment. They reported that nine of the 16 evaluable patients showed a significantly higher value for at least one of morning PEFR, evening PEFR or daily inhaled bronchodilator usage. Values were only presented on graphs in the publication, and no significance values were reported.

The cross-over study by Kaur and colleagues[201] reported a significant change from baseline value for both BDP and BUD treatment, but did not report a significant difference between the two treatments. Mean change from baseline FEV_1 after six weeks was 0.58L with BDP treatment and 0.55L with BUD treatment. This study did not report individual morning or evening PEFR values.

Symptoms

Neither of the cross-over studies[79;201] reported days or nights without symptoms or overall daily symptom scores.

Health related quality of life

Health related quality of life was not reported by either of the two RCTs.

Use of rescue medication

Ebden and colleagues reported that there were three exacerbations of asthma which required oral corticosteroid treatment. One patient required oral corticosteroids during the BDP phase, and a second patient required oral corticosteroids during both treatment phases. The use of inhaled bronchodilator during the last 21 days of treatment was significantly greater during BDP treatment than during BUD treatment. Median daily number of puffs was 6.72 (range 0-22) during BUD and 7.81 (0-26) during BDP ($p<0.05$). Kaur and colleagues did not report use of rescue medication.

Exacerbations

Exacerbations were not reported by either of the RCTs.

Adverse events

Ebden and colleagues[79] did not report the overall rate of side effects, but commented that any side effects of treatment were considered to be minimal by patients and physicians and did not require cessation of treatment or withdrawal from the study. Kaur and colleagues[201] did not report rates of adverse events in the two trial arms, but did report changes in serum cortisol. The mean 9 a.m. serum cortisol level increased by 0.4µg per 100ml in the BDP group and decreased by 0.85µg per 100ml in the BUD group. The mean 4 p.m. serum cortisol level decreased by 0.04µg per 100ml in the BDP group and decreased by 0.96µg per 100ml in the BUD group. The changes in serum cortisol level were not found to be statistically significant for either the 9 a.m. level or the 4 p.m. level. Analysis of individual patient data by Kaur and colleagues[201] found no significant difference between the two treatment groups for the number of patients with a > 20% fall in either 9 a.m. serum cortisol level ($p>0.5$) or 4 p.m. serum cortisol level ($p>0.1$).

5.2.3.1.3 Summary

Two small, double-blind cross-over trials compared 1500µg - 2000µg BDP with 1600µg - 2000µg BUD. There was limited reporting of outcome measures appropriate for this systematic review. Neither of the trials found a statistically significant difference in lung function following treatment with the two drugs. One of the studies reported that the mean

daily number of puffs of rescue medication was statistically significantly higher in the BDP group. In general, the two RCTs indicated that BDP and BUD are similar in effects when used at 1:1 daily dose ratios, except for use of rescue medication.

5.2.3.2 FP and BDP (review Q2 – high dose ICS)

5.2.3.2.1 Study characteristics

Ten RCTs tested high doses of FP compared to BDP.[189;202-210] The studies were predominantly parallel in design but three trials used cross-over designs.[208-210] The studies varied considerably in size (from 21 participants to 340) and length (from six weeks to two years). Only two were undertaken in single centres.[207;210] All appeared to be superiority trials.

There were two parallel group trials comparing FP with BDP in a nominal 1:1 dose ratio. Boe and colleagues[203] randomised participants (stratified by their pre-trial dose of ICS) to either 2000µg of FP daily or 1600µg of BDP daily for three months. The study drugs were delivered by Diskhaler DPI (Rotadisk, GlaxoSmithKline – not explicitly stated but deduced from the text). Fabbri and colleagues[202] randomised participants to either 1500µg of FP daily or 1500µg of BDP daily, delivered by MDIs (no further details about devices reported), for 12 months. After three months investigators were allowed to increase the dose of the study drug to 2000µg either transiently or long term.

Five parallel group trials compared FP with BDP in a nominal 1:2 (FP: BDP) dose ratio. Barnes and colleagues[204] randomised participants to either 1000µg FP or 2000µg of BDP daily, delivered by pressurised inhalers (no further details of devices reported), for six weeks. Egan and colleagues[207] compared 1000µg of FP or 2000µg of BDP, daily by MDI (no further details of devices reported) for two years. The trial also contained three open control groups of the same age although these are not discussed here. Lorentzen and colleagues[206] randomised participants to either 1000µg of FP or 2000µg BDP daily, using MDIs(no further details of devices reported), for one year. Lundback and colleagues[205] study had three arms. Participants took 500µg of FP daily by either DPI Diskhaler (Rotadisk, GlaxoSmithKline - not explicitly stated by deduced from the text) or a pressurised inhaler, or 1000µg of BDP daily by pressurised inhaler (the DPI Diskhaler group is not reported here). The randomised section of the trial lasted for six weeks. At the end of this initial period the participants had

the option of continuing the trial on the same study drugs for 12 months in order to assess long term efficacy (the participants on the FP Diskhaler had to convert to a pressurised inhaler. The results of this non-randomised second phase are not reported here). Medici and colleagues' study[189] had four treatment arms comparing 400µg of FP, 800µg of BDP, 750µg of FP and 1500µg of BDP, all daily by MDI (no further details reported), for a period of one year. The lower doses of BDP and FP are reported in an earlier section of this report (review question 1 – low dose ICS, Section 5.2.2.2)

All three of the cross-over trials compared FP with BDP in a 1:2 dose ratio (FP : BDP). Bootsma and colleagues[210] compared 750µg FP daily with 1500µg BDP daily, using MDIs (no further details of devices reported), for 12 weeks. Participants took placebo for three weeks during the washout period. In the study by Pauwels and colleagues,[209] which had two arms, participants were randomised to three different strata, depending on their original dose of ICS: 500µg FP or 1000µg BDP, 750µg FP or 1500µg BDP, and 1000µg FP or 2000µg BDP. All were delivered by MDI (no further details reported) and the trial lasted for 12 months, with no washout period. Malo and colleagues[208] study had two arms. Participants were randomised to 1000µg, 1500µg or 2000µg of BDP and half the corresponding dose of FP daily, depending on their previous levels of ICS. The drugs were delivered using MDIs (no further details reported) and there was no washout period.

The average/median age of participants in the trials ranged from mid-thirties to early fifties. Almost all participants (except one patient[210]) were previously taking either BDP or BUD with doses ranging from 400µg to 2000µg per day. A number of trials did not present data on baseline FEV_1 % predicted. However, for those that did, the mean value ranged from 57 to 90%. Where stated, authors generally described participants as suffering from "moderate to severe" asthma.

Study quality was mixed. Although all trials described themselves as randomised and double blinded, these procedures were rarely described in any detail. Concealment of allocation was not discussed in any of the trials. Unfortunately, most trials did not state a primary outcome. Whilst most focussed on clinical efficacy outcomes, there were a number of trials whose principal aim was to determine effects on bone density/metabolism and other possible systemic side effects of steroids.[189;207-209] Pauwels and colleagues[209] study was the only study analysed on an intention to treat basis. In the study by Bootsma and colleagues[210] no carry-over effects were detected for any variables.

TABLE 23 *Study characteristics (FP and BDP)*

Study ID	Design	Intervention	Patients	Outcomes
Fabbri et al. (1993)[202]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 750µg b.i.d. (daily total 1500µg) 2. BDP 750µg b.i.d. (daily total 1500µg) After first 3 mths dose could be increased to 2000µg q.d. if needed *Delivery device:* 1, 2. MDI ± spacer *Duration:* 52 wks *Run in period:* 2 wks	*Number randomised* 274 *Age Range* 1. 17-77 2. 19-80 *Baseline FEV_1 % predicted* Not stated *Previous ICS treatment (drug and dose)* BUD or BDP ≥1000µg but <2000µg q.d.	*Outcomes* PEFR (am & pm) FEV_1 L Clinic PEFR FVC Day & night symptom scores Use of study medication Use of rescue medication Adverse events Morning plasma cortisol 24 hour urinary free cortisol Asthma exacerbations
Barnes et al (1993)[204]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 250µg 2 puffs b.i.d. (daily total 1000µg) 2. BDP 250µg 2 puffs b.i.d. times 2 inhalers (daily total 2000µg) *Delivery device:* 1,2. MDI + placebo *Duration:* 6 wks *Run in period:* 2 wks	*Number randomised* 154 *Median (years) age (range)* 1. 50 (18-78) 2. 52 (20-75) *Baseline FEV_1 % predicted* 1. 61 2. 57 *Previous ICS treatment (drug and dose)* BDP or BUD 1500-2000µg q.d.	*Outcomes* PEFR (am & pm) FEV_1 L, (% predicted) FVC Clinic PEFR Day & symptom scores Use of rescue medication Patient assessed asthma Adverse events Plasma cortisol

Study ID	Design	Intervention	Patients	Outcomes
Boe et al (1994)[203]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 1000µg b.i.d. (daily total 2000µg) 2. BDP 800µg b.i.d. (daily total 1600µg) *Delivery device:* 1. Diskhaler (Rotadisk, GlaxoSmithKline*) 2. Diskhaler (Rotadisk, GlaxoSmithKline*) *Duration:* 3 mths *Run in period:* 2 wks	*Number randomised* 134 *Mean (years) age (range)* 1. 51 (20-74) 2. 51 (27-75) *Mean baseline FEV_1 litres (± sd)* *1. 2.04 (± 0.66)* *1. 2.10 (± 0.93)* *Previous ICS treatment (drug and dose)* BDP or BUD 400-2000µg q.d.	*Primary outcome* PEFR (am & pm) *Secondary outcomes* Clinic PEFR FEV_1 L FVC Day &d night symptom score Use of bronchodilator Serum cortisol Plasma adrenocorticotropic hormone Adverse effects Asthma exacerbations

Study ID	Design	Intervention	Patients	Outcomes
Lundback et al (1993)[205]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 125µg 2 puffs b.i.d. (daily total 500µg) 2. FP 125µg 2 puffs b.i.d. (daily total 500µg) 3. BDP 250µg 2 puffs b.i.d. (daily total 1000µg) *Delivery device:* 1, 3. MDI + placebo 2. DPI Diskhaler® (Rotadisk, GlaxoSmithKline*) + placebo Only groups 1 and 3 considered here *Duration:* 6 wks *Run in period:* 2 wks	*Number randomised* 585 *Mean age (±sd, range)* *1. 46 (± 15, 18-78)* *2. 45 (± 16, 16-91)* *3. 46 (± 16, 15-90)* *Baseline FEV_1 % predicted* Not stated *Previous ICS treatment (drug and dose)* ICS 400-1000µg q.d.	*Outcomes* PEFR (am & pm) FEV_1 L FVC Clinic PEFR Day & night symptoms Use of rescue medication Plasma cortisol Asthma exacerbations
Lorentzen et al (1996)[206]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 250µg 2 puffs b.i.d. (daily total 1000µg) 2. BDP 250µg 4 puffs b.i.d. (daily total 2000µg) *Delivery device:* 1,2. MDI ± spacer + placebo *Duration:* 52 wks *Run in period:* 2 wks	*Number randomised* 213 *Median (years) age (range)* 1. 51 (18-77) 2. 54 (21-76) *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* BDP or BUD 1000-2000µg q.d.	*Outcomes* Clinic PEFR FEV_1 L FVC Adverse events Asthma exacerbations Morning plasma cortisol

Study ID	Design	Intervention	Patients	Outcomes
Egan et al (1999)[207]	RCT Single-centre Parallel-group Double-blind	*Drugs:* 1. FP 500µg b.i.d. (daily total 1000µg) 2. BDP 1000µg b.i.d. (daily total 2000µg) *Delivery device:* 1, 2. MDI + spacer *Duration:* 108 wks *Run in period:* 2 wks	*Number randomised* 33 *Mean age (± sd, range)* *1. 36 (± 8, 20-48)* *2. 33 (± 10, 20-50)* *Mean baseline FEV_1 litres (sd)* 1. 2.91 (0.7) 1. 3.13 (1.1) *Previous ICS treatment (drug and dose)* BDP or BUD 1000-2000µg q.d.	*Primary outcome* Absolute bone mineral density values *Secondary outcome* Biochemical markers of bone turnover Clinic PEFR Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Medici et al (2000)[189]	RCT Multi-centre Parallel-group Double-blind	*Drug(s):* 1. FP 200µg b.i.d. (daily total 400µg) 2. BDP 400µg b.i.d. (daily total 800µg) 3. FP 375µg b.i.d. (daily total 750µg) 4. BDP 750µg b.i.d. (daily total 1,500µg) Only groups 3 and 4 reported in this section *Delivery device:* 1, 2, 3, 4. MDI + spacer *Duration:* 52 wks *Run in period:* 4 wks	*Number randomised* 69 *Mean (years) age (±sd)* *1. 39 (± 8)* *2. 38 (± 8)* *3. 38 (± 10)* *4. 40 (± 10)* *Baseline FEV_1 % predicted (±sd)* *1. 79.9 (± 18.9)* *2. 90.2 (± 14.0)* *3. 75.0 (± 20.7)* *4. 78.2 (± 14.8)* *Previous ICS treatment (drug and dose)* ICS 400-1600µg q.d.	*Primary outcome* Bone mineral density of the distal radius *Secondary outcome* PEFR (am & pm) FEV_1 L Serum cortisol Markers of bone metabolism (serum & urine) Use of rescue medication

Study ID	Design	Intervention	Patients	Outcomes
Malo et al (1999)[208]	RCT Multi-centre Cross-over (no washout) Double-blind	*Drugs:* 1. FP daily dose half dose of BDP* 2. BDP 1000, 1500 or 2000µg q.d.* *3 different doses of FP and BDP in each group depending on normal dose of ICS *Delivery device:* 1,2. MDI *Duration:* 4 months for each treatment *Run in period:* 2 wks	*Number randomised* 67 *Mean age (range)* 48,4 (14.5) yr *Baseline FEV_1 % predicted (± sd)* *76 (± 18)* *Previous ICS treatment (drug and dose)* BDP or BUD 800-2000µg q.d.	*Outcomes* Daily asthma symptoms FEV_1 L, (% predicted) FVC Use of rescue medication Skin bruising Short synacthen test Urinary cortisol, phosphorus, calcium, N-telopeptides Serum intact osteocalcin Serum procollagen & specific alkaline phosphatise
Pauwels et al (1998)[209]	RCT Multi-centre Cross-over (no washout) Double-blind	*Drugs:* 1 FP 500 or BDP 1000µg q.d.* 2. FP 750 or BDP 1500µg q.d.* 3. FP 1000 or BDP 2000µg q.d.* *Dose received depended on dose of current ICS *Delivery device:* 1, 2, 3. MDI ± spacer *Duration:* 52 wks *Run in period:* 4wks	*Number randomised* 340 *Mean (years) age (±sd)* *FP/BDP 46.6 (± 14.6)* *BDP/FP 46.2 (± 15.0)* *Baseline FEV_1 % predicted (±sd)* *FP/BUD 78.4 (± 21.1)* *BUD/FP 80.0 (± 20.7)* *Previous ICS treatment (drug and dose)* BDP 1000-2000µg q.d. or BUD 800-1600µg q.d.	*Primary outcome* Serum cortisol level *Secondary outcomes* FEV_1 (% predicted) FVC PEFR (am & pm) Use or rescue medication Symptom scores Quality of life – Hyland's Living With Asthma Questionnaire (LWAQ) Urinary bone markers Dual energy X-ray absorptiometry (DEXA) – BMD L2 to L4, hip (femoral neck, trochanter, and Ward's triangle) Adverse effects Asthma exacerbations

Study ID	Design	Intervention	Patients	Outcomes
Bootsma et al (1995)[210]	RCT Single-centre Cross-over (3 wks washout period) Double-blind	*Drugs:* 1. FP 125µg 3 puffs b.i.d. (daily total 750µg) 2. BDP 250µg 3 puffs b.i.d. (daily total 1500µg) *Delivery device:* 1, 2. MDI + placebo *Duration:* 12 wks *Run in period:* 3 wks	*Number randomised* 21 *Mean (years) age (±sd)* *30.3 (± 7.4)* *Baseline FEV_1 % predicted (±sd)* *74.7 (± 18.1)* *Previous ICS treatment (drug and dose)* All but one used ICS before entering the study (mean daily dose 790µg q.d. (SE 54)	*Outcomes* PEFR (am & pm) FEV_1 Histamine & ultrasonically nebulised distilled water provocation test Use of rescue inhaler Asthma symptoms Adverse events Severity of symptoms (day & night) Eosinophils Serum cortisol Serum & urinary markers of bone turnover

* not stated explicitly, but deduced from the text

5.2.3.2.2 Results

A meta-analysis was not undertaken due to variation in the length of the trials, and also due to limitations in the data reported.

Lung function

FEV_1 L

Parallel design, 1:1 dose ratio

Boe and colleagues[203] reported an increase in FEV_1 of 0.19L and 0.06L in the FP and BDP groups, respectively. The end-point mean values (SE) were 2.23L (0.11) and 2.16 L (0.13) respectively. There were no statistically significant differences between treatments at any of the clinic visits (no p value reported). In the study by Fabbri and colleagues,[202] mean FEV_1 increased from 2.14 L and 1.81 L for FP and BDP to 2.39 L and 1.97 L, respectively, over the one year treatment period. The adjusted mean difference was 0.15 L (95% CI 0.01, 0.29; $p<0.05$).

Parallel design, 1:2 dose ratio

In the study by Barnes and colleagues,[204] there was an increase in FEV_1 of 0.07 L and 0.16 L in the FP and BDP groups, respectively. At end-point the adjusted means were 1.95 L and 1.89 L, respectively. The adjusted mean difference in end-point FEV_1 was non-significant, 0.66 L (95% CI -0.07, 0.19), p=0.343. There was significant difference between groups at 12 months in the study by Lorentzen and colleagues,[206] in favour of FP (mean difference 0.12L, 95% CI 0.01, 0.24, p=0.044).

In the trial by Lundback and colleagues,[205] the adjusted mean change from baseline in FEV_1 was 0.13 L and 0.09 L in the FP and BDP groups respectively. End-point values were 2.44 L and 2.51 L, respectively. There was no significant difference between groups (no p value reported). Medici and colleagues[189] did not formally analyse lung function measures, but reported that mean FEV_1 values taken at bi-monthly intervals over the 12 month study either remained similar or tended to increase above baseline values. Egan and colleagues[207] did not measure this outcome.

Cross-over design, 1:2 dose ratio

Bootsma and colleagues[210] found no significant differences between the two groups; the mean difference (SE) between FP and BDP was 0.06 (0.07), 95% CI -0.08, 0.21. The other two trials did not report this outcome.

FEV_1 % predicted

Parallel design, 1:1 dose ratio

Neither of the two studies reported this outcome measure.

Parallel design, 1:2 dose ratio

Only Barnes and colleagues[204] reported this outcome measure. There was an increase in FEV_1 % predicted of 3% and 4% in the FP and BDP groups, respectively. At end-point the adjusted means were 64% and 61%, respectively (Mean difference 2% (95%CI -2, 6), p=0.358).

Cross-over design, 1:2 dose ratio

In the study by Malo and colleagues,[208] there was no significant difference in the mean (SD) end-point FEV_1 % predicted between FP, 77.5% (17.1), and BDP, 77.5% (17.5), p=0.7. Pauwels and colleagues[209] also found no significant difference (results were presented as a graph – it was not possible to determine the values accurately). Bootsma and colleagues[210] did not report this outcome measure.

Morning and evening PEFR (L/min)

Parallel design, 1:1 dose ratio

Boe and colleagues[203] only reported morning and evening PEFR as estimated increases per day over the treatment period. Baseline and end-point values are also reported, but for morning and evening PEFR combined.

The study by Fabbri and colleagues,[202] which only measured this outcome for the first 12 weeks, reported that changes in both morning and evening PEFR were significantly greater in the FP group. The mean difference, averaged over the 12 week period and adjusted for differences in baseline values, country and use of spacer device, for morning PEFR was 15 L/min (95% CI 6, 25), p<0.005, and 10 L/min (95% CI 0, 19; p<0.05) for evening PEFR.

Parallel design, 1:2 dose ratio

Barnes and colleagues[204] reported an increase in morning PEFR of 14 L/min and 30 L/min in the FP and BDP groups, respectively. At end-point adjusted mean values were 317 L/min and 324 L/min, respectively. The adjusted mean difference for morning PEFR at end-point was -7 L/min (95% CI -21, 7), p=0.346. For evening PEFR there was a decrease of 1 L/min in the FP group, compared to an increase of 15 L/min in the BDP group, respectively. At end-point adjusted mean values were 336 L/min and 348 L/min, respectively. The adjusted mean difference for evening PEFR at end-point was -13 L/min (95% CI -26, 1). The p value reported for the evening PEFR (p=0.07) was incompatible with the other values.

Lundback and colleagues[205] found no significant difference between the different treatment arms in either morning or evening PEFR. The adjusted mean change from baseline in morning PEFR was 19 L/min and 14 L/min in the FP and BDP groups, respectively. End-point values were 383 L/min and 394 L/min, respectively. For evening PEFR the adjusted mean change from baseline was 11 L/min and 14 L/min in the FP and BDP groups, respectively. End-point values were 400 L/min and 411 L/min, respectively. No p values were reported for between-group comparisons. Medici and colleagues[189] did not perform a formal statistical analysis on lung function data. However, mean daily morning and evening PEFR values either remained similar or tended to increase slightly above baseline values (no data shown). Egan and colleagues[207] only reported clinic PEFR, rather than morning and evening PEFR.

Cross-over design, 1:2 dose ratio

The mean (SE) difference in treatment effect for morning PEFR between FP and BDP in the study by Bootsma and colleagues[210] was 5.57 L/min (5.5), 95% CI 6.31 to 17.5 (nb. it appears that the lower limit of the CI is incorrect). The corresponding figures for evening

PEFR were 2.69 L/min (6.5), 95% CI -10.9 to 16.3. The other two trials did not report this outcome measure.

Symptoms

Days and nights without symptoms

Parallel design, 1:1 dose ratio

Fabbri and colleagues[202] reported an increase in mean percentage of symptom-free days of 19% in both the FP and BDP groups, respectively between run-in and 12 weeks treatment. Over the 12 weeks, values were 38% and 41% for the two groups, respectively. There were no significant differences between groups (no p values presented). Increases in mean percentage of symptom-free nights were also reported, 14% and 13% in the treatment groups, respectively. Over the 12 weeks values were 61% and 63% respectively. Again, there were no significant differences between groups (no p values presented). Boe and colleagues[203] did not report this outcome measure.

Parallel design, 1:2 dose ratio

In the study by Barnes and colleagues[204] there was an increase in the percentage of symptom-free days of 14% in the FP group, and 9% in the BDP group. At end-point the mean percentage of symptom-free days for FP was 52% and BDP was 37%, p=0.212. There was an increase in percentage of symptom-free nights of 13% and 12% respectively. At end-point the mean percentage of symptom-free nights for FP was 59% and BDP was 50%, p=0.854. Lundback and colleagues[205] reported that there were no statistical differences between the groups for either symptom-free days or nights. However, no data or p values were provided. The remaining three trials did not report on this outcome.

Cross-over design, 1:2 dose ratio

The percentage of symptom-free days or nights in the study by Pauwels and colleagues[209] did not differ significantly (no p values reported). The percentage (SD) of symptom-free days at six months was 69.1% (41.1) for FP and 70.3% (39.4) for BDP. The corresponding figures

for symptom-free nights were 81.0 (33.3) and 79.0 (35.4). The other two trials did not report on this outcome measure.

Daily symptom scores

Parallel design, 1:1 dose ratio

Boe and colleagues[203] measured both day and night symptom scores using a scoring instrument (no reference supplied). Day symptoms were measured on a six point scale (0= no symptoms during the day, 5 = symptoms so severe that you could not go to work or perform normal daily activities). Night symptoms were measured on a five point scale (0= no symptoms during the night, 4 = symptoms so severe that you did not sleep at all). At baseline mean (SEM) daily scores were 1.70 (0.11) and 1.94 (0.11) and night scores were 0.77 (0.08) and 0.85 (0.08) in the FP and BDP groups, respectively. Over the 12 week treatment period these reduced significantly in both groups. Corresponding values were 1.35 (0.13) and 1.60 (0.12) for daily scores; 0.62 (0.08) and 0.65 (0.08) for nightly scores. There were no significant differences between groups (no p value reported).

Fabbri and colleagues[202] measured day and night symptoms using a four point scale (0= no symptoms, 4= bad symptoms; no reference supplied). Changes in scores were not presented, other than that fewer than 10% of patients in either group had median symptom scores of 2 or more.

Parallel design, 1:2 dose ratio

Barnes and colleagues[204] measured day and night symptoms on a four point scale (0=none, 3=poor; no reference supplied). Changes in scores were not reported, although the proportion of patients with a day time or night time symptom score of 0 was reported. Lundback and colleagues[205] measured day and night symptoms using a four point scale (0= no symptoms, 3= bad symptoms; no reference supplied). Limited data were reported. Over weeks 1 to 6, median day time scores were significantly lower for BDP than the scores for FP (p=0.03).

Cross-over design, 1:2 dose ratio

Bootsma and colleagues[210] measured symptom scores (dyspnoea) using a visual analogue scale ranging from 0 to 100mm (reference supplied). Lower scores indicate fewer symptoms. There were no significant differences between FP and BDP (no p value given). The end-point day score (SE) for FP was 7.3 (21) and for BDP 6.4 (1.9). Corresponding values for night scores were 5.6 (2.0) and 5.9 (2.2) respectively. The other trials did not report this outcome measure.

Health related quality of life

Parallel design, 1:1 dose ratio

Neither study presented data on these outcomes.

Parallel design, 1:2 dose ratio

No trials reported this outcome.

Cross-over design, 1:2 dose ratio

In the study by Pauwels and colleagues,[209] quality of life was measured using the Hyland's Living with Asthma questionnaire (reference supplied). There was a small significant difference in favour of FP. The mean difference between end point scores after six months was 0.02 (95% CI 0.00, 0.04), $p<0.05$. The other two studies did not report this outcome measure.

Use of rescue medication (mean puffs per day)

Parallel design, 1:1 dose ratio

Boe and colleagues[203] reported a decrease in mean puffs per day of SABA use of 0.51 and 0.57 in the FP and BDP groups, respectively. The end-point mean (SE) numbers of puffs per day were 2.24 (0.24) and 2.35 (0.25) respectively. Reductions in night use were 0.04 and 0.25 in the FP and BDP groups, respectively. End-point mean (SE) number of puffs per night were 0.73 (0.14) and 0.51 (0.09). There were no significant differences between

groups (no p values reported). Fabbri and colleagues[202] did not present results for rescue medication use in terms of mean puffs per day.

Parallel design, 1:2 dose ratio

In the study by Barnes and colleagues[204] both treatment groups reduced their use of rescue medication (salbutamol) by three times a day. End-point values were 10 for FP group and 11 for the BDP group, p=0.866. There was a reduction of one and two times a night for the groups respectively. Corresponding end-point values were 5 and 6, p=0.875. Lundback and colleagues[205] did not report use of rescue medication in terms of mean puffs per day. The other three trials did not report this outcome measure.

Cross-over design, 1:2 dose ratio

In the study by Bootsma and colleagues[210] the mean (SE) difference in number of puffs per day between FP and BDP was -0.25 (0.22), 95% CI -0.72 to 0.21. The other two trials did not report this outcome measure.

Exacerbations

Parallel design, 1:1 dose ratio

In the study by Fabbri and colleagues,[202] asthma exacerbations were defined as increasing asthma symptoms requiring a change in therapy other than inhaled SABA rescue therapy. There were 33 exacerbations in 23 (16%) people in the FP group and 62 exacerbations in 37 (28%) people in the BDP group, p<0.05. The numbers of patients experiencing a severe exacerbation were three (2%) and 13 (10%) in the groups, respectively (p<0.02). Boe and colleagues[203] reported that there were three exacerbations during treatment in the FP group, and eight in the BDP group. During follow-up there were one and two exacerbations, respectively.

Parallel design, 1:2 dose ratio

Barnes and colleagues[204] reported that six patients taking FP and two taking BDP were withdrawn due to exacerbations. During the study by Egan and colleagues,[207] 11 (65%)

patients in the FP group and six (38%) patients in the BDP group had one or more exacerbations requiring a short course of oral corticosteroids on at least one occasion (p value not reported).

Lundback and colleagues[205] only reported exacerbation data for the non-randomised 12 month study period, as opposed to the six week randomised period of interest to the current report. In the study by Lorentzen and colleagues,[206] 62 (39%) patients in the FP group and 26 (48%) patients in the BDP group had at least one exacerbation (defined as an increase in asthma symptoms necessitating a change in therapy other than inhaled SABA). There was no statistical difference between the two groups (p value not reported). Medici and colleagues[189] reported that there was no significant difference between exacerbation rates in the high dose groups (no values were reported).

Cross-over design, 1:2 dose ratio

In the study by Malo and colleagues,[208] there were nine exacerbations requiring oral steroids in the FP group and eight in the BDP group, p=0.4. An exacerbation was noted by the use of more than eight puffs of rescue salbutamol in a 24 hour period, effectiveness of rescue salbutamol lasting more than three hours, waking due to asthma symptoms, or loss of a day at work because of asthma symptoms. Pauwels and colleagues[209] reported that exacerbation of asthma was the reason for withdrawal in ten of 28 patients. Withdrawals due to exacerbation were numerically more frequent under BDP compared to FP (seven and three, respectively. No statistically significant difference, p value not reported). Bootsma and colleagues[210] did not report this outcome measure.

Adverse events

Parallel design, 1:1 dose ratio

Boe and colleagues stated that the number of side-effects was similar in both groups and no life-threatening side-effects or deaths occurred during the study. However, it was not possible to extract data on the total number of side-effects or the number of people experiencing them. In the study by Fabbri and colleagues,[202] there were 276 adverse events in 70% of FP participants and 267 adverse events in 73% of BDP participants. Sixteen percent of patients in the FP group experienced a serious adverse event, compared with

23% of patients in the BDP group. Eight percent of patients withdrew from both groups due to adverse events.

Parallel design, 1:2 dose ratio

In the study by Barnes and colleagues,[204] there were 71 adverse events in 43 (52%) patients in the FP group and 60 adverse events in 37 (51%) patients in the BDP group, p>0.15. Eight (10%) patients in the FP group and five (7%) patients in the BDP group had serious adverse events. The numbers of withdrawals due to adverse events were eight (10%) and five (7%) respectively.

Egan and colleagues[207] reported that the adverse events profile and overall incidence of adverse events were similar for both groups, but no data were provided. In the trial by Lorentzen and colleagues,[206] equal proportions of patients reported adverse effects, FP 114 (72%) and BDP 39 (72%). The number of patients experiencing serious adverse events in the FP group was 11 (7%) and three (6%) in the BDP group. The corresponding number of patients withdrawing from the trial because of adverse events was 20 (13%) and five (9%) respectively.

In the study by Lundback and colleagues,[205] the numbers of people experiencing adverse events in the MDI FP group and MDI BDP group were 97 (50%) and 89 (46%) respectively. There was no statistically significant difference between the groups (p value not reported). The corresponding values for the number of people withdrawing due to adverse events (including exacerbations) were 13 and 16. Medici and colleagues[189] reported a similar number of patients from both groups experiencing adverse events but no further details were provided. There were no serious adverse events.

Cross-over design, 1:2 dose ratio

In the study by Bootsma and colleagues,[210] there were no serious adverse events, however, it was not possible to extract any further data. Pauwels and colleagues[209] found a similar number of adverse events in both groups (FP, 217 in 66.8% of patients, and BDP, 215 in 66.2% of patients), which was not statistically significant (p value not reported). There were 13 serious adverse events in 4% of patients in the FP group and 10 serious adverse events in 3% of patients in the BDP group. Twenty-eight patients discontinued the study due to

adverse events; thirteen in the FP group and 15 in the BDP group. Malo and colleagues[208] did not report on this outcome measure.

Cortisol levels

Parallel design, 1:1 dose ratio

In the trial by Boe and colleagues,[203] mean (SE) change from baseline to end of treatment in serum cortisol was -133.5 nmol l^{-1} (26.5) and 40.4 nmol l^{-1} (26.9) in the FP and BDP groups, respectively ($p<0.001$, from ANCOVA). At 14 week follow up the difference was not statistically significant (p value not reported). Fabbri and colleagues[202] found no difference in the analysis of geometric mean cortisol levels between groups (adjusted ratio of FP to BDP 1.10, 95% CI 0.89-1.37). There was no difference in the 24 hour urinary cortisol levels between the groups.

Parallel design, 1:2 dose ratio

In the study by Barnes and colleagues,[204] the ratio of the FP adjusted geometric mean to the BDP mean for plasma cortisol concentration was 1.27 (95% CI 1.03, 1.56), p=0.026. Egan and colleagues,[207] did not find a statistically significant treatment difference between FP and BDP at 12 months (data provided in a figures, but reviewers were unable to estimate the values). In the study by Lorentzen and colleagues(C2007} the ratio of the FP adjusted geometric mean to BDP was significantly increased, 1.22 (95%CI 1.05 to 1.43), p=0.01. Lundback and colleagues[205] did not find a statistically significant difference between geometric mean plasma cortisol levels. End-point values for MDI FP and MDI BDP were 377 and 364 nmol/L, respectively (no p values reported). The geometric mean of the morning serum cortisol concentration (in nmol/L) estimated by Medici and colleagues[189] remained within the normal range for both FP and BDP-treated patients throughout the 12-month study period.

Cross-over design, 1:2 dose ratio

Bootsma and colleagues[210] found no significant difference between groups (no p value reported). The mean cortisol end-point value was 0.61µmol/L for FP and 0.51µmol/L for BDP. In the study by Malo and colleagues[208] there was no significant difference in urinary or

plasma cortisol levels between treatments. The end-point mean plasma cortisol levels (SD) for FP and BDP were 410 (249) µmol/dl and 418 (245) µmol/dl, p=0.7. The corresponding values for mean 24 hour urinary cortisol levels were 105 (64) µmol/dl and 109 (80)µmol/dl, p=0.6. Pauwels and colleagues found no significant difference between treatments. The mean serum cortisol end-point values (SD) for FP and BDP were 13.31 (6.88) µg% and 13.29 (6.26) µg%, respectively (authors state no differences between groups, no p values reported).

Parallel design, 1:2 dose ratio

Egan and colleagues[207] found a significant difference in single energy quantitative computed tomography (QCT) of vertebral trabecular (T12 to L3) at 12 (p=0.006) and 24 (p=0.004) months in favour of FP. The mean (SD) end-point value for bone mineral density in the FP group at 12 months and 24 months was 154 (29.2) mg/cm^3 and 153 (26.8) mg/cm^3 respectively. The corresponding values for BDP were 144 (19.5) mg/cm^3 and 145 (19.6) mg/cm^3. There was a statistically significant difference between groups in favour of FP in dual energy QCT at 24 months (p=0.033) but not at 12 months (no p value given). The mean (SD) end-point value in the FP group at 12 and 24 months was 155 (30.6) mg/cm^3 and 161 (24.2) mg/cm^3 respectively. The corresponding values for BDP were 148 (21.3) mg/cm^3 and 148 (24.6) mg/cm^3 respectively. Dual energy X-ray absorptiometry of the spine, femoral neck and whole body were essentially unchanged at 6, 12 and 24 months. Single photon absorptiometry of the forearm increased slightly over baseline at 6, 12 and 24 months in both groups but there were no significant differences.

Medici and colleagues[189] provided a detailed evaluation of the impact of FP and BDP on bone mineral density (in g/cm^3) and other bone metabolism markers. Peripheral quantitative computed tomographic (pQCT) of the distal radius showed no significant difference in the bone mineral density between the two groups at six or 12 months. Overall, compared with baseline, there was no loss of trabecular or integral bone in the radius or tibia in any patients over 12 months. Some negative changes were recorded in the median bone density of compact bone of the radius and tibia in the high dose FP group but this was not thought to be clinically significant as the changes did not exceed -2%. The only result of borderline statistical significance was compact bone density of the radius at 12 months which was in favour of BDP, although not thought to be clinically significant (p=0.048). Dual energy X-ray

absorptiometry of the lumbar verterbrae showed no differences between the high dose treatments at six or 12 months. There were no statistically significant differences between groups on biochemical markers of bone formation or resorption except for carboxy terminal cross linked telopeptide of type 1 collagen (ICTP) (measured in lµg/L) which suggested greater bone resporption activity in patients taking FP than those taking BDP (p=0.031).

The other three trials did not report this outcome measure.

Cross-over design, 1:2 dose ratio

Pauwels and colleagues[209] measured bone mineral density (BMD) in the lumbar spine (L2 to L4) and hip (femoral neck, femoral trochanter, and femoral Ward's triangle) by dual energy X-ray absorptiometry. After six months the mean end-point BMD (SE) in the lumbar spine was 1.118 (0.016) g/cm^2 and 1.116 (0.018) g/cm^2 in the FP and BDP group respectively. In the neck of the femur the results for FP were 0.932 (0.015) g/cm^2 and for BDP were 0.912 (0.014) g/cm^2. The corresponding values for the trochanter were 0.736 (0.013) g/cm^2 and 0.741 (0.013) g/cm^2. The values for Ward's triangle were 0.728 (0.017) g/cm^2 and 0.693 (0.018)g/cm^2. The treatments were not directly compared and no other values were presented.

Pauwels and colleagues[209] also reported biochemical markers of bone metabolism. Mean end-point (SD) values for osteocalcin were 1.72 ng/mL (1.40) and 1.53 ng/mL (1.02) in the FP and BDP groups, respectively (mean difference 0.28 ng/mL; 95% CI0.12, 0.44, p<0.001).

Of the biochemical markers of bone metabolism measured by Malo and colleagues,[208] there was only one statistically significant difference. Osteocalcin was significantly lower when patients were on BDP compared to FP. Mean end-point (SD) values were 3.5 (1.9) ngmL^{-1} and 2.8 (1.7) ngmL^{-1} respectively, p=0.003.

Bootsma and colleagues[210] did not report this outcome measure.

5.2.3.2.3 Summary

Ten studies comparing FP with BDP at high doses (according to BTS/SIGN Guidelines) were identified. There was variability in design, length of treatment, doses and size. The studies were predominantly parallel-group in design, but three trials used cross-over designs. Two

parallel-group trials compared 1500µg -2000µg FP with 1500µg -1600µg BDP in a nominal 1:1 dose ratio. Five parallel group trials compared 500µg -1000µg FP with 1000µg -2000µg BDP in a nominal 1:2 (FP: BDP) dose ratio. The cross-over trials compared 500-1500µg FP with 1000-2000µg BDP in a 1:2 dose ratio.

Of the two studies comparing the drugs at a nominal dose ratio of 1:1, one of the trials reported significant differences in FEV_1 and morning and evening PEFR, and exacerbations in favour of FP. There were no statistically significant differences between groups for use of rescue medication and symptoms. The adverse effects profile did seem similar, except cortisol levels which were significantly lower for FP.

The five parallel-group studies comparing FP and BDP at a nominal 1:2 dose ratio found few statistically significant differences in efficacy outcomes. Adverse effects profile seemed to be similar. However, cortisol levels were increased in the FP group and the results for impact on bone mineral density were mixed.

One of the three cross-over trials comparing FP and BDP at the 1:2 ratio found a small significant increase in health related quality of life. However, neither drug demonstrated clear superiority on efficacy outcomes. The adverse effects profile appeared similar.

5.2.3.3 HFA BDP and HFA FP (review Q2 – high dose ICS)

5.2.3.3.1 Study characteristics

One study, by Aubier and colleagues,[211] published in 2001, compared high doses of HFA BDP with HFA FP (*Table 24*). Both drugs were administered as metered-dose aerosols with HFA propellants (BDP - Qvar Easi-Breathe, 3M ; – no further details of FP device provided) The study was a two-arm trial comparing BDP against FP for a total of 198 patients. The drugs were compared in a nominal 1:1 daily dose ratio (800µg/day HFA-BDP versus 1000µg/day HFA-FP).

The patients' ages ranged from 19 to 78 years, with mean ages in the trial arms of approximately 50-52 years. Patients in the two trial arms were generally similar at baseline. However, the mean eosinophil count was significantly higher in the HFA-BDP group (p=0.03) and the mean corrected urine cortisol/creatine ratio was significantly higher in the HFA-FP group (p<0.05).[211]

The study was an open label trial, without any blinding of the patients or the researchers to the drug treatments. The study did not report details of the procedures for randomisation or concealment of allocation. The study was designed to achieve 80% power to detect differences between the drugs for the change in morning PEFR from baseline.

The objective of Aubier and colleagues[211] was to test the equivalence of HFA-BDP with an HFA-formulation of FP. Their null hypothesis was that the mean change from baseline in the morning PEFR would differ between the drugs by more than ± 25 L/min. The remainder of the outcomes were analysed using statistical tests to detect significant differences between treatments.

TABLE 24 *Study characteristics (HFA BDP and FP)*

Study ID	Design	Intervention	Patients	Outcomes
Aubier et al (2001)[211]	RCT Parallel-group Open-label	1. BDP 800µg q.d. 2. FP 1000µg q.d. *Delivery device:* 1. HFA-MDI (Extrafine aerosol, Qvar Autohaler®, 3M) 2. HFA-MDI (no further details reported) *Duration:* 8 wks *Run in period:* 7-14 days ± 2 days	*Number randomised* ITT total 198 *Mean (years) age (range)* 1. 50.1 [b] (19-76) 2. 51.9 [b] (20-78) *Baseline FEV_1 % predicted* 1. 71.7 [b] 2. 71.8 [b] *Previous ICS treatment (drug and dose)* 500-1000 µg q.d. CFC-BDP (or equivalent) [b] Assumed by the reviewers to be mean values (not stated in trial report)	*Outcomes* Change from baseline in am & pm PEFR FEV_1 Asthma symptom scores Sleep disturbances scores Rescue medication usage

5.2.3.3.2 Results

Lung function

Change from baseline to end-point in FEV_1

The mean change (SD) from baseline in FEV_1 was slightly larger for HFA-BDP than for HFA-FP (0.11 [0.5] vs. 0.07[0.49], respectively; p=0.21).

Change from baseline in morning and evening PEFR

The mean (± SD converted from SE by reviewers) change from baseline to end-point (8 weeks) in the morning PEFR was 29.59 ± 52.16 L/min for HFA-BDP and 17.13 ± 53.68 L/min for HFA-FP. The difference (12.46 L/min) had a 90% CI of -0.02 to 24.91, which was within the defined equivalence interval of ±25 L/min $^{-1}$. However, in the per protocol analysis the difference exceeded the equivalence limits. The change from baseline to end-point in evening PEFR was 24.9 L/min for HFA-BDP and 12.0 L/min for HFA-FP; this difference is not statistically significant (*p*=0.13; test of difference).

Symptoms

Aubier and colleagues[211] reported that the mean (± SD calculated by reviewers) change from baseline to end-point in the percentage of days without asthma symptoms was 24.32 ± 44.1% for HFA-BDP and 18.20 ± 39.4% for HFA-FP. This difference between the drugs was not statistically significant (*p*=0.23; test of difference). However, the change did differ significantly between the drugs part-way through the study (at 3 weeks): the change in the days without asthma from baseline to three weeks was 18.32 ± 34.2 for BDP and 6.84 ± 25.6 for FP (*p*=0.03). Aubier and colleagues[211] commented, without providing data, that changes from baseline to end-point in the percentage of days without wheeze, cough, shortness of breath, chest tightness, or nights without disturbed sleep, did not differ significantly between the treatments.

Use of rescue medication

Although Aubier and colleagues[211] reported change in use of rescue medication, this was not presented as number of puffs per day, so is not included here.

Exacerbations

Asthma exacerbations were not reported explicitly, but worsening asthma symptoms resulted in the withdrawal from treatment of four patients (see below).

Adverse events

A slightly higher proportion of adverse effects occurred among patients treated with HFA-FP than among patients treated with HFA-BDP (24.8% vs. 38.3%. Three patients in the HFA-BDP group (7.8%) withdrew from the study due to adverse events (dysphonia and headache, cough, and asthma symptoms), whilst one patient in the HFA-FP treatment withdrew due to adverse events (dysphonia and increasing asthma symptoms).

5.2.3.3.3 Summary

The systematic review included one parallel-group RCT[211] which compared 800µg/day HFA BDP with 1000µg/day FP in a nominal 1:1 dose ratio. It was designed to demonstrate the equivalence / non-inferiority of the two treatments with respect to the primary outcomes. However there were limitations in methodology and the quality of reporting was poor. The limited information available suggests that there were few differences in clinical efficacy or safety between HFA-BDP and FP. The study demonstrated equivalence / non-inferiority on the primary outcome measure. For most of the outcomes, HFA-BDP was favoured over the comparator but the differences were generally small and not statistically significant.

5.2.3.4 FP and BUD (review Q2 – high dose ICS)

5.2.3.4.1 Study characteristics

Six parallel group RCTs[212-217] evaluated the effectiveness of BUD compared to FP, published between 1995 and 2005 (*Table 25*). One study[217] reported additional data in a secondary publication.[218] Four studies were multi-centre studies where study sample sizes ranged

between 395 and 671 participants, while two studies were single centre studies where sample sizes ranged between 59 and 197. Four of the trials reported undertaking a power calculation, where adequate power in the sample was met.[212;213;215;217]

Four included trials had two-arm comparisons of BUD versus FP.[212;213;215;216] The remaining trials were three-arm comparisons; one had two FP groups (at different doses)[214] and the other had a BDP treatment group (not described here).[217]

Two trials had a nominal dose ratio of 1:1,[212;213] three a nominal dose ratio of 1:2,[215-217] and the three arm trial with two doses of FP had a 1:2 nominal dose ratio and a 1:1 nominal dose ratio comparison.[214] Of the three 1:1 nominal dose ratio comparisons two were of higher doses (one comparing 2000µg FP with 2000µg BUD,[212] and one 2000µg FP with 1600µg BUD,[214] and one was of a lower dose comparison (800µg FP versus 800µg BUD[213]). In the four 1:2 nominal dose ratio comparisons the dose of FP was 1000µg compared with BUD 1600µg in three,[214;216;217] and FP 800µg versus BUD 1600µg in one.[215]

The devices used in four studies were DPIs (FP: Flixotide Diskhaler®, GlaxoSmithKline; BUD: Pulmicort Turbuhaler®, AstraZeneca)[212;213;215;217] and MDIs in two studies (no further details of devices reported by either study).[214;216] The treatment duration in the studies ranged from five weeks[213] to 12 months.[216] Two of the three studies with 1:1 dose comparisons were of short duration (five weeks[213] and six weeks[214] respectively) and one a long duration (24 weeks).[212] Two of the four studies with 1:2 dose comparisons were of medium length duration (12 weeks)[215;217] and one of a long term duration.[216] The fourth comparison was from a study with a shorter six week duration.[214]

All included trials aimed to compare the clinical efficacy and safety of the two drugs. The trial by Ringdal and colleagues[215] was reported to be an equivalence trial, assessing morning PEFR as their primary outcome. The longer term study (Hughes and colleagues[216] was designed to assess the effect of long term use of the drugs on measures of bone markers and bone density. The study by Kuna[213] was designed to estimate the minimal effective doses of the two drugs.

The ages of participants in the trials are similar with mean ages ranging from 41-53 years. The severity of asthma varied across the six studies and is reflected in the differences in the doses (see above). In the 1:1 dose ratio comparisons participants were described as mild to

moderate in severity in one trial[213] and severe in two trials.[212;214] In the 1:2 dose ratio comparisons participants were described as moderate to severe in three trials,[215-217] and severe in one.[214] This latter trial is the trial that also had a 1;1 dose ratio comparison. In the included trials all or most participants were already prescribed various ICS. Baseline FEV_1 % predicted varied in the included trials and was related to the severity of the participants.

The quality of reporting and methodology of the included trials was generally good. Five of the six trials were assessed to have used an adequate method of randomisation, no details were reported for the method of randomisation in the one remaining trial.[212] In addition four of the included trials were assessed to have an adequate method of concealment of allocation, in the other two trials the method was unclear.[212;216] These factors limit the possibility of selection bias. Five studies report that their analyses were based on an intent-to-treat population which minimises the possibility of measurement bias.

TABLE 25 *Characteristics of studies: FP versus BUD*

Study ID	Design	Intervention	Patients	Outcomes
Heinig et al (1999)[212]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 1000µg b.i.d. (daily total 2000µg) 2. BUD 1200µg am & 800µg pm (daily total 2000µg) *Delivery device:* 1. DPI (Flixotide Diskhaler®, GlaxoSmithKline) + placebo Turbuhaler 2. DPI (Pulmicort Turbuhaler®, AstraZeneca) + placebo Diskhaler *Duration:* 24 wks *Run in period:* 2 wks	*Number randomised* 395 *Mean age (years)* 1, 2. 48 *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment* *(drug and dose)* Not defined	FEV_1 PEFR Symptoms Exacerbations Rescue medication Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Kuna (2003)[213]	RCT: Single-centre Parallel-group Double-blind	*Drugs:* 1. FP 400µg b.i.d.* (daily total 800µg) 2. BUD 400µg b.i.d.* (daily total 800µg) * At 5 wk intervals dose was reduced to 200 & then 100µg b.i.d. if asthma control maintained *Delivery device:* 1. DPI (Flixotide Diskhaler®, GlaxoSmithKline) 2. DPI (Pulmicort Turbuhaler®, AstraZeneca) *Duration:* 5 wks *Run in period:* 4-6 wks	*Number randomised* 197 *Mean age (years)* 1, 2. 41 *Baseline FEV_1 % predicted* 79.4% *Previous ICS treatment* *(drug and dose)* 800-1600µg b.i.d. ICS other than FP or BUD	Time to withdrawal Morning PEFR FEV_1 Tolerability
Ayres et al (1995)[214]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 125µg 4 puffs b.i.d. ex actuator (daily total 1000µg) 2. FP 250µg 4 puffs b.i.d. ex actuator (daily total 2000µg) 3. BUD 200µg 4 puffs b.i.d. ex actuator (daily total 1600µg) *Delivery device:* 1,2,3. MDI (no further details reported) *Duration:* 6 wks *Run in period:* 2 wks	*Number randomised* 671 *Mean age* 49 years *Baseline FEV_1 % predicted* <80% *Previous ICS treatment* *(drug and dose)* BDP 1000-2000µg q.d. or BUD 800-1600µg q.d.	FEV_1 PEFR (am & pm) Symptom-free days Symptom-free nights Daytime symptom score Night-time symptom score Rescue SABA free days Asthma exacerbations Morning plasma cortisol Biochemical markers of bone turnover

Study ID	Design	Intervention	Patients	Outcomes
Ringdal et al (1996)[215]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 800µg q.d. 2. BUD 1600µg q.d. *Delivery device:* 1. DPI (Flixotide Diskhaler®, GlaxoSmithKline*) 2. DPI (Pulmicort Turbuhaler®, AstraZeneca*) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 518 *Mean (years) age (sd)* 1. 47.6 (14.8) 2. 48.3 (14.0) *Baseline FEV_1 % predicted* 1, 2. 45-90 *Previous ICS treatment* *(drug and dose)* BDP 400-2000µg q.d., BUD 400-2400µg q.d. or FP 400-1000µg q.d.	FEV_1 PEFR (am & pm) Daytime symptom score Night-time symptom score % symptom-free days % symptom-free nights % rescue SABA free days % rescue SABA free nights Morning plasma cortisol
Hughes et al (1999)[216]	RCT Single-centre Parallel-group Open-label	*Drugs:* 1. FP 500µg b.i.d. (daily total 1000µg) 2. BUD 800µg b.i.d. (daily total 1600µg) *Delivery device:* 1, 2. MDI + large spacer (no further details reported) *Duration:* 52 wks *Run in period:* 2 wks	*Number randomised* 59 *Mean (years) age (range)* 1. 50 (29-70) 2. 56 (25-68) *Baseline FEV_1 % predicted* >30 *Previous ICS treatment* *(drug and dose)* BDP 1500-200µg q.d. or BUD 1600µg q.d. or equivalent doses of other ICS	Bone mineral density assessment Biochemical markers of bone turnover Change in urinary free cortisol level Change in plasma cortisol level

Study ID	Design	Intervention	Patients	Outcomes
Molimard et al (2005)[217]	RCT Multi-centre Parallel-group Open-label	*Drugs:* 1. BDP 800µg q.d. 2. FP 1000µg q.d. 3. BUD 1600µg q.d. *Delivery device:* 1. HFA-MDI (QVAR Autohaler®, 3M) 2. DPI (Flixotide Diskhaler®, GlaxoSmithKline) 3. DPI (Pulmicort Turbuhaler®, AstraZeneca) Only groups 2 and 3 considered here *Duration:* 12 wks *Run in period:* unclear	*Number randomised* 460 (although only 446 included in "ITT" population *Mean (years) age (sd)* 1. 42.4 (14.1) 2. 42.1 (13.5) 3. 42.9 (13.8) *Baseline FEV_1 % predicted (± d)* *1. 76.6 (± 18.5)* *2. 76.7 (± 16.8)* *3. 79.3 (± 18.0)* *Previous ICS treatment* *(drug and dose)* FP ≤ 500µg q.d., BUD ≤ 1000µg q.d. or BDP ≤ 1000µg q.d.	*Primary outcome* Change from baseline in asthma control score, assessed with Juniper questionnaire (ACQ), incorporating FEV1% predicted value & rescue medication usage *Secondary outcomes* FEV_1 (L) Adverse events

* not stated explicitly, but deduced from the text

5.2.3.4.2 Results

Lung function

Parallel design, 1:1 dose ratio

One trial[214] reported data on change from baseline on FEV_1 although did not report any measure of variance around the point estimates. Adjusted for baseline differences, the mean change from baseline after six weeks treatment was 0.28 L in the FP 2mg/d arm compared with 0.12 L in the BUD 1.6mg/d arm. The difference between the study groups was shown to be statistically significant, $p<0.05$. This analysis was not on an intention-to-treat population.

After 24 weeks, participants in the Heinig and colleagues[212] trial had similar end-point FEV_1 values regardless of treatment (2.30 (SD 0.90) L FP 2mg versus 2.30 (SD 0.90) L BUD 2mg). Similar end-point values of FEV_1 were also seen in both arms of the five week study by Kuna.[213] No point estimates were provided but the mean FEV_1 was 2.63 L in the FP (800µg) arm compared to 2.61 L in the BUD (800µg) arm. The study reports no statistically significant difference between treatments, $p=0.69$. In this latter study no statistically significant differences between treatments were demonstrated on FEV_1 % predicted: FP 80.7% versus BUD 79.7%, $p=0.48$.

Change in morning PEFR was 3.36 (SD 43.62) L/min in the FP arm of the Kuna[213] trial and –0.81 (SD 41.05) L/min in the BUD arm. The treatment difference (4.17 L/min) was not statistically significantly different (95% CI –7.65, 15.99). Evening PEFR in the same study was reported as an end-point value rather than the change from baseline, and it can be seen that these values were also not statistically significantly different between the two treatment groups (FP 407 L/min, BUD 392 L/min, $p=0.08$).

Parallel design, 1:2 dose ratio

Two trials[214;217] reported data on change from baseline on FEV_1. Molimard and colleagues[217] reported that the mean change in FEV_1 after 12 weeks was 0.28 (SD 0.49)L in the FP arm compared with 0.21 (SD 0.4) L in the BUD arm. Molimard and colleagues[217] found no statistically significant differences between groups ($p=0.250$), but the significance test included a third treatment arm not discussed here. In the trial by Ayres and colleagues,[214]

the adjusted mean change from baseline after six weeks treatment was 0.22 L in the FP 1000µg/d arm compared with 0.12 L in the BUD 1600µg/d arm. The difference between the study groups was shown to be statistically significant, p<0.05. This analysis was not on an intention-to-treat population.

FEV_1 at end-point in the Ringdal and colleagues[215] trial was 2.38 (SD 0.77) L in the FP arm and 2.27 (SD 0.77) L in the BUD arm after 12 weeks of treatment. The treatment difference was not shown to be statistically significantly different (0.11 L [95% CI –0.02, 0.24]).

Change in morning PEFR was shown to be statistically significantly better after 12 weeks of treatment with FP compared to BUD after 12 weeks of treatment with BUD in the Ringdal and colleagues trial (p=0.003).[215] Change in morning PEFR was 20.90 L/min (SD 37.92) and 12.40 (SD 35.45) L/min, respectively (treatment difference 8.50 L/min [95% CI 2.18, 14.83]). This confidence interval was not provided by Ringdal and colleagues,[215] and was calculated by a reviewer. Ringdal and colleagues[215] stated in their paper that treatment groups were considered equivalent if the 95% CI for the diference between treatments was ≤ 15L/min. The confidence interval presented here falls within this limit, suggesting that the two treatments are clinically equivalent.

Symptoms / health related quality of life

Parallel design, 1:1 dose ratio

Percentage of symptom-free days in the Heinig and colleagues[212] trial at end-point (after 24 weeks) showed a trend for improved symptoms in the FP arm (29.90 [SD 38.70]%) compared to BUD (23.30 [SD 36.40]%) the treatment difference was not statistically significantly different between groups (difference 6.60 [95% CI –1.48, 14.68]).

Symptom ratings on a 4-point scale in the Kuna[213] study showed no statistically significant differences between treatment groups after five weeks of treatment. In the FP arm the rating at end-point was 0.46 and in the BUD arm this was 0.56, p=0.44.

Although Ayres and colleagues[214] reported some data on symptoms in their trial, inadequate information was provided for the purposes of the present review.

Parallel design, 1:2 dose ratio

Molimard and colleagues[217] reported data on the Juniper Asthma Control Questionnaire (ACQ). This measure is a seven-item questionnaire; six items evaluate day and night symptoms and use of rescue medication, and one item evaluates FEV_1 as a percent predicted value. The study reported that this is a validated measure. Change from baseline was shown to be similar between the two groups after 12 weeks of treatment (FP –0.8 SD 1.0); BUD –0.8 (SD 0.9)).

Although Ayres and colleagues[214] reported some data on symptoms in their trial for the comparison between 1000µg FP and 1600µg BUD, inadequate information was provided for the purposes of the present review.

Use of rescue medication

Parallel design, 1:1 dose ratio

Although Ayres and colleagues[214] and Kuna[213] reported some data on use of rescue medication, this was not reported in terms of puffs per day as required for the purposes of the present review.

Parallel design, 1:2 dose ratio

Although Ayres and colleagues[214] reportedsome data on use of rescue medication, this was not reported in terms of puffs per day as required for the purposes of the present review.

Exacerbations

Parallel design, 1:1 dose ratio

The proportion of patients experiencing exacerbations in the Ayres and colleagues[214] trial was slightly higher in the BUD 1.6mg/d group compared to the FP 2mg/d group (16% FP versus 22% BUD, p-value not reported).

Parallel design, 1:2 dose ratio

The proportion of patients experiencing exacerbations in the Ayres and colleagues[214] trial was slightly higher in the BUD 1600µg/d group compared to the FP 1000µg/d group (17% FP versus 22% BUD, p-value not reported).

Adverse events

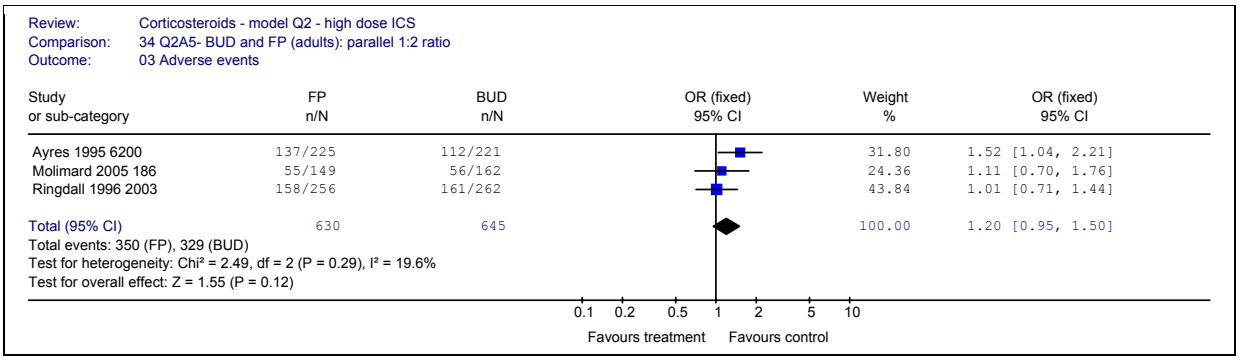
Parallel design, 1:1 dose ratio

Adverse events were experienced by 49% of the participants in the FP arm and 51% of participants in the BUD arm of the Ayres and colleagues trial.[214]

Parallel design, 1:2 dose ratio

Three trials reported the number of participants experiencing an adverse event, and these data were combined in a meta-analysis (*Figure 11*). Using a fixed-effects model, the meta-analysis showed a trend to better odds of not having an adverse event in the BUD treatment groups, but this was not statistically significant (OR 1.20 [95% CI 0.95, 1.50]). Two of these studies were of 12 weeks duration and the other six weeks duration.

FIGURE 11 *Adverse events FP vs. BUD, parallel 1:2 dose ratio*



In the Ringdal and colleagues[215] study, 10/256 participants in the FP group and 13/262 participants in the BUD group discontinued due to adverse events. This was not statistically significantly different (OR 0.78 [95% CI 0.34, 1.81]).

Cortisol levels and bone mineral density

In the Hughes and colleagues[216] study, no statistically significant differences were found between treatment groups on mean change in urinary free cortisol levels (FP –14.8% versus BUD –6.2%, p=ns). The study also reports that the mean change in serum cortisol levels was not statistically significantly different between groups, but no data were presented to support this. No decline in bone mineral density at the spine, neck or trochanter were observed in participants treated with either FP or BUD in the Hughes and colleagues[216] study.

5.2.3.4.3 Summary

Six parallel group RCTs[212-217] evaluated the effectiveness of BUD compared to FP. Two trials had a nominal dose ratio of 1:1,[212;213] three a nominal dose ratio of 1:2, and a three arm trial with two doses of FP had both a nominal 1:2 dose ratio and a nominal 1:1 dose ratio comparison.[214] The nominal 1:1 dose ratio comparisons compared 800µg-2000µg FP with 800µg -2000µg BUD. The nominal 1:2 dose ratio comparisons compated 800µg -1000µg FP with 1600µg BUD.

Parallel design, 1:1 dose ratio

On measures of lung function, the results generally showed no statistically significant differences between treatment with FP and treatment with BUD, although in one trial a significant difference in favour of FP was observed on FEV1. This was not on an intention-to-treat population and therefore may be subject to measurement bias. No statistically significant differences between treated groups were observed on measures of symptoms, exacerbations or adverse events.

Parallel design, 1:2 dose ratio

The results of the included trials generally showed no statistically significant differences between treatment with FP and treatment with BUD on measures of lung function. In one trial, a significant difference in favour of FP was observed on FEV1, however, care is required in interpreting this data as it was not on an intention-to-treat population and therefore may be subject to measurement bias. One other trial reported a difference in

favour of FP on morning PEFR. This latter trial was an equivalence trial and therefore power calculations may have been based on testing equivalence rather than superiority. However the sample size was large. No differences between study groups were observed on measures of symptoms or exacerbations although data were limited on these outcomes. There were no differences in the adverse event profiles of the groups.

5.2.3.5 MF and BUD (review Q2 – high dose ICS)

5.2.3.5.1 Study Characteristics

One trial reported a comparison of MF and BUD, by Bousquet and colleagues[197] (*Table 26*). This study had four treatment arms; 100µg MF twice daily plus placebo; 200µg MF twice daily plus placebo; 400µg MF twice daily plus placebo, and 400µg BUD twice-daily. Daily dose ratios were therefore 1:4, 1:2 and 1:1, respectively. Only the comparison between 400µg MF twice daily plus placebo, and 400µg BUD twice-daily is presented here (i.e. the 1:1 dose ratio). The other comparisons, which are within the 'low dose' category, are presented under Review question 1 (Section 5.2.2.5).

Patients in the MF arms took one inhalation from each of two DPIs (either one active and one placebo, or two active DPIs) in the morning and again in the evening. Patients randomised to BUD took one inhalation from each of two Turbohaler DPI devices (Pulmicort Turbuhaler®, AstraZeneca), morning and evening. No placebo Turbohaler was available, so only evaluators were blind to treatment group allocation (no details OF devices reported, MF made by Schering-Plough).

Further details on the characteristics of this study can be found in Section 5.2.2.5.

TABLE 26 *Characteristics of studies (MF and BUD)*

Study ID	Design	Intervention	Patients	Outcomes
Bousquet et al (2000)[197]	RCT Multi-centre Parallel-group Evaluator-blind Active-controlled	1. MF 100µg b.i.d. (daily total 200 µg) + placebo 2. MF 200µg b.i.d. (daily total 400µg) + placebo 3. MF 400µg b.i.d. (daily total 800µg) + placebo 4. BUD 400µg b.i.d. (daily total 800µg) *Delivery device:* 1, 2, 3. MF-DPI (made by Schering-Plough) 4. DPI (Pulmicort Turbuhaler®, AstraZeneca) *Duration:* 12 wks *Run in period:* Not defined	*Number randomised* 730 *Mean (years) age (range)* 1. 39 (14-71) 2. 42 (14-76) 3. 41 (12-74) 4. 42 (12-76) *Baseline FEV_1 % predicted (sd)* 1. 76.2 (0.7) 2. 77.1 (0.8) 3. 77.9 (0.7) 4. 76.0 (0.7) *Previous ICS treatment (drug and dose)* ICS as previously prescribed (moderate to persistent asthma)	*Primary outcome* Change from baseline to end-point in FEV_1 (L) *Secondary outcomes* FVC PEFR Symptom scores Nocturnal awakenings requiring salbutamol use as rescue medication Daily salbutamol use Physician evaluation of response to therapy Adverse event

5.2.3.5.2 Results

Lung function

The 400µg b.i.d. MF group in the study by Bousquet and colleagues[197] reported a mean change from baseline FEV_1 that was statistically significantly greater than change in the BUD group (0.16L ±0.03 for 400µg b.i.d. MF vs. 0.06L± 0.03 in the BUD group, $p<0.05$). Similarly, the end-point percent of predicted FEV_1 was statistically significantly different between the 400µg b.i.d. MF group (83.0%± 1.2) and BUD (77.9%± 1.1); $p<0.05$.

Bousquet and colleagues[197] did not find a statistically significant difference between MF and BUD in terms of change in morning PEFR. Change from baseline to end-point was 24.75L/min ±5.3 in the BUD group, compared with 37.31L/min ± 5.2 in the 400µg b.i.d. MF group. Changes in evening PEFR were not presented, but were reported to be similar to changes in morning PEFR.

Symptoms

Bousquet and colleagues[197] reported change from baseline in mean number of nocturnal awakenings to be 0.41 in the 400µg b.i.d. MF group and 0.30 in the BUD group (P=NS).

Use of rescue medication

Bousquet and colleagues[197] reported relief use of salbuterol as change from baseline dose. Change from baseline in the BUD group was -33.90µg/day, compared with -72.13µg/day in the -400µg b.i.d. MF group. Whilst the decrease in use in the MF group was greater than that in the BUD group, the difference was not statistically significant.

5.2.3.5.3 Summary

One parallel-group compared MF with BUD in a 1:1 daily dose ratio. In this trial there were significant differences in FEV_1 between 400µg b.i.d. MF and 400µg b.i.d BUD, but not for morning PEFR, symptoms, or use of rescue medication.

5.2.3.6 CIC and FP (review Q2 – high dose ICS)

[redacted]

5.2.3.6.1 Study Characteristics

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Table with characteristics of study submitted by Altana and designated "commercial in confidence" has been deleted

5.2.3.6.2 Results

[redacted]

Lung function

[redacted]

[redacted]

[redacted]

Symptoms

[redacted]

[redacted]

[redacted]

Health related quality of life

[redacted]

[redacted]

Use of rescue medication

[redacted]

[redacted]

[redacted]

Exacerbations

[redacted]

Adverse events

[redacted]

[redacted]

[redacted]

5.2.3.6.3 Summary

[redacted]

[redacted]

5.2.3.7 MF and FP (review Q2 – high dose ICS)

5.2.3.7.1 Study characteristics

One trial comparing MF and FP at high doses was identified,

O'Connor and colleagues[200] (*Table 27*). The study comprised four arms in which three doses of MF (200, 400 and 800µg/day) were compared with one dose of FP (500µg/day). The comparisons of 200 and 400µg/day of MF with FP are reported under review question 1 – low dose ICS, see Section 5.2.2.7). The comparison of 800µg/day MF with 500µg/day FP approximates a rounded nominal dose ratio of 2:1.

O'Connor and colleagues[200] employed DPIs for both MF and FP, but these were of different types: a newly-developed DPI inhaler (MF-DPI, Schering-Plough) was used for MF whereas FP was administered using a standard Diskhaler formulation (Flixotide Diskhaler®, GlaxoSmithKline).

The study was a large-scale international dose-ranging trial (with 60 centres in 20 countries). Duration was relatively short, lasting 12 weeks. The age of patients included in the comparison ranged from 12 to 79 years, with a mean age per treatment group of 42 for MF and 40 for FP. The enrolled patients had moderate persistent asthma.

The objective of the work was to compare effects of MF and FP when administered with a drug-specific delivery device. The study design did not permit effects of the drugs to be evaluated independently of effects of the type of inhaler used.

TABLE 27 *Characteristics of the study comparing MF and FP*

Study ID	Design	Intervention	Patients	Outcomes
O'Connor et al. (2001)[200]	RCT Parallel-group Double-blind (dosage) Evaluator-blind (medication)	Drug(s): 1. MF 100µg b.i.d. (daily total 200µg) 2. MF 200µg b.i.d. (daily total 400µg) 3. MF 400µg b.i.d. (daily total 800µg) 4. FP 250µg b.i.d. (daily total 500µg) Delivery device: 1, 2, 3. MF-DPI (made by Schering-Plough) 4. DPI (Flixotide Diskhaler®, GlaxoSmithKline) Duration: 12 wks Run in period: 1-2 wks	*Number randomised* 733 *Mean (years) age (range)* 1. 42 (14-75) 2. 42 (12-79) 3. 42 (12-75) 4. 40 (12-79) *Baseline FEV_1 % predicted* 1, 2, 3. 75 4. 76 *Previous ICS treatment (drug and dose)* BDP 400-100µg q.d., BUD 400-800µg q.d., flunisolide 500-100µg q.d., FP 200-500 or triamcinolone acetonide 600-800µg q.d.	*Primary outcome* mean change in FEV_1 from baseline to end-point *Secondary outcomes* PEFR FEF25-75% FVC Asthma symptom scores Rescue medication use Nocturnal awakenings Physician evaluation Adverse events

5.2.3.7.2 Results

Parallel 2:1 dose ratio studies

The study by O'Connor and colleagues[200] has a parallel design and provides a single comparison of high-dose (800µg/day) MF with high-dose (500µg/day) FP, at a nominal dose ratio of (approximately) 2.1.

Lung function

The change in FEV_1 (mean ± SD) was 0.19 ± 0.54 L for MF (800µg/day) and 0.16 ± 0.54 L for FP (500µg/day). The change in morning PEFR (mean ± SD) was 30 ± 67.8 L/min for MF (800µg/day) and 32 ± 67.8 L/min for FP (500µg/day). Neither of these differences between the drugs in lung function outcomes was statistically significant.

Symptoms

The change from baseline in the number of nocturnal awakenings was -0.06 for MF-treated patients and -0.14 for FP-treated patients. This difference was not statistically significant. The change in the incidence of morning coughing, morning wheezing or difficulty breathing also did not differ statistically significantly between the MF and FP patient groups.

Use of rescue medicine

The change from baseline in the use of albuterol rescue medication was -38.10µg/day for MF-treated patients and -52.06µg/day for FP-treated patients. This difference between the treatments was not statistically significant.

Exacerbations

Aggravated asthma was one of the most frequent adverse events leading to the discontinuation of treatment, but was not reported separately from other adverse events (summarised below).

Adverse events

Fifty-five out of 184 patients (30%) who were treated with 800µg/day MF experienced treatment-related adverse events. Fifty-three out of 184 patients (29%) who were treated with 500µg/day FP experienced treatment-related adverse events. Nine patients who received 800µg/day MF and eight patients who received 500µg/day FP did not complete their treatment because of adverse events. The most frequent adverse events leading to discontinuation were aggravated asthma, bronchitis, pharyngitis and upper respiratory tract infection.

5.2.3.7.3 Summary

One parallel-group RCT compared 800µg/day MF and 500µg/day FP in a nominal 2:1 dose ratio. This was one pair-wise comparison from a four arm trial. Overall, no differences in clinical efficiency or safety between MF and FP were observed when these drugs were compared at a nominal dose ratio of 2:1.

5.2.3.8 Summary of Q2 – relative effectiveness of high dose ICS

According to the BTS/SIGN Guidelines, BDP and BUD are comparable at the same daily dose. FP and MF comparable at half the daily dose of BDP and BUD. It is assumed that CIC is also comparable at half the daily dose of BDP and BUD. Thus at Step 4 of the guidelines the following drugs at the following doses (excluding considerations of device) are equivalent:

BUD 800µg/BDP 800µg/FP 400µg/MF 400µg/CIC 400µg.

The exception to this is for HFA propelled pMDI BDP compared to FP which, it is suggested,[171] is equivalent at a 1:1 dose ratio rather than a 1:2 dose ratio. This is due to the extra fine particle size resulting in altered lung deposition. This applies to the QVAR HFA BDP preparation, but may not apply to other HFA BDP brands.

In general, all of the ICS in this assessment were associated with favourable changes from baseline to end-point across efficacy and safety outcomes. However, when evaluated in pair-wise comparisons, there were few statistically significant differences between them in terms of the outcomes prioritised for this assessment (although it was not always possible to

discern whether significance testing had been performed). From the head-to-head comparisons of these drugs there is little evidence to reject the hypothesis that there is no difference in clinical effectiveness between them.

As with review question 1, there were few differences between the ICS (where statistical tests had been reported). In some cases non-inferiority was assessed and demonstrated.

- BDP vs BUD (2 RCTs, 1:1 dose ratio) – The only significant difference was for exacerbations in favour of BUD
- FP vs BDP (10 RCTs, 2 at 1:1 dose ratio, 8 at 1:2 dose ratio) – Significant differences in favour of FP for lung function and exacerbations, otherwise few significant differences.
- HFA BDP vs HFA FP (1 RCT, 1:1 dose ratio) – No significant differences. Non-inferiority demonstrated for lung function (in intention-to-treat analysis, but not per-protocol analysis)
- FP vs BUD (6 RCTs, 3 at 1:1 dose ratio, 3 at 1:2 dose ratio) – FP significantly favourable for lung function, from 1 RCT (at 1:1 and 1:2 rounded nominal dose ratios, FP : BUD). No significant differences for adverse events based on meta-analysis of 3 RCTs.
- MF vs BUD (1 RCT, 1:1 dose ratio) – Significant difference in favour of MF for lung function.
- [redacted]
- MF vs FP (1 RCT, 1:2 dose ratio) – No significant differences on any outcomes.

The following tables provide a visual illustration of the results of pair-wise comparisons.

BUD vs BDP n=2 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
1500µg BDP) vs. 1600µg BUD)	Ebden *et al.* Cross-over (no washout) 6 weeks pMDI + spacer N=28	BDP	NSD	C	C								
		BUD									+		
2000µg BDP vs. 2000µg BUD)	Kaur *et al.* Cross-over 6 weeks MDI + spacer N=15	BDP	NSD										
		BUD											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

FP vs BDP n=10 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
1500µg vs 1500µg	Fabbri *et al* Parallel 12 months MDI N=274	*FP*	+	+	+		NSD	NSD				+	70%
		BDP											73%
2000µg vs 1600µg	Boe *et al* Parallel 3 months DPI N=134	*FP*	NSD						NSD		NSD	F	C
		BDP											
500µg vs 1000µg	Lundback *et al* Parallel 6 weeks MDI N=585	*FP*	NSD	NSD	NSD		NSD	NSD					97 (50%)
		BDP							+				89 (46%)
750µg vs 1500µg	Medici *et al* Parallel 12 months MDI N=69	*FP*										NSD	C

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
1000µg vs 2000µg	Barnes *et al* Parallel 6 weeks MDI N=154	*FP*	NSD	NSD	NSD		NSD	NSD			NSD		43 (52%)
		BDP											37 (51%)
	Lorentzen *et al* Parallel 12 months MDI N=213	*FP*										NSD	114 (72%)
		BDP											39 (72%)
	Egan *et al* Parallel 2 years MDI N=33	*FP*											C
		BDP										F	
BDP 1000µg, 1500µg or 2000µg FP half	Malo *et al* Cross-over 4 months MDI N=67	*FP*	NSD									NSD	
		BDP											

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
the BDP dose	Pauwels *et al* Cross-over 12 months MDI N=340	*FP*	NSD				NSD	NSD		+		NSD	66.8%
		BDP											66.2%
750µg vs 1500µg	Bootsma *et al* Cross-over 12 weeks MDI N=21	*FP*	NSD		NSD				NSD		NSD		
		BDP											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

HFA BDP vs FP n=1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800µg BDP vs. 1000µg FP	Aubier *et al.* Parallel 28 weeks DPI N=503	*BDP*	NSD	NSD NID (in ITT but not PP)	NSD	NSD	NSD						38.3%
		FP											24.8%

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported; NID=non-inferiority demonstrated. Blank cells signify no data reported on that outcome.

FP vs BUD n=6 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
2000µg FP vs. 2000µg BUD	Heinig *et al.* Parallel 24 weeks DPI (Diskhaler or Turbuhaler) N=395	FP	C				F						
		BUD											
800µg FP vs. 800µg BUD	Kuna *et al.* Parallel 5 weeks DPI Diskhaler or Turbuhaler, N=197	FP	NSD	NSD	NSD				NSD				
		BUD											

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800µg - 1000µg FP vs. 1600µg BUD	**Meta analysis** Ayres (*1000 µg FP arm)*; Molimard; Ringdal	FP											NSD
		BUD											
1000µg FP 2000µg FP 1600µg BUD	Ayres *et al.* Parallel 6 weeks MDI N=671	1. 1000 µg FP	+ 1 vs. 3								F 1 vs. 3		
		2. 2000 µg FP	+ 2 vs. 3								F 2 vs. 3		49%
		3. BUD											51%

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800µg FP vs. 1600µg BUD	Ringdal *et al.* Parallel 12 weeks DPI (Diskhaler or Turbuhaler) N=518	FP	NSD	+									
		BUD											

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
1000µg FP vs. 1600µg BUD	Molimard *et al.* Parallel 12 weeks DPI (Diskhaler or Turbuhaler) N=460	FP	NSD						NSD				
		BUD											
	Hughes *et al.* Parallel 52 weeks MDI+ spacer N=59	FP											
		BUD											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

MF vs. BUD n=1 study

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800 µg MF 800 µg BUD	Bousquet *et al.* Parallel 12 weeks DPI N=730	*MF*	+	NSD		NSD					F		
		BUD											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

FP vs CIC n=3 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse event % of patien
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
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		Confidential information removed											Confidential information removed
Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed		Confidential information removed		Confidential information removed	Confidential information removed	Confidential information removed
		Confidential information removed							Confidential information removed		Confidential information removed		Confidential information removed
		Confidential information removed										Confidential information removed	Confidential information removed

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adver event % of patien
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed	Confidential information removed		
		Confidential information removed						Confidential information removed					

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported; NID=non-inferiority demonstrated. Blank cells signify no data reported on that outcome.

FP vs MF n=1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
MF 800µg FP 500µg	O'Connor Parallel 12 weeks DPI N=733	*MF*	NSD	NSD		NSD					NSD		30%
		FP											29%

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

5.2.4 Review Question 3a – ICS vs ICS+LABA (ICS dose higher when used alone)

To re-cap, 10 RCTs evaluated ICS vs ICS+LABA, where the ICS alone arm used a higher dose than that used in the combination inhaler arm (*Table 28*). The following sub-sections describe the characteristics and results of these trials.

TABLE 28 *Breakdown of studies for Review Question 3a – ICS vs ICS+LABA (ICS dose higher when used alone)*

Pair-wise comparison	Number of RCTs included
FP vs FP/SAL	2
BUD vs FP/SAL	3
BUD vs BUD/FF	4
FP vs BUD/FF	1
Total	10

5.2.4.1 ICS vs ICS+LABA (FP vs FP/SAL)

5.2.4.1.1 Study Characteristics

Two RCTs evaluated the effectiveness of FP/SAL in a combination inhaler compared to FP alone, and were published in 2003[222] and 2004.[223] They were both large multi-centre studies, ranging in size from 365 to 558 participants. The trials were double-blind, parallel group design, containing two intervention arms (*Table 29*).

The trials differed in the doses of FP/SAL administered to patients. Bergmann and colleagues[223] compared FP/SAL in a single inhaler with a total daily dose of 500µg/100µg, with FP given at a dose of 1,000µg/day. The total daily doses of FP in the study by Busse and colleagues[222] were lower, with patients receiving 200µg/100µg FP/SAL in a single inhaler compared to 500µg/day FP alone. Both trials used Diskus inhaler devices (all by GlaxoSmithKline) to deliver both the combination drugs and the ICS alone (Busse and colleagues[222] used Advair and Flovent Diskus, whilst no further details are reported by Bergmann and colleagues.[223]

The treatment duration was 12 weeks in the Bergmann and colleagues study.[223] Busse and colleagues[222] randomised participants to each of the two treatments for either 12 or 24 weeks

to determine whether asthma control was maintained for a longer period. The RCTs differed with respect to the study aims. Bergmann and colleagues[223] aimed to determine whether combination therapy with FP/SAL was superior to FP alone in terms of efficacy and tolerability. The trial by Busse and colleagues[222] was an equivalence trial and was designed to evaluate whether FP/SAL delivered via a single inhaler was ICS-sparing in patients requiring 500µg/d FP for asthma stability.

The mean age of participants was similar, ranging from around 40-50 years. Patients in both trials had previously been managed on medium dose ICS therapy of 500-1000µg BDP or equivalent (*Table 29*). Patients were described as having moderate asthma in one trial,[223] but severity was not reported in the other trial. Baseline FEV_1 % predicted was similar, around 75-80%.

Bergmann and colleagues[223] reported change in morning PEFR as their primary outcome measure. The trial was designed to identify a difference of 15 L/min between treatment groups with a power of 80% at α=0.05, requiring 174 patients in each group. Busse and colleagues[222] reported the proportion of patients without worsening asthma (i.e. those who did not withdraw from the study because of lack of efficacy) as the primary outcome. The study was designed such that a sample size of ≥250 patients per treatment group provided at least 80% power to ensure that a 90% CI of the difference between survival proportions at week 12 was contained within the margin of equivalence (Δ=0.15, assuming survival rates of 0.85 and 0.80 for FP/SAL and FP respectively).

The quality of reporting and methodology of the included RCTs was mixed. The trial by Bergmann and colleagues[223] was of good methodological quality. The trial reported a randomisation procedure that assured true random assignment to treatment groups, and which was also adequately concealed. The trial by Busse and colleagues[222] was of lower quality. The study did not describe the method of randomisation, and the method to conceal allocation to groups was unclear. The analysis was reported to be by the intention-to-treat principle in both studies.

TABLE 29 *Study Characteristics (FP vs FP/SAL)*

Study ID	Design	Intervention	Patients	Outcomes
Bergmann et al (2004)[223]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 250µg/50µg b.i.d. (daily total 500µg/100µg) 2. FP 500µg b.i.d. (daily total 1000µg) *Delivery device:* 1,2. DPI Diskus® (GlaxoSmithKline*) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 365 *Mean (years) age (±sd)* 1. 49.8 (± 14.2) 2. 48.9 (± 13.9) *Baseline FEV_1 % predicted (±sd)* 1. 74.5 (± 19.3) 2. 75.7 (± 20.2) *Previous ICS treatment (drug and dose)* BDP or BUD 800-1000µg q.d. or FP 500µg q.d.	*Primary outcome* Change in morning PEFR *Secondary outcomes* Evening PEFR FEV_1 (% predicted) FVC Asthma symptom score % symptom-free days/nights Use of rescue medication Adverse events Quality of life

Study ID	Design	Intervention	Patients	Outcomes
Busse et al (2003)[222]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 100µg/50µg b.i.d. (daily total 200µg + 100µg) 2. FP 250µg b.i.d. (daily total 500µg) *Delivery device:* 1. Advair Diskus® 2. Flovent Diskus® (both GlaxoSmithKline) *Duration:* 12 to 24 wks *Run in period:* 3 run-in periods: 10-14 days 5-28 days 26-30 days	*Number randomised* 558 (12wks treatment n=250; 24wks treatment n=308) *Mean (years) age (range)* 1. 38 (12-77) 2. 39 (12-72) *Baseline FEV_1 % predicted (±sd)* *1. 80.5 (± 9.7)* *2. 80.9 (± 9.4)* *Previous ICS treatment (drug and dose)* Medium dose of ICS BDP 504-840µg q.d., BUD 400-800µg q.d., FP 440-660µg q.d., flunisolide 1000-1500µg q.d. or triamcinolone acetonide 1200-1600µg q.d.	*Primary outcome* Proportion of patients with no worsening asthma *Secondary outcomes* FEV_1 (L) PEFR (am & pm) Asthma symptom score % symptom-free days Rescue medication use Rescue medication-free days Adverse events

* not stated explicitly, but deduced from the text

5.2.4.1.2 Results

For a number of outcomes, Busse and colleagues[222] reported that differences between treatment groups were within the 90% CI for equivalence but failed to define what the confidence limits were. In addition, it is not clear whether the reported *p*-values were for a test of difference or a test of equivalence.

For some outcome measures, sufficient data were reported in the two trials to be combined in meta-analyses. However, it should be noted that the doses of FP administered to patients in the Bergmann and colleagues[223] trial was twice that administered in the Busse and colleagues trial.[222] This should be taken into consideration when interpreting the results of the meta-analyses.

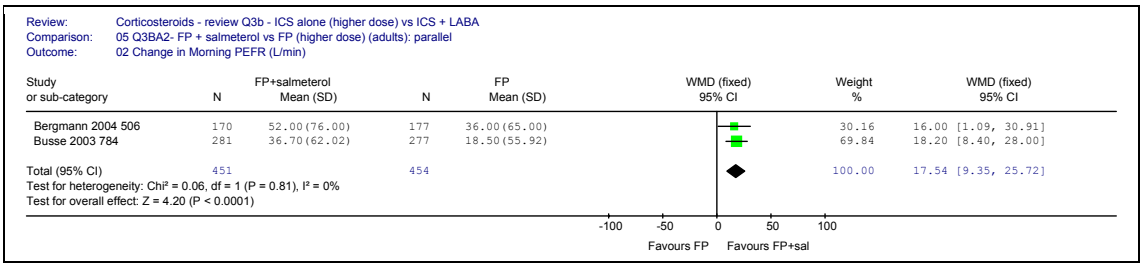
Lung function

Data on FEV_1 was reported in different ways by the two studies. Busse and colleagues[222] reported a mean change from baseline to end-point at 12 weeks in FEV_1 of 0.07 (±0.17) L in the FP/SAL group compared to -0.03 (±0.17) L ($p \leq 0.001$) in the FP group. In the sub-group of patients who received treatment for 24 weeks, improvements from baseline in FEV_1 were 0.10 (±SEM 0.02) L and 0.00 (±SEM 0.02) L ($p \leq 0.007$) in the FP/SAL and FP groups respectively. The authors stated that differences between treatments were within the 90% CIs for equivalence (although the CIs were not reported).

Bergmann and colleagues[223] reported a mean change from baseline in FEV_1 % predicted of 12.30% (±1.70) in the FP/SAL group compared to 8.40% (±1.40) in the FP group, with no statistically significant differences between groups (*p*-value not reported).

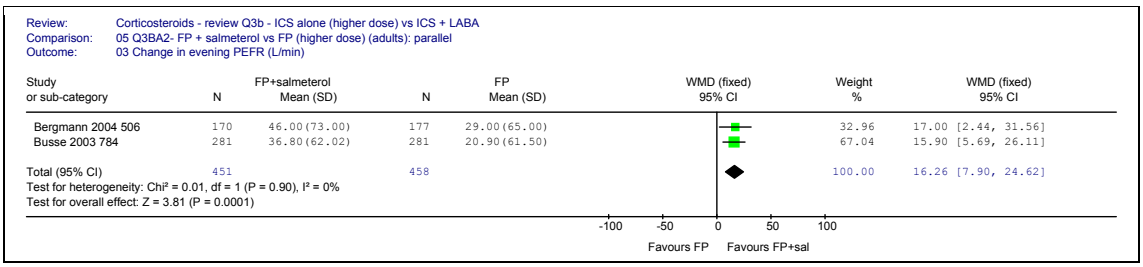
Change in morning PEFR (L/min) was reported by both trials, and data at 12 weeks has been combined in a meta-analysis (*Figure 12*). Pooling the data using a fixed-effects model showed a statistically significant improvement with FP/SAL treatment compared with FP (WMD 17.54 [95% CI 9.35, 25.72]; p<0.0001). Heterogeneity was not statistically significant (p=0.81, I^2=0%).

FIGURE 12 *Change in morning PEFR (L/min), FP/SAL vs FP*



Change in evening PEFR (L/min) from baseline to end-point at 12 weeks was also reported by both trials. Combining the data in a meta-analysis (*Figure 13*) using a fixed-effects model showed a statistically significant improvement with FP/SAL treatment compared with FP (WMD 16.26 [95% CI 7.90, 24.62]; p<0.0001). Heterogeneity was not statistically significant (p=0.90, I^2=0%).

FIGURE 13 *Change in evening PEFR (L/min), FP/SAL vs FP*



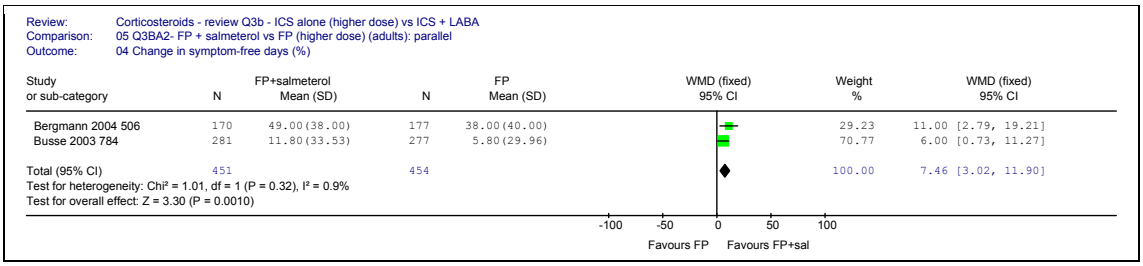
In the Busse and colleagues trial,[222] the change from baseline to end-point at 24 weeks in morning PEFR was 45.2 (±SEM 5.9) L/min in the combination treatment group compared with 32.5 (±SEM 6.8) L/min in the FP group (p=0.180). Differences between groups in evening PEFR (24 week data) were 49.4 (±SEM 5.9) L/min and 31.3 (±SEM 6.2) L/min respectively (p=0.039). For both morning and evening PEFR, differences between treatments were reported to be within the 90% CIs for equivalence (the CIs were not reported).

Symptoms

Data for the two trials on the change from baseline to end-point at 12 weeks in symptom-free days were combined in a meta-analysis (*Figure 14*). Pooling the data using a fixed-effects model showed a statistically significant improvement with FP/SAL treatment compared with

FP (WMD 7.46 [95% CI 3.02, 11.90]; p=0.001). Heterogeneity was not statistically significant (p=0.32, I^2=0.9%).

FIGURE 14 *Change in symptom-free days (%), FP/SAL vs FP*



For patients receiving treatment for 24 weeks,[222] the mean change from baseline was 11.6 (±SEM 3.0) days for FP/SAL compared to 6.0 (±SEM 2.9) days for FP (p=0.078). Differences between treatments were within the 90% CIs for equivalence (the CIs were not reported).

Total daily asthma symptom scores were reported differently in the two trials, and therefore data could not be combined in a meta-analysis. Busse and colleagues[222] used a six-point Likert scale (0=no symptoms, 5=severe symptoms, no reference supplied). Both treatments resulted in improvements in the daily asthma symptom scores at 12 weeks (-0.20 (±SEM 0.04) vs -0.12 (±SEM 0.04), p=0.232 for FP/SAL vs FP respectively), and at 24 weeks (-0.22 (±SEM 0.06) vs -0.14 (±SEM 0.06), p=0.137 for FP/SAL vs FP respectively). Differences between treatments were within the 90% CIs for equivalence (the CIs were not reported). In the trial by Bergmann and colleagues,[223] daytime and night-time asthma symptoms were recorded using a five-point rating scale (0=none, 4=severe, no reference supplied), which were combined to give a total asthma symptom score. Combined FP/SAL therapy was statistically significantly superior to double dose FP with respect to the improvement in asthma symptoms. The mean difference between treatment groups at the 12-week end-point was -0.5 points (95% CI -0.78 to -0.22, p=0.0005).

Quality of life

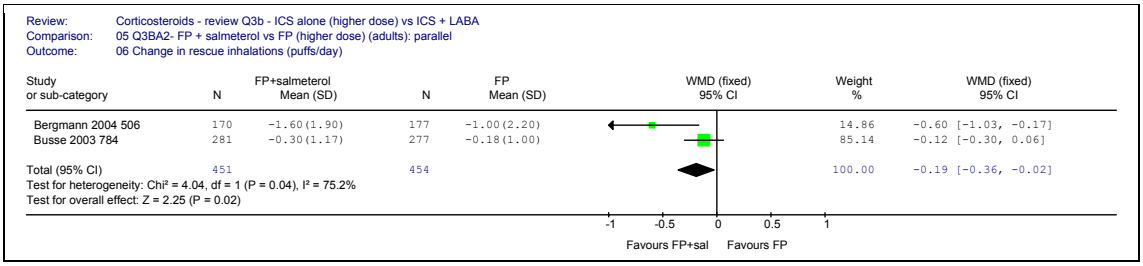
Data on health-related quality of life were reported by one trial[223] using a validated asthma quality of life questionnaire (reference supplied). The questionnaire consists of four dimensions: asthma symptoms, physical activity, environment and emotions, and is scored

from 0 to 7 (0=most severe impairment, 7=least impairment). The scores at week 12 were presented as the average of the preceding 21 days. Improvements were seen in both groups. For the FP/SAL group, the mean change from baseline quality of life score (mean score for all four dimensions) was 1.1 compared to 0.8 for patients in the increased dose FP group (values read from a bar chart, no *p* value given).

Use of rescue medication

Meta-analysis of the change in the use of salbutamol or albuterol rescue medication (mean number of puffs/day) at 12 weeks showed a statistically significant difference in favour of FP/SAL treatment (*Figure 15*). Using a fixed-effects model, the WMD was -0.19 puffs [95% CI -0.36, -0.02]; p=0.02). However, heterogeneity was statistically significant (*p*=0.04, I^2=75.2%). Using a random-effects model, treatment with FP/SAL was no longer statistically significantly superior to treatment with FP alone (WMD -0.32 [95% CI -0.78, 0.14]), and heterogeneity remained. Therefore, care needs to be taken in interpreting this outcome. *Figure 15* provides an illustration of the direction of the results.

FIGURE 15 *Change in use of rescue medication (puffs/day), FP/SAL vs FP*



For patients receiving treatment for 24 weeks,[222] both treatments resulted in a reduced need for supplemental albuterol. The mean change from baseline was -0.43 (±SEM 0.11) for FP/SAL compared to -0.21 (±SEM 0.07) for FP (*p*=0.022). Differences between treatments were within the 90% CIs for equivalence (the CIs were not reported).

Exacerbations

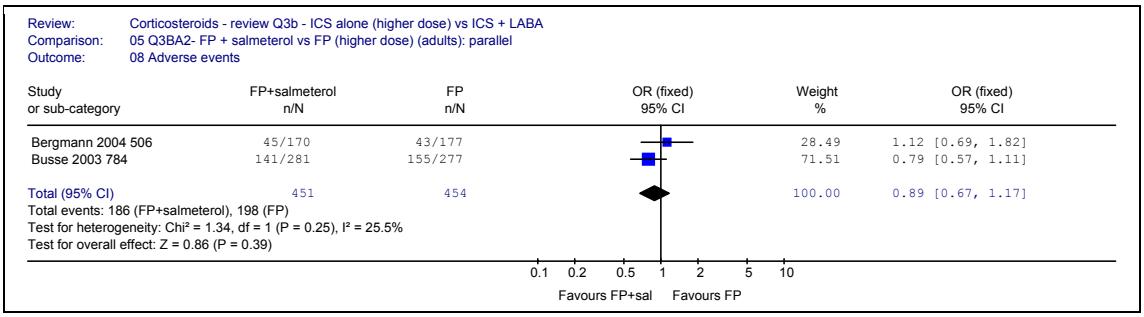
In both studies, similar proportions of patients experiencing exacerbations of asthma were reported in each treatment group. In the Bergmann and colleagues trial,[223] one (0.6%) patient in the combination therapy group compared to four (2.3%) patients in the FP group

were reported as having an asthma exacerbation (*p* values not reported). In the Busse and colleagues trial,[222] proportions were 3% and 2% at 12 weeks (*p*=0.820), and 2% and 0 (*p*=0.104) at 24 weeks in the FP/SAL and FP groups respectively.

Adverse events

Sufficient data on numbers of adverse events were reported in the two trials to be combined in a meta-analysis (*Figure 16*). The fixed-effects model's pooled odds ratio was 0.89 [95% CI 0.67, 1.17] suggesting no statistically significant difference between the two treatments (p=0.39). Heterogeneity was not statistically significant (*p*=0.25, I^2=25.5%).

FIGURE 16 *Adverse events, FP/SAL vs FP*



In the sub-group of patients who received treatment for 24 weeks, the incidence of adverse events was also similar for the two treatment groups (44% of FP/SAL patients vs 47% of FP patients reported one or more adverse events).[222]

Discontinuations due to adverse events were similar for the two treatment groups in one trial.[222] One patient (<1%) receiving combination therapy and two patients (<1%) receiving FP withdrew from the study as a result of adverse events (no *p* value reported).

5.2.4.1.3 Summary

Two large, parallel-group RCTs compared 200-500µg/day FP and 100µg/day SAL in a combination inhaler with 500-1000µg/day FP in adult participants. The Busse and colleagues study[222] assessed clinical equivalence, and although the general trend was that FP/SAL was more effective than FP, for most relevant outcomes the differences between treatments were within the confidence intervals for clinical equivalence (but the data to support this were not provided).

Treatment with FP/SAL was significantly more favourable compared with FP treatment alone on measures of PEFR but not FEV_1. Data on symptoms was also mixed, with combination treatment being significantly more favourable in terms of change in symptom-free days, but not quality of life. Improvement in total daily asthma scores was significantly better with FP/SAL therapy in one trial, but not in the other. On the whole, combination therapy was reported to be as safe as double dose FP. There were no statistical differences between the two therapies for adverse events, and no observed differences for exacerbations or discontinuations due to adverse events where reported. Although patients receiving FP/SAL had a significantly reduced need for rescue medication, the trials were statistically heterogenous and this difference did not remain when the data were analysed in a random-effects model.

5.2.4.2 ICS vs ICS+LABA (BUD vs FP/SAL)

5.2.4.2.1 Study characteristics

Three RCTs, published between 2000 and 2004,[224-226] evaluated BUD compared to FP/SAL combination therapy (*Table 30*). All three studies were multi-centre trials with two-arm parallel designs. The number of subjects randomised ranged from 349 to 398.

Two studies, by Johansson and colleagues[225] and Zhong and colleagues,[226] compared the combination of 200µg/100µg/day FP/SAL with 800µg/day BUD (representing a low dose of BUD). The third study, by Jenkins and colleagues[224] compared the combination of 500µg/100µg/day FP/SAL with 1600µg/day BUD (representing a high dose of BUD). All doses reported here are ex-valve.

In all three trials the BUD delivery device was a Turbohaler™ (Pulmicort Turbuhaler®, AstraZeneca). All three studies delivered the FP/SAL via a Diskus™ combination inhaler (Seretide Accuhaler®, GlaxoSmithKline). Two studies also used a placebo Turbohaler™ with the FP/SAL treatment and a placebo Diskus™ inhaler with the BUD treatment.[224;225] The studies were relatively short, at six, 12 and 24 weeks. Two of the studies evaluated the superiority of FP/SAL combination therapy compared to BUD.[224;226] Zhong and colleagues[226] assessed the efficacy and safety of the treatments in patients with asthma that was uncontrolled with low-dose ICS treatment. Jenkins and colleagues[224] compared treatment with a combination of a LABA and ICS with another ICS alone via a different inhaler. The

third study (Johansson and colleagues[225]) compared the lowest strength of the combination treatment with BUD at a four-fold higher dose in patients who remained uncontrolled on existing therapy.

The age range of patients included in the RCTs varied from 12 to 80 years, with mean ages from 36 to 48 years. All trial patients had previously been treated with low to medium dose ICS. One trial reported patients as having been previously treated with 400 to 600µg daily of FP or 800 to 1200µg daily of BUD or BDP.[224] Two trials reported patients as having been previously treated with a daily dose of 500µg BUD or BDP.[225;226] In two of the studies mean baseline FEV_1% predicted is reported as between 68 to 77.[224;225] The third study did not report FEV_1 % predicted.[226] Johansson and colleagues[225] described patients as suffering from mild to moderate asthma, whist the other two studies described patients as suffering from moderate to severe asthma.[224;226]

Two studies reported their primary outcome as the mean morning PEFR,[225;226] whilst Jenkins and colleagues[224] did not specify a primary outcome. The quality of the studies appeared to be good overall. The three studies each aimed to achieve 90% power for demonstrating a difference of 15 L/min in the PEFR with 95% confidence, based on the assumption that the maximum SD of the PEFR is 40 L/min and that the minimum number of subjects per treatment group would be 150. One study provided no details of their randomisation procedure,[224] whist the other two studies used computer-generated randomisation codes.[225;226] Johansson and colleagues[225] provided full details of blinding and concealment of treatment allocation, while no details of treatment allocation concealment were provided by the other two studies.[224;226] All three studies reported an intention-to-treat analysis, using the ITT population for analysis.

TABLE 30 *Characteristics of studies (BUD vs FP/SAL)*

Study ID	Design	Intervention	Patients	Outcomes
Jenkins et al. (2000)[224] Lundbäck et al. (2000)[227] *Juniper et al.* (2002)[228]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. FP/SAL 250/50µg b.i.d. (daily total 500/100µg) 2. BUD800µg b.i.d. (daily total 1600µg) *Delivery device:* 1. DPI Diskus™ (Seretide Accuhaler®, GlaxoSmithKline) + placebo Turbuhaler 2. DPI Turbuhaler™ (Pulmicort Turbuhaler®, AstraZeneca) + placebo Diskus *Duration:* 24 wks *Run in period:* 2 wks	*Number randomised* 353 *Mean (years) age (range)* 1. 45 (16-75) 2. 48 (14-80) *Baseline FEV_1 % predicted (range)* 1. 68 (33-105) 2. 72 (37-109) *Previous ICS treatment (drug and dose)* BUD 800-1200µg q.d.	*Outcomes* change in PEFR (am & pm) change in FEV_1 symptom-free days and nights % salbutamol free days in each group % exacerbations
Johansson et al. (2001)[225]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. FP/SAL 100/50µg b.i.d. (daily total 200/100µg) 2. BUD 400µg b.i.d. (daily total 800µg) *Delivery device:* 1. DPI Diskus™ (Seretide Accuhaler®, GlaxoSmithKline) + placebo Turbuhaler 2. DPI Turbuhaler™ (Pulmicort Turbuhaler®, AstraZeneca) + placebo Diskus *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 349 *Mean (years) age (±sd)* 1. 36 (± 16) 2. 36 (± 17) *Mean baseline FEV_1 % predicted (±sd)* 1. 77 (± 10) 2. 76 (± 11) *Previous ICS treatment (drug and dose)* BDP or BUD up to 500µg q.d.	*Primary outcome* Morning PEFR *Secondary outcomes* Evening PEFR Rescue salbutamol usage Day& night-time symptom scores Asthma exacerbations

Study ID	Design	Intervention	Patients	Outcomes
Zhong et al (2004)[226]	RCT Multi-centre Parallel-group Open-label	1. FP/SAL 100/50µg b.i.d. (daily total 200/100µg 2. BUD 400µg b.i.d. (daily total 800µg) *Delivery device:* 1. DPI Diskus™ (Seretide Accuhaler®, GlaxoSmithKline) 2. DPI Turbuhaler™ (Pulmicort Turbuhaler®, AstraZeneca) *Duration:* 6 wks *Run in period:* 2 wks	*Number randomised* 398 *Mean (years) age (range)* 1. 46 (44-47) 1. 46 (44-47) *Mean Baseline FEV_1 (litres)* 1. 1.91 2. 1.90 *Previous ICS treatment (drug and dose)* Mild to moderate asthma (uncontrolled with low-dose ICS)	*Primary outcome* Morning PEFR *Secondary outcomes* Evening PEFR Use of rescue medication Day & night-time asthma symptoms scores % symptom-free days and nights FEV_1

5.2.4.2.2 Results

Some of the symptom scores reported by Jenkins and colleagues[224] were also summarised briefly in a secondary publication by Lundbäck and colleagues.[227] Quality of life scores originating from the study carried out by Jenkins and colleagues are reported in a secondary publication by Juniper and colleagues.[228]

Lung function

FEV_1

Two studies reported the FEV_1 at end-point,[224;225] one study reported the change in FEV_1 from baseline to end-point[226] and one study briefly mentioned the percent predicted FEV_1 at end-point.[224]

Johansson and colleagues[225] reported that the mean ± SD of the FEV_1 at end-point (12 weeks) was 2.79 ± 0.81 L for FP/SAL and 2.83 ± 0.86 L for low-dose (800µg/day) BUD; however, this difference was not tested statistically. Jenkins and colleagues[224] reported that the FEV_1 at end-point (24 weeks) differed significantly between FP/SAL (mean 2.53 L) and high-dose (1600µg/day) BUD (mean 2.44 L); the treatment difference was 0.091 L, (95% CI 0.0,0.17; p<0.05). Zhong and colleagues[226] reported a change in FEV_1 from baseline to end-point of 310 ml for subjects on FP/SAL and 280 ml for subjects on low-dose (800µg/day) BUD. This difference was not statistically significant (p=0.2614). Jenkins and colleagues[224] commented (without presenting data) that the percent predicted FEV_1 at end-point (week 24) was higher for subjects in the FP/SAL group, although the difference between treatments was not statistically significant.

Morning PEFR

The change from baseline in the morning and evening PEFR was reported in all three studies but the data and statistics were presented in different ways that precludes combining the studies in a meta-analysis. Johansson and colleagues[225] reported a change in the morning PEFR from baseline to end-point (12 weeks) of 383 to 426 L/min in subjects receiving FP/SAL, and of 382 to 415 L/min in subjects receiving low-dose (800µg/day) BUD. Statistics presented by Johansson and colleagues[225] appear to refer to the difference in

morning PEFR between the drugs at end-point (11 L/min, 95% CI from 2 to 20 L/min, *p*=0.022) rather than the difference of the change in morning PEFR from baseline (10 L/min). Accordingly, it is unclear in that study whether the changes from baseline in the morning PEFR differed significantly between the treatments. Johansson and colleagues[225] also reported that the predicted percent morning PEFR differed significantly between the treatments, with a change from baseline to end-point of 83 to 94% in the FP/SAL subject group, and of 80 to 89% in the BUD subject group (95%CI 1%, 5%; *p*=0.009).

Zhong and colleagues[226] reported that the mean change from baseline to end-point (six weeks) in the morning PEFR was 52.4 L/min for subjects on FP/SAL (95% CI from 44.2 to 60.6 L/min) and 29.9 L/min for subjects on low-dose (800µg/day) BUD (95% CI from 22.2 to 37.6 L/min). This difference between the drugs was statistically significant (*p*<0.0001). At end-point, the least-squares-adjusted mean morning PEFR was 326 L/min (95% CI from 318 to 334 L/min) for the FP/SAL group and 303 L/min (95% CI from 295 to 311 L/min) for the BUD group (no *p*-value reported).

Jenkins and colleagues[224] presented data on the morning PEFR for several time periods during their 24-week study. The closest data to the end-point that they provided was for weeks 13-24. During this period, the mean ± SD change in the morning PEFR from baseline (adjusted by ANCOVA for sex, age and country) was 410 ± 4.49 L/min for subjects on FP/SAL and 384 ± 4.69 L/min for subjects on high-dose (1600µg/day) BUD. The difference between treatments of 26 L/min (95% CI 14, 38) L/min was statistically significant (*p*<0.001). The corresponding figures for the morning PEFR averaged over the whole study (weeks 1-24) showed a similar pattern, with a mean ± SD change from baseline of 406 ± 3.67 L/min for FP/SAL subjects and 380 ± 3.81 L/min for BUD subjects. This difference of 25 (95% CI 15, 35; *p*<0.001) L/min was statistically significant.

Evening PEFR

Johansson and colleagues[225] reported (without giving details) that the change from baseline in the evening PEFR was significantly larger (by 11 L/min) for subjects on FP/SAL than for subjects on low-dose (800µg/day) BUD (95% CI 3,20 L/min; *p*=0.008). The predicted percent evening PEFR was also significantly larger in the FP/SAL subject group (95 CI 1%, 5%; *p*=0.003).

Zhong and colleagues[226] reported that the mean change from baseline to end-point (six weeks) in the evening PEFR was 45.6 L/min for subjects on FP/SAL and 32.1 L/min for subjects on low-dose (800µg/day) BUD. This difference between the drugs was statistically significant (p=0.0066).

For weeks 13-24 of their study, Jenkins and colleagues[224] reported a mean ± SD change from baseline in the evening PEFR (adjusted in ANCOVA for sex, age and country) of 420 ± 3.85 L/min for subjects on FP/SAL and 401 ± 4.03 L/min for subjects on high-dose (1600µg/day) BUD. This difference of 19 (95% CI 9, 29) L/min was statistically significant (p<0.001). The corresponding figures for the evening PEFR averaged over the whole study (weeks 1-24) show a similar pattern, with a mean ± SD change from baseline of 416 ± 3.14 L/min for the FP/SAL subject group and 398 ± 3.25 L/min for the BUD subject group. This difference of 18 (95% CI 9, 26) L/min was statistically significant (p<0.001).

Symptoms

All three studies[224-226] reported the percentage of symptom-free days and nights. Johansson and colleagues[225] reported the mean ± SD percentage of symptom-free days and nights for weeks 1-4 and weeks 1-12 of their study but not at the end-point. For weeks 1-4, the mean percentage of symptom-free days was 46 ± 38% in the FP/SAL subject group and 48 ± 38% in the low-dose (800µg/day) BUD treatment. Over the study as a whole (weeks 1-24), there were 53 ± 38% symptom-free days for subjects on FP/SAL and 55 ± 38% symptom-free days for subjects on BUD. The mean percentage of symptom-free nights for weeks 1-4 was 65 ± 37% for the FP/SAL subject group and 66 ± 35% for the BUD subject group. Over the study as a whole (weeks 1-12), the percentage of symptom-free nights for the respective drugs was 68 ± 36% and 72 ± 33%. Johansson and colleagues commented that the improvement in daytime or night-time symptoms did not differ between the drugs (no p-value provided).

In their study, Zhong and colleagues[226] reported that the mean percentage of symptom-free days at end-point (six weeks) was 57% for subjects treated with FP/SAL and 41.0% for subjects on low-dose (800µg/day) BUD. The corresponding percentages of symptom-free nights for the respective drugs were 65.9% and 47.7%. When symptom-free days and nights were combined, the mean percentage of symptom-free 24-hour periods at end-point was 66.5% for subjects treated with FP/SAL and 46.6% for subjects on BUD. For each of these

three outcomes (symptom-free days, symptom-free nights and symptom-free 24-h periods) the difference between the drugs was statistically significant (p<0.001).

Jenkins and colleagues[224] did not report symptoms at the end-point but did report the mean percentage of symptom-free days for several time periods during their study. In the time period closest to the end of the study (weeks 13-24), the median percentage of symptom-free days was 75% for subjects who received FP/SAL and 40% for subjects who received high-dose (1600µg/day) BUD (these data were estimated by the reviewers from Fig. 3a of Jenkins and colleagues[224]). The respective median percentages of symptom-free days over the whole study (weeks 1-24) for these drugs were 60% and 34% (with a 95% CI from 2 to 11). For each of these time periods the difference in the percentage of symptom-free days between the drugs is statistically significant (p<0.001). The differences between drugs were also statistically significant for other time periods: weeks 1-4 (p<0.001), weeks 5-8 (p<0.001), and weeks 9-12 (p=0.019), in all cases with the highest percentage of symptom-free days being in the FP/SAL subject group. The median percentage of symptom-free nights was reported by Jenkins and colleagues[224] only for the overall study period (weeks 1-24). This was 86% for subjects on FP/SAL and 79% for subjects on BUD; the difference between the drugs was reported as not being statistically significant.

Health-related quality of life

Health-related quality of life was analysed in one study. Juniper and colleagues[228] calculated asthma quality of life scores based on a 32-item asthma quality of life questionnaire (AQLQ), for a subset of the subjects in the study reported by Jenkins and colleagues[224] (these were subjects who completed both baseline and end-point questionnaires: n=55 for FP/SAL and n=58 for BUD). Mean scores were calculated for four domains: activity limitation, asthma symptoms, emotional functioning and environmental exposure, as well as an overall ALQL score. A threshold score change from baseline of 0.5 was used to represent a clinically important change to identify subject improvement (a decrease in the score of ≥ 0.5 from baseline), deterioration (a score increase of ≥ 0.5) or no change (a score change of -0.49 to +0.49).

The mean ± SEM change in the overall AQLQ score was 0.89 ± 0.11 for subjects treated with FP/SAL and 0.44 ± 0.10 for subjects treated with high-dose (1600µg/day) BUD, indicating

that a clinically important improvement occurred only in the former subject group (ANCOVA model with country and baseline scores as covariates). The difference of the baseline to end-point score changes between the drugs was 0.45 ± 0.14, which is statistically significant (95% CI 0.17, 0.72; *p*=0.002). Improvements in all the AQLQ domain scores were significantly greater for the FP/SAL subject group than for the BUD group, with the largest differences being in the symptoms and emotional functions domains. Approximately 70% of the subjects on FP/SAL experienced an improvement in their health-related quality of life scores, 30% remained unchanged and 0% deteriorated. For BUD, scores for 43% of subjects improved, 45% remained unchanged, and 12% deteriorated.

Use of rescue medication

All three studies[224;227;228] reported the percentage of salbutamol-free days and the percentage of salbutamol-free nights, but did not report mean puffs per day.

Exacerbations

Two of the studies reported asthma exacerbations. Johansson and colleagues[225] reported that seven participants in the FP/SAL group and ten participants in the low-dose (800µg/day) BUD group experienced exacerbations. Of these, three in the FP/SAL group were withdrawn due to exacerbations after randomisation.

Jenkins and colleagues[224] reported that 65 patients in the FP/SAL group and 58 patients in the high-dose (1600µg/day) BUD group experienced at least one exacerbation. Of these subjects, 36 (20%) and 27 (16%), respectively, had mild exacerbations (95% CI 0.74, 2.25; *p*=0.382 for the difference between treatments); 28 (16%) and 29 (17%), respectively, had moderate exacerbations (95% CI 0.54,1.73; *p*=0.913 for the difference between treatments); and one (0.6%) and two (1%), respectively, had severe exacerbations. Six of the subjects treated with FP/SAL and five of the subjects treated with BUD withdrew from the study due to exacerbations after randomisation.

Adverse events

The numbers of subjects experiencing adverse events in the FP/SAL and in the BUD groups were not tested statistically in the three studies but appear similar between the drugs (*Table*

31). The largest difference was in the comparison with high-dose (800µg/day) BUD (Johansson and colleagues[225]), where six more subjects in the BUD group than in the FP/SAL group experienced at least one adverse event (a difference of 4%). Three serious adverse events in the FP/SAL group reported by Johansson and colleagues[224] were acute asthma, asthma exacerbation, and cough and sputum production. The serious adverse events reported by Zhong and colleagues[226] (one in each treatment group) and by Jenkins and colleagues[225] (six in each treatment group) were not considered to be related to the study treatment. Withdrawals due to adverse events that were possibly or probably related to the study treatment (*Table 31*) included cough and sputum production in one subject receiving FP/SAL (Johansson and colleagues[224]), headache, palpitation and ankle oedema in three FP/SAL subjects, and rash and chest pain in two BUD subjects (Zhong and colleagues[226]). Jenkins and colleagues[224] did not specify whether seven withdrawals due to adverse events in their study were related to the study treatments.

TABLE 31 *Adverse events reported in comparisons of FP/SAL against BUD (number of subjects experiencing at least one adverse event)*

Study	Adverse events (AE)		Serious AE		Withdrawals due to AE	
	FP/SAL	BUD	FP/SAL	BUD	FP/SAL	BUD
Johansson *et al.*[224]	67 (38%)	65 (38%)	3	0	1	0
Zhong *et al.*[226]	47 (24%)	45 (24%)	1	1	3	2
Jenkins *et al.*[225]	25 (14%)	31 (18%)	6	6	3	4

5.2.4.2.3 Summary

Three parallel-group RCTs demonstrated larger improvements in lung function outcomes for subjects treated with 200-500 µg/day SAL + 100µg/day FP than for subjects treated with 800-1600µg/day BUD. Estimates of the FEV_1 at end-point, the change in FEV_1 from baseline, the percent predicted FEV_1, morning and evening PEFR at end-point and the change from baseline in the PEFR were larger in the FP/SAL group in all cases, although statistically significant differences were not reported by all studies. A notable finding from the study of Jenkins and colleagues[224] was that the percent predicted FEV_1 differed statistically significantly between the two drugs prior to the end-point (at four weeks) but did not differ statistically significantly at end-point (24 weeks), highlighting the problem that short-duration studies may not adequately predict longer-term clinical effects.

In cases where the frequency of symptom-free days or nights and salbutamol-free days or nights differed statistically significantly between the drugs, the frequency was consistently highest for the group that received FP/SAL. The asthma quality of life questionnaire scores were also statistically significantly in favour of the FP/SAL treatment. Although Jenkins and colleagues reported a larger number of exacerbations in subjects receiving FP/SAL, the difference between drugs was not statistically significant.

Overall, the findings reported here favour FP/SAL over BUD but all the studies were of relatively short duration (6 to 24 weeks). Accordingly, the longer-term relevance of the findings is unclear.

5.2.4.3 ICS vs ICS+LABA (FP vs BUD/FF)

5.2.4.3.1 Study Characteristics

One RCT, by Bateman and colleagues published in 2003, evaluated the combination of BUD/FF compared to FP alone.[229] It was a multi-centre study conducted in 37 centres across six countries, and involving the recruitment of 373 patients. Only 344 patients were randomised. The trial was a double-blind, parallel-group design, containing two arms.

Patients were randomised to BUD/FF 160/4.5 µg b.i.d (total daily dose 320/9µg) or to FP 250µg (b.i.d) (total daily dose 500 µg/day). It was reported that a BUD metered dose of 200µg was equivalent to 160µg delivered dose. The BUD/FF combination was delivered via a single Turbohaler inhaler (Symbicort® Turbuhaler®, AstraZeneca) plus a placebo device, whilst the FP was delivered via a Diskhaler (Flixotide Diskhaler®, GlaxoSmithKline), plus a placebo device. The rationale of the trial was to compare the efficacy of the combination treatment with a higher dose of the corticosteroid FP. The authors did not explicitly state whether the intention was to test equivalence or superiority. The primary outcome measure was morning PEFR. A power calculation is reported to detect a significant difference between groups on this outcome. Treatment lasted for 12 weeks.

The study included men and women aged 17 to 75, with a mean age of 42.6 years for the BUD/FF group and 41.8 years for the FP group (*Table 32*). All patients had previously received a range of ICS therapy at a consistent daily dose of 200 -1000µg for at least 30 days. Authors described patients as suffering from moderate persistent asthma, with a mean

baseline FEV_1 % predicted of 77.2 for the BUD/FF treatment group and 79.2 for the FP treatment group.

On the whole, the study was of adequate quality. The intention-to-treat analysis only included all subjects who received at least one dose of study drug. Details of the randomisation procedure and concealment of allocation were lacking. The study provided information of withdrawals and drop-outs for each treatment group, but did not offer explanations for all the reasons.

TABLE 32 *Characteristics of study (BUD/FF and FP)*

Study ID	Design	Intervention	Patients	Outcomes
Bateman et al (2003)[229]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. BUD/FF 200/6µg b.i.d. ex-valve (daily total 320/9µg ex-actuator) + placebo 2. FP 250µg b.i.d. (daily total 500µg) + placebo *Delivery device:* 1. DPI (Symbicort® Turbuhaler®, AstraZeneca) + placebo Diskhaler 2. DPI (Flixotide Diskhaler® GlaxoSmithKline) + placebo Turbuhaler *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 344 *Mean (years) age (range)* 1. 42.6 (18-75) 2. 41.8 (17-74) *Baseline FEV_1 % predicted* 1. 77.2 2. 79.2 *Previous ICS treatment (drug and dose)* Moderate to persistent asthma: 200-1000µg ICI therapy daily	*Primary outcome* PEFR (am) *Secondary outcome* PEFR (pm) FEV_1 Reduction in reliever medication (inhalations/ day) % of reliever free days % symptom-free days % night-time awakenings % asthma control days

5.2.4.3.2 Results

Lung function

A significantly greater mean change from baseline in morning PEFR was reported for the BUD/FF treatment group compared to the FP group (27.4 vs 7.7 L/min; p < 0.001). Similar increases were also found for evening PEFR (24.0 vs 6.8 L/min; *p*<0.001). Geometric means of average FEV_1 increased significantly across clinic visits in the BUD/FF group compared with the FP group (2.57L vs 2.46L; *p*<0.001).

Symptoms

The percentages of symptom-free days were calculated from diary cards. A symptom-free day was defined as a day and night without asthma symptoms and no night-time awakening due to asthma. Although the BUD/FF group had a higher slightly higher percentage of symptom-free days compared with the FP group (60.4% vs 55.5%), these differences were not statistically significant (no p value reported). The percentages of night-time awakenings due to asthma was lower in the BUD/FF group compared with the FP group (7.9% vs 9.6%), however the differences were also not statistically significant (no p value reported).

Use of rescue medication

Patients were provided with either terbutaline sulphate or albuterol if preferred, as rescue medication. There was a statistically significantly higher reduction in reliever medication use (inhalations/day) for the BUD/FF group compared with the FP group (0.31 vs 0.13; p=0.04).

Exacerbations

Bateman and colleagues[229] reported that patients treated with BUD/FF had a lower incidence of mild asthma exacerbations than patients treated with FP, occurring in 50 patients (29.8%) and 74 patients (42.0%) respectively. Mild exacerbations were defined as awakening due to asthma on two consecutive nights, morning PEFR at least 20% below that at baseline on two consecutive days, or the need to use at least four inhalations of reliever medication. Severe asthma exacerbations, defined as the need for oral corticosteroids, a 30% decrease in PEFR

from baseline on two consecutive days, or discontinuation due to asthma worsening, were reported to be low. The trial reported a lower incidence of severe asthma exacerbations in patients treated with the BUD/FF combination compared to patients treated with FP alone, occurring in 13 patients (8%) and 19 patients (11%) retrospectively. No statistical tests were reported.

Adverse events

Bateman and colleagues[229] reported that adverse event profiles were similar between the two treatments (no data given on rate of adverse events). Out of five serious adverse events occurring during the trial, two were in the BUD/FF group and three in the FP group. No other data were supplied, but the authors reported that the adverse events were asthma exacerbations and not considered to be treatment-related.

5.2.4.3.3 Summary

One large parallel-group RCT compared 500µg/day FP with 400µg/day BUD and 12µg/day FF in a combination inhaler. There were statistically significant differences between groups in favour of the combination inhaler on measures of morning and evening PEFR, and FEV_1 (L), and use of rescue medication, but not for symptoms. There appeared to be a slightly lower incidence of mild exacerbations for the combination inhaler group, although this was not confirmed statistically. Incidence of severe exacerbations was low, and appeared to be similar between treatments, as were adverse events.

5.2.4.4 ICS vs ICS+LABA (BUD vs BUD/FF)

5.2.4.4.1 Study Characteristics

Four trials[230-233] compared BUD/FF in a combined inhaler with higher doses of BUD. There was considerable variation in overall design and quality. The trials were all parallel group, multinational studies except for Pohl and colleagues,[231] which was undertaken in a single country. The number of participants randomised ranged from 133 to 2760. The length of the trials was between 20 weeks to one year. All were designed as superiority trials but with different aims and objectives depending on the specific treatment comparisons.

The study by Lalloo and colleagues[230] had two arms comparing BUD 80µg/FF 4.5µg twice daily with BUD 200µg twice daily. Patients in the combined treatment arm used a Symbicort inhaler (Symbicort® Turbuhaler®, AstraZeneca), but the delivery device for the other arm was not documented. They used terbutaline as a reliever.

Pohl and colleagues[231] compared two different treatments, BUD 1280µg per day (two inhalations twice per day) and BUD 640µg/FF 18µg per day (two inhalations twice per day) using either Symbicort or Pulmicort Turbohalers (AstraZeneca). After week 4 adjustable maintenance dosing was introduced. The total number of inhalations per day was adjusted in each group at the doctor's discretion depending on symptoms (two to four inhalations per day in weeks five to eight, and one to four inhalations per day in weeks nine to 20). Participants were free to choose between terbutaline and salbutamol as reliever medication.

O'Byrne and colleagues'[232] trial had three arms. The first arm was BUD 80µg/FF 4.5µg twice daily with the combination inhaler as reliever. The second arm was BUD 80µg/FF 4.5µg twice daily with terbutaline as reliever, and the final arm was BUD 320µg twice daily with terbutaline as reliever. All study medication was delivered by Turbohaler (BUD - Pulmicort Turbuhaler®, AstraZeneca).

There were two treatment arms in the study by Scicchitano and colleagues.[233] Patients in the first group received ex-actuator doses of 320µg BUD plus 9µg FF per day (metered doses of 400µg and 12µg, respectively). The drugs were delivered via a combined DPI Turbohaler (Symbicort®, Turbuhaler®, AstraZeneca) as two inhalations each evening. Patients could take up to ten additional inhalations per day as needed. Patients in the second treatment arm took two inhalations of BUD twice a day (total daily dose ex-actuator 640µg/day, metered dose 800µg/day) delivered via a DPI Turbohaler (Pulmicort Turbuhaler®, AstraZeneca). Patients were permitted to take up to ten inhalations of 0.4µg per day (metered dose 0.5µg).

The ages of patients in the study by Lalloo and colleagues[230] ranged from 18 to 78 (average age around 40 years), had a baseline mean FEV_1% predicted of over 80%, and required ICS at a dose between 200 to 500µg per day (any brand) prior to study entry. The patients' ages in the study by Pohl ranged from 20 to 82 (average age 45 years). Patients had a baseline mean FEV_1% predicted in the mid sixties and all had a requirement for ICS or combination therapy with a LABA as judged by the trial investigator (it is not clear if they were actually

receiving this medication prior to the study). The patients in the study by O'Byrne and colleagues included children (aged 4 to 11 years). The age range of all patients was from 4 to 79 years. The mean baseline FEV_1% predicted was 73. Prior to entry, children had to be treated with 200 to 500µg per day of ICS and adults with 400 to 1000µg per day. In the study by Scicchitano and colleagues,[233] patients had a mean age of 43 years, ranging from 11 to 80 years. Patients suitable for inclusion had moderate-to-severe asthma, and had previously received a mean ICS daily dose of 746µg (range 250-2000 µg). The mean baseline FEV_1% predicted was 70% and 83% of patients were classified as having severe asthma.

All trials were classified as randomised controlled and double blind; however, details were generally sparse in the reports. Neither Lalloo and colleagues[230] nor Scicchitano and colleagues[233] provided any further details on randomisation, concealment and blinding. In the study by Pohl and colleagues,[231] a computer generated random number list was used, but no other details are available. O'Byrne and colleagues[232] used a computer generated random number list (they were randomised in balanced blocks and there were separate lists for children and adults) and the treatment delivery devices were indistinguishable – no other details were available. All studies reported using intention-to-treat analysis. However, the study by Pohl and colleagues did not include patients with missing data.

All were superiority trials. A primary outcome was not specified in the study by Lalloo and colleagues.[230] In the study by Pohl and colleagues,[231] the primary outcome was the number of people who had one or more treatment failures. Both O'Byrne and colleagues[232] and Scicchitano and colleagues[233] used time to first severe asthma exacerbation as the primary outcome.

TABLE 33 *Study characteristics (BUD vs. BUD/FF)*

Study ID	Design	Intervention	Patients	Outcomes
Lalloo et al (2003)[230]	RCT Multi-centre Parallel-group Double-blind	1. BUD/FF 80µg/4.5µg b.i.d. (daily total 160µg/9µg) 2. BUD 200µg b.i.d. (daily total 400µg) *Delivery device:* 1. DPI (Symbicort® Turbuhaler®, AstraZeneca) 2. BUD inhaler not specified *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 467 *Mean (years) age (range)* 1. 42 (18-77) 2. 40 (18-78) *Baseline mean FEV_1% predicted (range)* 1. 82 (38-117) 2. 81 (42-157) *Previous ICS treatment (drug and dose)* ICS at constant dose of 200-500µg/day for at least 1 month	*Outcomes* FEV_1 FEV_1% predicted FVC PEFR (am & pm) Day & night-time symptom scores Use of reliever medication Night time awakenings Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Pohl et al (2005)[231]	RCT Multi-centre Parallel-group Double-blind Adjustable dose maintenance (ADM)	1. BUD 320µg 2 puffs b.i.d. fixed dosing for wk1-4 (daily total 1280µg). ADM from wk4. 2-4 puffs/day, wks 5-8, then 1-4 puffs/day wks 9-20) 2. BUD/FF 160µg/4.5µg 2 puffs b.i.d. (daily total 640µg/9µg). ADM from wk4. 2-4 puffs/day, wks 5-8, then 1-4 puffs/day wks 9-20) *Delivery device:* 1. DPI (Symbicort®, Turbuhaler®, AstraZeneca) 2. DPI (Pulmicort Turbuhaler®, AstraZeneca) *Duration:* 20 wks *Run in period:* none	*Number randomised* 133 *Mean (years) age (range)* 1. 45 (20-82) 2. 45 (20-80) *Baseline mean FEV_1 % predicted (range)* 1. 65 (39-85) 2. 67 (35-88) *Previous ICS treatment (drug and dose)* ICS or ICS/LABA combination therapy within the given starting dose	*Primary outcome* The number of patients per treatment group who experienced ≥1 treatment failure *Secondary outcomes* FEV_1 PEFR HRQL (SF36) Treatment satisfaction Dose of study medication % days patients required reliever medication Adverse events

Study ID	Design	Intervention	Patients	Outcomes
O'Byrne et al (2005)[232]	RCT Multi-centre Parallel-group Double-blind N.B. This trial also examines the effects of the combination inhaler as a reliever. 12% are children (4-11 yrs)	1. BUD/FF 80µg/4.5µg b.i.d. plus 80µg/4.5µg as needed (daily total 160µg/9µg) + combination inhaler as reliever 2. BUD/FF 80µg/4.5µg b.i.d. (daily total 160µg/9µg) + terbutaline as reliever as needed 3. BUD 320µg b.i.d. (daily total 640µg) + terbutaline as reliever as needed *Delivery device:* 1, 2, 3. DPI (Pulmicort Turbuhaler®, AstraZeneca) *Duration:* 12 mths *Run in period:* 14-18 days	*Number randomised* 2760 *Mean (years) age (range)* 1. 35 (4-77) 2. 36 (4-79) 3. 36 (4-79) *Baseline mean FEV_1% predicted (range)* 1. 73 (43-108) 2. 73 (46-108) 3. 73 (49-100) *Previous ICS treatment (drug and dose)* Adults 400-1000µg q.d. - children 200-500µg q.d.	*Primary outcome* The time to first severe asthma exacerbation. *Secondary outcomes* FEV_1 PEFR (am & pm) Asthma symptom scores (day/night) Awakenings Reliever medication use Symptom-free days Rescue medication free days Asthma control days Study drug use Adverse events Height (children) Morning plasma cortisol Mild exacerbations

Study ID	Design	Intervention	Patients	Outcomes
Scicchitano et al (2004)[233]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. BUD/FF, 400ug/6ug† 2 puffs q.d. (total 320µg/9µg/day*) + additional puffs as needed 2. BUD 200ug† 2 puffs b.i.d. (total 640µg/day*) + terbutaline as needed † ex-valve ** ex-actuator* *Delivery device:* 1. DPI (Symbicort®, Turbuhaler®, AstraZeneca) 2. DPI (Pulmicort Turbuhaler®, AstraZeneca) *Duration:* 52 wks *Run in period:* 2 wks	*Number randomised* 1890 *Mean (years) age (range)* 43 (11-80) *Baseline FEV_1 % predicted* 70 (37-102%) *Previous ICS treatment (drug and dose)* ICS 400-1600µg/day	*Primary outcome* The time to first severe asthma exacerbation. *Secondary outcomes* FEV_1 PEFR (am & pm) Asthma symptom scores (day/night/total) Awakenings Symptom-free days Reliever medication use Reliever medication free days Asthma control days Adverse events Severe exacerbations requiring medical attention Mild exacerbations

5.2.4.4.2 Results

Meta-analysis was not possible due to insufficient reporting of data. When reading this section it also needs to be acknowledged that the study by Pohl and colleagues[231] was an adjustable maintenance dosing study. Furthermore, one of the three arms in the study by O'Byrne and colleagues[232] used the combination inhaler as both maintenance and reliever. In addition, 12% of the patients in this trial were aged between 4-11 years. However, the majority of results reported by the trial were for all ages combined. Results pertaining to children, where reported separately, are presented in our accompanying assessment report for the efficacy and safety of ICS in children.[179]

Lung function

FEV_1, L

Lalloo and colleagues[230] reported that mean FEV_1 increased from baseline values in both treatment groups. A comparison of the ratios of geometric means from a multiplicative model showed no significant between-group differences. No values were presented. Pohl and colleagues[231] found that improvements in FEV_1 were comparable: 0.36 and 0.47 for patients treated with BUD/FF and BUD respectively (p-values, 95% CI, and other measures were not presented). In the trial by O'Byrne colleagues[232] baseline mean of FEV_1 (range) was 2.14 (0.64-4.02), 2.10 (0.62-4.50), and 2.13 (0.65-4.28) for patients treated with BUD, BUD/FF and terbutaline reliever, and BUD/FF as maintenance and reliever respectively. The mean of the data over the 12 month period was used as the treatment mean and analysed using analysis of variance with the baseline value as covariate. The respective values were 2.41, 2.43 and 2.51. P-values for the comparison were 0.09, and <0.001 for BUD/FF with terbutaline compared to BUD, and BUD/FF as maintenance and reliever compared to BUD. Scicchitano and colleagues[233] reported mean FEV_1 throughout the study, but did not report change from baseline. A statistically significant mean difference between the groups of 0.1L was reported (p<0.001). Patients using the combined inhaler treatment of BUD/FF had a mean FEV_1 level of 2.54L, compared with 2.45L in those receiving BUD plus terbutaline.

Morning and evening PEFR

Lalloo and colleagues[230] presented data on morning and evening PEFR. The baseline value was the average value over the last ten days of run in and treatment was the average value for the entire treatment period. These were analysed using analysis of covariance. For morning PEFR, the change from baseline was 16.5 L/min and 7.3 L/min for BUD/FF and BUD only, respectively (other statistics for these values were not provided). The between group difference was 9.2 (95% CI, 3.4 to 14.9) L/min, p=0.02. For evening PEFR, the change from baseline was 13.7 L/min and 4.2 L/min; the between group difference was 9.5 L/min (95%CI, 4.0 to 15.0), p<0.001).

In the study by Pohl and colleagues,[231] the mean morning PEFR for patients in the BUD/FF and BUD treatment groups was 407 L/min and 398 L/min respectively; corresponding values for mean evening PEFR were 411 L/min and 404 L/min. Other statistics for these values were not provided. No baseline values were presented in the trial by O'Byrne and colleagues.[232] End-point values were analysed using analysis of covariance and were based on the mean of data over the 12 month period. Morning PEFR was 339 L/min, 346 L/min and 355 L/min for BUD, BUD/FF with terbutaline reliever and BUD/FF as maintenance and reliever, respectively. P values for the comparisons of BUD/FF with terbutaline reliever versus BUD, and BUD/FF as maintenance and reliever versus BUD were all less than 0.001, showing statistical significance. The equivalent values for evening PEFR were 345 L/min, 349 L/min and 360 L/min. As with morning PEFR, between group comparisons showed statistical significance (p<0.001 for all comparisons). Other statistics for these values were not provided.

Scicchitano and colleagues[233] reported the mean and range of treatment PEFR values. People who received BUD/FF had a mean treatment morning PEFR value of 372.1 L/min (range 100-751 L/min) compared with 348.5 L/min (range 93-805 L/min) in the BUD with terbutaline group. The mean difference of 20.3L/min (95%CI 17, 24) was statistically significantly different (p<0.001). A slightly smaller but still statistically significant difference of 14L/min (95% CI 10, 18) was seen between the two groups' evening PEFR values (p<0.001). In the BUD/FF group, the treatment mean was 369.6 L/min (range 99-720 L/min) compared with 354.7 L/min (range 91-808 L/min) in the BUD with terbutaline group.

Symptoms

Symptom-free days

Lalloo and colleagues[230] reported improvements in the proportion of symptom-free days of 16% versus 10% for BUD/FF and BUD groups, respectively. The estimated between group difference was 6% (95%CI, 2 to 11%), which was statistically significant (p=0.007). The percentage of symptom-free days (range) at baseline in the study by O'Byrne and colleagues[232] was 23.5% (0-100), 24.0% (0-100) and 23.1% (0-100) in the BUD, BUD/FF with terbutaline reliever and BUD/FF as maintenance and reliever, respectively. End-point values were analysed using ANCOVA, and were based on the mean of data over the 12 month period. The respective values were 46%, 53% and 54%. Comparisons of BUD/FF with terbutaline reliever versus BUD, and BUD/FF as maintenance and reliever versus BUD were both statistically significantly different (p <0.001 for both comparisons). Other statistics for these values were not presented. Pohl and colleagues[231] did not present data on this variable. The percentages of symptom-free days and nocturnal awakenings reported by Scicchitano and colleagues[233] ranged from 0-100% for both treatment groups. In the BUD/FF group, the mean on-treatment percentage of symptom-free days was 41.7%, compared with 34% in the BUD/terbutaline group. This difference of 7.5 days (95% CI 5, 10) was statistically significantly different (p<0.001). Similarly, the difference in nocturnal awakenings between groups was statistically significant (9.4 in the BUD/FF vs. 13.0 in the BUD/terbutaline group; p<0.001).

Symptom scores

Pohl and colleagues[231] did not present data on this variable. Lalloo and colleagues[230] presented very limited data. Daytime and night time symptoms were scored from 0, no symptoms, to 3, severe symptoms. There were reductions from the run-in baseline of 24% versus 6% for asthma symptoms (probably a combined evening and morning score but it is not clear in the paper) in patients treated with BUD/FF and BUD respectively. Other statistics for this variable were not presented.

O'Byrne and colleagues[232] presented data on daytime and night time symptom scores. The symptoms were scored from 0 (no symptoms) to 3 (unable to undertake normal activities/sleep)(no reference supplied). Daytime and night time symptom scores at baseline

were not available. End-point values were analysed using ANCOVA and were based on the mean of data over the 12 month period. The values for daytime scores were 0.59, 0.50, and 0.48 for BUD, BUD/FF with terbutaline reliever and BUD/FF as maintenance and reliever, respectively. P values for the comparisons of BUD/FF with terbutaline reliever versus BUD, and BUD/FF as maintenance and reliever versus BUD were <0.001 and <0.001 and respectively, showing statistical significance. Corresponding values for night time symptom scores were 0.42, 0.36, and 0.31. P values were 0.01, and <0.001, respectively. Other statistics for these values were not presented.

Scicchitano and colleagues[233] reported the mean total asthma symptom score using a seven point scale (0-6, 0-3 for daytime score +0-3 for night-time score, where 0=no symptoms; no reference given for scale used).The treatment means were 1.08 in the BUD/FF group and 1.90 in the BUD/ terbutaline group, with a range of 0-6 in both groups. The difference between groups was statistically significant (p<0.001).

Health related quality of life

Pohl and colleagues[231] measured health related quality of life using the Short-Form Health survey (SF-36). Significant and clinically relevant differences between the two treatment groups were apparent in physical functioning (6.0 units; p=0.025) and emotional role functioning (12.1 units; p=0.035) with participants in the BUD/FF group performing better. The other studies did not report this variable.

Use of rescue medication

In the study by Lalloo and colleagues;[230] the change from baseline in the number of inhalations used in 24 hours was -0.33 and -0.1 in the BUD/FF group and BUD group respectively. Other statistics for these values were not presented. The between-group difference was -0.2 (95% CI, -0.4, 0), which was statistically significant (p=0.025). In the study by O'Byrne and colleagues,[232] baseline mean of number of inhalations per day was 1.69 (0.0-7.0), 1.69 (0.0-9.4), and 1.74 (0.0-8.0) for patients treated with BUD, BUD/FF and terbutaline reliever, and BUD/FF as maintenance and reliever, respectively. The corresponding figures for night time use were 0.72 (0.0-3.7), 0.73 (0.0-6.6) and 0.72 (0.0-5.7), repectively. End-point values were analysed using ANCOVA and were based on the

mean of data over the 12 month period. Daytime values were 1.03, 0.84, and 0.73. P values for the comparisons of BUD/FF with terbutaline reliever versus BUD, and BUD/FF as maintenance and reliever versus BUD were all less than 0.001, showing statistical significance. The equivalent values for night time were 0.43, 0.37 and 0.28, respectively. The P value for the comparison of BUD/FF with terbutaline versus BUD was 0.003, and for the comparison of BUD/FF as maintenance and reliever versus BUD was <0.001.

Other statistics for these values were not provided. Neither Pohl and colleagues[231] nor Scicchitano and colleagues[233] reported data for this outcome.

Exacerbations

In the study by Lalloo and colleagues,[230] fewer patients in the BUD/FF arm (110 out of 230) experienced at least one mild asthma exacerbation (defined as two consecutive mild exacerbation days which were defined as either night time awakenings, 20% decrease in PEFR from baseline or more than four inhalations of reliever medication in a 24 hour period) compared with those in the BUD group (136 out of 237). The patients in the BUD group had a shorter time to first mild exacerbation, p=0.02, log-rank test. A Cox proportional hazards model indicated that the estimated relative risk of having a mild asthma exacerbation was 26% lower for patients treated with BUD/FF (p=0.02). There were no between group differences (7% in each group) in the proportion of patients with severe exacerbations (defined as the need for oral steroids, or a ≥30% decrease in PEFR on two consecutive days or discontinuation due to asthma worsening) or time to first severe exacerbation.

In the study by Pohl and colleagues,[231] the number of exacerbations was not documented very clearly. However, in the BUD/FF group 5 out of 63 (8%) of patients had treatment failures (all used nebulised beta$_2$-agonists); in the BUD group there were 2 out of 63 (3%) patients (both were treated with oral steroids). The rate of treatment failure in the BUD group was less than the value of 25% that had been assumed for the calculation of the sample size.

In the study by O'Byrne and colleagues,[232] the percentages of patients experiencing a severe exacerbation (including a fall in PEFR of 70% or less of baseline on two consecutive days) were 28%, 27% and 16% in the groups taking BUD, BUD/FF with terbutaline and BUD/FF as maintenance and reliever, respectively. Comparison of the BUD/FF with terbutaline group

and the BUD group showed no statistically significant difference (p=0.74). Comparison of the BUD/FF as maintenance and reliever group with the BUD group showed a statistically significant difference (p<0.0001). The percentages of patients experiencing a serious adverse event requiring medical attention were 19%, 21% and 11% in the groups taking BUD, BUD/FF with terbutaline and BUD/FF as maintenance and reliever, respectively. The p values were 0.37 and <0.001 for the comparison of BUD/FF with terbutaline to BUD, and BUD/FF as maintenance and reliever to BUD, respectively.

A statistically significantly lower percentage of people in Scicchitano and colleagues[233] BUD/FF group reported an acute exacerbation than those in the BUD/terbutaline group (18% vs. 27%; HR 0.61[95% CI 0.50, 0.74]; p<0.001). Similarly, 14% of those in the BUD/FF group had an exacerbation requiring medical intervention, compared with 22% in the BUD/terbutaline group. The hazard ratio was 0.61(95% CI 0.49, 0.75; p<0.001).

Adverse events

In the study by Lalloo and colleagues,[230] there were no between-group differences in the profile and frequency of all adverse events. There were 134 adverse events in 230 patients in the BUD/FF group and 128 adverse events in 237 patients in the BUD group. There were five serious adverse events in the BUD/FF group and two in the BUD group. Three patients withdrew from each group because of adverse events.

In the study by Pohl and colleagues,[231] there were 74 adverse events in the BUD/FF group and 81 in the BUD group (the total number of patients included in the analysis of each group is not stated). Three patients reported serious adverse events, two in the BUD/FF group and one in the BUD group; none was treatment related. A total of four patients withdrew because of adverse events (not split by group).

In the trial by O'Byrne and colleagues,[232] the proportion of patients experiencing one or more adverse events was 52 (57%) for BUD, 475 (52%) for BUD/FF with terbutaline, and 496 (54%) for BUD/FF as maintenance and reliever. Corresponding proportions of patients experiencing one or more serious adverse events were 48 (5%), 62 (7%), and 46 (5%), respectively. Fourteen patients in the group taking BUD/FF with combination reliever, 29 taking BUD/FF with terbutaline and 24 in the BUD group discontinued because of adverse events. The study reported no significant findings in plasma cortisol in the subgroup of

patients aged 12 to 80, but data were not presented in sufficient detail to include here.

No statistically significant differences between groups were reported by Scicchitano and colleagues[233] for the rate of adverse events, serious adverse events, or withdrawals due to adverse events. Adverse events were experienced by 56% of the BUD/FF group, compared with 57% of the BUD/terbutaline group (p=0.677). The rate of serious adverse events was 6% in both groups (p=0.846). Discontinuations due to adverse events were low; 3% of the BUD/FF group and 4% of the BUD/terbutaline group (p=0.072).

5.2.4.4.3 Summary

Four parallel-group RCTs were identified which compared 400-1280µg BUD to 160-640µg BUD with 9-18µg FF in a combination inhaler. There was variability in the design, rationale and reporting of the studies, prohibiting meta-analysis. It is difficult to draw any firm conclusions from the study by Pohl and colleagues[231] as it was underpowered to detect a difference in the primary outcome. Overall, the combination inhaler appeared to perform better than BUD alone for most efficacy outcomes. In one trial there were no significant differences in the proportion of patients experiencing severe exacerbations between BUD and the combination inhaler, with terbutaline as relief in both groups. However, exacerbations were significantly reduced for patients taking the combination inhaler as both maintenance and reliever, compared to BUD with terbutaline as a reliever. There did not appear to be any difference in adverse effects between the different combinations.

5.2.4.5 Summary of Q3a – ICS vs ICS+LABA (ICS dose higher when used alone)

Five RCTs evaluated FP/SAL combination inhaler vs higher dose of ICS, and five evaluated BUD/FF combination inhaler vs higher dose of ICS. The general finding is that ICS+LABA in a combination inhaler is significantly superior to increasing the dose of the ICS, across a range of outcomes. This applied to both of the combination inhalers. The following tables provide a visual illustration of the results of pair-wise comparisons.

FP vs. FP/SAL n=2 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
	Meta-analysis Bergmann + Busse	*FP*											NSD
		FP/SAL		+	+		+				+		
1000µg vs 500µg/100µg	Bergmann 12w parallel group DPI n=365	*FP*	NSD										
		FP/SAL							+	F		F	

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results									
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
500µg vs 200µg/100µg	Busse 12-24w parallel group DPI n=558	*FP*							NSD			NSD	
		FP/SAL	+										

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

BUD vs. FP/SAL n=3 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
1600µg vs. 500µg/100µg	Jenkins 24w parallel group DPI n=353	*BUD*						NSD				NSD	18%
		FP/SAL	+	+	+		+			+			14%
800µg vs. 200µg/100µg	Johansson 12w parallel group DPI n=349	*BUD*	C				C	C					38%
		FP/SAL		+*	+							F	38%
	Zhong 6w parallel group DPI n=398	*BUD*	NSD										24%
		FP/SAL		+	+		+	+					24%

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

* see main text

FP vs. BUD/FF n=1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
500µg vs. 400µg/9µg	Bateman 12w parallel group DPI n=344	*FP*				NSD	NSD						
		BUD/FF	+	+	+						+	F	

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

BUD vs. BUD/FF n=4 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
400µg vs. 200µg/9µg	Lalloo 12w parallel group DPI n=467	*BUD*	NSD										54%
		BUD/FF		+	+		+				+	+	58%
1600µg vs 800µg/18µg ADM	Pohl 20w parallel group DPI n=133	*BUD*	C	F	F							C	81 events
		BUD/FF								+			74 events
800µg vs 200µg/9µg	O'Byrne 52w parallel group DPI n=2760	*1.BUD*	NSD 1 vs. 2									NSD 1 vs. 2	57%
		*2.BUD/FF***		+ 2 vs. 1	+ 2 vs. 1		+ 2 vs. 1		+ 2 vs. 1		+ 2 vs. 1		52%
		*3.BUD/FF****	+ 3 vs. 1	+ 3 vs. 1	+ 3 vs. 1		+ 3 vs. 1		+ 3 vs. 1		+ 3 vs. 1	+ 3 vs. 1	54%

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800µg vs. 400µg/9µg	Scicchitano 52w parallel group DPI n=1890	*BUD*											NSD
		BUD/FF	+	+	+	+	+		+			+	

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies); ADM = adjustable dose maintenance

C = results stated to be comparable between treatment arms, but no other data presented; NSD = no significant difference between trial arms; + indicates results favour this trial arm; F indicates that results favour this trial arm but no significance testing has been reported. Blank cells signify no data reported on that outcome.

** terbutaline only used as reliever in this arm

*** combination inhaler used as both maintenance and reliever in this arm.

5.2.5 Review Question 3b – ICS vs ICS+LABA (ICS dose similar in both groups)

To re-cap, nine RCTs evaluated ICS vs ICS+LABA, where a similar ICS dose has been used in both trial arms (*Table 34*). The following sub-sections describe the characteristics and results of these trials.

TABLE 34 *Breakdown of studies for Review Question 3b – ICS vs ICS+LABA (ICS dose similar in both treatments)*

Pair-wise comparison	Number of RCTs included
FP vs FP/SAL	6
BUD vs BUD/FF	3
Total	9

5.2.5.1 ICS vs ICS+LABA (FP vs FP/SAL)

5.2.5.1.1 Study Characteristics

Six parallel group RCTs evaluated the effectiveness of FP/SAL in a combination inhaler compared to FP alone.[234-239] The trials were published between 1999 and 2006 (*Table 35*). Four were multi-centre studies and two single-centre studies. Sample sizes were 54 and 282 in the two single centre studies[237;238] respectively, and ranged between 349 and 3421 participants in the multi-centre studies. All but one trial[234] reported that a power calculation was undertaken and sample sizes suggest that adequate power was met. However, in the Koopmans and colleagues study[237] analysis was based on sputum eosinophils as the primary outcome, with lung function and symptoms as secondary outcomes. The sample size of 54 may not be powered for these secondary outcomes.

Four trials[234;236;238;239] also included other intervention arms, such as SAL monotherapy and placebo, but these arms are not reported here. One trial, the GOAL study by Bateman and colleagues,[235] stratified patients into three groups based on previous ICS therapy. Data for the first stratum (no previous ICS) are not reported here as these patients do not meet the inclusion criteria of the present review.

There was variability in the doses used in the trials, with the FP dose varying from 200µg to 1000µg per day (both as monotherapy and combined with SAL).

One trial compared 200µg per day of FP with FP/SAL combination 100/200µg per day.[236] Three trials compared 500µg per day FP with FP/SAL 500/100µg per day.[237-239] One trial compared FP 1000µg per day with FP/SAL 1000/100µg per day.[234]

In the GOAL trial by Bateman and colleagues,[235] a variable dose was applied through two phases of treatment therapy. In the stratum with participants previously on lower dose ICS therapy (≤ 500µg day) the FP/SAL arm in phase one was stepped-up between 200/100µg, 500/100µg or 1000/100µg per day, until total control was met or the highest dose reached. Then in phase two, participants continued on the final dose reached in phase one. The FP arm was similarly stepped-up between 200, 500, or 1000µg per day (until control or highest dose) in phase one and continued in phase two. In the stratum with participants previously on higher dose ICS therapy (500-1000µg day) the dose ranges were 500/100µg and 1000/100µg per day for both treatments and both phases of treatment respectively.

The treatment duration across the included trials varied. Two trials lasted 12 weeks,[236;239] one trial lasted 28 weeks[234] and three trials lasted one year.[235;237;238] The inhaler devices used were DPIs in all six trials

(for all trials - FP/S: Seretide Accuhaler®, GlaxoSmithKline – not explicitly stated in most trials, but deduced from the text; FP: Flixotide Diskhaler®, GlaxoSmithKline – also not explicitly stated in most trials, but deduced from the text).

The aims of the trials were mostly to compare the safety and efficacy of the two treatments (and, in some cases, other treatments). In the Bateman and colleagues[235] study, where stepped-up dose of the treatments were given, the aim was to compare the efficacy of increasing doses of the two treatments to achieve asthma control as defined by Global Initiative for Asthma/National Institutes of Health guidelines (reference given).

The ages of participants in the six trials are likely to be largely similar, but differences in methods of reporting ages make summarising the data difficult. Where reported, mean ages were in the region of 34-50 years. One trial reported a mean age of 40 years but a range of 9-83 years, and as such may have included some children.[235] The severity of asthma was mild to moderate in three of the trials,[237-239] and moderate in three.[234-236] Baseline FEV_1 % predicted was between 40-92% but in most trials was between 67-77%.

The quality of reporting and methodology of the included RCTs was generally poor. The method of randomisation was unknown in all but one included study[235] and the method to conceal allocation to groups was similarly only assessed to be adequate in this one trial. In the other trials the method was either not reported or judged to be an inadequate method. These factors, if adequately met, reduce the risk of selection bias. Intention-to-treat analysis was assessed to be adequate in only three included studies.[234;235;238] This factor limits the possibility of measurement bias.

TABLE 35 *Characteristics of studies (FP versus FP/SAL)*

Study ID	Design	Intervention	Patients	Outcomes
Aubier et al (1999)[234]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP/SAL 500/50µg b.i.d. (daily total 1000/100µg) 2. FP 500µg + SAL 50µg b.i.d. (daily total 1000/100µg) 3. FP 500µg b.i.d. (daily total 1000µg) Only group 1 and 3 relevant to this section *Delivery device:* 1. Diskus® (Seretide Accuhaler®, GlaxoSmithKline*) + placebo 2. Diskus® inhaler (Flixotide Diskhaler®, GlaxoSmithKline*) 3. Diskus® inhaler (Flixotide Diskhaler®, GlaxoSmithKline*) + placebo *Duration:* 28 wks *Run in period:* 2 wks	*Number randomised* 503 *Mean age (years)* 1. 46 3. 50 *Baseline FEV1 % predicted (±sd)* 1. 73 (± 1.2) 3. 73 (± 1.4) *Previous ICS treatment:* *(drug and dose)* BDP or BUD 1500-2000µg q.d. or FP 750-1000µg q.d.	PEFR (am & pm) Daytime asthma score Night-time asthma score Adverse events Serum cortisol Urinary cortisol

Study ID	Design	Intervention	Patients	Outcomes
Bateman et al (2004)[235]	RCT Multi-centre Parallel-group Double-blind Stratified	*Drugs:* Stratum 1: no ICS therefore not included here Stratum 2: previous low ICS use ≤ 500µg BDP or equivalent daily. 1. FP/SAL - Phase I: 100/50, 250/50 or 500/50µg b.i.d. step-up until total control or highest dose reached. Phase II: continued on the final dose reached in phase I. 2. FP - Phase I: dose 100, 250 or 500µg b.i.d. step-up until total control or highest dose reached. Phase II: continued on the final dose reached in phase I. Stratum 3: previous moderate ICS use >500 to ≤ 1000µg BDP or equivalent daily. 1. FP/SAL - Phase I: 250/50 or 500/50µg b.i.d. step-up until total control or highest dose reached. Phase II: continued on the final dose reached in phase I. 2. FP - Phase I: 250µg or 500µg b.i.d. step-up until total control or highest dose reached. Phase II: continued on the final dose reached in phase I. *Delivery device:* 1. DPI (Seretide, Advair, GlaxoSmithKline) 2. DPI (Flixotide Diskhaler®, GlaxoSmithKline) *Duration:* 52 wks *Run in period:* 4 wks	*Number randomised* 3421 *Mean (years) age (range)* Stratum 1: 1. 36.1 (12-80) 2. 36.4 (12-82) Stratum 2: 1. 40.4 (12-78) 2. 40.3 (9-80) Stratum 3: 1. 44.1 (12-83) 2. 42.7 (12-80) *Baseline FEV1 % predicted (±sd)* Stratum 1: *1. 77 (± 18.7)* *2. 79 (± 18.8)* Stratum 2: 1. 78 (18.2) 2. 77 (18.4) Stratum 3: 1. 75 (18.6) 2. 76 (17.6) *Previous ICS treatment* *(drug and dose)* Continued on their usual dose of ICS if any	Proportion of patients who achieved well-controlled asthma during phase I Cumulative proportion of patients achieving control in phase II Dose of ICs & time to achievement of the first well-controlled asthma week Proportion of patients & dose to achieve totally controlled asthma Time to achieve the first totally controlled week Asthma quality of life (using AQLQ) Exacerbation rates Morning pre-dose FEV_1 Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Kavuru et al (2000)[236]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP/SAL 100/50µg b.i.d. (daily total 200/100µg) 2. SAL 50µg b.i.d. (daily total 100µg) 3. FP 100µg b.i.d. (daily total 200µg) 4. Placebo b.i.d. Only group 1 and 3 reported here. *Delivery device:* 1. Diskus® (Seretide Accuhaler®, GlaxoSmithKline*) 2. Diskus (GlaxoSmithKline) 3. Diskus® (Flixotide Diskhaler®, GlaxoSmithKline) 4. Diskus (GlaxoSmithKline) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 356 *Mean (years) age (range)* 1. 38 (12-70) 2. 37 (12-67) 3. 39 (12-67) 4. 35 (12-66) *Baseline FEV_1 % predicted* 1, 2, 3, 4. 64 *Previous ICS treatment.* *(drug and dose)* BDP 252-420µg 6-10 puffs q.d. or flunisolide 1000µg 4 puffs q.d. or FP 176µg 4 puffs q.d.	FEV_1 (Under the 12 hr serial curve relative to baseline) Morning pre-dose FEV_1 Probability that patients be in the study without withdrawn for worsening asthma PEFR Daily patient-rated diary card symptom scores Albuterol use Night-time awakenings requiring albuterol
Koopmans et al (2006)[237]	RCT Single-centre Parallel-group Double-blind	*Drugs:* 1. FP 250µg b.i.d. (daily total 500µg) 2. FP/SAL 250/50µg b.i.d. (daily total 500/100µg) *Delivery device:* 1. Diskus (Flixotide Diskhaler®, GlaxoSmithKline*) 2. Diskus (Seretide Accuhaler®, GlaxoSmithKline*) *Duration:* 52 wks *Run in period:* 4 wks	*Number randomised* 54 *Median (years) age (range)* 1. 32 (19-57) 2. 32 (21-59) *Baseline FEV1 % predicted (±sd)* *1. 89.9 (± 14)* *2. 88.8 (± 18)* *Previous ICS treatment:* *(median daily dose) (range)* 1. ICS 593µg q.d. (200-1200) 2. ICS 619µg q.d. (200-1000)	FEV_1 PEFR Symptom scores Rescue medicine use

Study ID	Design	Intervention	Patients	Outcomes
Lundback et al. (2006)[238]	RCT Single-centre Parallel-group Double-blind	*Drugs:* 1. FP/SAL 250/50µg b.i.d. (daily total 500/100µg) 2. FP 250µg b.i.d. (daily total 500µg) 3. SAL 50µg b.i.d. Only group 1 and 2 reported here *Delivery device:* 1. Diskus™ (Seretide Accuhaler®, GlaxoSmithKline*) 2. Diskus™ (Flixotide Diskhaler®, GlaxoSmithKline*) 3. Diskus™ (GlaxoSmithKline*) *Duration:* 12 mths *Run in period:* 2 mths	*Number randomised* 282 *Mean (years) age (±sd)* *1. 39.9 (± 11.9)* *2. 39.1 (± 12.0)* *3. 40.7 (± 12.3)* *Baseline FEV1 % predicted* 1. 92.1 2. 93.0 3. 94.9 *Previous ICS treatment* *(drug and dose)* 68% patients had previously received ICS - BUD median dose 500µg or equivalent	No of pts requiring an increase in study medication No of pts experiencing ≥2 exacerbations Morning PEFR PEFR diurnal variation FEV_1 Day & night-time symptom scores Rescue medication use Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Shapiro et al (2000)[239]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP/SAL 250/50µg b.i.d. (daily total 500/100µg) 2. FP 250µg b.i.d. (daily total 500µg) 3. SAL 4. Placebo Only group 1 and 2 reported here *Delivery device:* 1. Diskus (Seretide Accuhaler®, GlaxoSmithKline*) 2. Diskus (Flixotide Diskhaler®, GlaxoSmithKline*) 3, 4. Diskus *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 349 *Mean (years) age (range)* 1. 38 (12-69) 2. 40 (12-67) 3. 39 (12-68) 4. 38 (12-69) *Baseline FEV1 % predicted* 1. 69 2. 66 3. 67 4. 68 *Previous ICS treatment:* *(drug and dose)* BDP 462-672µg q.d. or Triamcinolone acetonide 1100-1600µg q.d. or FP 440µg q.d. or Flunisolide 1250-2000µg q.d.	FEV_1 (Under the 12 hr serial curve relative to baseline). Morning pre-dose FEV_1 Probability of remaining in study PEFR Symptom scores Albuterol use Night-time awakenings Safety

* not stated explicitly, but deduced from the text

5.2.5.1.2 Results

Lung function

FEV_1 (L)

Four of the six studies report mean change from baseline in FEV_1 (L).[234;236;238;239] In the Kavaru and colleagues[236] trial (FP doses of 200µg per day) the mean change in FEV_1 L was 0.51 (SD 0.46) in the combination FP/SAL group compared with 0.28 (SD 0.46) in the FP group (mean difference 0.23 [95% CI 0.09, 0.37], p <0.001). Two studies that treated participants with doses of 500µg FP per day (in the combination and FP alone arms respectively) showed greater improvement in patients treated with combination treatment compared to FP alone.[238;239] In the Lundback and colleagues[238] study this was not statistically significantly different (actual p values were not reported) and as no measure of variance was reported these two studies could not be combined to give a pooled treatment effect. The treatment duration also differed between these two studies, Lundback and colleagues[238] was a 12 month study whereas Shapiro and colleagues[239] was shorter at 12 weeks. Lundback and colleagues[238] reported that FEV_1 L change from baseline was 0.09 in the FP/SAL group compared to 0.02 in the FP arm. Shapiro and colleagues[239] demonstrated a mean change in FEV_1 L of 0.48 (SD 0.45) in the FP/SAL arm compared with 0.25 (SD 0.45) in the FP arm (p=0.003).

The study by Aubier and colleagues,[234] which used daily doses of 1000µg FP in both combination and monotherapy arms, found no statistically significant difference between groups (figures derived from graphs; FP/SAL 0.25 L vs FP 0.18 L, p=0.061). This was a 28-week study.

FEV_1 % predicted

FEV_1 % predicted was reported in the trial by Koopmans and colleagues[237] but the data presented was only the mean difference between the FP/SAL and FP groups (2.7 (SE 1.5)) and this was reported as not statistically significantly different, p=0.07.

Results for the Bateman and colleagues[235] trial were reported for the stratified groups and for the two phases of treatments separately. In the lower dose stratum the adjusted mean

change in FEV_1 % predicted was 0.35% in the FP/SAL group in phase one and 0.22% in the FP treatment group. During phase two these were 0.37% and 0.24% for the two treatments respectively. In the higher dose stratum the adjusted mean change in FEV_1 % predicted in phase one was 0.29% in the FP/SAL group and 0.17% in the FP group. For phase two mean changes were 0.32% and 0.18% respectively. In each phase it is apparent that the combination treatment gave higher rates of change but no statistical analysis was undertaken of the two groups in these two strata alone. Rather, data were combined with data from stratum one, the latter not being relevant to present review.

Morning PEFR

Data on change in morning PEFR (L/min) were reported in three of the included RCTs[234;236;239] but due to wide variation in the doses meta-analysis was not appropriate. Using daily fluitcasone doses of 200µg the Kavaru and colleagues trial[236] demonstrated a statistically significant difference in change in morning PEFR. The mean change was 52.50 (SD 49.44) L/min in the FP/SAL arm compared with 17.30 (SD 40.57) L/min in the FP arm (mean treatment difference 35.20 (95% CI 21.70, 48.70), $p \leq 0.025$). The Shapiro and colleagues[239] trial similarly showed a statistically significant difference in change in morning PEFR between combination treatment group and the FP alone group (FP/SAL 53.50 (SD 50.40) L/min versus FP 15.20 (SD 41.40) L/min, mean difference 38.30 [95% CI 24.10, 52.50] L/min, p=0.015). The dose of FP in this study was 500µg per day. Lundback and colleagues trial[238] (also using FP 500µg/day) reported data on mean change from baseline in morning PEFR (L/min) but no measures of variance around the point estimates were presented. The mean change was 38 L/min in the FP/SAL group and 21 L/min in the FP group ($p<0.01$).

Using higher doses of FP (1000µg per day) Aubier and colleagues[234] also showed a statistically significant difference in change in morning PEFR, although the magnitude of this difference was less than in the other studies (FP/SAL 38.00 (SD 50.40) L/min versus FP 22.00 (SD 51.40) L/min, mean difference 16.00 [95% CI 5.04, 26.95] L/min. This latter study was of a 28 week duration whereas the Kavaru and colleagues[236] and Shapiro and colleagues[239] studies were of12 weeks' duration.

At end-point in the Koopmans and colleagues[237] trial, morning PEFR was 459 (SD 67.50) L/min in the FP/SAL arm compared to 419 (SD 67.50)L/min in the FP arm. No statistical analysis of the difference between groups was undertaken.

Evening PEFR

Change in evening PEFR was reported in three included trials,[234;236;239] but differences in doses prevented a meta-analysis. Using daily doses of 200µg FP, the Kavaru and colleagues trial[236] demonstrated a statistically significant difference in change on evening PEFR (as observed by the 95% CI). The mean change was 35.00 (SD 43.84) L/min in the FP/SAL arm compared with 18.00 (SD 12.40) L/min in the FP arm (mean treatment difference 17.00 (95% CI 7.42, 26.58) L/min, p ≤ 0.025). The Shapiro and colleagues[239] trial similarly showed a statistically significant difference in change in evening PEFR between combination treatment group and the FP alone group (FP/SAL 45.40 (SD 46.80) L/min versus FP 7.90 (SD 40.50) L/min, mean difference 37.50 [95% CI 24.02, 50.98] L/min (p=0.015). The dose of FP in this study was 500µg per day. In the study which used higher doses of FP (1000µg per day)[234] there was a statistically significant difference in change in evening PEFR, although the magnitude of this difference was less than in the previous studies (FP/SAL 31.00 (SD 49.10) L/min versus FP 13.00 (SD 50.10) L/min, mean difference 18.00 [95% CI 7.33, 28.67] L/min (p <0.01). This latter study was of a 28 week duration whereas the Kavaru and colleagues[236] and Shapiro and colleagues[239] studies were 12 weeks in duration.

In the trial by Koopmans and colleagues trial[237] mean change in evening PEFR (L/min) was only reported in terms of the treatment difference. The difference between FP/SAL and FP alone was 36 (SE 9) L/min (p<0.001).

Symptoms / health related quality of life

Two of the included trials reported data on the change from baseline in symptom-free days.[236;239] One study used treatment doses of FP of 200µg/day[236] and one 500µg/day.[239] In both studies there was a statistically significant difference between groups in favour of FP/SAL combination therapy. In the Kavaru and colleagues[236] study, the mean change in percentage of symptom-free days was 22.60 (SD 42.81) in the combination treatment arm

compared with 7.20 (SD 37.70) in the FP arm (mean difference 15.40 [95% CI 3.35, 27.45], p ≤ 0.025). Corresponding values for mean change in percentage of nights with no awakenings were 4.6 (SD 16.1) and 2.4 (SD 21.6) (mean difference 2.2 [95% CI -3.50, 7.90], (no statistically significant difference, no p value reported)).

In the Shapiro and colleagues[239] study the mean change in percentage of symptom-free days was 33.80 (SD 41.40) in the FP/SAL arm compared with 15.40 (SD 37.80) in the FP arm (mean difference 18.40 [95% CI 6.19, 30.61]; p=0.015). Corresponding values for percentage of nights without awakenings were 7.2 (SD 17.1) and 2.8 (SD 21.6) (mean difference 4.4 [95% CI -1.60, 10.40]; p=0.015).

Symptom-free days were reported in the Aubier and colleagues study[234] but no measure of variance were reported for the data. In the FP/SAL treatment group the proportion of symptom-free days was 38%, compared to 28% in the FP group. This was not statistically significantly different between the two groups (no p value given).

Three studies reported symptom scores.[236;237;239] In the study by Koopmans and colleagues[237] morning symptoms were measured on a five point scale (0 – 4; no further detail reported). Only mean differences were reported for the change over the one year treatment period. The mean difference between the groups for morning symptoms was -0.1 (SE 0.1; p=0.02). Evening symptoms scores were measured on a six point scale (0-5; no further detail reported). The mean difference between groups was -0.2 (SE 0.1; p=0.01).

In the study by Kavaru and colleagues[236] symptoms were measured on a six point scale (0= no symptoms, 5=symptoms that severely interfered with daily activities, no reference supplied). In the FP/SAL group there was a change in score of -0.7 (SE 0.11) compared to a change of -0.2 (SE 0.09) in the FP group (p≤ 0.025). Shapiro and colleagues[239] also reported changes in symptom scores using a scoring system which appears to be identical to that of Kavaru and colleagues.[236] In the FP/SAL group there was a change in score of -0.8 (SE 0.12) compared to a change of -0.4 (SE 0.09) in the FP group (p=0.015).

Bateman and colleagues[235] reported data on the Asthma quality of life (AQLQ) scale. Results were presented for the stratified groups and for the two phases of treatments separately. In the lower dose stratum, the adjusted mean change in AQLQ score was 1.3 in the FP/SAL treatment group in phase one and 1.0 in the FP treatment group. During phase

two treatments these were 1.3 and 1.2 for the two treatments, respectively. In the higher dose stratum the adjusted mean change in AQLQ score in phase one was 1.1 in the FP/SAL treatment group and 0.8 in the FP treatment group. For phase two treatment these mean changes were 1.2 and 1.0 respectively. In each phase there were slightly higher rates of change in the combination treatment arms but no statistical analysis was undertaken of the two groups in these two strata alone, rather was combined with the data from stratum one which was not included in the present review.

Use of rescue medication

Change in the use of rescue medication in terms of inhalations per day was also shown to be statistically significantly better with FP/SAL treatment versus FP treatment alone in two trials. In the Kavaru and colleagues trial[236] there was a –1.90 (SD 2.43) change in inhalations per day in the combination treatment arm compared to a –0.40 (SD 1.94) change in the FP treatment arm (difference –1.50 [95% CI –2.16, -0.84] p≤ 0.025). This trial used low doses of FP in both treatment groups (200µg per day). In the Shapiro and colleagues trial[239] (using doses of 500µg/day of FP in each treatment group) there was a –2.30 (SD 3.60) change in inhalations per day in the FP/SAL group compared to a –0.90 (SD 1.80) change in inhalations per day in the FP group (difference –1.40 [95% CI –2.28, -0.52], p=0.015).

The treatment difference between the FP/SAL group and the FP group of the Koopmans and colleagues trial[237] for use of rescue medication was -0.9 (SE 0.3) puffs per day. This difference was reported to be statistically significantly different, p<0.001 but the study may be underpowered to detect a difference on this outcome.

Exacerbations

Four of the trials reported this outcome, with variability in definitions, and limited reported data. Shapiro and colleagues[239] reported that 2% and 7% of patients withdrew due to clinical exacerbations in the FP/SAL and the FP groups, respectively. A clinical exacerbation was defined as requiring emergency room treatment, hospitalisation, or use of asthma medication not allowed by the study protocol. In the trial by Kavaru and colleagues[236] no patients in the FP/SAL group withdrew because of clinical exacerbations, compared with 4% of patients in

the FP group. The definition of clinical exacerbation was the same as that used by Shapiro and colleagues.[239]

In the trial by Lundback and colleagues[238] exacerbations were defined as any deterioration in asthma that required an increase in rescue medication use (SABA) over that used during the run-in period of >6 puffs/d for ≥2 consecutive days, or an increase of ≥2 doses/d 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 (25mg) for five days. The percentage of patients experiencing two or more acute exacerbations was 4.2% for FP/SAL combination, compared to 17.4% for FP, p<0.01.

Bateman and colleagues[235] defined exacerbations as deterioration in asthma requiring treatment with an oral corticosteroid or an emergency department visit or hospitalisation, based on the Global Initiative for Asthma (GINA)/National Institutes of Health guidelines. The mean annual rates of exacerbations were low in both treatment groups but were significantly lower in the FP/SAL group in each stratum (p ≤0.009). Rates for each stratum were not reported.

Adverse events

Numbers of participants experiencing adverse events were reported in three trials. In the Shapiro and colleagues[239] trial, no adverse events were experienced in either treatment group. In the Lundback and colleagues[238] trial, 92/95 (96%) participants in the combination treatment group and 88/92 (95%) participants in the FP treatment group experienced an adverse event. In the Aubier and colleagues[234] trial, 28/167 (16%) participants in the FP/SAL arm experienced an adverse event compared to 32/165 (19%) participants in the FP arm. The variation in the proportions of patients experiencing adverse events between the studies may be related to differences in the way events are classified by different studies.

Three trials[234;236;239] provided data on numbers discontinuing due to adverse events. In the Shapiro and colleagues[239] trial, no participants were classed as withdrawing due to adverse events in either treatment arms. In the Kavaru and colleagues[236] trial, one participant in the FP arm discontinued due to an adverse event compared on no participants in the

combination arm. In the Aubier and colleagues[234] trial,16/167 participants in the FP/SAL arm discontinued due to adverse events (9%) compared to 22/165 (13%) in the FP arm.

5.2.5.1.3 Summary

Six parallel-group RCTs were identified comparing FP/SAL in a combination inhaler compared to FP. These trials varied in terms of FP dose ranging from 200µg to 1000µg per day (both as monotherapy and combined with SAL), and duration (between 12 weeks to one year).

FP/SAL treatment was generally more favourable compared with FP treatment alone on measures of lung function, and statistically significant differences were reported by some studies. Data on symptoms generally favoured the combination treatment but this was not always statistically significant. Use of rescue medication, where reported, was statistically significantly different between treatment arms, again in favour of the FP/SAL. Exacerbations, which were defined and reported in a variety of ways, appeared similar between treatments. In two studies there were statistically significant differences in favour of the combination treatment. Generally similar rates of adverse events and discontinuations due to adverse events were reported between the two treatment options, where data were reported.

5.2.5.2 ICS vs ICS+LABA (BUD vs BUD/FF)

5.2.5.2.1 Study characteristics

Three trials were included in this comparison[240-242] (*Table 36*). All of them used parallel-group designs and were published between 2001 and 2006. All were international multi-centre trials and generally large in size, ranging from 362 to 1272 patients. The length of treatment was 12 weeks in all three trials.

All trials had multiple arms, testing various regimens. Buhl and colleagues[241] compared two regimens of BUD combined with FF against BUD. In one of the regimens patients took two inhalations (160/4.5µg) once a day, whilst in the other they inhaled twice a day (160/4.5µg) (a total daily dose of 320/9µg per day). Patients receiving BUD only took 400µg/day. The trial by Kuna and colleagues[242] tested similar regimens, but with higher doses. They compared BUD/FF (80µg/4.5µg) two inhalations once a day (evening), BUD/FF (80µg/4.5µg) one

inhalation twice a day (total BUD/FF dose of 160µg/9µg/day in both groups), and BUD 200µg/day. The comparison between the once and twice daily regimens of BUD/FF in both of these trials is not relevant to this review. Finally, one study, by Zetterström and colleagues,[240] compared BUD/FF in a combination inhaler (160µg/4.5µg two inhalations b.i.d; total daily dose total 640µg/18µg/day), with the two agents in separate inhalers (200µg/4.5µg two inhalations b.i.d; total daily dose total 800µg/18µg/day), and with BUD monotherapy (200µg two inhalations b.i.d (total 800 µg/day). For the purposes of this section, only the combination inhaler and the BUD monotherapy arms are compared. See Section 5.2.6.3 for a comparison of the combination inhaler and the separate inhalers. In summary, the three trials compared BUD/FF combination inhaler with BUD. The dose of BUD was similar in both comparisons, ranging from 200µg to 800µg per day.

In all studies a Turbohaler DPI was used to deliver BUD/FF. Metered doses (ex-actuator) are reported for some arms, and delivered doses (ex-valve) are reported for others. This reflects changes in labelling whereby the combination inhalers (Symbicort® Turbuhaler®, AstraZeneca – not explicitly stated in only one study,[241] but deduced from the text) express doses as delivered, compared to the separate inhalers (BUD: Pulmicort Turbuhaler®, AstraZeneca - not explicitly stated in any of the three studies, but deduced from the text) for BUD/FF which express doses as metered. An inhalation of BUD/FF 160µg/4.5µg from the combination inhaler delivers the same quantity as a 200µg metered inhalation of BUD and as a 4.5µg metered inhalation of FF.

Two of the trials had similar rationales. The aim of the study by Buhl and colleagues[241] was to evaluate the efficacy of once daily combination therapy compared to twice daily combination therapy, and to once daily BUD. It was suggested that a 'simple treatment regimen' (i.e. one inhaler taken once a day) would be effective in patients with moderate persistent asthma. Similarly, Kuna and colleagues[242] also compared once daily combination therapy, with twice daily combination therapy and with BUD alone, but with lower doses and in patients with mild to moderate asthma. The rationale was that patients with milder chronic asthma, who may experience fewer symptoms and who may under-estimate their condition, may be more likely to use their medication if taken once a day. The third trial, by Zetterström and colleagues,[240] aimed to compare the then new BUD/FF combination inhaler with the two drugs administered in separate inhalers, and with BUD alone.

The average age of patients in the trials was generally between 30 to 40 years, ranging from 18 to 80. All patients had previously been treated with ICS, although doses varied across the trials. One of the studies included patients who were receiving 'lower dose' ICS (according to the BTS/SIGN Guidelines).[1] Patients in the trial by Kuna and colleagues[242] were defined by the authors as having mild to moderate asthma which was not optimally controlled despite taking 200-500µg per day of inhaled steroids (unspecified as to which steroid). The other two trials included patients who had been managed on higher doses: 400-1000µg per day of any corticosteroid in the trial by Buhl and colleagues[241] (patients described by the authors as having moderate persistent sub-optimally controlled asthma), and ≥500 µg per day in the trial by Zetterström and colleagues[240] (patients described as having symptomatic asthma despite treatment with ICS). Mean baseline FEV_1 as a percentage of predicted was between 70 to 80% across the trials, suggestive of moderate asthma.[2]

Only one of the trials specified a primary outcome measure. Kuna and colleagues[242] measured mean change in morning PEFR from baseline as their primary outcome. A power calculation is reported for this outcome. The remaining outcomes in these and the other two studies comprised lung function (FEV_1 and PEFR), measures of symptoms (symptom scores, symptom-free days, nocturnal awakenings), use of reliever medication, mild and severe exacerbations, and adverse events.

In terms of methodological quality the trials had some limitations. Only one provided details of the randomisation procedure used, and the method used for concealment of allocation.[240] However, in this particular study sealed envelopes were used to conceal individual treatment codes until data analysis. This method is potentially open to subversion. All trials employed an intention-to-treat analysis.

TABLE 36 *Study Characteristics: BUD vs BUD/FF*

Study ID	Design	Intervention	Patients	Outcomes
Kuna et al. (2006)[242]	RCT Multi-centre Double-blind Double-dummy	*Drugs:* 1. BUD/FF 80/4.5µg* 2 puffs q.d. PM (daily total 160/9µg) 2. BUD/FF 80/4.5 µg* b.i.d. (daily total 160/9 µg) 3. BUD 200µg† q.d. PM * ex-actuator † ex-valve *Delivery device:* 1. DPI Turbuhaler (Symbicort® Turbuhaler®, AstraZeneca) 2. DPI Turbuhaler (Symbicort® Turbuhaler®, AstraZeneca) 3. DPI Turbuhaler (Pulmicort Turbuhaler®, AstraZeneca*) *Duration:* *12 wks* *Run in period:* 2 wks	*Number randomised* 617 *Mean (years) age (range)* 1. 45.8 (18-80) 2. 43.9 (19-80) 3. 45.1 (18-78) *Baseline FEV_1 % predicted* mean baseline % 1. 79.3 2. 77.9 3. 78.3 *Previous ICS treatment (drug and dose)* ICS 200-500µg q.d.	*Primary outcome* Mean change in morning PEFR from baseline *Secondary outcomes* Evening PEFR Symptom-free days Use of reliever medication Nocturnal awakenings Asthma control days FEV_1 (L) Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Buhl et al (2003)[241]	RCT Multi-centre Parallel-group Double-blind Double-dummy	*Drugs:* 1. BUD/FF 160/4.5µg* 2 puffs q.d. (daily total 320/9µg) 2. BUD/FF 160/4.5µg* b.i.d. (daily total 320/9µg) 3. BUD 400µg† q.d. * ex-actuator † ex-valve *Delivery device:* 1. DPI Turbuhaler (Symbicort® Turbuhaler®, AstraZeneca*) 2. DPI Turbuhaler (Symbicort® Turbuhaler®, AstraZeneca*) 3. DPI Turbuhaler (Pulmicort Turbuhaler®, AstraZeneca*) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 523 *Mean (years) age (range)* 1. 42.7 (18-77) 2. 44.8 (18-74) 3. 45.5 (18-78) *Baseline FEV_1 % predicted* 1. 77.1 2. 77.6 3. 77.6 *Previous ICS treatment (drug and dose)* ICS 400-1000µg q.d.	*Outcomes* PEFR PEFR (am & pm) FEV_1 (L) Day & night-time asthma symptoms Totally daily asthma symptom score Night-time awakenings Use of relief medication Mild & severe exacerbations Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Zetterström et al (2001)[240]	RCT Multi-centre Parallel-group Double-blind Double-dummy	*Drugs:* 1. BUD/FF 160/4.5µg* 2 puffs b.i.d. (daily total 640/18µg) (combination inhaler) 2. BUD+ FF 200µg† + 4.5µg 2 puffs b.i.d. (daily total 800µg + 18µg) (separate inhalers) 3. BUD 200µg† 2 puffs b.i.d. (daily total 800µg) ** ex-actuator* † ex-valve Only groups 1 and 3 relevant here *Delivery device:* 1. DPI Turbuhaler (Symbicort® Turbuhaler®, AstraZeneca) + placebo 2. DPI Turbuhaler (Pulmicort Turbuhaler®, AstraZeneca*) + placebo 3. DPI Turbuhaler (Pulmicort Turbuhaler®, AstraZeneca*) + placebo *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 362 *Mean (years) age (range)* 1. 46.7 (18-78) 2. 44.7 (18-77) 3. 48.5 (21-78) *Baseline FEV_1 % predicted* 1. 73.6 2. 74.7 3. 73.1 *Previous ICS treatment (drug and dose)* ICS $\geq$ 500 µg	*Outcomes* PEFR FEV_1 (L) Day & night-time symptoms scores Symptom-free days Night-time awakenings Asthma control days Use of relief medication Mild & severe exacerbations Adverse events

* not stated explicitly, but deduced from the text

5.2.5.2.2 Results

Results are reported narratively by outcome in the following sections. Meta-analysis was not possible due to limitations in the trial data, and due to differences between the trials in dose.

Lung function

All trials reported FEV_1 in terms of litres, with results generally favouring BUD/FF compared to BUD. In the trial by Kuna and colleagues[242] increases in FEV1 (geometric mean) from baseline to end-point were 0.08L and 0.12L for the once daily and twice daily BUD/FF groups respectively. In the BUD group there was a decrease of 0.01L. No statistical significance values are reported, although it is stated that there was a 3.8% difference between the two combination inhaler groups and the BUD group in terms of FEV_1 as a percentage of the baseline value at end-point ($p<0.05$). In the trial by Buhl and colleagues[241] there was no change in FEV_1 between baseline and end-point for the once daily BUD/FF group, an increase of 0.12L in the twice daily group, and a decrease of 0.06L in the BUD group. There was a statistically significant difference between the once daily group and the twice daily group compared to the BUD group in end-point values (2.32 L; 2.37L and 2.21L respectively, $p<0.001$). Increases in FEV1 in the study by Zetterström and colleagues[240] were 0.19L for the combination inhaler group, and 0.11L for the BUD group. The difference between the groups was statistically significant for end-point values, 2.47L (95%CI 2.40 – 2.55) and 2.35L (95%CI 2.28 – 2.43) respectively ($p<0.05$).

FEV_1 as a percentage of predicted was not reported as an outcome in any of the trials.

All three trials reported changes from baseline in morning PEFR, and in all cases increases were statistically significant for BUD/FF compared to BUD. Increases of 23.4 L/min (95%CI 18.1, 28.6), 24.1 L/min (95%CI 19.0, 29.2) and 5.5 L/min (95%CI 0.3, 10.6) were reported for the BUD/FF once daily group, twice daily group and BUD group respectively in the trial by Kuna and colleagues[242] ($p<0.001$ for both combination inhaler groups compared to the BUD group). In the trial by Buhl and colleagues,[241] statistically significant increases of 27.4 L/min, 22.8 L/min, were reported for the once daily and twice daily BUD/FF groups compared to the BUD group (values not provided for this group) ($P<0.001$). Increases of 35.7 L/min (95%CI 28.4, 43.0) and 0.2 L/min (95%CI -7.1, 7.6) were reported for the BUD/FF group and the BUD group respectively in the trial by Zetterström and colleagues[240] ($p<0.01$).

Evening PEFR was also reported by all three trials. As with morning PEFR, increases were statistically significant for BUD/FF compared to BUD. Increases of 9.6 L/min (95%CI 4.4, 14.8), 18.3 L/min (95%CI 13.2, 23.4) and a decrease of 1.7 L/min (95%CI -6.8, 3.5) was reported for the BUD/FF once daily group, twice daily group and BUD group respectively in the trial by Kuna and colleagues.[242] The difference was statistically significant for both combination inhaler groups compared to the BUD group, $p<0.01$ and $p<0.001$, respectively. In the trial by Buhl and colleagues,[241] increases of 11.8 L/min and 18.8 L/min and a decrease of 4.8 L/min were reported for the once daily, twice daily BUD/FF groups and the BUD group, respectively. Mean differences between the combination inhaler groups and the BUD group were statistically significant ($p<0.001$). An increase of 24.8 L/min (95%CI 18.2, 31.4) and a decrease of 3.7 L/min (95%CI -10.3, 3.0) was reported for the BUD/FF group and the BUD group respectively in the trial by Zetterström and colleagues[240] ($p<0.01$).

Symptoms

Two of the trials reported asthma symptom scores. Buhl and colleagues[241] and Zetterström and colleagues[240] measured day and nighttime symptom scores on a scale of 0-3 (0=none; 3=severe), and summed these to provide a total score (0-6). In both studies there were statistically significant differences favouring BUD/FF. In Buhl and colleagues, scores decreased (indicating fewer symptoms) by, 0.24, 0.32 and 0.2 in the once daily, twice daily BUD/FF groups and the BUD group, respectively. The difference in end-point values was statistically significant for the BUD/FF once daily group compared to the BUD group ($p<0.05$), but not for the twice daily group compared to BUD. In the trial by Zetterström and colleagues[240] scores decreased by 0.52 (95%CI, -0.65, -0.39) and by 0.20 (95%CI, -0.33, -0.07) in the BUD/FF group and the BUD group respectively ($p<0.01$).

All three trials reported the proportion of symptom-free days, using slightly different definitions. In all cases there were statistically significant differences between groups favouring BUD/FF. Kuna and colleagues[242] defined a symptom-free day as a day and a night with no asthma symptoms and no night time awakenings due to asthma. The increase in percentage of symptom-free days between baseline and end-point was 12.2%, 14.2% and 5.3% in the BUD/FF once daily group, twice daily group and BUD group respectively ($p<0.05$ for end-point values for both combination inhaler groups compared to BUD). Buhl and colleagues[241] used the definition of a day and a night with a total symptom score of zero.

The increase in percentage of symptom-free days between baseline and end-point was 14.3%, 14.7%, and 11.9% for the once daily, twice daily BUD/FF groups and the BUD group, respectively ($p<0.05$ for end-point values for both combination inhaler groups compared to BUD). Zetterström and colleagues[240] used the definition of days with a total asthma score of 0 and no nighttime awakening. The increase in percentage of symptom-free days between baseline and end-point was 25.0% (95%CI 19.5, 30.6) and 8.0% (95%CI 2.4, 13.6) for the BUD/FF group and the BUD group respectively ($p<0.01$).

Nighttime awakenings were reported in all three trials. In the trial by Kuna and colleagues[242] the reduction in the percentage of awakenings was 4.5%, 4.7% and 5.9% in the BUD/FF once daily group, twice daily group and BUD group respectively. Differences between groups were not reported to be statistically significant (no p value provided). Buhl and colleagues[241] reported percentage nights with awakenings. There was a reduction of 4.6% for the BUD/FF once daily group, an increase of 2.1% for the twice daily group, and a reduction of 1.4% for the BUD group. The end-point value was statistically significant for the twice daily group compared to the BUD group ($p<0.05$). Zetterström and colleagues[240] reported changes in the percentage of nighttime awakenings due to asthma. Reductions were 8.4% (95% CI, -11.4, -5.4) and 5.8% (95%CI -8.8, -2.7) for the BUD/FF group and the BUD group respectively. Differences between groups are not reported to be statistically significant (no p value provided).

Use of rescue medication

All three trials reported this outcome, although only two reported it in terms of puffs per day. For both of these trials differences between groups were statistically significant, in favour of BUD/FF. In the trial by Buhl and colleagues[241] reductions in the number of inhalations/day from baseline to end-point were 0.37, 0.45 and 0.10 for the once daily, twice daily BUD/FF groups and the BUD group, respectively ($p<0.01$ for the once daily group compared to the BUD group; $p<0.001$ for the twice daily group compared to the BUD group). In the trial by Zetterström and colleagues[240] reductions in puffs/day from baseline to end-point were 0.99 (95%CI -1.29, -0.69) and 0.44 (95%CI -0.74, -0.13) for the BUD/FF group and the BUD group respectively ($p<0.01$).

Exacerbations

Two of the trials reported this outcome. Buhl and colleagues[241] reported mild and severe exacerbations. Mild exacerbations were defined as two consecutive mild exacerbation days (for the same criterion), the latter being defined as a nighttime awakening due to asthma; ≥ 20% decrease in PEFR from baseline; or ≥ four inhalations of reliever medication over a 24 hour period. Severe exacerbation was defined as asthma deterioration requiring oral corticosteroid treatment; or ≥ 30% decrease in PEFR from baseline on two consecutive days; or discontinuations due to worsening of asthma. Rates of severe exacerbations were 8%, 9% and 11% for the once daily, twice daily BUD/FF groups and the BUD group, respectively. A similar pattern across treatment groups was reported for mild exacerbations (no data reported).

Zetterström and colleagues[240] defined severe exacerbations as the need for oral steroids; discontinuations due to worsening asthma, or PEFR <70% of run-in mean on two consecutive days. Rates were 6.5% and 8.9% for the BUD/FF group and the BUD group respectively. The authors reported that too few severe exacerbations occurred during the study to detect differences between the treatments.

Adverse events

The rate of adverse events, where reported, appeared similar between treatments. No statistical significance values were reported in any of the trials.

In the trial by Kuna and colleagues,[242] 76 (38%), 78 (38%) and 74 (36%) of patients experienced at least one adverse event in the BUD/FF once daily group, twice daily group and BUD group respectively. Seven serious adverse events were reported: two, one and four in the study groups respectively. The proportion of patients experiencing at least one adverse event in the trial by Buhl and colleagues[241] was 71 (40%), 60 (34%) and 78 (46%) in the once daily, twice daily BUD/FF groups and the BUD group, respectively. None of the five serious adverse events were considered to be related to treatment. The number of patients experiencing at least one adverse event was not reported by Zetterström and colleagues.[240] However, it is reported that the number, nature and intensity of adverse events were similar across the treatment groups. None of the five serious adverse events were considered to be related to treatment.

5.2.5.2.3 Summary

Three large parallel-group RCTs compared BUD/FF combination inhaler with BUD in patients with mild to moderate asthma not controlled despite regular treatment with ICS (doses generally in the range of 200 to 1000 /day). The dose of BUD was similar in both comparisons, ranging from 200µg to 800µg per day.

There were statistically significant differences between treatment groups favouring BUD/FF in nearly all outcomes (morning and evening PEFR; symptom scores; symptom-free days; use of rescue medication; FEV_1). Statistically significant differences between treatments in nighttime awakenings were reported in only one of the three trials. The incidence of mild exacerbations (reported in one trial) severe exacerbations (reported in two of the trials) appeared similar between treatments, although no statistical significance values were reported. Incidence of adverse events appeared similar between treatments (no statistical significance values reported).

The trials therefore suggest that BUD/FF is superior to BUD alone in controlling asthma in patients with mild to moderate asthma symptomatic despite treatment with ICS.

5.2.5.3 Summary of Q3b – ICS vs ICS+LABA (ICS dose similar in both groups)

Six RCTs evaluated FP/SAL combination inhaler vs similar dose of ICS, and four evaluated BUD/FF combination inhaler vs similar dose of ICS. In all trials the same ICS was used in both comparators. ICS and LABA was statistically superior to ICS alone across most outcomes. The following tables provide a visual illustration of the results of pair-wise comparisons.

FP vs. FP/SAL n=6

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
1000µg vs. 1000µg/100µg	Aubier 28w parallel group DPI n=503	*FP*	NSD				NSD						19%
		FP/SAL		+	+								16%

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
500µg vs. 500µg/100µg	Koopmans 52w parallel group DPI n=54	*FP*	NSD										96%
		FP/SAL		F	+				+		+		95%
	Lundback 52w parallel group DPI n=282	*FP*	NSD										
		FP/SAL		+								+	
	Shapiro 12w parallel group DPI n=349	*FP*											0
		FP/SAL	+	+	+	+	+		+		+	F	0
200µg vs. 200µg/100µg	Kavaru 12w parallel group DPI n=356	*FP*				NSD							
		FP/SAL	+	+	+		+		+		+	F	

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
Variable	Bateman 52w parallel group DPI n=3421	*FP*											
		FP/SAL	F							F		+	

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

BUD vs. BUD/FF n=3 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800µg vs. 800µg/9µg	Zetterström parallel group DPI n=362	*BUD*											C
		BUD/FF	+	+	+	F	+		+		+	F	
400µg vs. 400µg/9µg	Buhl 12w Parallel group DPI n=523	*1. BUD*				NSD 1 vs. 2							46%
		2. BUD/FF od	+ 2 vs. 1	+ 2 vs. 1	+ 2 vs. 1		+ 2 vs. 1		+ 2 vs 1		+ 2 vs. 1	F 2 vs. 1	40%
		3. BUD/FF bd	+ 3 vs. 1	+ 3 vs. 1	+ 3 vs. 1	+ 3 vs. 1	+ 3 vs. 1		NSD 3 vs. 1		+ 3 vs. 1	F 3 vs. 1	34%

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
200µg vs. 200µg/9µg	Kuna 12w DPI n=617	*1. BUD*				F 1 vs. 2 1 vs. 3							36%
		2. BUD/FF od	+ 2 vs. 1	+ 2 vs. 1	+ 2 vs. 1		+ 2 vs. 1						38%
		3. BUD/FF bd	+ 3 vs. 1	+ 3 vs. 1	+ 3 vs. 1		+ 3 vs. 1						38%

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies); ADM = adjustable dose maintenance; od = once daily; bd = twice daily

C = results stated to be comparable between treatment arms, but no other data presented; NSD = no significant difference between trial arms; + indicates results favour this trial arm; F indicates that results favour this trial arm but no significance testing has been reported. Blank cells signify no data reported on that outcome.

Summary

As expected, adding a LABA to an ICS without increasing the dose of ICS alone produces a beneficial effect in terms of lung function, symptoms and use of rescue medication. These effects are apparent whether the ICS and LABA combination used is FP/SAL or BUD/FF. Few trials reported exacerbations, which might be expected to exhibit a similar pattern. No difference in adverse events is noted for FP vs FP/SAL, but this effect is less certain for BUD vs BUD/FF.

5.2.6 Review Question 4 – ICS+LABA in combination vs separate inhalers

To re-cap, six RCTs compared ICS and LABA in a combination inhaler to the two drugs delivered in separate inhalers (*Table 39*). The following sub-sections describe the characteristics and results of these trials.

TABLE 37 *Breakdown of studies for Review Question 4 – combination inhaler vs separate inhalers*

Pair-wise comparison	Number of RCTs included
FP/SAL (combination) vs BUD+FF (separate)	1
FP/SAL (combination) vs FP+SAL (separate)	3
BUD/FF (combination) vs BUD+FF (separate)	2
Total	6

5.2.6.1 FP/SAL in a combination inhaler vs BUD+FF in separate inhalers

5.2.6.1.1 Study characteristics

One parallel group RCT[243] evaluated the effectiveness of FP/SAL in combination compared to BUD+FF given concurrently and was published in 2002 (*Table 38*). This study was a multi-centre trial with 11 centres and the study sample size was 428 participants. The study was powered to assess non-inferiority of the FP/SAL combination and adequate power in the sample was met.

The trial compared FP/SAL 100/500µg per day in via DPI (Seretide® Diskus®, GlaxoSmithKline) in one trial arm with BUD 800µg (Pulmicort Turbuhaler®, AstraZeneca – not

explicitly stated but deduced from the text) per day and FF 12µg per day also via DPI Turbohaler in the second trial arm. The treatment duration was for 12 weeks.

The aim of the study was to compare safety and efficacy of the two groups to demonstrate similar efficacy between treatments but using less than one third of ICS dose in the combination therapy group.

The mean ages of the participants in the trial were 46.5 years in the FP/SAL group and 48.1 years in the BUD+FF group respectively. The severity of asthma was moderate to severe with participants on daily ICS doses between 1,000-1600µg per day of BDP or equivalent. The mean baseline FEV_1 % predicted in all participants was 69%.

The quality of reporting and methodology of the study was generally good. The methods of randomisation and allocation concealment were assessed to be adequate. This factor minimises the risk of selection bias in the trial. The study reported that data were analysed on the intention-to-treat population however the method undertaken was assessed to be inadequate. This factor, when adequate, helps to minimise the risk of measurement bias.

TABLE 38 *Characteristics of study (FP/SAL vs BUD+FF)*

Study ID	Design	Intervention	Patients	Outcomes
Ringdal et al (2002)[243]	RCT Multi-centre Parallel-group Double-blind	*Drug(s):* 1. FP/SAL 250/50 µg b.i.d. (daily total 500/100µg) 2. BUD+FF 800µg + 12µg b.i.d. (daily total 1600µg + 24µg) *Delivery device:* 1. DPI (Seretide® Diskus®, GlaxoSmithKline) + 2 placebo Turbuhalers 2. DPI Turbuhaler (BUD -Pulmicort Turbuhaler®, AstraZeneca*) + placebo Diskus *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 428 *Mean (years) age (sd)* 1. 46.5 (14.0) 2. 48.1 (13.9) *Baseline FEV_1 % predicted (sd)* 1. 69.2 (10.7) 2. 69.0 (10.1) *Previous ICS treatment* *(drug and dose)* BUD/BDP or flunisolide 1000-1600µg q.d. or FP 500-800 µg q.d.	Mean am PEFR PEFR (am & pm) at other time-points PEFR % diurnal variation Clinical FEV_1, rate Severity of exacerbations Day & night-time symptom scores Night-time awakenings Use of rescue salbutamol Withdrawals from study Asthma-related health-care resource utilisation (Norwegian health-care system & costs - not data extracted) Adverse events

* not stated explicitly, but deduced from the text

5.2.6.1.2 Results

Lung function

The Ringdal and colleagues[243] trial present data on the mean change from baseline in FEV_1. This was shown to be similar between the two groups (FP/SAL 0.27, BUD+FF 0.26, difference –0.01, 95% CI –0.09, 0.07m p=0.796) suggesting that lower doses of the combination therapy was not inferior to higher doses of BUD+FF therapy.

Morning PEFR changes from baseline were also reported to be similar between the two groups, but no p-value was reported for the intention-to-treat population (FP/SAL 43 L/min, BUD+FF 47 L/min) only for a per-protocol population (not reported here).

Symptoms / health related quality of life

Symptom-free days were reported to be similar between groups in the Ringdal and colleagues[243] trial but no data were reported in the publication to support this. The proportion of nights without awakenings was only reported as a median and hence is not reported here.

Use of rescue medication

Ringdal and colleagues[243] reported that there were no differences between the FP/SAL and BUD+FF groups on the need for rescue medication, but no data were presented to support this.

Exacerbations

The total number of acute exacerbations during treatment was 129 in the FP/SAL arm and 206 in the BUD+FF arm of the Ringdal and colleagues trial.[243] No statistical analysis was reported to have been undertaken of the difference between the groups. The mean rate of exacerbation per patient per 84 days of treatment was 0.47 in the FP/SAL group compared to 0.73 in the BUD+FF group and was shown to be statistically significantly different (ratio 0.64, 95% CI 0.51, 0.80, p<0.001).

Adverse events

There were 91 adverse events in total in the FP/SAL group and 78 in the BUD+FF group of the Ringdal and colleagues.[243] trial No analysis of statistical significance was undertaken on this data. Serious adverse events were reported by two participants in the FP/SAL group and three in the BUD+FF group.

5.2.6.1.3 Summary

One RCT compared 500µg/day FP and 100µg/day SAL with 1600µg/day BUD and 24µg/day FF. Lower doses of the combination FP/SAL were shown to be similar to treatment with higher dose BUD/FF on measures of lung function. Rates of exacerbations were better in the combination treatment arm compared to the separate inhaler arm of the included trial. Adverse events appeared to be greater in the FP/SAL arm but this was not tested for statistical significance compared to the BUD/FF arm.

5.2.6.2 FP/SAL in a combination inhaler vs FP+SAL in separate inhalers

5.2.6.2.1 Study Characteristics

Three parallel group RCTs[234;244;245] evaluated the effectiveness of FP/SAL in combination compared to FP+SAL taken concurrently and were published between 1998 and 1999 (*Table 39*). All three studies were multi-centre trials where study sample sizes ranged between 224 and 503 participants. None of the included trials report undertaking a power calculation.

All three included trials had comparisons of FP/SAL in combination with FP+SAL separately. One of the included trials also had a third arm comparison with FP alone (reported in Section 5.2.5.1). The three trials used the same dose of SAL but varying doses of FP. One trial compared FP/SAL 200/100µg per day with FP 200µg per day + SAL 100µg per day.[244] Another compared FP/SAL 500/100µg per day with FP 500µg per day + SAL 100µg per day[245] and the third study FP/SAL 1000/100µg per day with FP 1000µg per day + SAL 100µg per day.[234]

The devices used in all three studies were DPIs for both the combination treatment groups (Seretide® Diskus®, GlaxoSmithKline) and the separate treatment groups (Flixotide, Accuhaler®, GlaxoSmithKline, deduced from the text for Aubier and colleagues) respectively.

The treatment duration was 12 weeks in one study[244] and 28 weeks in the other two studies.[234;245]

All three trials were reported to be assessing whether the treatments given in combination inhalers were clinically equivalent to the treatments given in separate inhalers. Treatment equivalence was tested using the 90% CI of the difference between the combination and separate therapies on morning PEFR in all three included trials[234;244;245] where *a priori* equivalence was regarded as a 90% CI within ± 15 L/min (reported to be defined and validated in previous clinical studies, references given).

The ages of participants in the trials are reasonably similar ranging in the three studies between 33 years to 48 years. All trials reported that their participants were symptomatic on their previous ICS treatments but on inspection of the doses of the previous treatments patient severity was likely to be different across the three trials. These previous treatments were 400-500µg per day of BDP or equivalent drug in the Bateman and colleagues[244] trial, 800-1200µg per day BDP or equivalent in the Chapman and colleagues trial[245] and 1500-2000µg BDP or equivalent in the Aubier and colleagues[234] trial. This would also be reflected in the range of doses of FP and SAL treatments given across the three trials as noted above. Baseline FEV_1 % predicted was reported as being 73% in one trial.[234] The other two trials report absolute FEV_1 as 2.4[244] and 2.5[245] litres respectively although this is reported as % predicted (assume a typographical error).

The quality of reporting and methodology of the included trials was mixed. The method of randomisation was reported and assessed as being adequate in only one of the trials[244] but not reported in the other two trials.[234;245] The means by which allocation was concealed was not reported in any of the three trials. Where adequate these factors minimise the potential for selection bias in trials. Finally, the analysis was reported to be by an intention-to-treat principle in all three trials but the method used was only assessed as being adequate in two of these[234;244] as participants appeared to be excluded from some of the analyses in the other trial.[245] An intention-to-treat analysis minimises the potential for measurement bias.

TABLE 39 *Characteristics of studies (FP/SAL vs FP+SAL)*

Study ID	Design	Intervention	Patients	Outcomes
Aubier et al (1999)[234]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 500/50µg b.i.d. (daily total 1000/100µg) 2. FP+SAL 500µg + 50µg b.i.d. (daily total 1000 + 100µg) 3. FP 500µg b.i.d. (daily total 1000µg) Only group 1 & 2 reported here *Delivery device:* 1. DPI (Seretide® Diskus®, GlaxoSmithKline) + placebo 2, 3. DPI Diskus® (Flixotide, GlaxoSmithKline*) + placebo *Duration:* 28 wks *Run in period:* 2 wks	*Number randomised* 503 *Mean (years) age (range)* 1. 46 (12-78) 2. 48 (19-79) 3. 50 (12-76) *Baseline FEV_1 % predicted (± d)* *1. 73 (± 1.2)* *2. 73 (± 1.2)* *3. 73 (± 1.4)* *Previous ICS treatment* *(drug and dose)* BDP 1500-200µg/day or FP 750-100µg/day	PEFR (am & pm) Daytime asthma score Night-time asthma score Adverse events Serum cortisol Urinary cortisol

Study ID	Design	Intervention	Patients	Outcomes
Bateman et al (1998)[244]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 100/50µg b.i.d.+ placebo (daily total 200/100µg) 2. FP+SAL 100µg + 50µg b.i.d. (daily total 200µg + 100µg) *Delivery device:* 1. DPI (Seretide® Diskus®, GlaxoSmithKline) 2. DPI (Flixotide, Accuhaler®, GlaxoSmithKline*) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 244 *Mean (years) age (range)* 1. 33 (12-78) 2. 33 (12-76) *Baseline FEV_1 % predicted* 1. 75 2. 76 *Previous ICS treatment* *(drug and dose)* Various ICS therapies (no details)	PEFR (am & pm) FEV_1 Use of rescue salbutamol Daytime and night-time symptom score
Chapman et al (1999)[245]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 250/50µg b.i.d. (daily total 500/100µg) + placebo 2. FP+SAL 250µg + 50µg b.i.d. (daily total 500µg + 100µg) *Delivery device:* 1. DPI (Seretide® Diskus®, GlaxoSmithKline) 2. DPI (Flixotide Accuhaler®, GlaxoSmithKline) *Duration:* 28 wks *Run in period:* 2 wks	*Number randomised* 371 *Mean (years) age (range)* 1. 42.8 (13-73) 2. 41.4 (15-75) *Baseline FEV_1 % predicted* 1. 75 2. 77 *Previous ICS treatment* *(drug and dose)* BDP or BUD 800-1200 µg q.d. or FP 400-600µg q.d.	PEFR (am & pm) FEV_1 Use of salbutamol Daily and nightly symptom score Compliance Adverse events

* not stated explicitly, but deduced from the text

5.2.6.2.2 Results

Lung function

The adjusted mean change from baseline in FEV_1 in the Aubier and colleagues[234] study (estimated from figures) was 0.25 L in the combination FP/SAL arm and 0.15 L in the separate FP+SAL arm at 28 weeks. This was not statistically significantly different, p=0.45. At 28 weeks the mean change from baseline in FEV_1 in the Chapman and colleagues[245] trial was 0.26 L in the combination treatment group and 0.24 L in the separate inhaler group. The 90% CI of the treatment difference (-0.02) was –4 to -1. FEV_1 adjusted change from baseline was also reported after 12 weeks of therapy in the Bateman and colleagues[244] trial. Although values appear to be similar, no statistical analysis of equivalence or superiority was undertaken and no measure of variance was reported (FP/SAL 0.20 L, FP+SAL 0.17 L).

The change from baseline in morning PEFR was measured for the first 12 weeks to be 38 (SD 50.4) L/min in the FP/SAL arm compared with 36 (SD 49.7) L/min in the FP+SAL arm of the Aubier and colleagues trial.[234] The 90% CI around the mean difference (-2 L/min) was -10, 7 L/min, p=0.77. This was within pre-defined equivalence limits (± 15 L/min^{-1}). In the Chapman and colleagues[245] trial, the change from baseline in morning PEFR was also measured for just the first 12 weeks of therapy. This was reported to be 43 L/min in the combination inhaler group and 36 L/min in the separate inhaler group. The treatment difference 90% CI was within the equivalence definition of the study (-6, 90% CI –13, 0). The results of these studies suggest no difference between treatment with a combination inhaler and separate inhalers on morning PEFR. In the Bateman and colleagues[244] trial, adjusted mean change in morning PEFR was 47 L/min in the FP/SAL arm compared with 39 L/min in the FP+SAL arm after 9-12 weeks of therapy. The difference between the two groups was not statistically significantly different (p=0.22) although the study reports that the 90% CI of weeks 1-12 combined (lower -17 to higher 0) were outside the defined equivalence interval, showing superiority of the combination treatment therapy.

The change from baseline in evening PEFR was measured for the first 12 weeks to be 31 (SD 49.1) L/min in the FP/SAL arm compared with 26 (SD 48.4) L/min in the FP+SAL arm of the Aubier and colleagues trial.[234] These figures were not statistically significantly different (p=0.27). In the Chapman and colleagues[245] trial the change from baseline in evening PEFR

was also measured for just the first 12 weeks of therapy. This was reported to be 36 L/min in the combination therapy group and 26 L/min in the separate therapy group respectively. The treatment difference was reported to be statistically significantly different (p=0.008) favouring the combination product. In the Bateman and colleagues[244] trial, adjusted mean change in evening PEFR was 39 L/min in the FP/SAL arm compared with 34 L/min in the FP+SAL arm after 12 weeks of therapy. The difference between the two groups was not statistically significantly different (p=0.39). The equivalence interval was not defined on the outcome of evening PEFR although the study stated that the results were equivalent (we therefore assume this is because there is no evidence that either treatment is superior).

Symptoms / health related quality of life

The mean proportion of symptom-free days were 38% in both comparison groups in the Aubier and colleagues[234] trial (not statistically significantly different), where data points were estimated from figures in the publication. Similarly the mean proportion of symptom-free nights was not statistically significantly different between the two comparison groups (FP/SAL 58% versus FP+SAL 55%, estimated from figures) in the Aubier and colleagues[234] trial.

Use of rescue medication

No appropriate data were reported.

Exacerbations

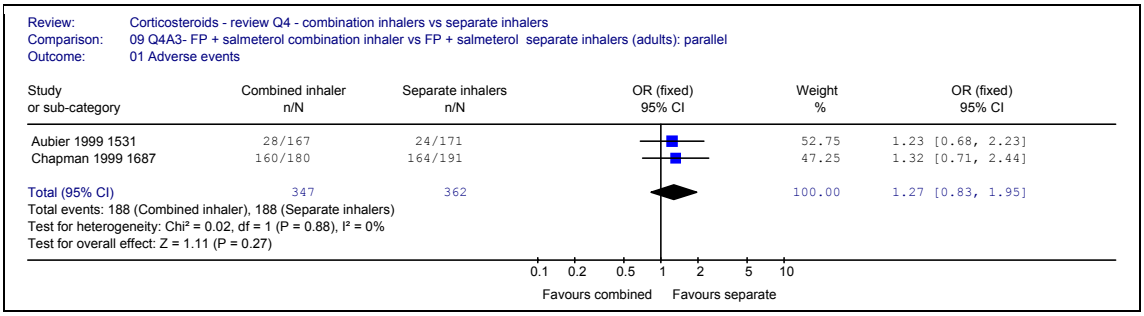
No appropriate data were reported.

Adverse events

Sufficient data on numbers of adverse events were reported in the two 28 week trials to be combined in a meta-analysis (*Figure 17*). The severity of the participants' asthma was likely to be slightly different as the patients in the trial by Aubier and colleagues[234] recieved higher doses than the patients in the Chapman and colleagues[245] trial, and this needs to be considered when interpreting the results of the meta-analysis. The fixed-effects pooled odds

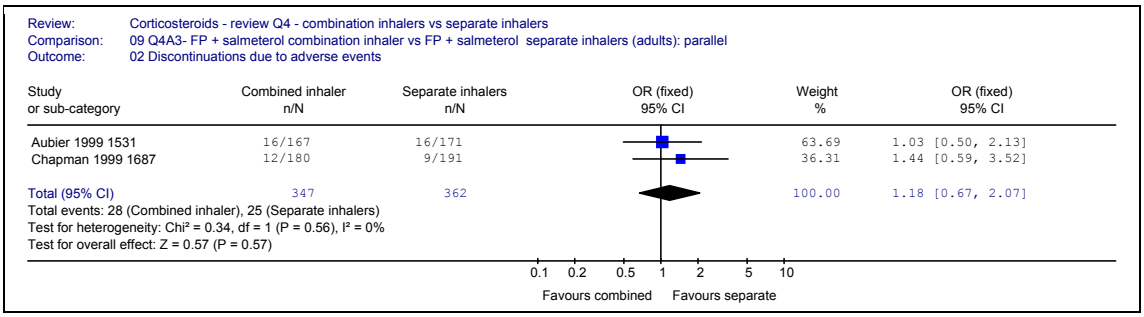
ratio was 1.27 (95% CI 0.83, 1.95; p=0.27), suggesting no statistically significant difference between the combination FP/SAL treatment and the separate FP+SAL treatment. Heterogeneity was not statistically significant (p=0.88, I^2 = 0%).

FIGURE 17 *Adverse events, FP/SAL versus FP+SAL*



Data on discontinuations due to adverse events were also reported in the two 28 week trials and combined in a meta-analysis (*Figure 18*). The fixed-effects pooled odds ratio was 1.18 (95% CI 0.67, 2.07; p=0.57), similarly suggesting no statistically significant difference between the combination therapy and the separate therapies. Heterogeneity was not statistically significant (p=0.56, I^2 = 0%).

FIGURE 18 *Discontinuations due to adverse events, FP/SAL vs FP+SAL*



5.2.6.2.3 Summary

Three parallel-group RCTs compared combination use of 200-1000µg/day FP /100µg/day SAL with separate use of 200-1000µg/day FP and 100µg/day SAL.

On measures of lung function, no statistically significant differences were observed between treatment with FP/SAL in a combination inhaler compared to treatment with FP+SAL in separate inhalers. These trials were mostly designed to show equivalence therefore results are in line with this assumption. Similarly, where reported, there were no statistically

significant differences between the two treatments on measures of symptoms. The adverse event profiles of the two treatments were not statistically significantly different.

5.2.6.3 BUD/FF in a combination inhaler vs BUD+FF in separate inhalers

5.2.6.3.1 Study Characteristics

Two RCTs[240;246] evaluated the effectiveness of BUD/FF in a combination inhaler compared to BUD+FF administered via separate inhalers, and were published in 2001[240] and 2002.[246] They were both international, multi-centre studies with sample sizes ranging between 362 and 586 participants. One study was double-blind and the other open-label, both of parallel group design (*Table 40*).

The doses of BUD and FF were the same in the two studies. One study[246] compared BUD/FF in a single inhaler with a total daily dose of 640µg/18µg (160µg/4.5µg, two inhalations b.i.d.), with BUD+FF delivered via separate inhalers but with the same total daily dose of 640µg + 18µg (160µg + 4.5µg, two inhalations b.i.d.). Zetterström and colleagues[240] also compared BUD/FF in a single inhaler with a total daily dose of 640µg/18µg (160µg/4.5µg, two inhalations b.i.d), with the two agents in separate inhalers and a total daily dose of 800µg BUD + 18µg FF (200µg + 4.5µg, two inhalations b.i.d). This trial also had a third arm comparison with BUD alone (200µg, two inhalations b.i.d; total 800 µg/day). For the purposes of this section, only the combination inhaler and the separate inhaler arms are compared. See section 5.2.5.2 for a comparison of the combination inhaler and the BUD monotherapy arms.

The devices used in the two trials were Turbohaler DPIs for both the combination treatment groups and the separate treatment groups (BUD/FF - Symbicort® Turbuhaler®/Oxis Turbuhaler®, BUD - Pulmicort Turbuhaler®, all AstraZeneca). In the Zetterström and colleagues trial,[240] metered (ex-actuator) doses are reported for the separate inhalers and BUD monotherapy arms, and delivered (ex-valve) doses are reported for the single inhaler. This reflects changes in labelling for newer inhaled drugs which require the delivered dose rather than the metered dose to be reported. An inhalation of BUD/FF 160µg/4.5µg from the single inhaler (Symbicort® Turbuhaler®, AstraZeneca) delivers the same quantity as a 200µg metered inhalation of BUD (Pulmicort Turbuhaler®, AstraZeneca) and a 4.5µg metered inhalation of FF from separate inhalers.

The treatment duration was six months in one study[246] and 12 weeks in the second study.[240] Zetterström and colleagues[240] aimed to compare the then new BUD/FF combination inhaler with the two drugs administered in separate inhalers, and with BUD alone. Rosenhall and colleagues[246] also aimed to compare the single inhaler with treatment administered via separate inhalers, but the focus in this study was more on the longer term safety (as well as efficacy) of the single inhaler, particularly in terms of health-related quality of life.

The ages of the participants in the trials ranged from 18 to 81 years, with a mean age of approximately 45 years in both studies. Patients in both trials had previously received ICS therapy and remained symptomatic. Previous treatment was approximately 700µg/d[246] and 950µg/d[240] of ICS in the two trials. The severity of asthma was not specifically stated in either trial, but was likely to be comparable across the studies based on previous ICS therapy. Baseline FEV_1 % predicted was around 94% in one trial,[246] and 74% in the other trial.[240]

Rosenhall and colleagues[246] reported safety (adverse events) as their primary outcome measure, whilst Zetterström and colleagues[240] reported change in morning PEFR as the primary outcome.

The quality of reporting and methodology of the included RCTs was mixed. In the Zetterström and colleagues trial[240] the method of randomisation was reported and assessed as being adequate, and the method used to conceal allocation to groups was also adequate. In the Rosenhall and colleagues trial,[246] details of the randomisation procedure and concealment of allocation were unknown. The analysis was reported to be by intention-to-treat principle in both trials.

TABLE 40 *Characteristics of studies (BUD/FF vs BUD+FF)*

Study ID	Design	Intervention	Patients	Outcomes
Rosenhall et al (2002)[246]	RCT Multi-centre Parallel-group Open-label	1. BUD/FF 160/4.5µg 2 puffs b.i.d. ex-actuator (daily total 640/18µg) 2. BUD+FF 160µg + 4.5µg 2 puffs b.i.d. ex-actuator (daily total 640µg +18µg) *Delivery device:* 1. DPI (Symbicort® Turbuhaler®, AstraZeneca) 2. DPI (Pulmicort Turbuhaler® + Oxis Turbuhaler®, AstraZeneca) *Duration:* 6 mths *Run in period:* Not reported	*Number randomised* 586 *Mean (years) age (range)* 1. 45.2 (18-81) 2. 44.4 (18-78) *Baseline FEV_1 % predicted (range)* 1. 94.1 (37-149) 2. 95.4 (50-155) *Previous ICS treatment (drug and dose)* ICS 400-1200µg/day	*Primary outcome* Adverse events *Secondary outcome* FEV_1 FVC Adverse events Exacerbations HRQOL/symptoms

Study ID	Design	Intervention	Patients	Outcomes
Zetterström et al (2001)[240]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. BUD/FF 160/4.5µg* 2 puffs b.i.d. (daily total 640/18µg) 2. BUD+FF 200µg† + 4.5µg 2 puffs b.i.d. (daily total 800µg + 18 µg) 3. BUD 200µg† 2 puffs b.i.d. (daily total 800µg) ** ex-actuator* † ex-valve Only groups 1 & 2 reported here *Delivery device:* 1. DPI (Symbicort® Turbuhaler®, AstraZeneca) 2,3. DPI (Pulmicort Turbuhaler®, AstraZeneca*) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 362 *Mean (years) age (range)* 1. 46.7 (18-78) 2. 44.7 (18-77) 3. 48.5 (21-78) *Baseline FEV_1 % predicted* 1. 73.6 2. 74.7 3. 73.1 *Previous ICS treatment (drug and dose)* ICS ≥ 500µg/day	*Outcomes* PEFR (am & pm) FEV_1 (L) FVC Day time & night-time symptom score Symptom-free days Night-time awakenings Asthma control days Use of rescue medication Adverse events Exacerbations

* not stated explicitly, but deduced from the text

5.2.6.3.2 Results

Lung function

Differences in the way in which measures of lung function were reported by the two trials meant that combining data in a meta-analysis was not possible.

Only limited data on FEV_1 were reported in the trials. Zetterström and colleagues[240] reported a mean FEV_1 of 2.28 L at baseline and 2.47 L at end point in the BUD/FF group (a change of 0.19 L), compared to 2.33 L at baseline and 2.50 L at end point (a change of 0.17 L) in the separate BUD+FF arm, with no statistically significant difference between groups (p>0.05). Rosenhall and colleagues did not report the data at end point but stated that mean FEV_1 increased approximately 5-6% compared with baseline in both the combination inhaler and separate inhaler treatment groups.

Data on change in morning and evening PEFR was reported by one study.[240] Change from baseline in morning PEFR was 35.7 (95% CI 28.4 - 43.0) L/min in the BUD/FF single inhaler group, and 32.0 (95% CI 24.5 - 39.4) L/min in the BUD+FF separate inhaler group. These differences were not statistically significant (p>0.05). Similarly, change from baseline in evening PEFR was 24.8 (95% CI 18.2 - 31.4) L/min and 22.3 (95% CI 15.5 - 29.0) L/min in the single inhaler and separate inhaler groups respectively. Again, this difference was not statistically significant (p>0.05).

Symptoms / health-related quality of life

Only the Zetterström and colleagues trial[240] reported data on symptoms.

The mean change from baseline in percentage of symptom-free days was 25.0% in the BUD/FF single inhaler group compared to 22.3% in the BUD+FF separate inhaler group. The difference was not statistically significant (p>0.05). Daytime and night-time asthma symptoms were recorded using a 4-point rating scale (0=none, 3=severe, no reference supplied), and these were combined to give a total asthma symptom score (0-6). Asthma symptoms were shown to reduce in both groups with a change from baseline of -0.52 vs -0.44 for BUD/FF combination and separate BUD+FF respectively. Again, there was no statistically significant difference between treatment groups.

Rosenhall and colleagues[246] did not report specifically on symptoms, but did report data on health related quality of life using the Mini Asthma Quality of Life Questionnaire (MiniAQLQ). The MiniAQLQ consists of four domains: symptoms, activity limitations, emotional function and environmental stimuli and is scored from 0 to 7 (0=severe asthma problems, 7=mild/no problems, reference supplied). The scores were presented as the change from baseline to the average of the values at weeks 13 and 26 (end point). Improvements were seen in both groups. For the BUD/FF single inhaler group, the mean change from baseline total MiniAQLQ score was 0.48 compared to 0.45 for patients in the BUD+FF separate inhaler group. There was no statistically significant difference between groups (no *p* value given).

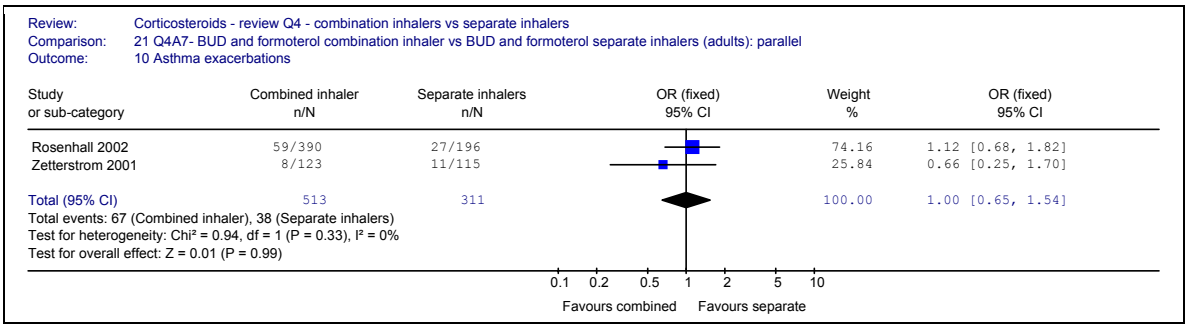
Use of rescue medication

The mean reduction from baseline in the use of terbutaline sulphate or salbutamol rescue medication (number of puffs per day) was similar in both treatment groups in the Zetterström and colleagues trial (-0.99 vs -1.13 for BUD/FF and BUD+FF respectively, $p>0.05$).[240]

Exacerbations

Sufficient data on numbers of serious adverse events were reported in the two trials to be combined in a meta-analysis (*Figure 19*). However, it should be noted that in the Rosenhall and colleagues trial,[246] an exacerbation was defined as the need for oral corticosteroids, and the authors did not describe the severity of the exacerbations. In the Zetterström and colleagues trial,[240] a severe asthma exacerbation was defined as the need for oral steroids, discontinuation due to worsening of asthma, or PEFR <70% of the run-in mean on two consecutive days. In addition, the duration of treatment was different in the two studies and these factors will need to be considered when interpreting the results of the meta-analysis. The fixed-effect pooled odds ratio was 1.00 [95% CI 0.65, 1.54] suggesting no statistically significant difference between the combination treatment and the separate treatment (p=0.33). Heterogeneity was not statistically significant ($p=0.33$, $I^2=0\%$).

FIGURE 19 *Asthma exacerbations, BUD/FF versus BUD+FF*

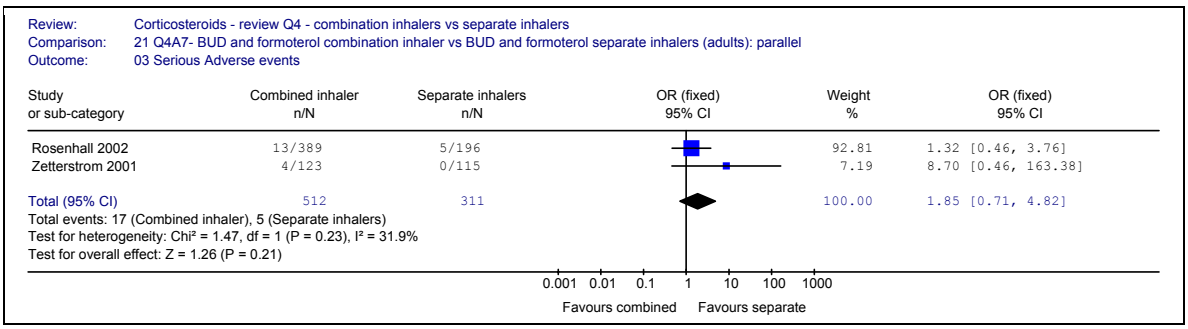


Adverse events

Neither trial reported the total number of adverse events experienced by each treatment group. In the Rosenhall and colleagues trial,[246] at least one adverse event was reported by 77% of patients treated with the combination inhaler compared to 69% treated with the separate inhalers. Zetterström and colleagues[240] reported that the number, nature and intensity of adverse events was similar across groups.

Sufficient data on numbers of serious adverse events were reported in the two trials to be combined in a meta-analysis (*Figure 20*). The duration of treatment was different in the two studies and this will need to be considered when interpreting the results of the meta-analysis. The fixed-effect pooled odds ratio was 1.85 [95% CI 0.71, 4.82] suggesting no statistically significant difference between the two treatments (p=0.21). Heterogeneity was not statistically significant (p=0.23, I^2=31.9%).

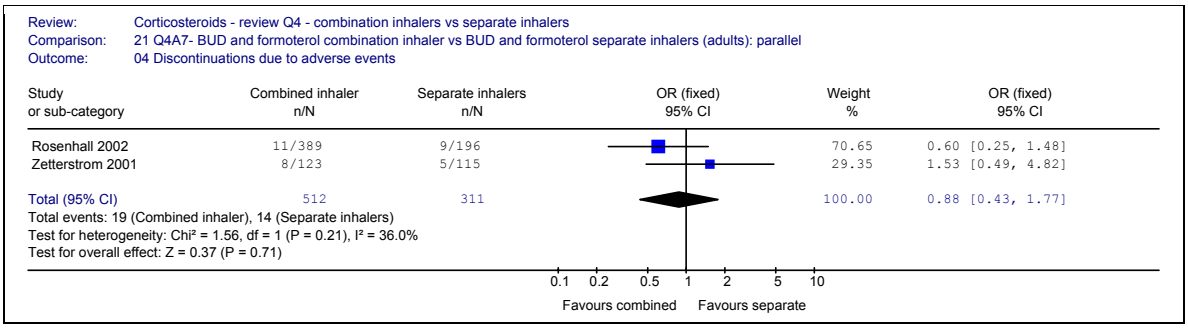
FIGURE 20 *Serious adverse events, BUD/FF versus BUD+FF*



Data on discontinuations due to adverse events were also reported in the two trials and combined in a meta-analysis (*Figure 21*). The fixed-effects pooled odds ratio was 0.88 [95%

CI 0.43, 1.77] similarly suggesting no statistically significant difference between treatments (p=0.71). Heterogeneity was not statistically significant (p=0.21, I^2=36.0%).

FIGURE 21 *Discontinuations due to adverse events, BUD/FF versus BUD+FF*



5.2.6.3.3 Summary

Two parallel-group RCTs compared BUD and FF in a combination inhaler with the the same doses of the drugs used in separate inhalers. No statistically significant differences were observed in measures of lung function. Similarly, where reported, there were no differences between the two treatment groups on measures of symptoms or health-related quality of life. Furthermore, the adverse event profiles of the two treatments were also found to be comparable, with no statistically significant differences between them for serious adverse events, and discontinutations due to adverse events.

5.2.6.4 Summary of Q4 – ICS+LABA in combination vs separate inhalers

Three RCTs compared the FP/SAL combination inhaler against the two drugs delivered in separate inhalers. Two compared BUD and FF combination inhaler against the two drugs in separate inhalers. One compared FP/SAL combination inhaler against BUD+FF in separate inhalers. There were very few statistically significant differences between the treatments across the various efficacy outcomes. For some outcomes (e.g. lung function) non-inferiority was demonstrated. Meta-analysis of adverse events found no statistically significant differences in adverse events, serious adverse events and discontinuations in adverse events. The following tables provide a visual illustration of the results of pair-wise comparisons.

FP/SAL in a combination inhaler vs. BUD+FF in separate inhalers n=1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
500/100µg vs. 1600+24µg	Ringdal 12w parallel group DPI n=428	*FP/SAL comb*	NSD	C			C				C	+	91 events
		BUD+FF sep											78 events

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

FP/SAL in a combination inhaler vs FP+SAL in separate inhalers n= 3 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
	Meta-analysis Aubier, Chapman	*FP/SAL comb*											NSD
		FP+SAL sep											
1000/100µg vs. 1000+100µg	Aubier 28w parallel group DPI n=503	*FP/SAL comb*	NSD	NSD NID	NSD		NSD	NSD					
		FP+SAL sep											
200/100µg vs. 200+100µg	Bateman 12w parallel group DPI n=244	*FP/SAL comb*	C	NSD	NSD								
		FP+SAL sep											

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
500/100µg vs. 500+100µg	Chapman 28w parallel group DPI n=371	*FP/SAL comb*	NSD	NSD NID	+								
		FP+SAL sep											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported; NID=non-inferiority demonstrated. Blank cells signify no data reported on that outcome.

BUD/FF in a combination inhaler vs BUD+FF in separate inhalers n= 2 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800/18µg vs. 800+18µg	Rosenhall 26w parallel group open label DPI n=586	*BUD/FF comb*	C							NSD			77%
		BUD+FF sep											69%
	Zetterström 12w parallel group DPI n=362	*BUD/FF comb*	NSD	NSD	NSD		NSD		NSD		NSD		C
		BUD+FF sep											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies)

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

5.2.7 Review question 5 – Combination inhaler compared to combination inhaler

To re-cap, three RCTs compared the two combination inhalers head-to-head (*Table 41*). The following sub-section describes the characteristics and results of these trials.

TABLE 41 *Breakdown of studies for Review Question 5 – combination inhaler vs combination inhaler*

Pair-wise comparison	Number of RCTs included
FP/SAL (combination) vs BUD/FF (combination)	3
Total	3

5.2.7.1 BUD / FF vs FP / SAL

5.2.7.1.1 Study Characteristics

Three large, parallel-group RCTs compared the use of BUD/FF, delivered via a Turbohaler DPI, with FP/SAL, delivered via a Diskus DPI (*Table 42*). There were 706 patients in the 52-week trial by FitzGerald and colleagues,[247] and 2143 in the 52-week trial by Vogelmeier and colleagues.[248] The RCT by Aalbers and colleagues[249] included 658 patients. For the first four weeks of treatment, patients in the BUD/FF AMD group did not adjust their dose. Aalbers and colleagues[249] combined the results for this period for the AMD and FD BUD/FF groups. Following this double-blind month, there was a six month open-label extension during which patients were treated in the original three randomised groups i.e. FD BUD/FF, AMD BUD/FF or FD FP/SAL. Only data from the six-month extension phase will be discussed here, since these are the only data available for the three randomised groups.

The studies by FitzGerald and colleagues[247] and Vogelmeier and colleagues[248] were two-arm trials. However, Aalbers and colleagues[249] reported a three-arm trial comparing the FP/SAL arm with either fixed dose (FD) or adjustable maintenance dose (AMD) of BUD/FF. The studies all used the same standard doses of 250µg FP and 50µg SAL, delivered twice a day. Patients in this arm of the study by Vogelmeier and colleagues[248] could have the dose titrated up or down to improve control, and were also given salbutamol as required. Those in this arm of the study by FitzGerald and colleagues[247] were also required to take two doses of placebo via a Turbohaler twice a day. The standard doses of BUD/FF in the trials by

Vogelmeier and colleagues[248] and Aalbers and colleagues[249] were 320µg BUD and 9µg FF ex-actuator, delivered twice a day. Patients in the Vogelmeier study[248] could have their doses titrated up or down to improve control, plus additional inhalations for relief as needed. Doses for the third arm of the Aalbers and colleagues[249] study were adjustable to 160-640µg BUD and 4.5-18µg FF ex- actuator twice daily. The study by FitzGerald and colleagues[247] started with a higher dose of 400µg BUD plus 12µg FF ex valve twice a day, but these doses were halved after four weeks and subsequently adjusted according to self-management plans. Patients in this study arm were also required to take a placebo via a Diskus DPI twice a day (BUD/FF -Seretide® Diskus®, GlaxoSmithKline; FP/SAL - Symbicort® Turbuhaler®, AstraZeneca for all studies).

The aim of the trial by Vogelmeier and colleagues[248] was to compare the effectiveness of BUD/FF for maintenance (plus as-needed medication) with FP/SAL plus salbutamol as rescue medication. Aalbers and colleagues[249] investigated whether asthma control improved if patients adjusted the maintenance dose of BUD/FF according to asthma severity, compared with traditional fixed dosing regimens of either this combination or FP/SAL. Only comparisons between FP/SAL and either dosing regimen of BUD/FF will be included here; comparisons between FD and AMD BUD/FF will not be discussed in any detail. The aim of the FitzGerald study[247] was to compare the efficacy of stable dosing of FP/SAL with adjustable maintenance dosing of BUD/FF.

Patients were of similar mean ages across the trials (44-46 years), with age ranges of 12-84/85 reported by two trials[248;249] and a standard deviation of 14 years reported by FitzGerald and colleagues.[247] None of the included studies commented on the severity of asthma in the RCTs' populations, but all studies reported mean baseline FEV_1 values as a percentage of the predicted normal value. In the trial by Aalbers and colleagues,[249] the mean baseline FEV_1 was 84% of the predicted normal value. This was slightly lower in the study by FitzGerald and colleagues,[247] who reported a mean baseline FEV_1 value of 81% of the predicted normal value. Mean baseline FEV_1 was lowest in the patients enrolled into the study by Vogelmeier and colleagues[248] (73%). This suggests mild to moderate asthma, according to guidelines.

At entry to the study by Aalbers and colleagues,[249] 73% of all randomised patients already used LABAs or combinations of these with ICS. All of the patients in the study by FitzGerald and colleagues[247] had used either an ICS at a dose equivalent to 200-500µg BDP per day,

combined with a LABA, or an ICS alone at a dose equivalent to >500–1000µg BDP per day for at least 12 weeks before enrolment. Patients were eligible for inclusion in the study by Vogelmeier and colleagues[248] if they had used at least 500µg BUD or FP per day, or at least 1000µg per day of another ICS for at least a month before study entry.

The primary outcomes were different for the three included RCTs. Aalbers and colleagues[249] used the odds of having a well controlled asthma week, defined as: no night awakenings; no exacerbations; no change in treatment due to adverse effects; and at least two other criteria relating to asthma score of >1 on fewer than two days, fewer than two days or four instances of use of relief medication, and morning PEFR rate higher than 80% of predicted value every day. FitzGerald and colleagues reported the mean percentage of symptom-free days as the primary outcome measure, and Vogelmeier and colleagues[248] used time to first severe exacerbation.

All three studies reported adequate methods of randomisation and concealment of allocation to treatment groups. Two of the studies[247;248] were double-blind, but the study by Aalbers and colleagues[249] was open-label after an initial month of double-blind treatment. Analysis of outcome data by Aalbers and colleagues[249] was on an ITT basis, but the studies by FitzGerald and colleagues[247] and by Vogelmeier and colleagues[248] excluded small numbers of randomised patients from efficacy analyses.

TABLE 42 *Characteristics of studies comparing BUD/FF with FP/SAL*

Study ID	Design	Intervention	Patients	Outcomes
Aalbers et al (2004)[249]	RCT Multi-centre Parallel-group Double blind Double-dummy Open-extension	1. BUD/FF FD160/4.5µg* 2 puffs b.i.d. (daily total 800/24µg) 2. BUD/FF AMD *160/4.5µg* 2 puffs b.i.d. (daily total 800/24µg - adjustable to 1puff b.i.d. at end of double-blind – up to 4 puffs b.i.d. in open extension period for 7-14 days if needed)* 3. FP/SAL 250/50µg b.i.d. (daily total 500/100µg) * ex-actuator *Delivery device:* 1, 2. DPI (Symbicort® Turbuhaler®, AstraZeneca) 3. DPI (Seretide® Diskus®, GlaxoSmithKline) *Duration:* 1 mth (double-blind) + 6 mths (open-label) *Run in period:* 10-14 days	*Number randomised* 658 *Mean (years) age (range)* 46 (12-85) *Baseline FEV_1 % predicted* 84% -85% *Previous ICS treatment (drug and dose)* BUD 500-1200µg (with or without beta^2-agonist)	*Primary outcome* 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 ≤2d ≤2d with reliever use ≤4 reliever uses AM PEFR ≥80% of predicted every day *Secondary outcome* PEFR (am & pm) 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 AM PEFR ≥80% of predicted every day Exacerbations (oral steroids for ≥3d, ER visits and/or hospitalisation)

Study ID	Design	Intervention	Patients	Outcomes
FitzGerald et al. (2005)[247]	RCT Multi-centre Parallel-group Double blind Double-dummy	*1. BUD/FF AMD 200/6µg† 2 puffs b.i.d. (daily total 800/24µg - adjustable to 1puff b.i.d. after 4wks – up to 4 puffs b.i.d. for 7-14 days if needed) +1 puff b.i.d. placebo* 2. FP/SAL 250/50µg 1 puff b.i.d. (daily total 500/ 100µg) + 2 puffs placebo b.i.d. † ex-valve *Delivery device:* 1. DPI (Symbicort®, Turbuhaler®, AstraZeneca) + placebo Diskus 2. DPI (Seretide® Diskus®, GlaxoSmithKline*) + placebo Turbuhaler *Duration:* 52 wks *Run in period:* 2 wks	*Number randomised* 706 *Mean (years) age (±sd)* *1. 44 (± 14)* *2. 46 (± 14)* *Baseline FEV_1% predicted (±sd)* *1. 81 (± 13)* *2. 82 (± 21)* *Previous ICS treatment (drug and dose)* ≈200-500µg/day BDP + LABA or ICS dose equivalent to >500–1000µg/day BDP	*Primary outcome* Mean % of symptom-free days (over 24hr period) on daily record card *Secondary outcome* % rescue-free days Daily rescue medication use Daily asthma symptom score % nights awoken due to asthma Mean morning PEFR % well controlled asthma weeks Incidence of asthma exacerbations (hospital treatment or oral corticosteroids, either in the opinion of the investigator or based on a morning PEFR <70% of the mean of the last 7 days in weeks 1 through 4 for >2 consecutive days) Adverse events Compliance

Study ID	Design	Intervention	Patients	Outcomes
Vogelmeier et al 2005[248]	RCT Multi-centre Parallel-group Open-label	*1. BUD/FF 160/4.5 µg* x 2 puffs b.i.d. (daily total 800/24µg - titrated up to 4 puffs or down to 2 puffs to improve control + plus additional inhalations for relief as needed)* *2. FP/SAL 250/50µg b.i.d. (daily total 500/100µg - titrated up or down to 100/ 50µg b.i.d to improve control + salbutamol relief)* ** ex-actuator* *Delivery device:* 1. DPI (Symbicort®, Turbuhaler®, AstraZeneca) 2. DPI (Seretide® Diskus®, GlaxoSmithKline) *Duration:* 52 wks *Run in period:* 2 wks	*Number randomised* 2143 *Mean (years) age (range)* 45 (12-84) *Baseline FEV_1 % predicted (range)* 73 (28 -115 across groups) *Previous ICS treatment (drug and dose)* ≥ 500µg/day BUD or FP or ≥ 1000µg/day for another ICS (and LABA, if appropriate)	*Primary outcome* 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 outcome* Pre and post terbutaline FEV_1 As needed medication use Symptoms (Asthma Control Questionnaire ACQ-5) HRQOL (Asthma Quality of Life Questionnaire AQLQ(S)) Adverse events Severe exacerbations (no. of days with exacerbations & days with oral steroids)

* not stated explicitly, but deduced from the text

5.2.7.1.2 Results

Lung function

Aalbers and colleagues[249] reported mean change from baseline in morning PEFR as a secondary outcome measure. FEV_1 was only reported for the first month of the study, which was not fully randomised, so will not be discussed here. Changes in morning PEFR were estimated from a graph. Mean values changed by 27.5L/min in the BUD/FF AMD group, by 34L/min in the BUD/FF FD group, and by 35L/min in group the FP/SAL group. The study reported no statistically significant differences between the three treatment groups. Aalbers and colleagues also reported that evening PEFR was significantly lower in the BUD/FF AMD group compared with both FD groups. The mean difference between the BUD/FF AMD group and the FP/SAL group was 8.4L/min (95%CI 0.7, 16.1; $p<0.05$).

FitzGerald and colleagues[247] reported morning PEFR, but not FEV_1, as measures of lung function. The average morning PEFR at end-point was 395 L/min (SD 104) in the FP/SAL group and 390 L/min (SD 100) in the BUD/FF group. FitzGerald and colleagues[247] then adjusted these values using ANCOVA to allow for treatment, baseline, group country, sex and age. The resulting values (400.1 L/min for the FP/SAL group and 390.6 L/min for the BUD/FF group) were statistically significantly different (p=0.006).

Vogelmeier and colleagues[248] measured lung function using pre- and post-terbutaline FEV_1 changes from baseline, but did not report morning or evening PEFR. There was a statistically significant difference between the two treatment groups for both pre- and post-terbutaline FEV_1 mean change from baseline. Adjusted mean change from baseline pre-terbutaline FEV_1 was 0.17L in the BUD/FF group and 0.14L in the FP/SAL group (p=0.066). For the post-terbutaline FEV_1 mean change from baseline, values of 0.07L and 0.04L were reported for the BUD/FF group and the FP/SAL group, respectively (p=0.045).

Symptoms

Aalbers and colleagues[249] measured asthma symptoms using daytime symptom score and number of nocturnal awakenings. Nocturnal awakenings were reported by 12.5% of the BUD/FF AMD group, 19.5% of the BUD/FF FD group, and 16% of the FP/SAL group.

Significance values were not reported for the differences between the BUD/FF groups and the FP/SAL group. Data were not reported for asthma symptom scores, but were described as being comparable between groups during the open-label phase.

Patients in the study by FitzGerald and colleagues[247] recorded daily asthma symptom scores on a daily record card, from which mean percentage of symptom-free days was calculated. They also reported the percentage of nights at end-point in which patients were awoken due to asthma. The mean daily asthma scores at end-point were 0.8 (SD 0.8) in the FP/SAL group and 0.9 (SD 0.8) in the BUD/FF group; no p value was reported. The median percentage of symptom-free days at end-point was 58.8 (IQR 1.5, 90.6) in the FP/SAL group and 52.1 (IQR 0, 83.5) in the BUD/FF group. The difference between the two groups was statistically significant (p=0.034). There was no statistically significant difference between the two groups in terms of median percentage of nighttime awakenings (p=NS). Patients in the FP/SAL group were awakened by their asthma symptoms 1.1% of the nights (IQR 0, 6.3), compared with 1.4% of the nights in the BUD/FF group (IQR 0, 6.3).

Asthma symptoms were recorded on the Asthma Control Questionnaire (ACQ-5) by patients in the study by Vogelmeier and colleagues.[248] The questionnaire has five questions on the burden of symptoms, and each question is scored on a scale of 0 to 6 (where 0=no symptoms). There was no statistically significant difference between the two treatment groups in mean adjusted change from baseline in overall ACQ-5 score, although both groups reported a slight mean decrease (i.e. an improvement in symptoms). Patients in the BUD/FF group had a mean decrease of 0.64 points, compared with a mean decrease of 0.58 in the FP/SAL group (p=0.069). Vogelmeier and colleagues[248] considered these changes to be clinically relevant (references cited).

Health related quality of life

Health related quality of life was only reported by Vogelmeier and colleagues,[248] who used the Asthma Quality of Life Questionnaire (AQLQ(S)). The questionnaire consists of 32 questions, each of which is scored on a scale of 1-7 (7=least impairment) and then summed to give the total. Vogelmeier and colleagues[248] reported that a change in AQLQ(S) overall score of at least 0.5 is considered to be clinically relevant (references cited). Both treatment groups had a mean adjusted change from baseline in AQLQ(S) score which indicated a

clinically significant improvement in quality of life. The BUD/FF group had a mean increase of 0.60 points, compared with a mean increase of 0.57 points in the FP/SAL group (p=0.51).

Use of rescue medication

Aalbers and colleagues[249] did not report use of rescue medication. FitzGerald and colleagues[247] reported daily rescue medication use as the median daily puffs of salbutamol per day. The FP/SAL had a median of 0.11 puffs per day (IQR 0.02, 0.43), which was statistically significantly lower than the 0.18 puffs taken by the BUD/FF group (IQR 0.04, 0.59; p=0.006). Vogelmeier and colleagues[248] reported the percentage of patients requiring either up to four or more than four inhalations of rescue medication in the last two weeks of the study, but they did not report mean number of puffs per day.

Exacerbations

All three studies reported the rates of asthma exacerbations experienced by the patients in their trials. Aalbers and colleagues[249] defined an exacerbation as an event requiring three or more days of oral steroids, an emergency room (ER) visit and/or hospitalisation. The rates of exacerbations per month were 0.024 in the BUD/FF AMD group, 0.036 in the BUD/FF FD group and 0.041 in the FP/SAL group. The rate reduction between the BUD/FF AMD group and the FP/SAL group was 39.7% (95% CI 8.3, 60.3%; p=0.018).

FitzGerald and colleagues[247] defined asthma exacerbations as deterioration requiring hospital treatment or treatment with oral corticosteroids, either in the opinion of the investigator or based on a morning PEFR that was <70% of the mean of the last seven days (during the first four weeks), for more than two consecutive days. The adjusted annual mean exacerbation rate was statistically significantly lower in the FP/SAL group than in the BUD/FF group (0.18 vs. 0.33; p=0.008).

Vogelmeier and colleagues[248] defined a severe exacerbation as a deterioration requiring hospitalisation or ER treatment, oral steroids for at least three days, or an unscheduled visit leading to treatment change. The annual exacerbation rate per patient was 0.24 for the BUD/FF group and 0.31 for the FP/SAL group (p=0.0025). Excluding unscheduled clinic visits, the annual exacerbation rate per patient was slightly lower, at 0.19 for the BUD/FF group and 0.23 for the FP/SAL group (p=0.0023).Vogelmeier and colleagues[248] also reported

the annual rate of severe exacerbations due to ER visits/hospitalisations per patient, which was 0.04 in the BUD/FF group and 0.05 in the FP/SAL group (p=0.38).

Adverse events

The studies by Aalbers and colleagues[249] and Fitzgerald and colleagues[247] reported data on rate of adverse events, which were pooled for meta-analysis using a fixed-effects model (*Figure 22*). The two trials show small differences in direction of effect, and statistical tests indicate that heterogeneity is significant for this outcome measure (χ^2=5.33, p=0.07; I^2 = 62.5%). A random-effects model was also used to pool the trials, but resulted in the same χ^2 and I^2 values. The trials were of different length (seven months vs. one year), which could have an effect on the results. The odds ratio from the pooled results was 1.09 (95% CI 0.87, 1.36; p=0.45) using the fixed-effects model and 1.18 (95% CI 0.80, 0.73; p=0.41) using the random-effects model. This suggests that there is no statistically significant difference between the two drug regimens, in terms of rate of adverse effects, but the studies' heterogeneity suggests that this result should be interpreted with caution.

FIGURE 22 *Rate of adverse events*

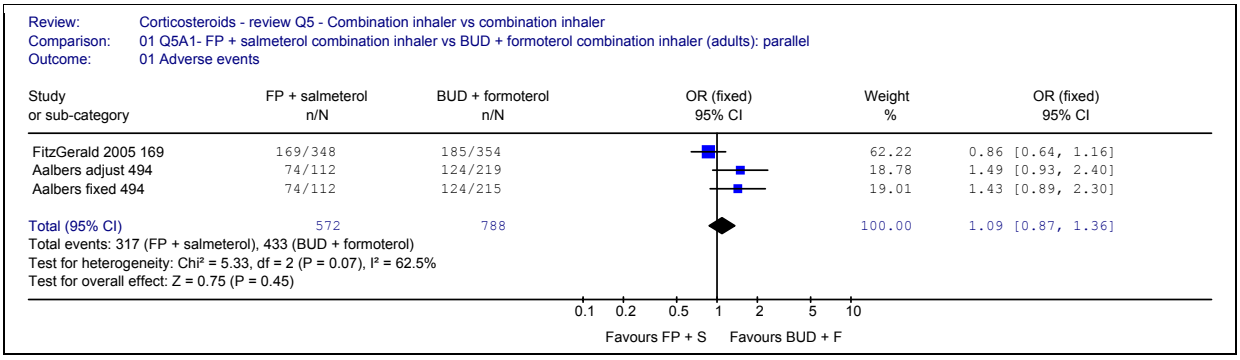
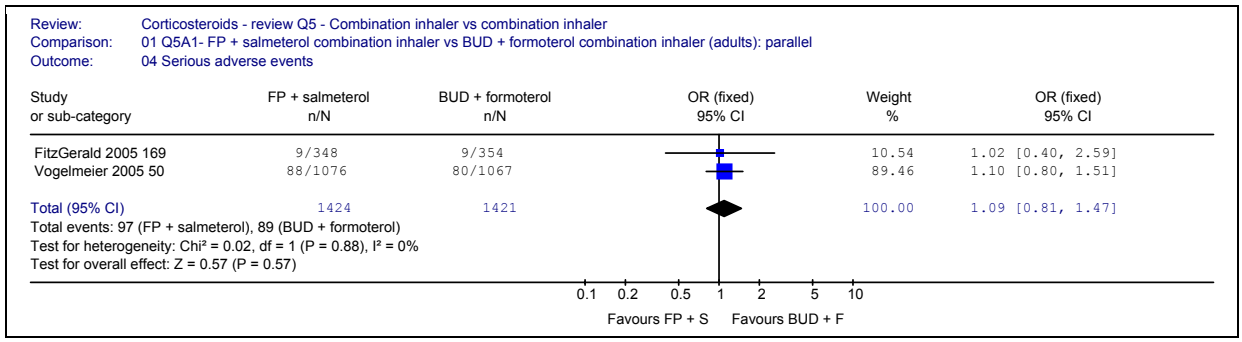


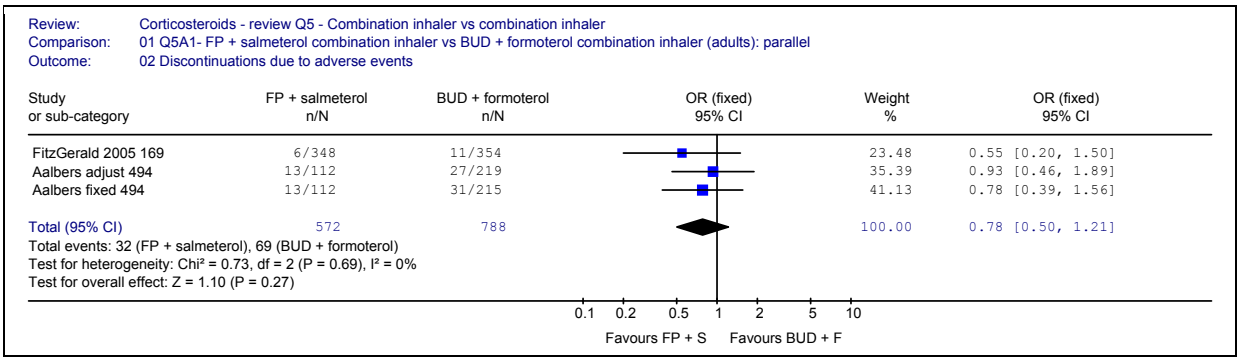
FIGURE 23 *Rate of serious adverse events*



The studies by FitzGerald and colleagues[247] and Vogelmeier and colleagues[248] reported rates of serious adverse events. These were pooled for meta-analysis using a fixed-effects model (*Figure 23*). Statistical tests indicated that there was no significant heterogeneity (χ^2=0.02, p=0.88; I^2 = 0%). Although the pooled results slightly favour BUD/FF, the odds ratio was 1.09 (95% CI 0.81, 1.47) and there was no statistically significant difference between the two treatments (p=0.57).

The studies by FitzGerald and colleagues[247] and Aalbers and colleagues[249] reported rate of withdrawals due to adverse events, and these were pooled using a fixed-effects model (*Figure 24*). Statistical tests did not indicate any significant heterogeneity (χ^2=0.73, p=0.69; I^2 = 0%). Both of the studies indicated a slightly higher rate of withdrawals due to adverse events in the BUD/FF arms, and the overall treatment effect favours FP/SAL for this outcome, with an odds ratio of 0.78 (95% CI 0.50, 1.21). However, the difference between the two treatment arms was not found to be statistically significant (p=0.27).

FIGURE 24 *Rate of withdrawals due to adverse events*



5.2.7.1.3 Summary

Three large, parallel-group RCTs compared the use of fixed or adjustable dose BUD/FF, delivered via a Turbohaler DPI, with fixed or adjustable dose FP/SAL, delivered via a Diskus DPI. Daily doses were approximately 800µg BUD, 24µg FF, 500µg FP and 100µg SAL. The studies were generally of good methodological quality, but lack of ITT analysis in the two of the studies,[247;248] and lack of blinding in the six-month extension period of the other trial[249] may have allowed some bias to affect results. The trials tended to show conflicting results for the drug comparisons, suggesting that the two drug combinations are probably of similar efficacy.

There were mixed results for measures of lung function. Aalbers and colleagues[249] reported no statistically significant difference between the three treatment groups in morning PEFR change from baseline value. However, evening PEFR was significantly lower in the BUD/FF AMD group compared with the FP/SAL group. FitzGerald and colleagues[247] reported similar average morning PEFR values in both treatment groups, but found that values were statistically significantly higher in the FP/SAL group after adjusting for various factors. By contrast, Vogelmeier and colleagues[248] reported statistically significantly higher mean change from baseline FEV_1 in the BUD/FF group.

The three trials reported conflicting effects in terms of asthma symptoms. One study reported that daily symptom scores were similar in the treatment arms, and another found no statistically significant difference between the groups in ACQ-5 score. By contrast, the third study found that the median percentage of symptom-free days was statistically significantly higher in the FP/SAL group. Patients in the BUD/FF groups tended to require more rescue medication than those in the FP/SAL groups. The rate of asthma exacerbations per month

was statistically significantly lower in the BUD/FF AMD groups than in the FP SAL group in two trials. However, the adjusted annual mean exacerbation rate was statistically significantly lower in the FP/SAL group than in the BUD/FF group in the third trial. Results pooled for meta-analyses indicated that there were no significant differences between the treatment groups in rates of adverse events, serious adverse events or withdrawals due to adverse events.

5.2.7.2 Summary of Q5 – Combination inhaler compared to combination inhaler

Three RCTs compared the two combination inhalers head to head. Results were mixed, with the FP/SAL combination significantly superior on some outcomes, and BUD/FF combination superior on others. Meta-analysis found that there were no significant differences between the treatment groups in rates of adverse events, serious adverse events or withdrawals due to adverse events

BUD/FF vs FP/SAL both in combination inhalers, n=3 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
	Meta-analysis Aalbers Fitzgerald	*BUD/FF*											NSD
		FP/SAL											

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS				
800/18µg vs. 500/100µg	Aalbers 4w/26w parallel group double blind/open ext DPI n=658	*1. BUD/FF*		NSD					C				
		2. BUD/FF AMD			+ 2 vs. 1 2 vs. 3	F 2 vs. 1 2 vs. 3						+ 2 vs. 3	
		3. FP/SAL				F 3 vs. 1							
	Fitzgerald 52w parallel group DPI n=706	*BUD/FF*				NSD	+						
		FP/SAL		+							+	+	
	Vogelmeier 52w parallel group DPI n=2143	*BUD/FF*	+						NSD	NSD		+	
		FP/SAL											

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies) ; AMD = adjustable maintenance dosing.

NSD = no significant difference between trial arms; + indicates results favour this trial arm; N number of events; C=results appear to be comparable between treatment groups, but no tests of statistical significance reported; F=results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.

5.2.8 Related systematic reviews

5.2.8.1 Cochrane systematic reviews

Five Cochrane systematic reviews[54;168-171] evaluating various ICS treatments for chronic asthma in adults and children were identified in searches. The reviews were published between 2000 and 2006 and are briefly described individually below.

It is important to note that these reviews had slightly different inclusion criteria to the current assessment (e.g. when comparing ICS and LABA to ICS alone, the former could be delivered in separate inhalers as well as combination inhalers). Further, the reviews include studies of adults and children under the age of 12, although there were comparatively few studies of children. Their results are provided here as context within which to interpret the results of the current assessment.

Adams and colleagues[168] – FP versus BDP or BUD

This review[168] evaluated the effectiveness and safety of three ICS - FP was compared with either BDP or BUD. The review was first published in Issue 1, 2001 and was last updated in May 2005 (searches up to January 2005). The review included prospective RCTs of parallel or cross-over design in both adults and children (>2 years) with chronic asthma. The interventions included any dose of FP compared to any dose of BDP or BUD, with a treatment period of one week or longer.

The review found 57 studies which met the inclusion criteria, involving a total of 12,614 participants. Fourteen of the studies were in children, with the remaining studies conducted in adolescents and adults. The asthma severity of the participants in the trials varied from mild (8 studies), mild to moderate (12 studies), moderate (12 studies), moderate to severe (16 studies), severe (6 studies), and mild to severe (2 studies), with severity being unclear in one trial. In the majority of studies, some or all of the participants were using regular ICS at the time of enrolment.

Results

Dose ratio 1:2

FP resulted in a significantly greater absolute FEV_1 compared to BDP/BUD (mean difference 0.09 litres, 95% CI 0.03 to 0.15 litres). However, when reported as change from baseline, there was no significant difference between groups (mean difference 0.01 litres, 95% CI -0.02 to 0.05 litres). Similarly, there was no significant difference between groups in absolute FEV_1 % predicted (mean difference 0.50%, 95% CI -1.28 to 2.28%) or change from baseline FEV_1 % predicted (mean difference -1.04%, 95% CI -3.55 to 1.47%).

Treatment with FP led to a significantly greater morning PEFR compared to BDP/BUD (mean difference 9.32 L/min, 95% CI 5.96 to 12.69 L/min), but not evening PEFR (mean difference 4.67 L/min, 95% CI -1.36 to 10.7 L/min). When reported as change from baseline, there was no significant difference between groups (mean difference 1.68 L/min, 95% CI -1.93 to 5.29 L/min).

Symptoms and rescue medication use were widely reported but differences in the reporting of these outcomes precluded the pooling of data for meta-analysis. The review only reported on specific adverse events, and data on morning plasma cortisol and 24-hour urinary cortisol was limited. No significant differences were observed between FP and BDP/BUD for trial withdrawals (OR 0.76, 95% CI 0.53 to 1.09, 12 studies), or in the likelihood of experiencing an asthma exacerbation (OR 0.75, 95% CI 0.52 to 1.08, 3 studies).

Dose ratio 1:1

A significant difference in absolute FEV_1 was found in favour of FP (mean difference 0.09 litres, 95% CI 0.02 to 0.17 litres). However, when reported as change from baseline, there was no significant difference between groups (mean difference 0.04 litres, 95% CI -0.03 to 0.11 litres).

Morning PEFR was significantly better with FP compared with BDP (mean difference 8.78 L/min, 95% CI 5.14 to 12.41 L/min). Evening PEFR was also significantly better with FP (mean difference 6.37 L/min, 95% CI 2.75 to 9.99 L/min).

Treatment with FP resulted in a significant reduction in the odds of an asthma exacerbation (OR 0.77, 95% CI 0.59 to 0.99, 4 studies). However, when a random-effects model was applied to the meta-analysis due to study heterogeneity, the difference became insignificant. No significant differences were observed between FP and BDP/BUD for trial withdrawals (OR 0.72, 95% CI 0.38 to 1.35, 5 studies). Differences in the reporting of measures of symptoms and rescue medication use meant that only limited studies could be included in a meta-analysis. There was no significant difference between groups in the proportion of symptom-free days (3 studies), day time or night-time score (2 studies), the number of participants experiencing symptom-free days or nights (2 studies), or the use of rescue medication use (2 studies).

Lasserson and colleagues[171] – FP versus HFA-BDP for chronic asthma in adults and children

This review[171] aimed to determine the efficacy of FP compared to HFA-BDP. The review was first published in Issue 4, 2005 and was last updated in January 2006 (searches up to January 2006). The review included RCTs of parallel or cross-over design in both adults and children with chronic asthma. The interventions included CFC- or HFA-FP compared to HFA-BDP.

The review found eight studies which met the inclusion criteria, involving a total of 1,260 participants. Only one of the studies was conducted in children. The HFA-BDP used in all the studies was extra fine, and all the studies had a nominal dose ratio of 1:1. Treatment duration ranged from 3 to 12 weeks. The majority of participants were adults with baseline symptoms and lung function indicating moderate asthma.

Results

Parallel trials

No significant difference in change in FEV_1 was observed between the HFA-BDP and FP groups (WMD 0.04 litres, 95% CI -0.03 to 0.11). Similarly, no significant difference was observed in change from baseline in morning PEFR (WMD -2.31 L/min, 95% CI -12.53 to 7.91).

Differences in the way data were reported meant that meta-analysis was not undertaken for most of the other outcome measures. Individual studies reported no significant differences between treatment groups for symptom scores, health-related quality of life, nor asthma exacerbations. Whilst three trials found no difference in the use of rescue medication (reported in various ways), one trial reported a significant difference in the medians which favoured FP (0.28 vs 0 puffs/day, p=0.04). No significant difference was found in the rate of any adverse event (RR 0.88, 95% CI 0.72 to 1.08).

Cross-over trials

Of the three RCTs of cross-over design, one was a fully published paper and two were conference abstracts only. Therefore, there is limited data to report in this category.

One trial reported no significant difference between FP and HFA-BDP in FEV_1 % predicted or morning PEFR. One trial also reported in the text that there were no differences between treatment groups in FEV_1 or morning PEFR but did not present any data. The third study did not indicate whether reported FEV_1 data were significantly different.

The trials in this category did not report any data on symptoms, quality of life, rescue medication use, asthma exacerbations or withdrawals.

Ni Chroinin and colleagues[170] – LABAs versus placebo in addition to ICS in children and adults with chronic asthma

This review[170] assessed the effectiveness and safety of adding a LABA to ICS compared to ICS alone. The review was first published in Issue 4, 2005 and was last updated in June 2005 (searches up to April 2004). The review included RCTs of parallel or cross-over design in both adults and children (>2 years) with chronic asthma who had previously received ICS therapy. The interventions included a LABA (SAL or FF) or placebo administered daily for at least 30 days, added to ICS (e.g. FP, BDP, BUD, triamcinolone acetonide). The dose of ICS had to be the same in both the LABA and ICS alone groups.

The review included 26 studies involving 8,147 participants which met the inclusion criteria and provided data in sufficient detail. Eight of the studies were in children, with the remaining studies conducted in adolescents and adults. LABA was added to BUD in seven trials, to

BDP in three trials, to BDP or BUD in one trial, to FP in four trials, with the ICS being unspecified in 11 studies. Most of the studies used separate inhaler devices for ICS and LABA (n=19), and study duration was ≤4 months in most trials. Participants in the majority of trials had inadequate asthma control, and the severity of asthma was mild (n=8 trials) or moderate (n=18 trials). In adult studies, the mean age of participants ranged from 35 to 48 years, whilst in children the mean age ranged from 8.5 to 14 years.

Results

Compared to ICS alone, the addition of LABA to ICS provided significantly greater improvement in change from baseline FEV_1 (WMD 0.170 litres, 95% CI 0.11 to 0.24 litres) and change in FEV_1 % predicted (WMD 2.79%, 95% CI 1.89 to 3.69%). Similarly, treatment with ICS+LABA led to a significantly greater improvement in change from baseline in morning PEFR (WMD 23.28 L/min, 95% CI 18.38 to 28.18 L/min) and evening PEFR (WMD 21.33 L/min, 95% CI 14.53 to 28.12 L/min).

Use of ICS+LABA significantly reduced day time symptoms (SMD -0.34, 95% CI -0.44 to -0.23, 5 studies), night-time symptoms (SMD -0.18, 95% CI -0.31 to -0.05, 2 studies), and overall 24-hour symptoms (SMD -0.28, 95% CI -0.45 to -0.11, 2 studies). The addition of LABA was also significantly more favourable in terms of change from baseline in symptom-free days (WMD 17.21%, 95% CI 12.06 to 22.36%, 6 studies) and symptom-free nights (SMD 0.51, 95% CI 0.28 to 0.74, 4 studies). There were no significant differences between groups in change in percentage of nights with no awakenings or in night-time awakenings.

The addition of LABA to ICS significantly reduced the need for rescue-medication use in terms of the change in overall 24-hour use (WMD -0.81 puffs/day, 95% CI -1.17 to -0.44, 8 studies). The addition of LABA also significantly reduced the risk of asthma exacerbations requiring systemic steroids by 19% (RR 0.81, 95% CI 0.73 to 0.90, 17 studies). There was no group difference in the risk of overall adverse events (RR 0.98, 95% CI 0.92 to 1.05, 11 studies), serious adverse events (RR 1.16, 95% CI 0.30 to 4.42, 4 studies) or withdrawals due to adverse events (RR 1.29, 95% CI 0.96 to 1.75, 23 studies).

Adams and colleagues[54] – BDP versus BUD for chronic asthma

This review assessed clinical outcomes in studies which compared BDP with BUD delivered at the same nominal daily dose. The review was published in Issue 1, 2000 and was last updated in November 1999 (searches up to 1999, month not specified). The review included RCTs of either parallel-group or cross-over design. Studies were eligible for inclusion if they included adults or children over two years old with chronic asthma. The drugs could be delivered by different devices (pMDI, MDI+spacer, DPI), and there does not appear to have been any restriction on the length of treatment period.

The review found 24 studies (5 parallel-group and 19 cross-over trials) published between 1982 and 1988 which met the inclusion criteria. Four of these were only available in abstract form and did not report any outcome data. Two of the citations were not assessed for the review as they required translation. Eighteen of the studies were conducted in adults, and six studies were in children, with a total of 1174 participants in the included trials. The level of asthma control at randomisation was not well described in the majority of studies, and asthma severity at baseline was not well documented. One study stated that patients had asthma of moderate severity, one described patients as having fairly severe asthma, and two reported severe asthma. In 20 of the studies, patients were not previous regular users of oral corticosteroids (OCS). In three of the studies, prior OCS use was an inclusion criterion, and a proportion of patients in another trial had received OCS treatment at the time of enrolment. Twelve studies lasted from two to four weeks, ten treated patients from six to 12 weeks, and one study treated patients for two years. One of the studies had a complex trial design with treatment periods of variable length. Only two of the cross-over trials had a washout period. The majority of trials assessed daily doses of 400µg/day (n=10) or 800µg/day (n=7), although one study assessed doses of 200µg/day and two studies used higher doses of 1500-1600µg/day. An MDI device was used to deliver both drugs in eight of the studies, but the other 16 used different delivery devices for each drug.

Results

Meta-analysis by Adams and colleagues[54] found no statistically significant differences between BDP and BUD for any of the outcome measures relevant to the present review. Results were presented separately for cross-over trials with no prior OCS, parallel-group

trials, and cross-over trials with prior OCS. Comparisons reported below were for BDP vs. BUD.

FEV_1 was reported by six cross-over studies of people with no prior OCS and two parallel-group studies. The weighted mean difference was -0.08L[-0.27, 0.12] in the cross-over studies of people with no prior OCS and -0.02 [-0.23, 0.20] in the parallel-group studies. FEV_1 predicted was also reported by two cross-over studies of people with no prior OCS (WMD -5.04L[-11.98, 1.89]). Morning and evening PEFR reported in diary cards also showed no statistically significant difference between the two drugs. The pooled cross-over trials where patients had no prior OCS had a WMD of -2.99L/min [-28.43, 22.45] for morning PEFR (six trials) and -5.47L/min [-31.50, 20.56] for the five trials reporting evening PEFR. Similar, non-statistically significant differences were observed in three cross-over trials whose patients had previously received OCS. Corresponding analysis for one parallel-group RCT found a WMD of -18.00 L/min [-54.76, 18.76] for morning PEFR and -8.00 L/min [-49.29, 33.29] for evening PEFR.

The studies reported asthma symptoms using a range of measures, and no significant differences between treatments were reported for any of these measures. Meta-analysis of daily symptom score in five studies found no statistically significant difference between BDP and BUD (SMD 0.08 [95% CI -0.22, 0.39]). Similarly, use of rescue medication was not reported to differ statistically significantly between the two drugs. Adverse events were not pooled due to lack of clear reporting in the original trials. One parallel-group study reported a relative risk of 1.76 (BDP vs. BUD) for withdrawal due to an asthma exacerbation (95% CI 0.44, 7.10).

Greenstone and colleagues[169] – Combination of LABA and ICS vs. higher dose ICS in children and adults with persistent asthma

This review assessed clinical outcomes in studies which compared combination treatment of twice daily LABA and ICS against use of a higher dose of ICS. The review was published in Issue 4, 2005 and was last updated in July 2005 (searches up to April 2004). The review included RCTs of adults or children over two years old with chronic asthma, with a minimum duration of 30 days' treatment.

The review found 42 studies published as 26 full-text papers and 16 abstracts, 13 of which provided insufficient data to be included in the meta-analysis. One of the trials had two intervention groups compared to a control group, and these were analysed as separate trials, so the review was therefore based on data from 30 trials with a total of 9509 participants. One trial was a cross-over study, and the rest were of parallel-group design. The majority of trials (n=27) were based on adult participants, and three of the studies focussed on children. Participants' asthma was generally of moderate severity, and was inadequately controlled at baseline in all but two of the studies. Patients were required to have used ICS for at least one to three months before entry to all but one of the trials.

SAL was used as the LABA in 24 of the trials, with FF being used in the other eight trials. Standard doses of LABA were used in the majority of trials (n=27). Most of the trials (n=25) used the same ICS in both the LABA and control groups; 11 used CFC-BDP; four used BUD and ten FP. Three trials compared FP and LABA to CFC-BDP, BUD or HFA-BDP. One study compared the combination of LABA and the patients' usual ICS to additional FP in the higher ICS study arm, and one study compared BUD and LABA to FP. The median ICS dose in the combined LABA group was 400µg/day (range 200-1000µg/day) and 1000µg/day (range 400-2000µg/day) in the higher ICS dose group. ICS and LABA drugs were delivered via separate devices in 22 trials, but eight trials used a single device to deliver the drugs. Most of the trials lasted for 12 or 24 weeks (n=14, n=9), with others lasting four weeks (n=1), six weeks (n=1), 52 weeks (n=3) or 54 weeks (n=1).

Results

The review's main outcome measure was the risk of exacerbation requiring systemic corticosteroids, and this was reported by 15 of the trials. Pooled data gave a relative risk of 0.88 (95% CI 0.77, 1.02), with no significant group difference (RD=2% [95% CI 0% to 4%). Although the similarity between treatments did not meet Greenstone and colleagues'[169] *a priori* definition of equivalence, the upper confidence interval was reported to exclude the likelihood of a higher rate of exacerbations in patients who received LABA. Planned subgroup analyses found no effect of age group (children vs. adult), average baseline severity, type of LABA, ICS dose difference between groups, ICS dose associated with LABA, and trial duration. However, meta-regression of 13 trials found two independent

variables which significantly reduced the risk of exacerbation (low ICS dose used in combination with LABA [*p*=0.046] and trial duration of 24 weeks or less [*p*=0.01]).

Lung function showed a statistically significantly greater improvement in the combination LABA and ICS groups than in the high dose ICS group. Using pooled data from nine trials, the weighted mean difference in FEV_1 at end-point was 0.13 L (p5% CI 0.08, 0.19). Similarly, change from baseline FEV_1 showed a WMD of 0.10L (95% CI 0.07, 0.12; n=7 trials) and FEV_1 % predicted at end-point had a WMD of 3.93% (95% CI 1.33, 6.53; n= 4 trials). The WMDs for morning and evening PEFR at end-point were 27.33L/min (95% CI 21.39, 33.26; n=14 trials) and 20.18L/min (95% CI 12.75, 27.62; n=3 trials), respectively.

Patients treated with a combination of ICS and LABA had statistically significantly better changes from baseline total asthma symptom scores. Data from five trials were pooled, giving a SMD of -0.23 (95% CI -0.41, -0.05). The percent of symptom-free days at end-point also favoured combination therapy in pooled analysis of eight trials (WMD=11.9%, 95% CI 7.37, 16.44). Change in rescue inhalations over 24 hours favoured the combination treatment group (ICS+LABA) over the high dose ICS group. Data from eight trials were pooled to give a SMD of -0.22 (95% CI -0.29, -0.14). There were no statistically significant differences between the groups in daytime symptoms at end-point, nighttime symptoms, percentage of symptom-free days at end-point, change from baseline in nighttime awakenings, and QoL as measured by the Juniper Questionnaire. There were no group differences in overall side effects (RR=0.93 (95%CI 0.84, 1.03]; n=15 trials), serious adverse events (RR=1.54 [95% CI 0.72, 3.21]; n=5 trials) or withdrawals due to adverse events (RR=0.94 [95% CI 0.71, 1.24]; n=18).

5.2.8.2 Other systematic reviews

Two systematic reviews evaluating ICS treatments for chronic asthma in adults and adolescents (>12 years) were identified, published in 1999[250] and 2004.[251]

Kankaanranta and colleagues[251] aimed to systematically review the evidence that supports different treatment options for asthma, including increasing the dose of ICS, and the use of add-on therapy options such as a LABA, leukotriene antagonist or theophylline. Jarvis and Faulds[250] evaluated the therapeutic efficacy of FP at doses ≤500 µg/day, and included comparisons with placebo, non-steroidal, anti-inflammatory agents, other ICS drugs (BDP,

BUD, flunisolide and triamcinolone acetonide), and combination with SAL. Hence both reviews evaluated therapeutic options which are not relevant to the current assessment, and it should be noted that the description of the methodology and results which follow are only those which are applicable here.

Kankaanranta and colleagues[251] included 14 blinded RCTs with either parallel group or cross-over designs, whilst Jarvis and Faulds[250] included double-blind, parallel group RCTs, but did not specify the study design in the search criteria and so other study types may have been included. In addition, the authors stated that 'large, well-controlled trials with appropriate statistical methodology were preferred', and it is not clear whether smaller trials were excluded. The number of studies included which are relevant to our review was approximately 36, but this is not clear. The number of participants was not reported in either review. Participants included in the reviews were adults or adolescents (one review[251] defined adolescents as >12 years) with mild to moderate asthma[250] or asthma that was inadequately controlled with ICS[251] (results are reported for patients with mild, and moderate to severe asthma).

Neither of the reviews described their methodology in any detail. Details of procedures such as study selection, validity assessment and data extraction were not reported by either review, and assessment of publication bias was not carried out in one review[251] and not reported in the other review.[250] Heterogeneity between studies was partially described by Kankaanranta and colleagues,[251] but not by Jarvis and Faulds.[250] Both reviews were narrative and neither included a meta-analysis. The quality of the reviews was mixed. Kankaanranta and colleagues[251] clearly stated their research question, defined the search strategy and the inclusion/exclusion criteria, and reported the number and type of included studies. Jarvis and Faulds[250] were not clear in stating their research question, used only limited key words in their search strategy, did not clearly specify the inclusion/exclusion criteria, and were ambiguous in their reporting of the number and type of studies included in the assessment.

A brief summary of the main findings of each of the reviews are outlined below.

Results

Kankaanranta and colleagues review main findings:[251]

- In patients with moderate to severe asthma, addition of FF was superior to the increase in steroid dose in increasing FEV_1 and morning PEFR, and was equal or superior to the four-fold increase in ICS in reducing day- or night-time symptom scores or rescue medication use.
- In patients with moderate to severe asthma, addition of SAL was superior to the two- to four-fold increase in the dose of ICS in increasing FEV_1 and mean morning PEFR, improving symptom scores and reducing the need for rescue medication. However, a statistically significant difference was not always reached.
- A four-fold increase in the dose of BUD reduced severe and mild asthma exacerbations, as did the addition of FF to the lower dose of BUD. Addition of FF to BUD in patients with mild asthma significantly reduced the risk of the first asthma exacerbation and severe exacerbations.

Jarvis and Faulds review main findings:[250]

- In one study, morning PEFR and FEV_1 increased significantly in patients receiving FP (88µg or 220µg twice daily) compared with those receiving BDP (168µg twice daily). The increase in rescue medication-free days was significantly greater with BDP compared with FP in one study, but there was no statistical differences in the frequency of as-needed salbutamol usage between the two groups.
- Mean improvement in morning and/or evening PEFR in patients with FP, were similar or greater than in those receiving BUD; morning PEFR was significantly greater with FP than with BUD in two studies. There was no statistically significant difference in the frequency of as-needed rescue-medication usage between groups. In one study, treatment with FP resulted in a significant improvement in symptom-free days and nights, and rescue medication-free days and nights compared with BUD.
- There were no statistically significant differences in FEV_1 or morning PEFR in patients treated with FP+SAL in separate delivery devices compared with FP/SAL combined in the same delivery device in the two identified studies.

Summary

The review by Kankaanranta and colleagues[251] found that addition of a LABA was more effective than increasing the dose of ICS in improving asthma control. However, they reported that increasing the ICS dose was likely to be of small magnitude. The review by Jarvis and Faulds[250] found that FP was at least as effective as other ICS (BDP and BUD) administered at twice the FP dosage. The addition of inhaled SAL to FP allowed the use of lower maintenance doses of FP, and was well tolerated.

6. Economic analyses

SECTION CONTENTS

6.1 Purpose of this chapter

The purpose of this chapter is to:

1. Summarise existing published economic evaluations that are relevant to the decision problems specified in the project scope and protocol (section 6.2).

2. Summarise the industry-submitted economic evaluations provided as part of the NICE appraisal process, with particular focus on critically appraising those that are relevant to the decision problems specified in the project scope (section 6.3).

3. Describe the methods and results of the new economic evaluation(s), cost comparisons and other economic information which have been generated to try and help the NICE Appraisal Committee to consider the 'value for money' implications for the NHS of alternative guidance on the use of corticosteroids in adults with asthma (section 6.5)

Additionally, in section 6.4, we outline and justify the approach we have taken to assessing the cost-effectiveness or, more broadly - given the lack of clear evidence of differential effectiveness for all but one of the cost-effectiveness research questions - the 'value for money' to the NHS of the alternative asthma treatments evaluated. In this section we also explain why we have not presented a comprehensive model-based cost-utility analysis in the main body of the report (although, for the purpose of exploring uncertainty, we present a shortened version in an Appendix for one of the research questions). Finally, in section 6.5 we attempt to provide an overview of the economic evidence from the different analyses, and comment on any consistent or conflicting findings.

6.2 Systematic review of published economic evaluations

A systematic review of existing published economic evaluations was undertaken.

The aims of this systematic review were to (i) identify and critically appraise any high quality economic evaluations of the same (or very similar) decision problems to those specified in the NICE appraisal scope, and which are from an NHS or UK societal perspective, and (ii) gain some insights into the key 'trade-offs' or relationships between resources, costs and health outcomes in assessing the treatment of asthma, in order to inform our own economic analyses.

6.2.1 Search Strategy and Critical Appraisal Methods

Ten electronic daatabases including MEDLINE, EMBASE and the Cochrane Library (Issue 1, 2006) were searched for cost-effectiveness studies that assessed the cost-effectiveness of BDP, BUD, FP dipropionate, CIC and MF used alone or in combination with a LABA (SAL or FF) within their licensed indications and the appropriate step of the BTS/SIGN Guidelines.[1] The full search strategy is shown in *Appendix 3*. The original searches were conducted in April 2006 with updated searches in October 2006.

A total of 723 titles and abstracts were screened for inclusion in the review. This included studies that were potentially relevant to the present assessment, and also those relevant to the related technology assessment project on the clinical effectiveness and cost-effectiveness of ICS and LABAs for the treatment of chronic asthma in children under 12.[179] Of the titles and abstracts screened, 58 were ordered as full papers and assessed in detail.

Data extraction tables were designed to capture the standard information required for critically appraising the quality of methods of economic evaluation,[252] and for judging the policy/decision relevance of each study to this assessment.

6.2.2 Inclusion and exclusion criteria

Full, published cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-consequence analyses were eligible for inclusion in the cost-effectiveness review.

6.2.3 Results

Fifty-eight full papers were assessed for inclusion in the review. Of these, 15 met the inclusion criteria and are summarised in the following sections.

6.2.3.1 Summary of the included cost-effectiveness studies

A total of 15[227;253-266] published full-text studies were judged as full economic evaluations and met our inclusion criteria and involved adults with asthma. All of the 15 studies were published after 1994. They are summarised in the following section.

Appendix 7 provides more details of the study designs, model features (where relevant) and main results of the included studies..

6.2.3.2 Study types and settings

As *Table 43* and *Table 44* show, of the 15 included studies, four[254;261;265;266] compared ICS monotherapies with each other, and the rest compared ICS plus a LABA with the same ICS as monotherapy. There were also two other studies, by Stempel and colleagues[267] and Barnes and colleagues,[268] which compared FP with BUD, which were excluded because they mixed effectiveness evidence from both children and adults with asthma, and did not report the results for adults separately. It is also worth noting that in these two economic evaluations, amongst the six trials that were in adults there was substantial heterogeneity in terms of inhaler device types, asthma severity (mild, mild/moderate, to severe), and prior ICS use (both steroid naïve and not). None of this heterogeneity was recognised in their methods of meta-analysis of average cost-effectiveness ratios across the seven trials.

There is also duplicate publication in some of the studies comparing FP with FP/SAL from the Swedish health system perspective (with the analyses by Pieters and colleagues[263] and Palmqvist and colleagues[262] and Johansson and colleagues[258] also appearing in the paper by Lundbäck and colleagues[260]). The wide variation in the comparators in different studies, both in terms of the drug types and daily dosages, is such that few meaningful comparisons can be made between studies.

Of the eleven studies which compared ICS against ICS plus LABA, all except two studies (by Johansson and colleagues, 2006,[257] and Jönsson and colleagues, 2004[259]) involved adding a LABA to the same daily dose of ICS as in the ICS monotherapy it is compared with. Given that the more realistic clinical choice when faced with a poorly controlled asthma patient already on ICS, is between either increasing their ICS dose or adding a LABA (probably to the current ICS dose), the results of these evaluations are therefore of limited clinical relevance in the current context of the BTS/SIGN Guidelines.

There were no published economic evaluations which compare CIC or MF with other ICS or ICS plus LABAs.

For completeness, we have included the three economic evaluations which we found that compared ICS with ICS plus LABAs in separate inhalers.[253;259;263]

TABLE 43 *Comparisons between each of the five ICS, and the daily dosage (µg)*

	ICS as monotherapy				
Study	**BUD**	**BDP**	**FP**	**CIC**	**MF**
Booth et al. 1995[254]	800		400		
Marchetti *et al*. 2004[261]	*For moderate asthma*				
		1000	400		
	800	1000			
		400 extra-fine	400		
	800	400 extra-fine			
	For severe asthma				
		1500	1000		
	1600	1500			
		800 extra-fine	1000		
	1600	800 extra-fine			
Steinmetz *et al*. 1998[265]	500		1200		
Venables *et al*. 1996[266]	400		400		

TABLE 44 *Comparisons between ICS plus LABAs with ICS alone, and the daily dosage (µg)*

	ICS as monotherapy					ICS with LABA in combination inhaler		ICS with LABA in separate inhalers	
Study	**BUD**	**BDP**	**FP**	**CIC**	**MF**	**BUD/FF Symbicort®**	**FP/S Seretide®**	**BUD/FF**	**FP/S**
ICS+LABA in combination inhaler vs ICS									
Briggs *et al*. 2006[255]			100				100/50		
			250				250/50		
			500				500/50		
Ericsson *et al*. 2006[256]			400			400/12			
Johansson *et al*. 2006[257]						800/24 + additional inhalations as needed	500/100 + additional inhalations as needed		
Johansson *et al*. 1999[258]			200				200/100		
Lundbäck *et al*. 1999[260]			200				200/100		
			500				500/100		
			1000						1000/100
Lundbäck *et al*. 2000[227]	1600						500/50		
Palmqvist *et al*. 1999[262]			500				500/50		
Price and Briggs, 2002[264]			200				200/100		
ICS+LABA in separate inhalers vs ICS									
Andersson *et al*. 2001[253]	200							200/24	
	800							800/24	
Jönsson *et al*. 2004[259]	200 400							200/9 400/9	
Pieters *et al*. 1999[263]			500						500/50

Of the 15 economic evaluations, 12 were cost-effectiveness analyses (CEA), one[261] was a cost-utility analysis (CUA), one[266] was a cost-minimisation analysis, and one[255] contained

both CEA and CUA results. Some of the cost-effectiveness analyses reported cost-effectiveness ratios for more than one outcome measure.

Four studies[253-255;266] were analysed from a UK perspective (UK NHS). Of these however, only one was based on patient-level clinical trial and resource use data specifically collected from UK asthma patients. One[253] was based on trials conducted in the UK, Spain, and seven other countries and analysed from a societal perspective of the UK, Spain, and Sweden. The other studies were based mainly on patients in USA, 'North America' (unspecified), or in various European countries. The common convention of reporting that patients in trials come from a stated number of 'centres' in different countries, without elaboration on whether the patients' care was mainly managed via primary care or secondary care services, also limits our ability to judge the relevance of many of these clinical and cost-effectiveness studies to the UK context.

Most studies were based on clinical effectiveness results from a single clinical trial. The two (excluded) studies by Stempel and colleagues and Barnes and colleagues, comparing BUD with FP at half the dose.[267;268]

TABLE 45 *Summary of published full-text economic evaluation studies in adults*

Author, year	Study type	Analysis type	Country, Setting	Comparators [a]	Perspective
Andersson *et al*. 2001[253]	Trial-based	CEA	UK, Spain, etc., 9 countries. Setting NR	• BUD+FF (separate inhalers) • Bud	Society (Sweden, UK, and Spain)
Booth *et al*. 1995[254]	Trial-based	CEA	UK, in 57 general practices.	• FP • BUD	UK NHS
Steinmetz *et al*. 1998[265]	Trial-based	CEA	Germany. Ambulatory or outpatient centres.	• FP • BUD	German third-party payer
Venables *et al*. 1996[266]	Trial-based	CMA	UK, in general practice. Setting NR	• BUD • FP	UK NHS
Briggs *et al*. 2006[255]	Trial & regression model-based	CEA CUA	44 countries. General practice & hospital clinics	• FP/SAL • FP	UK NHS
Ericsson *et al*. 2006[256]	Trial-based	CEA	6 countries (4 in Europe). Setting NR	• BUD/FF • FP	Healthcare payer, society, and drug budget holder, respectively
Johansson *et al*. 2006[257]	Trial-based	CEA	16 countries (10 in Europe including the UK). Setting NR	• BUD/FF • FP/SAL	Societal perspective
Johansson *et al*. 1999[258]	Trial-based	CEA	North American clinical data Setting NR	• FP/SAL • FP	Swedish healthcare system
Jönsson *et al*. 2004[259]	Trial-based	CEA	17 countries (15 in Europe). Setting NR	• BUD+FF (separate inhalers) • BUD	Both healthcare payer and society
Lundbäck *et al*. 1999[260]	Trial-based	CEA	North American and European. Setting NR	• FP+SAL (both combination and separate inhalers) • FP	Swedish healthcare system
Lundbäck *et al*. 2000[227]	Trial-based	CEA	Sweden. Setting NR	• FP/SAL • BUD	Swedish healthcare system
Marchetti *et al*. 2004[261]	Decision model based	CUA	Italy. Setting NR	• BDP • BDP-extra-fine • FP • BUD	Both the Italian healthcare system and society

Author, year	Study type	Analysis type	Country, Setting	Comparators [a]	Perspective
Palmqvist *et al*. 1999[262]	Trial-based	CEA	North American. Setting NR	• FP/SAL • FP	Swedish healthcare system
Pieters *et al.* 1999[263]	Trial-based	CEA	France, Germany and The Netherlands. Setting NR	• FP+SAL (separate inhalers) • FP	Swedish healthcare
Price and Briggs, 2002[264]	Decision model based	CEA	42 centres in the US [b]. Setting NR	• FP/SAL • FP	UK healthcare system (implied by results in £)

[a] LABA with ICS in combination inhalers, unless otherwise specified.

[b] Data from supplement of the trial by Kavuru et al. J ALLERGY CLIN IMMUNOL, 2000; 105: 1108-16[269]

Palmqvist *et al*, 1999 ,[262] Pieters *et al*, 1999 ,[263] and Johansson *et al*, 1999[258] involve duplicate publication of the cost-effectiveness comparisons reported in Lundback 1999[260]

The time horizon of the studies ranged from six weeks to one year. Discounting was applied only in one study (and for utility only; Marchetti, 2004[261]). Most of the studies were funded by pharmaceutical companies; some also involved co-authors employed by such companies.

In summary, while there are a number of economic evaluations that could be relevant to the current decision problem, the very wide variation in health system settings and study perspectives, drug comparators, dose levels, outcome measures, and model structures or trial designs and durations, makes the evidence base relatively uninformative.

6.2.3.3 Economic evaluations from a UK NHS perspective

Of the 15 economic evaluations which met the review's inclusion criteria, only four were wholly conducted from a UK NHS perspective,[254;255;264;266] and another included an analysis from the UK NHS perspective[253] (as well as from the Swedish and Spanish health systems' perspectives). All five studies were funded by and included authors affiliated with the manufacturers of the products being evaluated; there is evidence that industry-funded published cost-utility analyses are more likely to produce favourable cost-effectiveness ratios.[270]

Summary information on the comparators, analysis design and results are shown in *Table 46*. Only the most recent study by Briggs and colleagues calculated an incremental cost per QALY, and two of the studies are over a decade old.

TABLE 46 *Published economic evaluations from a UK NHS perspective*

Study	Analysis year	Recruitment/model Setting	Source of effectiveness data	Comparison, daily doses	ICER[a]
Andersson et al. 2001[253]	1999	Not reported	1 year results of a 9 country RCT ('FACET' study)	(separate inhalers) BUD 200µg/FF 24µg *vs* BUD 200µg	£2.86 per SFD
				(separate inhalers) BUD 800µg/FF 24µg *vs* BUD 800µg	£4.06 per SFD
Booth et al. 1995[254]	1995	57 general practices in the UK	UK based 8-week RCT, of people with no or low ICS	BUD 800µg vs FP 400µg	Not reported
Briggs *et al*. 2006[255]	2003/04	GP & hospital clinics	1 year results of a 44 country RCT ('GOAL' study)	Combination inhaler of FP (100 or 250 or 500µg)+S 50µg *vs* FP 100 or 250 or 500µg (previously no ICS)	£7600 per QALY (95% CI £4800 to £10,700)
				Combination inhaler of FP (100 or 250 or 500µg)/S 50µg *vs* FP 100 or 250 or 500µg (previously on low-dose ICS)	£11,000 per QALY (95% CI £8600 to £14,600)
				Combination inhaler of FP (100 or 250 or 500µg)/S 50µg *vs* FP 100 or 250 or 500µg (previously on moderate dose ICS)	£13,700 per QALY (95% CI £11,000 to £18,300)
Price & Briggs 2002[264]	2000	Trial:US treatment 'centres' Model: health system perspective	12-week efficacy and safety RCT in 42 US 'centres'	Combination inhaler of FP/S 200/50µg *vs* FP 200µg	£20.83 per successfully controlled week (95% CI £-65* to £113 per SCW)
Venables et al. 1996[266]	1996	General practices in the UK	UK based 8-week RCT, of people with no or low ICS – which showed no significant differences in any outcome	BUD 400µg vs BUD 200µg vs FP 200µg	Not reported

Study	Analysis year	Recruitment/model Setting	Source of effectiveness data	Comparison, daily doses	ICER[a]
[a]All these ICERs are undiscounted and for ICS plus LABA compared with ICS alone. * negative because FP/S dominates FP. Using same exchange rate as used in the published paper, of 1 Euro = £0.613.					

The most recent UK NHS study, by **Briggs and colleagues**[255] based on the 'GOAL' study (see clinical effectiveness review),[235] examined the cost-utility of the combination of FP/S compared with FP alone. The analysis was trial-based but used regression models of individual patient trial data to estimate costs by subgroup (three prior levels of ICS usage), to estimate the relationship between control status and costs, and to enable 'adjustment for the UK analysis using the full GOAL dataset' (p.533 of their paper). Overall, this appears to be a good quality economic analysis, and is based on a complex trial which uses innovative dose step-up rules, and which also stratifies according to prior level of ICS usage. However, limitations include a lack of detail on the different regression analyses (e.g. goodness of model fit to trial data), an unusually low cost per 'week-with-exacerbation' of £32, and insufficient details on the methods used to derive utility values from the AQLQ instrument scores. In relation to the non-medication costs, for example, it would have been useful to see both the whole trial and UK-specific numbers and rates of secondary care visits, and primary care visits in the trial arms. It is well known that because of the distinctive organisation of primary care in the UK, patterns of self-care, and urgent care-seeking from general practitioners versus hospital services are different from many other countries. The authors acknowledge this to some extent, but in combination with the very small differences in the proportion of weeks spent with exacerbations (0-1%) and given that exacerbations were not a primary or secondary outcome of the main trial,[235] this probably deserved more description.

Another good quality study comparing FP/S with F from an implicit (not stated) UK NHS perspective (**Price and Briggs**, 2002[264]) mainly emphasised the development of the five-state Markov model, but also presented both deterministic and probabilistic incremental cost-effectiveness ratios for achieving 'successfully controlled weeks' (using a multi-criteria definition of successful control encompassing symptoms, lung function and exacerbations). However, given that this study was based on a single 12-week US-based trial of FP/S combination inhaler with FP at the same dose,[236] and also did not use a more generic measure of health-related quality of life it is less relevant to the present decision problem.

The economic analysis by **Andersson and colleagues**,[253] based on the FACET clinical trial, was a cost-consequence analysis. It compared the costs of BUD with FF or BUD (at the same dose) alone, with the average annual number of symptom-free days, episode-free days, mild exacerbations and severe exacerbations. However, ICERs were only presented for symptom-free days (and these have limited meaning in the context of decision-making by NICE). This study did reveal a very different cost breakdown between the countries; in the UK the additional cost of adding FF was only partially offset by reduced costs of treating exacerbations and other medications, whereas in Sweden and Spain the treatment cost savings due to the reduced number of exacerbations were greater than the additional 'study medication' costs. This highlights the risks in generalising the results of cost-effectiveness studies in this clinical area between different national health systems.

The similar cost-effectiveness analyses by **Booth and colleagues**[254] (of FP 200µg twice daily vs BUD 400µg twice daily) and by **Venables and colleagues**[266] (of FP 200µg twice daily vs BUD 400µg once daily vs BUD 200µg twice daily), were in a treatment setting which is highly relevant to this technology review, but both are over 10 years old. As well as only reporting average cost-effectiveness ratios (cost per 'successfully treated week/day' with each treatment) they also suffer from other important methodological limitations, such as the very short time horizon of eight weeks, omitting the non-medication care costs of treating exacerbations, and not being based on randomised controlled trials.

6.2.4 Summary of evidence from published economic evaluations

In summary, only the economic evaluation by Briggs and colleagues[255] comparing FP/S with FP at various dose-levels is sufficiently recent and potentially relevant to the decision problem of this assessment. That is, it is from a UK health system perspective, involves two of the relevant comparators and expresses effectiveness in terms of health-related quality of life (and QALYs). Although there are limitations of this study (see above), the analysis appears to have been carried out, and is mostly reported, according to currently accepted standards of good practice for economic evaluations. It also usefully defines subgroups on the basis of their previous level of use of ICS. On the basis of ICER estimates ranging from £4800 to £18300 per QALY gained, they concluded that achieving optimal asthma control via a combination of FP and S would be a cost-effective use of NHS resources for people at all three levels of previous ICS usage (according to current levels of willingness to pay for a

QALY, as indicated by NICE decision-making). However, their analysis pooled effectiveness and resource use data from patients in 44 countries. Although the multivariate statistical analyses employed claims to have partly adjusted for UK-specific factors, the generalisability of the cost-effectiveness results to a UK, dominantly primary care, treatment setting may still be limited.

6.3 Review of cost-effectiveness studies provided by industry

Seven submissions to NICE included cost-effectiveness analysis. Two of these included cost-effectiveness analysis (CEA) and five included cost minimisation analysis (CMA). Submissions were made by GlaxoSmithKline, Astra-Zeneca, ALTANA Pharma, Meda Pharmaceuticals Ltd., Ivax Pharmaceuticals Ltd., and Trinity-Chiesi Pharmaceuticals Ltd. *Table 47* below shows a summary of the submissions received by industry through the appraisal process. No submissions were received for the ICS MF.

TABLE 47 *Summary of the submissions received by industry through the appraisal process*

Manufacturer	Product	Generic name	Type of inhaler device	Type of analysis
GlaxoSmithKline	Becotide® Flixotide® Seretide®	BDP FP FP/SAL	pMDI pMDI / DPI	CEA
AstraZeneca	Pulmicort® Symbicort®	BUD BUD/FF	pMDI DPI	CEA
ALTANA Pharma	Alvesco®	CIC	MDI	CMA
Ivax Pharmaceuticals Ltd	QVAR®	BDP	pMDI / MDI	CMA
Meda Pharmaceuticals Ltd.	Novolizer®	BUD	DPI	CMA
Trinity-Cheisi Pharmaceuticals Ltd	Clenil® Modulite® Pulvinal®	BDP	pMDI	CMA

Below a review of each of the manufacturers' submissions (CEA, CMA) is presented. The reviews have been assessed using a checklist suggested for critical appraisal of cost-effectiveness analyses (Drummond and colleagues, 1997[252]), and the requirements of NICE for submissions on cost-effectiveness analysis (reference case) (NICE, 2004[271] and

where appropriate a suggested guideline for good practice in model-based cost-effectiveness analysis (Philips and colleagues, 2004[272]).

6.3.1 Review of the submission by GlaxoSmithKline (GSK)

6.3.1.1 Overview

The submission by GSK to NICE includes economics commentary and cost-effectiveness analysis to support three GSK products: BDP (Becotide®), FP (Flixotide®), and FP/SAL (Seretide®).

The submission includes some commentary on the clinical equivalence of ICS products, and the presentation of some price estimates. The submission does not include any cost-effectiveness analysis for BDP and FP versus other ICS products, with a cost-minimisation approach assumed due to clinical equivalence across these products.

The submission is focused on four specific research questions, which are:

Q1: For patients taking ICS alone, is FP the most clinically effective ICS?

Q2: For patients uncontrolled on ICS alone, is switching to FP/SAL more clinically effective than remaining on the same dose or increasing the dose of ICS alone?

Q3: Where a LABA and ICS are to be co-prescribed, is FP/SAL in a combination inhaler more clinically effective than FP+SAL delivered in separate inhalers?

Q4: In patients where combination therapy is appropriate what is the relative clinical effectiveness of FP/SAL (Seretide) compared to BUD/FF (Symbicort)?

The submission presents outline detail of a systematic search of the literature on cost-effectiveness analyses for treatment of asthma, and modelling of asthma. Appendix 9 of the submission provides information on this review. The literature is deemed unhelpful for the current submission and the submission presents specific cost-effectiveness analysis, and a 'generic' cost-effectiveness model to address cost-effectiveness in the context of questions 2 to 4, but question 1 is not covered further (as above, a CMA approach is assumed).

6.3.1.2 Model on cost-effectiveness of Seretide

In the submission a new model is developed by GSK to estimate cost-effectiveness of the alternative treatment scenarios. Below we outline the approach taken for the GSK model, and provide an outline review.

The model presented is a simple two state model applying effectiveness data on the % of symptom-free days (% SFDs), cost and outcome data associated with the two health states of 'symptom-free' and 'with symptoms'. The model is essentially a spreadsheet calculation to estimate cost-effectiveness from this related data across alternative treatments. In the model, at a given point in time, patients are either (1) symptom-free, or (2) with symptoms. Death is not included in the model (due to an assumption of no differential effect of treatments). Exacerbations are not included in the model. The model is not a disease progression model, and does not involve transitions between the two health states over time. The model presents a scenario, showing occupancy of states 'conditional on treatment choice', on the basis of a meta-analysis of the %SFD at trial endpoint. This endpoint is chosen as it was (1) commonly reported and considered, (2) based on clinical opinion, (3) judged to be more appropriate than lung function for representing patients' clinical response to treatment. This reported endpoint (%SFD) was taken to represent the proportion of time spent in the symptom-free state. (p52) The effectiveness data are taken from a subset of trials reported in the industry review of clinical effectiveness.

The model is based on a range of assumptions, including the assumptions that:

- Alternative therapies have the same mortality profile, and the same toxicity profile (including long-term effects).
- The differential proportion of time patients spend in the symptom-free state over their treatment lifetime would be the same as the differential proportion observed during the trial period (even though clinical trials are mainly 12-weeks)
- Trial based data is generalisable to wider patient populations
- There is no difference in effectiveness between different inhaler devices. Here the submission cites eight clinical trials to support the assumption of the equivalence of devices (i.e. MDI versus DPI; p.10)

The submission states that the time horizon is "nominally one year, corresponding to the duration of the GOAL trial used to estimate costs and utilities." (p53) However, given the nature of the model, it is a 'snap-shot' or cross-sectional approach to estimating cost-effectiveness analysis.

The model uses health state values of 0.97 for the 'symptom-free' health state, and 0.85 for the 'with symptoms' health state, a utility decrement of 0.12. These values are cited from the CEA study for the GOAL RCT reported by Briggs and colleagues (2006).[255] However, this study does not provide information on the methods used for estimating utility weights, citing a personal communication only, for a study mapping AQLQ to EQ-5D. The model works by placing proportions of patients (or patient time) in each health state, according to the effectiveness data, and calculating QALY differences as the product of these data [e.g. a 12.29% difference in % SFDs (low dose FP/SAL versus FP 200µg/day), results in a difference in QALYs between treatments of 0.014748].

Costs are comprised of the mean acquisition costs for products and an estimate of the annual mean 'other health service' costs for symptom-free time and time with symptoms. This latter 'other' cost excludes primary treatment costs. The cost estimates used for the health states are based on data from the GOAL clinical trial, which are comprised of resource use against secondary care visits, primary care visits and rescue medication used. The submission uses a linear regression model to estimate a mean annual cost, which is £79.83 for the health state 'with symptoms' and £1.57 for 'symptom-free'. The cost differences between alternatives are as per the above example for QALY differences, with estimated difference in costs for strategies multiplied by the percentage difference in SFDs.

The model is developed for use in both adult and child patient groups, and is arranged around 21 specific cost-effectiveness questions (5 for children, 16 for adults). All costs are reported as UK (£) sterling 2006.

6.3.1.3 Model / Cost-effectiveness Results

The cost-effectiveness analysis is arranged around the comparison of FP/SAL (at low, medium and high dose) to (i) ICS alone (at low, medium and high dose), (ii) ICS plus LABA in separate inhalers (at low, medium and high dose, and (iii) BUD/FF (at low, medium and high dose. The submission reports results for different product costs, and an average product

cost, therefore the analysis results in approx. 65 different summary statistics. These are summarised below:

FP/SAL versus ICS alone:-

- Low dose: FP/SAL 200µg/100µg per day versus FP 200 µg/day, results in small differences in incremental cost and QALYs, with an ICER range of £6,350 - £20,151
- Medium dose: FP/SAL 500µg/100µg versus FP 400/500µg/day, results in small differences in incremental cost and QALYs, with an ICER range of £12,100 - £24,020
- High dose: FP/SAL 1000µg/100µg versus FP 1000µg/day, results in small differences in incremental cost and QALYs, with an ICER range of £3,660 - £50,017
- Low dose versus medium dose: FP/SAL 200µg/100µg/day versus FP 400-500µg/day, results in small differences in incremental cost and QALYs, with 'FP/SAL dominant' in some instances; an ICER range of £51 - £15,997 in other cases.
- Medium dose versus high dose: FP/SAL 500µg/100µg/day versus FP 1000µg/day, results in small differences in incremental cost and QALYs, with an ICER range of 'FP/SAL dominance' to £14,567 per QALY.

FP/SAL combination versus ICS+LABA in separate components:-

- Low dose: FP/SAL 200µg/100µg/day versus separate inhalers 200µg+100µg/day (and BUD+SAL – 400µg/day), analysis shows FP/SAL as less costly (range -£80 to -£281), but with a small loss in utility (-0.0047), resulting in estimates for separates at ICERs of £16,519 to £59,442.
- Medium dose: FP/SAL combination 500µg/100µg/day versus separate inhalers 400-500µg+100µg/day (and also compared to BUD+SAL 800-1000µg/day) analysis shows FP/SAL as less costly (range -£62 to -£219), with a small utility gain (0.0044), resulting in a profile for FP/SAL combination inhaler dominating separates (comparators).
- High dose: FP/SAL combination 1000µg/100µg/day versus separate inhalers 1000µg+100µg/day (and also compared to BUD+SAL 1600-2000µg/day), results showed a varied cost profile (range -£343 to +128), and a small utility loss for FP/SAL combination (-0.0005), with separates (comparators) dominating combination therapy in some cases

(where seretide has increased cost) and in other cases the separate products having a very high ICER in excess of £166,000 per QALY.

FP/SAL (Seretide) versus BUD/FF (Symbicort):-

In these analyses CEA is only undertaken for one of the scenarios, with the submission stating 'data not available' for the other scenarios/analyses. Cost savings are estimated for those scenarios without CEA:

- Low dose: FP/SAL 200µg/100µg/day versus BUD/FF 400µg/100µg/day: No CEA - (estimated cost-saving; -£22 to -£183)
- Low dose: FP/SAL 200µg/100µg versus BUD/FF 400µg/200µg/day: No CEA - (estimated cost; -£11 to + £149)
- Medium dose versus high dose: FP/SAL 500µg/100µg/day versus BUD/FF 800µg/100µg/day: No CEA - (estimated cost-saving; -£357)
- Medium dose versus low dose: FP/SAL 500µg/100µg/day versus BUD/FF 800µg/200µg/day: CEA – FP/SAL stated to dominate BUD/FF (small cost saving, and very small utility gain (0.0005))
- Medium dose versus low dose: FP/SAL MD 500µg/100µg/day versus BUD/FF 800µg/400µg/day: No CEA - (estimated cost-saving; -£18)
- High dose versus low dose: fluticaseone/SAL 1000µg/100µg/day versus BUD/FF 1600µg/200µg: No CEA - (estimated cost-saving; -£164 to -£427)
- High dose versus low dose: FP/SAL 1000µg/100µg/day versus BUD/FF 1600µg/400µg/day: NoCEA - (estimated cost-saving;-£168 to -£431)

A number of factors are taken into account in the analysis (e.g. dose, price) resulting in a range of cost-effectiveness results. The TAR team suggest that policy makers should take note of the specific inputs for analysis and consider the interpretation of results. For example, where FP/SAL is said to be dominant when compared to BUD/FF this is based on a very small QALY gain (0.0005).

6.3.1.4 Appraisal of the cost-effectiveness analysis undertaken

TABLE 48 *Critical appraisal checklist of economic evaluation by GSK*

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	4 clinical questions stated (3 of which covered in CEA)
Is there a clear description of alternatives?	Yes	FP/SAL versus comparators (various options stated)
Has the correct patient group / population of interest been clearly stated?	Partial	
Is the correct comparator used?	Yes	Other comparators could also be appropriate
Is the study type reasonable?	Yes	CEA model used (CUA results presented).
Is the perspective of the analysis clearly stated?	Yes	Perspective stated as UK NHS
Is the perspective employed appropriate?	Partial Cost: Yes Outcomes: Partial	Submission appears to adopt a UK NHS and PSS perspective for costs (consistent with NICE reference case). Perspective on outcomes is that of the patient, but not all effects are considered.
Is effectiveness of the intervention established?	Yes	The CEA is based on clinical effectiveness data from a small number of trials reporting the chosen economic endpoint (%SFDs) – mainly over 12-weeks. Whilst the study demonstrates effectiveness over this one endpoint it does not discuss, in context of CEA, the other effectiveness endpoints across treatments. Study assumes differences seen in trials can be generalised to the lifetime treatment period.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	No	Nominal 1-year time horizon used (not lifetime) ICERS are based on 1-year cost and QALY differences.
Are the costs and consequences consistent with the perspective employed? *	Partial	Costs appear to be consistent with perspective employed, but limited information/justification provided.
Is differential timing considered?	No	Nominal 1-year time frame used.
Is incremental analysis performed?	Yes	

Is sensitivity analysis undertaken and presented clearly?	Yes	Yes sensitivity analysis is undertaken, probabilistic analysis. No scenario analyses undertaken to consider different mean input parameters.
* More on data inputs for costs and consequences in the review of modelling methods below		

TABLE 49 *NICE reference case requirements – GSK submission*

NICE reference case requirement		**Reviewer comment**
Decision problem: As per the scope developed by NICE (esp. technologies & patient group)	Partial	
Comparator: Alternative therapies routinely used in the UK NHS	Yes	
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	No	Only symptom-free days were used to consider QALY values
Type of economic evaluation: Cost-effectiveness analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Unclear	Method for estimating health state utilities is unclear
Method of preference elicitation for health state values: Choice-based method (e.g. TTO, SG, not rating scale).	Unclear	Method of preference elicitation is not reported
Source of preference data: Representative sample of the UK public	Unclear	
Discount rate: 3.5% pa for costs and health effects	NA	
N/A=not applicable		

6.3.1.5 Review of modelling approach

6.3.1.5.1 Model structure / structural assumptions

The model structure is based around the clinical endpoint of difference in the percentage of symptom-free days, and this is assumed, in the submission, to be a reasonable reflection of relative treatment effectiveness. This may not be the case, with it reflecting only part of the effectiveness profile of asthma treatments. Other important elements of asthma control include night time disturbances (and data presented in the submission indicates differences between SFNs may be smaller than % SFDs), lung function and exacerbations. The model

presented does not capture these items (at least directly). The model structure used is said to be based on the CEA for the GOAL clinical trial presented by Briggs and colleagues (2006),[255] however, the model differs from the approach of Briggs and colleagues in a number of ways (e.g. importantly Briggs and colleagues use patient level data to derive transition probabilities, their study uses a composite measure of asthma control, and their study captures exacerbations). The GSK model estimates of cost-effectiveness are simple spreadsheet calculations combining data on % SFDs and data estimated for relative costs and QALYs for patients in the health states used. The model uses a two-state approach covering time in a symptom-free state, and time with symptoms. This is a simplification of the disease process for asthma, and is said to be driven by the availability of data for comparative purposes, and on a review of the general literature on modelling asthma treatment. However, it may be that the endpoint chosen is more favourable for comparison of FP/SAL (Seretide) with other alternative strategies. For example, the effect of FP/SAL will be more immediate on SFDs than it will be from ICS alone (where impact will be felt over time). No discussion of other outcomes, in the context of the CEA, is provided in the discussing of model structure. Although there is brief coverage over the potential use of lung function as an alternative approach.

When considering the above points it is important to acknowledge that the literature on modelling cost-effectiveness in asthma treatment is sparse, and whilst there are guidelines for the treatment of asthma (e.g. BTS/SIGN[1]) it is generally difficult (given the current evidence base) to structure and populate a model which is driven by such guidelines.

6.3.1.5.2 Data inputs

The primary data inputs for effectiveness, costs and outcomes are presented in the submission. In the analysis, there is a lack of transparency in the calculations for 'other costs'. There are concerns with the methods used to identify and measure the 'other costs' associated with the cost-effectiveness analysis. Data used on resource for 'other costs' are taken from the GOAL trial by Bateman and colleagues (2004)[235]), but the specific data used are not presented in the submission. Furthermore, the generalisability of this study (a multi-national RCT, covering 44 countries) to the current analysis is not discussed. The GOAL CEA used data on resource use from all 44 countries in the trial, using a UK indicator variable in the analysis presented. However, this issue is not discussed in the context of the

current analysis. Unit costs for the resource use are taken from appropriate data sources. The submission uses a regression model to estimate other costs, based on an expected cost per week of £1.53 for people with asthma symptoms, a mean annual cost of £79.83. Where people with asthma are symptom-free this is reduce to £0.03, a mean annual cost of £1.57. These cost estimates appear to be very low and the submission does not offer the opportunity to consider the appropriateness of the resource use to the UK treatment group. The submission has referred to the economic evaluation undertaken alongside the GOAL trial (Briggs et al 2006[255]), however the publication for that particular evaluation does not offer detail on resource use. The regression analysis employed in the submission differs from that presented by Briggs and colleagues (2006).

The cost for FP/SAL (Seretide) is based on its availability in two different inhaler devices (Accuhaler and Evohaler), with both prices from the Drug Tariff, together with an average price, used to generate a range of data on cost-effectiveness. A drug 'cost per day' is estimated for all treatment options. For example, in the model the estimated cost per day for FP/SAL (Seretide) 200/100 via Accuhaler, FP/SAL 200/100 via Evohaler, and the average cost per day for these are set at £1.04, £0.60, and £0.79 respectively. For BUD/FF 400 (200/6), and ICS 400-500 (FP), the daily costs are estimated at £0.63 and £0.62 respectively. There are a range of approaches that can be taken to estimate daily costs, and the approach taken in the submission appears reasonable for the current analysis (Appendix 10 of the submission presents the methods used).

There is a lack of transparency over the calculation of health state utilities used in the model (with a citation to a personal communication). The general literature available to inform on health state values for asthma is sparse and undeveloped, and whilst the values used for symptom-free in the analysis seems relatively high (compared to some general population age-related values), the important issue is the incremental difference (0.12) used between health state with symptoms and symptom-free.

The effectiveness data used in the CEA are from a limited number of available trials, and this is justified in the submission on the basis of a lack of consistency in the reporting of common outcomes across relevant trials. The use of this limited data may introduce bias to the estimates used, but this has not been discussed or considered in the sensitivity analysis. The effectiveness data from the trials are assumed to be generalisable to the treatment group in England and Wales that are the focus of policy analysis. In addition, the treatment

effect from short term trials (mainly 12-weeks) is assumed to be appropriate over longer time periods (e.g. 1-year).

The meta-analysis reported in the analysis, to inform the cost-effectiveness analysis, presents the trials used according to the research question addressed. Where FP/SAL is compared to same dose ICS six trials from a possible 14 are used (three trials applied to each of three separate dosing options). Where FP/SAL is compared to increased dose ICS three from a possible six trials present data on % SFDs, but only two of these trials could be used in the cost-effectiveness analysis. Where FP/SAL is compared to ICS+LABA separates, there is one trial to inform each of the three possible dosing regimens. Only one trial is used (from two presented in the clinical review) to consider the effect of FP/SAL versus BUD/FF.

6.3.1.5.3 Assessment of uncertainty

Uncertainty in the analyses is addressed using probabilistic sensitivity analysis (PSA). The PSA considered parameter uncertainty for mean treatment effect, and for 'other cost' and utility model inputs. The report submitted does not present discussion on results of the sensitivity analysis (additional material was submitted, providing a cost-effectiveness plane and CEAC for each of the 80+ analyses undertaken). Additionally, the report does not present any deterministic sensitivity analysis, or address structural uncertainties via sensitivity analyses. Heterogeneity of the treatment group has not been considered against any defined sub-groups.

6.3.1.5.4 Model validation

The submission states that checks were undertaken to consider the validity of the model, with a re-build undertaken using a different software package. This presents evidence of the internal consistency (logic) of the model structure and data structure used.

6.3.1.6 Summary of general concerns

- The focus on % SFDs as a measure of asthma control, and treatment effect, may be limited and may not capture other important aspects of asthma control and/or effectiveness data (e.g. around exacerbations, quality of life).

- The use of a limited evidence base to populate the model (e.g. small number of trials used to derive effectiveness estimates)
- Assumptions over generalisability of trial data, and extrapolation of treatment effect are not discussed.
- Concerns over methods used and estimates used for 'other cost'.
- Concerns over the lack of transparency in estimating health state utilities, and other cost estimates.

6.3.2 Review of the submission by Astra-Zeneca (AZ)

6.3.2.1 Overview

The submission by AZ to NICE includes an economic commentary and cost-effectiveness analysis to support two AZ products; BUD (Pulmicort®) and BUD/FF in combination (Symbicort®).

The submission includes some commentary on the clinical equivalence of BUD with other ICS products, and the presentation of some price estimates. The submission does not include any cost-effectiveness analysis for BUD versus other ICS products. The submission states that BUD is the most extensively used ICS, and that "Pulmicort (budesonide) costs are well within the normal range of costs for maintenance asthma treatments with any ICS" (p32). There is limited discussion of the relative cost-effectiveness of different ICS products, with a cost-minimisation approach assumed due to clinical equivalence across these products.

The cost-effectiveness analysis presented in the submission is to support the use of BUD/FF. The submission refers to BUD/FF fixed dose (FD), BUD/FF adjustable maintenance dosing (AMD), and BUD/FF as both main maintenance and reliever therapy ('SMART'). The submission used BUD/FF FD as the base case for cost-effectiveness analysis, working on the basis that BUD/FF AMD and SMART have been shown to be superior to BUD/FF FD. The submission compares BUD/FF (covering the three BUD/FF dosing regimens of FD, AMD, SMART) to the use of ICS alone (high dose FP), BUD+FF in separate format, and to FP/SAL (Seretide;GSK combination product).

The submission consists of a brief discussion on the literature (covering CEAs, and modelling studies), and the presentation of the methods and results for a cost-effectiveness model developed for the submission to NICE.

A literature search is reported covering CEAs on BUD/FF. This search identified nine studies, all of which are stated to show BUD/FF AMD or SMART at an equivalent or increased efficacy compared to BUD/formoaterol FD (four studies), separates (three studies), FP (high dose ICS) (one study), or FP/SAL (one study). All except one of these identified studies is said to show cost savings from use of BUD/FF.

6.3.2.2 Model on cost-effectiveness of BUD/FF (Symbicort)

The submission reports a literature search to consider modelling studies relevant for the economic evaluation of asthma treatments. This identified nine studies. There is no discussion presented on these studies, other than that the study published by Price & Briggs (2002)[264] is reported to be the most appropriate approach for CEA considering the use of BUD/FF in UK practice.

Whilst the submission states that the approach presented by Price & Briggs is the most appropriate for the analysis of BUD/FF, it is also stated to have a number of limitations and a new model is developed by AZ for their submission. Below we outline the approach taken for the new model, and provide an outline review of the submission.

The model is developed to capture the difference in exacerbations between comparisons, and the difference in time spent in a non-exacerbation health state. The model is a Markov-type model with four health states; non-exacerbation, mild-exacerbation, severe-exacerbation, and treatment change. This latter state is an absorbing state which reflects withdrawal from the treatment allocated. Where patients withdraw from treatment (undergo treatment change) they are subject to a second-line treatment regimen and are modelled in a parallel process to the main (first-line) model. Where treatment is changed, it is in line with recommendations in the BTS/SIGN Guidelines. The model uses a cycle of 4-weeks, and has a time horizon of 1-year, with a 5-year time horizon considered in a sensitivity anlysis. The model uses transition probabilities derived from individual level patient data from a UK clinical trial of a 12-week duration that compared BUD/formoteraol FD with BUD/formoaterol AMD, [cited: Ind et al 2004/Unpublished AZ data]). The data on the relative effects of comparator

products (relative risks for severe exacerbation, mild exacerbation, and treatment change) were derived from unpublished clinical trial data for comparators (data are not presented, they are unpublished academic in confidence). Patient level trial data (over 12-weeks) allow the used of different transition probabilities for BUD/FF over months 1 to 3, and thereafter a constant transit probability matrix is used based on events occurring during months 1-3. Analysis is presented for an asthma treatment group aged 12 and above. In the model all persons start in the 'non-exacerbation' (controlled) health state. The perspective of the analysis is stated as stated as UK NHS & PSS. Prices for asthma treatment are at a 2005/06 price year.

Health state utilities used for the model are based on EQ-5D tariff values. Health state descriptions covering the health states used were collected from a sample of asthma patients, and EQ-5D tariff values for these states were used (the submission cites Kind and colleagues 1999).

[redacted]A monthly cost is applied in the model based on asthma medication cost and health service consultations and hospitalisations. Primary care NHS resource use (consultations) are assumed to be the same for each of the treatment options, and are not included in the model. The cost of managing a mild exacerbation is estimated at £50.42, for severe it is between £334 - £1,752.

The model assumes that exacerbations affect costs and utilities for 1-week only, with the remaining 3-weeks in that cycle based on non-exacerbation status.

6.3.2.3 Model / cost-effectiveness results

The submission presents summary results for outcomes and costs separately, in Tables 9 and 10 respectively, and in an incremental analysis in Table 11.

The submission presents results indicating that over a 12-month period BUD/FF FD resulted in very small incremental QALY gains, and prevented more exacerbations than both ICS alone and FP/SAL. Equivalence in effect was assumed when compared to ICS plus LABA separates. Over a 12-month period BUD/FF FD is reported to have a lower total cost than

FP/SAL (cost saving of -£8,185 per 1,000 persons). However, ICS alone is a lower cost compared to BUD/FF FD (with ICS alone showing a cost advantage of £245,152 per 1,000 persons).

In CEA results (Table 11), BUD/FF FD is stated to dominate FP/SAL, and to result in an additional cost per QALY of £40,234 when compared to ICS alone.

In the opinion of the TAR team, the differences in QALY gains for all comparisons are very small when considered at the level of the mean patient benefit (e.g. 0.00037 when BUD/FF compared to FP/SAL), and the mean cost difference per patient is also very small for comparisons with BUD/FF and FP/SAL, and ICS plus LABA as separates. It would appear that any comparison rests on the incremental costs and benefits associated with exacerbations. The use of 'non-exacerbation months' as an outcome will rest on the relative importance that is placed on mild exacerbations, as these are more frequent than severe exacerbations (roughly twice as frequent) other than for FP/SAL.

Whilst AZ state that BUD/FF dominates FP/SAL the TAR team would suggest that the difference between the two treatments, that is of interest, is the lower number of exacerbations predicted for BUD/FF versus FP/SAL (per 1,000 patients: BUD/FF had 60.19 fewer severe exacerbations, with an additional 10.28 mild exacerbations), with these differences being small at the mean patient level.

6.3.2.4 Appraisal of the cost-effectiveness analysis undertaken

TABLE 50 *Critical appraisal checklist of economic evaluation*

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	
Is there a clear description of alternatives?	Yes	BUD/FF versus comparators (various options stated).
Has the correct patient group / population of interest been clearly stated?	Partial	Adult patients 12 years and over. All patients in model start in non-exacerbation state (this may not be the case in practice with a proportion of patients being in an 'uncontrolled' asthma state)
Is the correct comparator used?	Partial	Comparators used are all appropriate; however other additional comparators could also be used.

Is the study type reasonable?	Yes	CEA model used (CUA results presented).
Is the perspective of the analysis clearly stated?	Yes	Perspective stated as UK NHS & PSS
Is the perspective employed appropriate?	Costs: Yes Outcomes: Partial	Submission appears to adopt a UK NHS and PSS perspective for costs (consistent with NICE reference case). Perspective on outcomes is that of the patient, but not all effects considered (focus on 'non- exacerbation' state).
Is effectiveness of the intervention established?	Partial	The CEA is based on clinical effectiveness data from a limited number of trials reporting the chosen economic endpoint (exacerbation related outcomes) – mainly over 12-weeks. Primary effectiveness data (for BUD/FF transition probabilties) from one UK RCT. Study assumes differences seen in trials can be generalised to the lifetime treatment period.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	No	1-year time horizon used (not lifetime) ICERS are based on 1-year cost and QALY differences. 5-yr horizon in sensitivity analysis
Are the costs and consequences consistent with the perspective employed? *	Partial	Costs appear to be consistent with perspective employed, but limited justification provided, and may not include all relevant costs (e.g. primary care not included) Consequences limited to exacerbations, and non-exacerbation months. Interpretation of non-exacerbation state from limited clinical evidence.
Is differential timing considered?	No	1-year time frame used – no discounting. (In sensitivity analysis 3.5% discount rate used)
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	Yes sensitivity analysis is undertaken, probabilistic analysis.
* More on data inputs for costs and consequences in the review of modelling methods below		

TABLE 51 *NICE reference case requirements – AZ submission*

NICE reference case requirement		**Reviewer comment**
Decision problem: As per the scope developed by NICE (esp. technologies & patient group)	Yes	
Comparator: Alternative therapies routinely used in the UK NHS	Yes	
Perspective on costs: NHS and PSS	Yes	

NICE reference case requirement		Reviewer comment
Perspective on outcomes: All health effects on individuals	Partial	health effects partly limited to effect of treatment on exacerbation rate
Type of economic evaluation: Cost-effectiveness analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes	
Method of preference elicitation for health state values: Choice-based method (e.g. TTO, SG, not rating scale).	Partial	Method of preference elicitation is explicit but a rating scale was used
Source of preference data: Representative sample of the UK public	Yes	
Discount rate: 3.5% pa for costs and health effects	N/A	base case is 1-year analysis, no discounting necessary. Sensitivity analysis at 5-years, with 3.5% rate used for costs and effects.
N/A=not applicable		

6.3.2.5 Review of modelling approach

6.3.2.5.1 Model structure / structural assumptions

The model structure is driven by the use of exacerbation data, and the characterisation of a 'non-exacerbation' health state, using clinical trial data. The non-exacerbation health state is made up of patients that are without symptoms and those patients with symptoms but not requiring any intervention from a health care professional. Mild exacerbation is defined as an exacerbation requiring primary care intervention, including oral corticosteroids if appropriate, but no secondary care intervention. Severe exacerbation (model state) is defined as an exacerbation requiring secondary care intervention, including hospital stay if appropriate.

Trial data have been used to estimate the transition probabilities between these states (and treatment change), but it is unclear how data may have been interpreted from different clinical trials, where methods may not have been homogeneous. For the non-exacerbation state the correlation with trial data is around controlled and symptom-free days. As BUD/FF is marketed at a sub-maximal dose with patients potentially able to use it as both SABA and

LABA, it is important to acknowledge that the non-exacerbation state used in the model is a combination of time with and without SABA rescue medication. Definitions for mild and severe exacerbations do not rely on use of SABA medication. Trial data for frequency of mild exacerbations are based on the use of oral corticosteroids. For severe exacerbations frequency of events in the trials used is based on exacerbations requiring hospitalisation or A&E visit. Much of the data to inform the model transitions have been taken from a limited evidence base, with citations to unpublished data on file at AZ.

The model structure is not discussed and justified in the context of a coherent theory of asthma, and the model is essentially based around the availability of data surrounding exacerbations for BUD/FF and comparators. It may be that AZ have adopted this approach due to the more positive profile of BUD/FF (against exacerbation rates), when use of an outcome related more directly to control, such as percentage of symptom-free days, may have seemed more favourable for comparator products (e.g. FP/SAL). The submission indicates that a review of published modelling studies was undertaken, but no discussion is presented on alternative approaches. Given the prominence in the clinical and economic literature of outcome measures/data around lung function and symptoms, it would have been useful for some discussion of competing approaches for the modelling of asthma treatment and cost-effectiveness to have been presented.

The model places emphasis on exacerbations, and exacerbation status (as a measure of control). The assumption in the model is that exacerbations affect utilities and costs for 1-week only.

Whilst not stated in the submission the model assumes the same toxicity profile for treatments, and the same profile for any longer-term adverse effects.

The cycle length and time horizon are justified on the basis of data available and an assumption that mortality rates (longer term outcomes) are similar across comparison treatments. Both of these assumptions seem reasonable. However, treatment effect is based primarily on 12-week trial data (ASSURE Trial), and the submission does not discuss the assumption that this treatment effect is assumed to continue for the time period of the model (1-year in base case), nor the generalisability of the trial data (importantly that from the BUD/FF trial used for transition probabilities) to the broader treatment population.

There is also no statement in the submission on the evaluation of the internal consistency of the model.

When making/considering the above points it important to acknowledge that the literature on modelling cost-effectiveness in asthma treatment is indeed sparse, and whilst there are guidelines for the treatment of asthma (e.g. BTS/SIGN[1]) it is generally difficult (given the current evidence base) to set up a model which is consistent with such guidelines.

6.3.2.5.2 Data inputs

The primary data inputs for effectiveness, costs and outcomes are presented in the submission. For effectiveness data, as above, the transition probabilities are estimated from a limited evidence base (BUD/FF FD arm of one RCT), and there is a lack of transparency over the calculation of relative treatment effect for comparator products. [redacted]

Medication costs are based on trial data for the number of inhalations per day, and drug costs from the Drug Tariff or eMIMs, and a weighted average cost per inhalation was estimated across the various drug formulations. [redacted]

Data on other costs are presented clearly, and whilst including a number of assumptions, appear reasonable. The estimated cost for managing a mild exacerbation was £50.42. The estimated cost for the management of a severe exacerbation ranged between £334 and £1,752 (dependent on need for hospitalisation); [redacted].

Whilst there may be some methodological limitations with the health state utility study (as with all studies of this nature) presented to inform the mode, data on health state utilities are consistent with the preferred approach of NICE, and C.I.C. data are provided to support this area of the model. The general literature available to inform on health state values for asthma is sparse and undeveloped.

6.3.2.5.3 Assessment of uncertainty

Uncertainty is addressed in the submission using deterministic sensitivity analysis and probabilistic sensitivity analysis. Probabilistic analysis has addressed parameter uncertainty in a number of cases, (number of inhalations, utility values, transition probabilities, relative risks). However, although the choice of distributions would seem to follow accepted methods, in many cases the uncertainty around parameter inputs is very small, [redacted] The report refers to the use of probabilistic methods for transition probabilities, however it is unclear how the probabilities were sampled (either re-scaled to sum to 1.00, or via some correlation matrix; the submission states "normalised to give a sum of one "p99"). [redacted]

The assessment of uncertainty does not address any issue of heterogeneity in the treatment group, and certain structural and methodological uncertainties are not addressed in the sensitivity analysis (e.g. impact of exacerbations on patients).

The deterministic analysis presented indicates very large changes in the cost per QALY results when assumptions over the proportion of time without SABA used are considered, and these results could have been further explained, with a breakdown of costs and consequences for these analyses (i.e. it maybe an issue related to very small incremental costs and effects, or a more substantive effect in analyses).

6.3.2.6 Summary of general comments on the submission:

- The focus on exacerbations (rate), and non-exacerbation defined control status may not capture other important aspects of asthma control and/or effectiveness data.
- There is the use of a limited evidence base to populate the model i.e. the arm of one RCT used to estimate the transition probabilities for BUD/FF.
- The lack of transparency over the estimation of relative treatment effect (unpublished, 'in-confidence' data cited).
- There are a number of assumptions made over the generalisability of the trial data, and issues around the extrapolation of treatment effect are not discussed.

6.3.3 Review of the submission by ALTANA Pharma

6.3.3.1 Overview

The submission by Altana Pharma to NICE includes economic analysis comprising a cost minimisation analysis comparing CIC (Alvesco®) versus FP (dose ratio 1:1), BDP (dose ratio 1:2) and BUD (dose ratio 1:2) within a UK context. The submission presents a discussion on the clinical effectiveness data available (some being commercial in confidence data on file at Altana) to compare CIC with FP, beclomethasome and BUD, and concludes that CIC 160µg once daily will be of comparable clinical effectiveness to FP100µg twice daily, BUD 200µg twice daily and BDP 200µg twice daily.

The submission also concludes that CIC 160µg/day will have a potentially lower overall cost to the UK NHS & PSS budget. The annual drug cost for patients prescribed CIC 160µg/day daily is estimated at £102.20. This cost is compared to estimates of £73-£219 for FP 200µg/day, £73-£138.70 for BUD 400µg/day and £14-£146 for BDP 400µg/day. Drug costs are estimated based on prices listed in the BNF (March 2006). The submission states that in the majority of cases where costs for comparators are lower than CIC 160µg/day they are based on products that use CFC propellants which will soon become obsolete (2007).[273;274] In table 10 presented in the submission appendices, a range of CFC-free products are listed for comparison; in 5 of the 16 CFC-free comparisons the estimated cost per year is lower than that presented for CIC. Costs other than medication costs are assumed to be constant across patients (regardless of the comparator ICS) and these costs are not discussed further in the submission.

The methodological rigour of the systematic review methods used to identify and review the clinical effectiveness data presented is open to some bias. The methods are not clear in all cases, and the search strategy is limited. Likewise, the methods used to estimate and compare costs are not comprehensive, and there are a number of assumptions of resource use profiles.

In a cost analysis, CIC 160µg/day is also compared to the combination therapies of FP/SAL and BUD/FF. For these cost comparisons CIC 160µg/day is estimated to cost £8.40 per month, with comparator doses of FP/SAL and BUD/FF at £31.19 and £19 per month

respectively. However, no discussion is presented on the clinical effectiveness of CIC versus combination therapies.

6.3.4 Review of the submission by Ivax Pharmaceuticals Ltd

6.3.4.1 Overview

The submission by Ivax to NICE includes a review of clinical effectiveness studies, and a review of existing cost-effectiveness studies which compare a specific HFA-propelled BDP product (Qvar®) to a range of alternative ICS products (BDP, HFA-propelled FP, and BUD via Turbuhaler®). Three of the published cost-effectiveness analyses are from a UK NHS perspective, and the submission does not present any cost-effectiveness analyses in addition to these.

6.3.4.2 Review of cost-effectiveness studies of Qvar®

The review of the cost-effectiveness of Qvar® summarises the results of three trial-based studies which compared Qvar® with other ICS preparations from a UK NHS perspective:

i. BDP – published in 2002 (Price and colleagues)[275]

ii. HFA-propelled FP – ERS conference poster presentation only

iii. BUD via Turbohaler® - ERS conference poster presentation only

Table 52 below summarises the main design features of these analyses. None include estimation of the longer term cost per QALY of using Qvar® in place of other ICS preparations. Limited sensitivity analyses were also presented.

TABLE 52 *Cost-effectiveness studies comparing Qvar with other ICS - study designs*

Comparator	Country Setting	Patients	Time	Outcomes	Costs
BDP	International, multicentre	n = 473 Aged	1 year	Symptom-free days HRQL (AQLQ > 0.5)	Study drugs; other respiratory drugs; 2 GP visits; hospitalisation and A & E visits

HFA-propelled FP	International, multicentre	n = 198 Age 18-75 years olds, on 500-1000µg/day (BDP equivalent)	8 weeks	Change in % Symptom-free days	Study drugs; other respiratory drugs; 2 GP visits;
BUD (Turbohaler)	International, multicentre	n = 209 Age 18-75 years olds, on 500-1000µg/day (BDP equivalent)	8 weeks	Change in % Symptom-free days	Study drugs; other respiratory drugs; 2 GP visits;

6.3.4.3 Cost-effectiveness results

The cost-effectiveness results of the studies summarised in the submission are as follows:

TABLE 53 *Cost-effectiveness studies comparing Qvar with other ICS: base case results*

Comparator	Costs per patient(£)	Effectiveness	ICER
BDP	Qvar = 226 CFC-BDP = 231	166 SFDs; 44% of patients >+0.5 change in AQLQ 128 SFDs; 36% of patients >+0.5 change in AQLQ	Qvar both slightly cheaper and more effective (more SFDs) than CFC-BDP.
HFA-propelled FP	Qvar = 143 HFA-propelled FP = 164	24% incr. in SFDs 18% incr. in SFDs	Qvar both cheaper and more effective (greater incr. in SFDs) than comparator.
BUD (Turbohaler)	Qvar = 174 BUD = 219	25% incr. in SFDs 12% incr. in SFDs	Qvar both cheaper and more effective (greater incr. in SFDs) than comparator.

These cost-effectiveness results should be treated with some caution because they use resource use data from a number of countries other than the UK, where standard clinical care for people with asthma may differ.

6.3.5 Review of the submission by Meda Pharmaceuticals Ltd

6.3.5.1 Overview

The submission by Meda Pharmaceuticals Ltd to NICE includes evidence summaries of the Novolizer® BUD (DPI) device's technical performance, tolerability, and acceptability to

patients as well as general discussion of the burden of asthma and the role of BUD in asthma. The emphasis throughout their report, including in their cost minimisation analysis (CMA), is on the documented or estimated patient benefits and NHS savings of the Novolizer® device compared to its main DPI competitor product, the Pulmicort® Turbohaler®. The majority of the submitted material, and the whole of the economic analysis, is therefore outside the scope of the NICE appraisal which is focused on comparing different ICS drug compounds with each other and selected 'add-on' therapies (rather than the different formulations or different delivery devices with the same compound).

Nevertheless, the submission does provide further useful insights into the mediating role of inhaler devices in the effectiveness of ICS and other inhaled asthma medications. In particular, better compliance with medication may result from devices which are easier to use correctly, and which also include features which clearly indicate correct inhaler technique.

For completeness in the following two tables we appraise the main features of the basic (two-page) economic evaluation submitted by Meda Pharmaceuticals Ltd.

TABLE 54 *Critical appraisal checklist of economic evaluation by Meda Pharmaceuticals Ltd.*

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	No	Implicitly compare the two device types
Is there a clear description of alternatives?	Yes	Novolizer (BUD) vs. Turbohaler (BUD) both at a dose of 400µg daily (=200µg bid)
Has the correct patient group / population of interest been clearly stated?	No	Not stated whether these typical doses are assumed to be for adults or children
Is the correct comparator used?	No	Comparison of devices not a part of NICE scope
Is the study type reasonable?	Yes - CMA	Assuming that claim of therapeutic equivalence with Turbohaler is valid
Is the perspective of the analysis clearly stated?	No	But implicitly NHS perspective
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	Yes(?)	Depending on the quality of RCT by Chuchalin et al. in Respiration 2002; 69(6): 502-508
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	No	CMA projects 1 year costs
Are the costs consistent with the perspective employed?	Yes	Only drug provision costs are included
Are the consequences consistent with the perspective employed?	N/A	
Is differential timing considered?	N/A	
Is incremental analysis performed?	Yes	Calculates per person annual NHS savings of switching from Turbohaler to Novolizer.
Is sensitivity analysis undertaken and presented clearly?	No	

TABLE 55 *NICE reference case requirements – Meda Pharmaceuticals Ltd submission*

NICE reference case requirement	Critical Appraisal	Reviewer comment
Decision problem: As per the scope developed by NICE (esp. technologies & patient group)	No	Inhaler devices compared, (i.e. not BUD with other ICS or ICS+LABAs)
Comparator: Alternative therapies routinely used in the UK NHS	Yes	BUT assessing inhaler devices outside NICE scope
Perspective on costs: NHS and PSS	Yes	Implicitly (source of costs = eMIMS)
Perspective on outcomes: All health effects on individuals	N/A	CMA
Type of economic evaluation: Cost-effectiveness analysis	CMA	
Adequate time horizon	No	1 year
Synthesis of evidence on outcomes: Based on a systematic review	Yes(?)	PubMed search obtained 1 trial; no stated inclusion or exclusion criteria
Measure of health benefits: QALYs	N/A	CMA
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	N/A	CMA
Method of preference elicitation for health state values: Choice-based method (e.g. TTO, SG, not rating scale).	N/A	CMA
Source of preference data: Representative sample of the UK public	N/A	CMA
Evidence on costs: prices relevant to NHS & PSS	Yes	Inhaler with drug and inhaler refill costs only
Discount rate: 3.5% pa for costs and health effects	No	

N/A=not applicable

* Health effects – just symptom-free days, used to consider QALY values

** Method for estimating health state utilities is unclear

6.3.6 Review of the submission by Trinity-Chiesi Pharmaceuticals Ltd

6.3.6.1 Overview of the submission for Clenil® Modulite®

The submission by Trinity-Chiesi focuses on the clinical effectiveness and cost of Clenil® Modulite®, an HFA-propelled BDP product for use with pMDIs.

The submission includes some discussion of evidence of the clinical equivalence of this product and the main CFC-propelled equivalent products that are licensed for adults, and the presentation of a cost-minimisation comparison with Qvar® (another HFA-propelled BDP product for use with pMDIs). There is also some discussion on the changing regulatory environment for these and related products, specifically the progressive banning of CFC-propelled asthma medications under the Montreal Protocol. The submission is based on a systematic search of the literature on a range of topics that include clinical effectiveness, tolerability and safety, and cost-effectiveness of the product. Two equivalence RCTs of the product relative to a standard CFC-containing pMDI (Becotide®) in adults with mild and mild-to-moderate persistent asthma are discussed.

Based on evidence summarised elsewhere in the submission (three unpublished Phase III studies) the cost-effectiveness section assumes the clinical equivalence of Clenil® Modulite® with Becotide®, which is one of the alternative BDP preparations available for inhalation via pMDI devices. It then proceeds with a cost comparison between Clenil® Modulite® and the only other CFC-free BDP product that is currently licensed for use in the UK, Qvar® (also via HFA-propelled pMDI).

They used a time horizon of a year and calculated the per patient incremental (NHS) medication costs of Clenil® Modulite® compared with Qvar®. In addition to the cost of the drugs, the main cost saving assumed to derive from switching to Clenil® Modulite® is avoiding the need for two therapeutic reviews, to re-titrate, and monitor response to new dosages, when switching to Qvar®. However, it should be noted that this is an analysis of the short-term benefits during the period when CFC-containing products are withdrawn from the market, and additionally comparisons are made amongst BDP products and it is therefore outside the scope of the present review. Below we only show the results without the assumed savings from avoided therapeutic reviews.

6.3.6.2 Cost-minimisation results

Table 56 below summarises the cost of Clenil® Modulite® (at the four available dose levels) and the cost of equivalent doses of Qvar®. The cost difference between using the two products, if the dose equivalence ratio of 2:1 is correct, is negligible.

TABLE 56 *Costs of Clenil® Modulite® and Qvar®.*

Product	Annual cost 50µg doses (£)	Annual cost 100µg doses (£)	Annual cost 200µg doses (£)	Annual cost 250µg doses (£)
Qvar® (at half dose of Clenil® Modulite®)	14.13	28.25	61.87	61.87
Clenil® Modulite®	14.05	28.18	61.43	61.87

6.3.6.3 Overview of the submission for Pulvinal®

The submission by Trinity-Chiesi to NICE focuses on the clinical effectiveness and cost of the following BDP product for use its own DPI device: Pulvinal®

The submission includes some discussion of evidence of the claimed clinical benefits of this product over other DPI products that are licensed for adults, and also summarise some evidence from published research literature to support the cost-effectiveness of inhaler devices that are easier to use or reduce dose wastage.

6.3.6.4 Analysis of cost of Pulvinal®

No economic evaluation is presented in the submission, but instead the estimated monthly and annual costs for Pulvinal® are compared with other BDP, BUD and FP dry powder products.

6.3.7 Summary of the cost-effectiveness submissions made by manufacturers

Our review of the industry submissions highlights a number of concerns in relation to providing a comprehensive and reliable evidence base for considering the present decision problem.

None of the submissions compared the cost-effectiveness of all five of the ICS products licensed for use in adults (and which are the scope for this assessment). All six submissions presented a cost minimisation analysis with a general assumption of an equivalent level of clinical effectiveness across ICS products being compared. The submissions by Ivax Pharmaceuticals Ltd and Trinity-Chiesi Pharmaceuticals Ltd, were both limited to a presentation of the costs of their respective BDP products, Qvar® and Clenil® Modulite®.

Likewise, the submissions by Altana Pharma and Meda Pharmaceuticals Ltd were limited to their products, CIC (Alvesco®) and BUD (Novolizer®) respectively.

The submissions by GSK and AZ for the cost-effectiveness of ICS products were limited to a cost minimisation analysis. The cost-effectiveness of the products included in the current appraisal was not apparent. Moreover, the methods used for estimating the product costs varied across the submissions, and were not transparent. This is particularly pertinent, as most ICS named preparations are usually sold in a variety of dose-strengths (e.g. 100µg, 200µg or 400µg per dose). Therefore there are usually a number of ways of achieving any given daily dose of a particular drug, with the method used to obtain the given daily dose determining the presented cost of the drug dose.

For the combination therapies of Seretide® (FP/SAL; GlaxoSmithKline) and Symbicort® (BUD/FF; Astra-Zeneca) more complex cost-effectiveness models were presented. However, once again both of the models were developed from a product-specific perspective.

6.4 Original economic analyses: introduction and rationale

The systematic review of economic evaluations in section 6.2 identified a number of limitations in the existing research literature on the relative cost-effectivenes of the five ICS, BDP, BUD, FP, CIC and MF, used as monotherapy. The published cost-effectiveness studies of FP or BUD in combination with LABAs (SAL or FF), also had some limitations in the UK NHS policy context, particularly within the appropriate step of the BTS/SIGN Guidelines.[1]

The cost-minimisation and other cost analyses submitted by industry mostly provide quite selective evidence pertaining to one or two of their own branded products; as opposed to a broader assessment of the relative effectiveness and cost-effectiveness of a broader range of alternative ICS drugs, or the cost-effectiveness of adding a LABA to ICS under different clinical circumstances. Some also did not fully meet the NICE reference case requirements for cost-effectiveness analyses (although, often this was partly because of the same lack of clear evidence of differential effectiveness that we have encountered).

For these reasons, we decided it was necessary to carry out further economic analyses. To address the project scope and the comparators specified in the project protocol, and in line with the clinical effectiveness research questions, we used five cost-effectiveness research questions which more accurately express the various decision problems that are implicit in the context of the BTS/SIGN Guidelines.

6.4.1 The cost-effectiveness research questions

The two research questions relating to the cost-effectiveness of the five ICS as monotherapy, are:

Q1. At low doses (200 - 800µg BDP per day or equivalent), which is the most cost-effective of the five ICS? (Step 2 of the guidelines)

Q2. At high doses (800 - 2000µg BDP per day or equivalent), which is the most cost-effective of the five ICS? (Step 4 of the guidelines)

The three research questions relating to the cost-effective use of ICS plus LABA, are:

Q3. a. Which is the more cost-effective approach to introducing a LABA in to a treatment regimen: to increase the dose of ICS alone or to add a LABA to treatment with the existing ICS dose? (steps 2-3 of the guidelines).

Question 3a is viewed as the more clinically relevant of the original two sub-questions for Q3, because if patients become uncontrolled on a given dose of ICS alone, staying on the same ICS dose is not a clinical option; in the context of the BTS/SIGN Guidelines either the ICS dose will be increased, or a LABA will be added to the existing dose of ICS. Although the clinical effectiveness literature contains some trials in which a LABA was added to the ICS treatment regimen without the included dose of ICS alone being increased, this sub-question (3b) is therefore not addressed in the cost-effectiveness evaluation.

Q4. Which is the more cost-effective treatment: FP and SAL in a combination inhaler or given in separate inhalers? and, BUD and FF in a combination inhaler or given in separate inhalers?

Q5. Which is the more cost-effective treatment: FP/SAL in a combination inhaler or BUD/FF in a combination inhaler? (at Step 3 of the BTS/SIGN Guidelines)

6.4.2 Types of analysis used

Given the lack of consistent evidence of differential clinical effectiveness for questions one, two, four, and five, yet the relatively consistent effectiveness evidence favouring combination inhalers over increased doses of ICS, we have taken a different approach to the economic analyses for each research question. Although the cost-effectiveness of asthma treatments can be assessed using more sophisticated modelling approaches, the data requirements and other challenges involved are considerable (*Appendix 10*). For most questions, the more pragmatic analytical approach used here inevitably focuses on the relative costs rather than the cost-effectiveness of the different drug treatments compared.

For each of the questions we present one of the following types of analysis:

1. A cost-comparison of the different ICS and ICS plus LABA preparations (for those questions where the clinical effectiveness review showed no consistent evidence of differential effectiveness). (for research questions 1,2, 4 and 5)

2. A cost-consequence comparison, to summarise the overall pattern of effectiveness differences identified in the systematic review and place them alongside the estimated current NHS preventer medication costs for each of the included trials. (for research question 3a)

3. A tentative model-based incremental cost-utility analysis, to explore the uncertainty surrounding choices in asthma drug treatment (particularly, here, the choice of whether to add a LABA or increase the ICS dose at Step 2/3 of the BTS/SIGN Guidelines).(as an exploration of research question 3a)

As mentioned, the review of the cost-effectiveness literature on asthma did not identify any studies whose results were applicable to either the research questions of interest or the UK context. Similarly, the limitations of published models of asthma meant they were not directly applicable in the decision problems and policy context of this review (or they relied on access to individual patient data from trials). We therefore developed a new model capable of addressing the specific research questions outlined previously, in the context of a UK adult

population and the BTS/SIGN Guidelines[1] A brief summary of the model design, input parameters and main probabilistic outputs is shown in *Appendix 10*. We decided not to present the full methods and results of the final model in the main body of the report for the following reasons (although the exact reasons for not modelling varied for each research question):

- a general lack of relevant, good quality and consistently reported trial evidence on the asthma outcomes of interest;
- an unavoidable over-reliance on exacerbation rates as the central driver of transition probabilities (nb. despite the inadequacy of other common trial outcomes, such as lung function or symptom-free days, as a basis for the cost-utility analyses for this assessment);
- considerable uncertainty surrounding the model outputs; in particular the sensitivity of central estimate ICERs to very small changes in effectiveness and medication cost assumptions relating to the controlled asthma state.

Two additional literature reviews were undertaken, mainly to inform the development of the cost-utility model; one of existing decision models for assessing treatment in asthma, and one of studies reporting health state utility values associated with defined asthma health states. However, since we have chosen to only present an abbreviated version of our cost-utility model and analysis (as *Appendix 10*), these two reviews are also presented in Appendices as background to that analysis and as a resource for future modelling studies in this area.

6.5 Original economic analyses

6.5.1 Rationale for cost comparisons

Cost comparisons, like cost-minimisation analyses, should normally be used when there is valid and reliable evidence of equivalent effectiveness of the alternative technologies being compared.[252] However, as previous sections of this report have concluded, amongst different ICS for asthma there is little conclusive evidence of equivalence. More often instead, there is inconclusive evidence concerning differential effectiveness.

Performing a cost comparison is not straightforward, as it is difficult to derive a single 'representative' cost figure for each ICS. This is because each drug is typically available in a range of named preparations (e.g. from different manufacturers, or for different inhaler devices), and also because each named preparation is usually sold in a variety of dose-strengths (e.g. 100µg, 200µg or 400µg per dose). There can therefore be a variety of ways of achieving any given daily dose of a particular drug. This is especially an issue for the long-established drugs like BDP and BUD.

In order to generate single cost figures for each ICS, we have made use of standard assumed ratios regarding dose equivalence and made some other simplifying assumptions to enable pooling of cost estimates. Also, given the likely withdrawal of CFC-containing products in the near future, we have calculated these cost estimates both including and excluding currently available CFC-containing products (this is an issue for BDP and BUD preparations only). During the period when CFC-containing products are withdrawn from sale in the UK, it is likely that the relative market shares of different named preparations will also alter, because many patients will need to switch between products, new products may simultaneously enter the market, and pack prices may also change.

6.5.2 Methods for cost comparisons

The mean weighted and unweighted annual cost of taking each type of ICS, or each type/combination of ICS with a LABA, is calculated in several stages.

First, we have calculated the **mean annual per patient cost** of taking each specific named preparation of each drug (or each combination of drugs), in order to achieve a given level of daily dosage. For each named preparation, this is calculated as:

£ per dose × doses per day × No. days in year

= (BNF £ pack price ÷ doses per pack)

× (Target daily dose ÷ No. µg BDP-CFC equivalent per dose)

× 365

Where **BNF £ pack price** is the specific British National Formulary per pack price for a specific preparation (e.g. 50, 100, 200, 250 or 400µg per dose).[276] The **doses per day** is

the number of doses of a given preparation needed to achieve a particular target daily dose level (e.g. 400µg/day of BDP-CFC equivalent ICS; see below).

Assumptions about target daily dosage

For adult patients with asthma, we have chosen to estimate costs for two 'low levels' and one 'high level' of daily dosage of ICS. The low level dosages we have costed are:

LD_{start}: Low dose starting dosage = 400µg CFC-BDP (or equivalent) per day

LD_{max}: Low dose maximum dosage = 800 µg CFC-BDP (or equivalent) per day

These equate to: the recommended starting dose for adult patients stepping up from mild intermittent asthma managed primarily by SABAs (i.e. those changing from Step 1 to Step 2 of the BTS/SIGN Guideline), and; the recommended maximum daily dose of ICS for adults before an add-on therapy (such as a LABA) should be tried (i.e. Step 3 'Add-on therapy').

For the 'high level' daily dosage we have costed is either 1500µg or 1600µg BDP-CFC (or equivalent) per day. This is assumed to approximate the median ICS dose of people being treated at Step 4 of the BTS/SIGN Guidelines.

Assumptions about number of doses per day

For simplicity, and unless otherwise recommended in the BNF, we assumed that the required daily dose of an ICS was achieved as either one dose taken twice daily or two doses twice daily. The base case assumptions are summarised in the table below.

TABLE 57 *Base case assumptions about number of doses per day*

Daily dosage (BDP-CFC equivalent)	taken either as	or as:
400µg	100µg* × 4 doses	200µg* × 2 doses
800µg	200µg* × 4 doses	400µg* × 2 doses
1500µg or 1600µg	250µg* × 6 doses	400µg* × 4 doses

* BDP-CFC or equivalent (see table below); except CIC (Alvesco®) and MF (Asmanex®) which are more usually prescribed as a single daily dose.

Assumptions about dose-equivalence with CFC-BDP

In order to compare the cost of alternative ICS preparations it is necessary to make some assumptions about the likely equivalent dose that would be required if controlled patients were switching between preparations. Because of product characteristics related to particle size and mode of action, the same quantities of different active ingredients do not achieve the same clinical effectiveness. For the practical puposes of informing dosage decisions when switching patients between ICS products, both the GINA Guidelines and the BTS/SIGN Guidelines publish ratios of dose-equivalence. These are summarised below.

TABLE 58 *Base case assumptions about dose-equivalence with CFC-BDP*

Drug	Equivalent amount of BDP-CFC (BTS/SIGN Guidelines)	Equivalent amount of BDP-CFC (GINA Pocket Guide to Asthma)	Ratio used in CMA
BDP-HFA-propelled[a]	× 2	× 2	× 2
BUD	Approx. × 1	Not shown	× 1
BUD-DPI	Approx. × 1[b]	Approx. × 1	× 1
FP	× 2	× 2	× 2
MF	× 2[c]	× 1.2[d]	× 1.2 to 2
CIC	Not established	Not stated	× 2[e]

Sources: section 4.2.3 of BTS/SIGN Guideline, and; Figure 7, p.19 of the GINA Pocket Guide 2005.

[a] Except Clenil Modulite which has been designed to have equivalent potency as BDP-CFC preparations.

[b] Despite some evidence that BUD-DPI via turbohaler is more effective than same dose of BDP-CFC.

[c] Suggested, according to the BTS/SIGN Guidelines, by 'a relatively limited number of studies'.

[d] Based on stated equivalence in the GINA Pocket Guide of 400µg MF with 500µg BDP-CFC, and 800µg MF with 1000µg BDP-CFC.

[e] A suggested dose ratio for CIC has not been pubished in any publicly available documents. The only published systematic review (March 2006), of a limited number (n = 5) of safety and efficacy trials, suggests there is no additional benefit from CIC compared with either FP or BUD, so it is potentially either as effective or twice as effective as BDP-CFC.[277] The assumption that 160µg CIC (ex actuator) = 200 µg CIC (ex valve) = 400 µg BDP-CFC is based on information supplied by Altana Pharmaceuticals Ltd. and based on the fact that trials have tended to compare once-daily CIC with other ICS at dose ratio of 1:2.

It should be noted that these ratios are fairly crude 'rules of thumb', for the main purpose of aiding doctors in deciding the starting dose of any new ICS drug when switching between drugs. They may not necessarily, therefore, reflect the relative doses actually used in the body of trials that have examined the clinical effectiveness of the different ICS drugs. Nor are they likely to reflect possible differences in the *de facto* clinical effectiveness within and between drugs due to different concordance or ease of use associated with different inhaler devices. In any case, it should be remembered that after a switch between drug treatments,

clinical guidelines recommend that the dose be adjusted upwards or downwards until the minimum dose required to maintain effective control is found.

However, to perform a cost comparison on the basis of a basic assumption of equivalent effectiveness we have to make use of these assumptions about how much of alternative ICS preparations people would probably need to take in order to maintain the same level of symptom control.

Assumptions about the mix of named preparations of each ICS drug

For some of the types of ICS drug (notably BDP) there is a wide range of named preparations, available in different physical form (aerosol vs dry powder), for different inhaler devices, and either propelled by CFC-containing or non-CFC propellents. To compare between ICS drugs it is therefore necessary to generate some single, average cost for a given level of daily dosage.

We have used two methods for doing this: (i) using an **unweighted mean annual cost**, and; (ii) using a **weighted mean annual cost**, weighted according to the current (2005) market share in terms of quantity of doses sold (in BDP-CFC equivalent units).

The unweighted mean annual cost is calculated as follows. First, for a given dose level (e.g. LDstart = 400µg BDP-CFC equivalent) calculate the annual cost of achieving this dose (e.g. all products available as 100µg BDP-CFC equivalent doses and/or 200µg BDP-CFC equivalent doses). Second, sum the annual costs for these preparations. Third, divide by the number of preparations available at these doses (i.e. the number of annual costs summed in step two).

The weighted mean annual cost is calculated as follows:

First, the adjusted quantity of each product of each ICS drug is calculated. For a product sold in 200 dose packs, for a drug where most products are available in 200 dose packs, this will simply be the quantity of packs sold (in thousands, as listed in the PCA 2005 database). However, for a product of this drug sold in a 100 dose packs, this PCA quantity sold will be multiplied by 0.5 (=100/200); similarly, for any products sold in 120 dose packs the PCA quantity sold will be multiplied by 0.6 (=120/200).

Second, using these adjusted sale quantities, total quantities are summed for each drug (BDP, BUD etc.). For each drug, total quantities are also calculated for three groupings of products: CFC-propelled aerosols (pMDI-CFC), HFA-propelled aerosols (pMDI-HFA) and products for dry powder inhalers (DPI). These total quantities are used as the denominators for the weighted mean percentages, and to calculate the proportion of adjusted sales of each subgroup of products (e.g. pMDI-HFA only, DPI only) accounted for by each product.

This has enabled the calculation of several different (weighted and unweighted) mean annual costs to estimate drug prices by broad inhaler type, and also according to whether the product contains a CFC propellant or not. This is particularly critical for estimating the mean annual cost of BDP and BUD, since CFC-containing products account for a substantial market share of these drugs, and will probably be withdrawn from the market in the near future.

For each of the five ICS drugs, and for each of the three dose levels, we have therefore estimated a weighted and unweighted mean annual cost of:

- All CFC-propelled (pMDI) products (where they exist)
- All HFA-propelled (pMDI) products (where they exist)
- All dry powder (capsule and loose powder) products
- All relevant products for that ICS (**including** CFC-propelled products)
- All relevant products for that ICS (**excluding** CFC-propelled products)

By 'relevant' products we mean those that achieve the specified daily dose in two or four doses per day, and excluding those specifically for use with nebulisers.

Note that because the combination inhaler products are only available in two named preparations (Symbicort® and Seretide®), and in a limited range of dose-strengths, we have calculated the mean cost for each separate product (instead of calculating an average cost across different combination products).

6.5.3 Results

6.5.3.1 Research question 1

Cost comparison: What is the cheapest ICS drug at treatment Step 2?

The cost comparisons presented below are justified on the basis that **we found no consistent evidence of differential effectiveness in trials comparing the two comparators of interest** (see section 5.2.2). *Table 59* and *Table 60* below summarise the unweighted and weighted cost of mean annual cost of the five ICS drugs, by inhaler and propellant type. Following the tables, *Table 59* and *Table 60* also plot the weighted and unweighted mean annual cost, and the estimated annual cost of using the cheapest and the most expensive product for each drug.

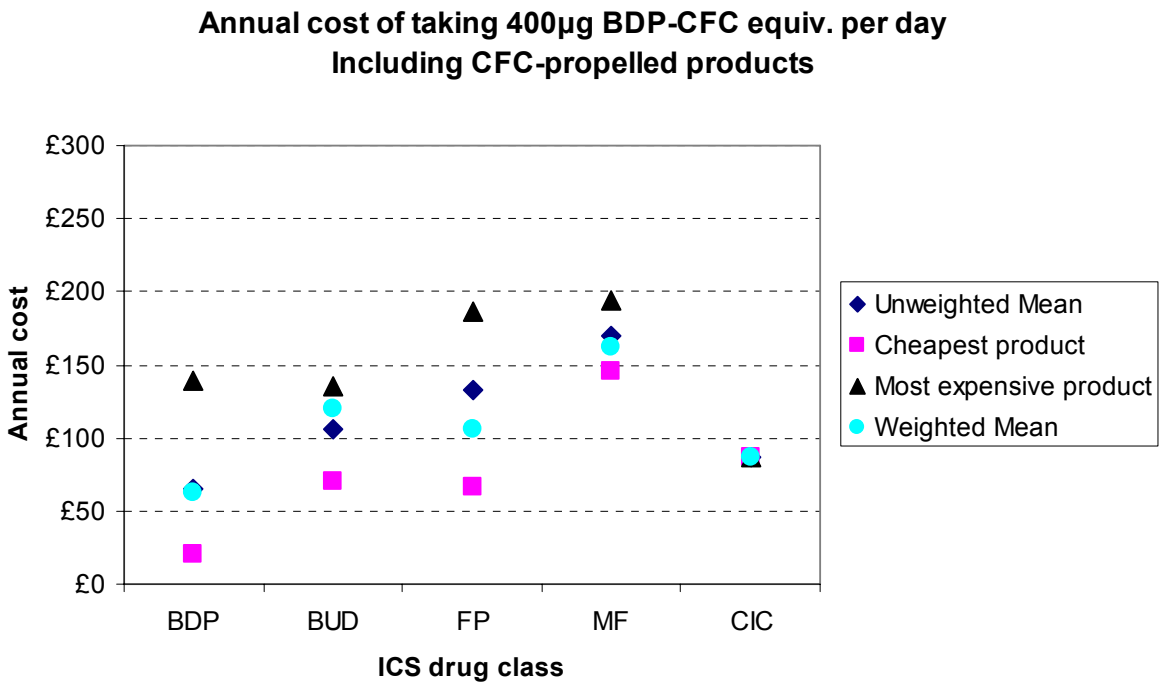
They show that overall BDP appears to be the current cheapest ICS drug at starting low doses (400µg BDP-CFC equivalent per day), costing on average £62 per year (weighted mean) or £65 per year (unweighted mean). If CFC-propelled products are excluded from the available products, BDP is still the cheapest but at a slightly higher annual cost. Excluding CFC-propelled products, and using current prices, causes a significant increase in the mean annual cost of taking BDP at this dose level since CFC-propelled products still account for over half of the product types and quantities of BDP sold. In contrast, for FP, MF and CIC no currently available products are CFC-propelled, so their exclusion does not alter the calculated mean annual cost. FP and MF are consistently the two most expensive drugs - at almost twice to three times the annual cost of taking BDP. It should be noted that the apparent relatively low cost of CIC, intermediate in cost between BDP and FP, is strongly dependent on the crude assumed dose-equivalence ratio of 1:2 with BDP-CFC products.

TABLE 59 *Unweighted mean annual cost of ICS by drug if on 400µg BDP equivalent per day*

	Preparations with same inhaler and propellant type (2006 £)			**All preparations of drug (2006 £)**	
	pMDI with CFC	**pMDI with HFA**	**DPI**	**Including CFC-propelled**	**Excluding CFC-propelled**
BDP	45	60	98	65	79
BUD	76	N/A	113	106	113
FP	N/A	66	149	133	133
MF	N/A	N/A	170	170	170
CIC	N/A	87	N/A	87	87

TABLE 60 *Weighted mean annual cost of ICS by drug if on 400µg BDP equivalent per day*

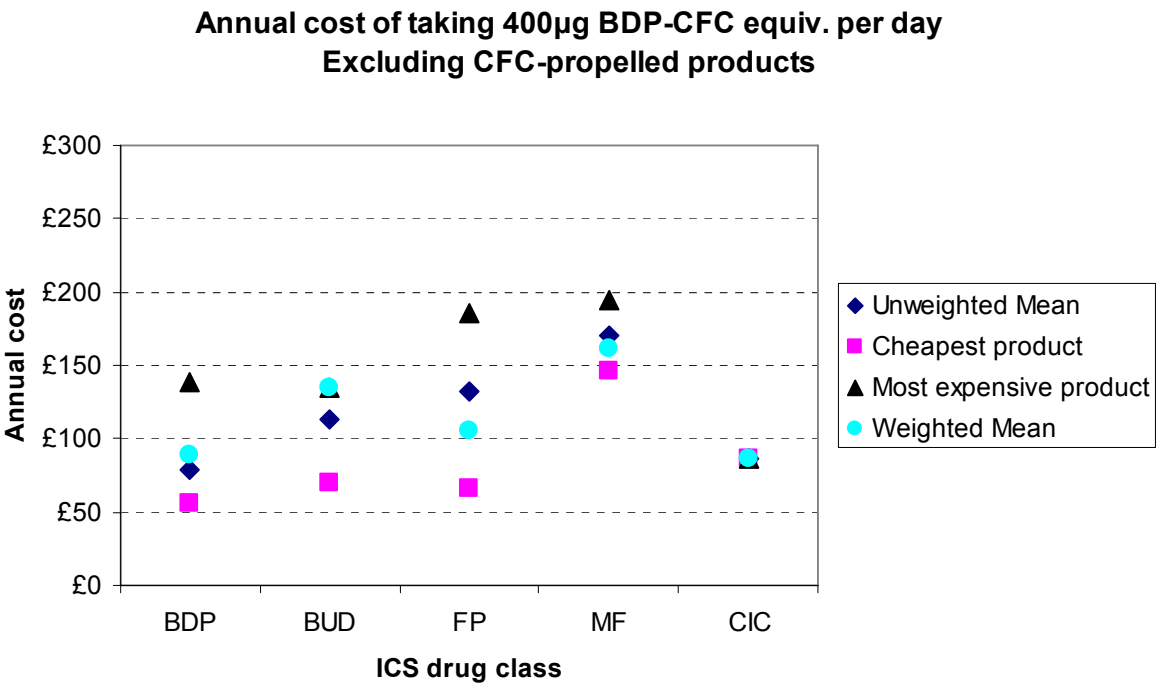
	Preparations with same inhaler and propellant type (2006 £)			**All preparations of drug (2006 £)**	
	pMDI with CFC	**pMDI with HFA**	**DPI**	**Including CFC-propelled**	**Excluding CFC-propelled**
BDP	50	61	121	62	90
BUD	76	N/A	134	120	134
FP	N/A	66	142	106	106
MF	N/A	N/A	162	162	162
CIC	N/A	87	N/A	87	87



Notes: Cheapest products of each drug: BDP = Becotide 100µg (200 D); BUD = Novolizer 200µg (100 D Ref.); FP = Flixotide Evohaler 50µg (120 D); MF = Asmanex Twisthaler 200µg (60 D); CIC = Alvesco 80µg (120 D).

Most expensive products of each drug: BDP = Becodisks 100µg (120 Ref.); BUD = Pulmicort Turbohaler 100µg (200 D); FP = Flixotide Disk 50µg (60 D Ref.); MF = Asmanex Twisthaler 200µg (30 D); CIC = Alvesco 80µg (120 D).

FIGURE 25 *Annual cost of 400µg ICS per day by ICS drug, including all products*



Notes: Cheapest products of each drug: BDP = Clenil Modulite 100µg (200 D); BUD = Novolizer 200µg (100 D Ref.); FP = Flixotide Evohaler 50µg (120 D); MF = Asmanex Twisthaler 200µg (60 D); CIC = Alvesco 80µg (120 D).

Most expensive products of each drug: BDP = Becodisks 100µg (120 Ref.); BUD = Pulmicort Turbohaler 100µg (200 D); FP = Flixotide Disk 50µg (60 D Ref.); MF = Asmanex Twisthaler 200µg (30 D); CIC = Alvesco 80µg (120 D).

FIGURE 26 *Annual cost of 400µg ICS per day by drug, excluding CFC-propelled products*

Table 61 and *Table 62* below summarise the unweighted and weighted mean annual cost of the five ICS drugs, by inhaler and propellant type, when taken at 800µg per day (BDP-CFC equivalent). Following the tables, *Figure 27* and *Figure 28* also plot the weighted and unweighted mean annual cost, and the estimated annual cost of using the cheapest and the most expensive product of each ICS.

They show that, overall at this dose level, BDP appears to be the current cheapest ICS drug, costing on average £157 per year (weighted mean) or £130 per year (unweighted mean). If CFC-propelled products are excluded from the available products, BDP is still the cheapest according to the unweighted mean, but FP becomes the cheapest according to the weighted mean amongst CFC-free products. Excluding CFC-propelled products, and using current prices, causes a substantial increase in the weighted mean annual cost of taking BDP and

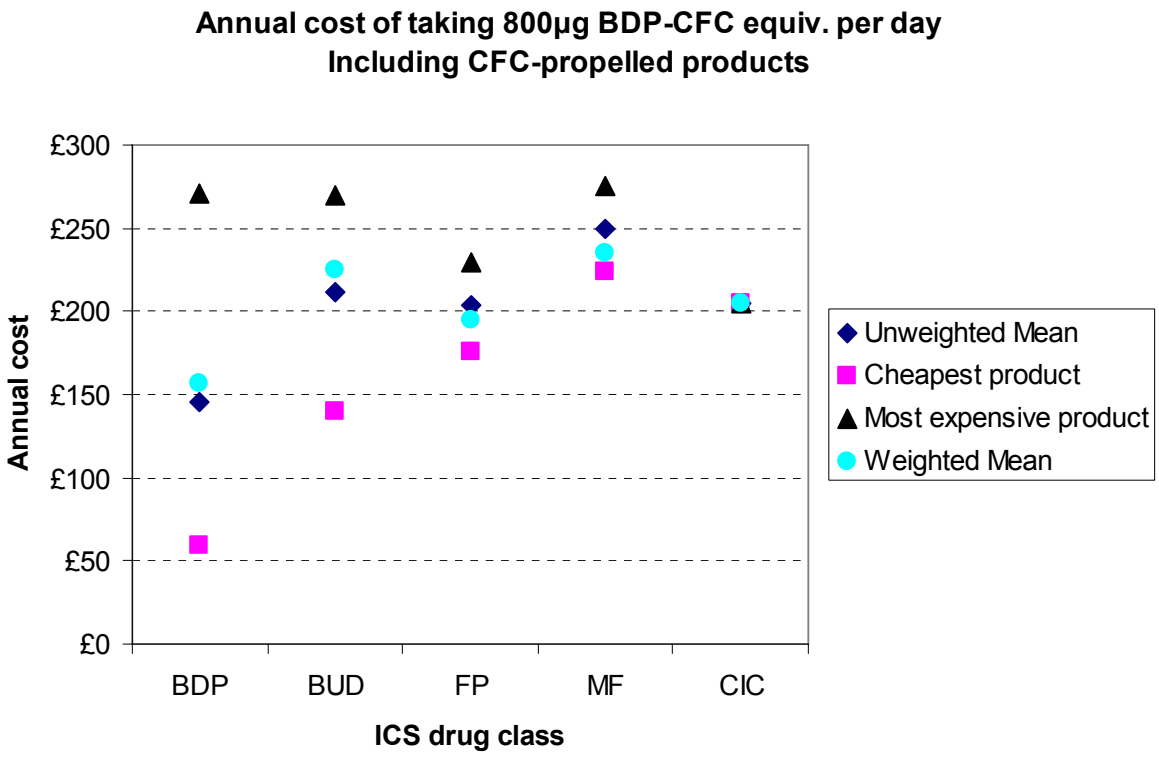
BUD at this dose level, since typically cheaper CFC-propelled products still account for over half of the product types and quantities of BDP sold. In contrast, for FP, MF and CIC no currently available products are CFC-propelled, so their exclusion does not alter the calculated mean annual cost. Although MF is the most expensive ICS drug according to the unweighted mean costs, non-CFC BUD is the most expensive if weighted according to the quantities of different products sold. It should be noted that the apparent relatively low cost of CIC, intermediate in cost between BUD and FP, is strongly dependent on the crude assumed dose-equivalence ratio of 1:2 with BDP-CFC products.

TABLE 61 *Unweighted mean annual cost of ICS by drug if on 800µg BDP equivalent per day*

	Preparations with same inhaler and propellant type (2006 £)			**All preparations of drug (2006 £)**	
	pMDI with CFC	**pMDI with HFA**	**DPI**	**Including CFC-propelled**	**Excluding CFC-propelled**
BDP	59	128	166	130	153
BUD	153	N/A	227	212	227
FP	N/A	176	218	204	204
MF	N/A	N/A	249	249	249
CIC	N/A	204	N/A	204	204

TABLE 62 *Weighted mean annual cost of ICS by drug if on 800µg BDP equivalent per day*

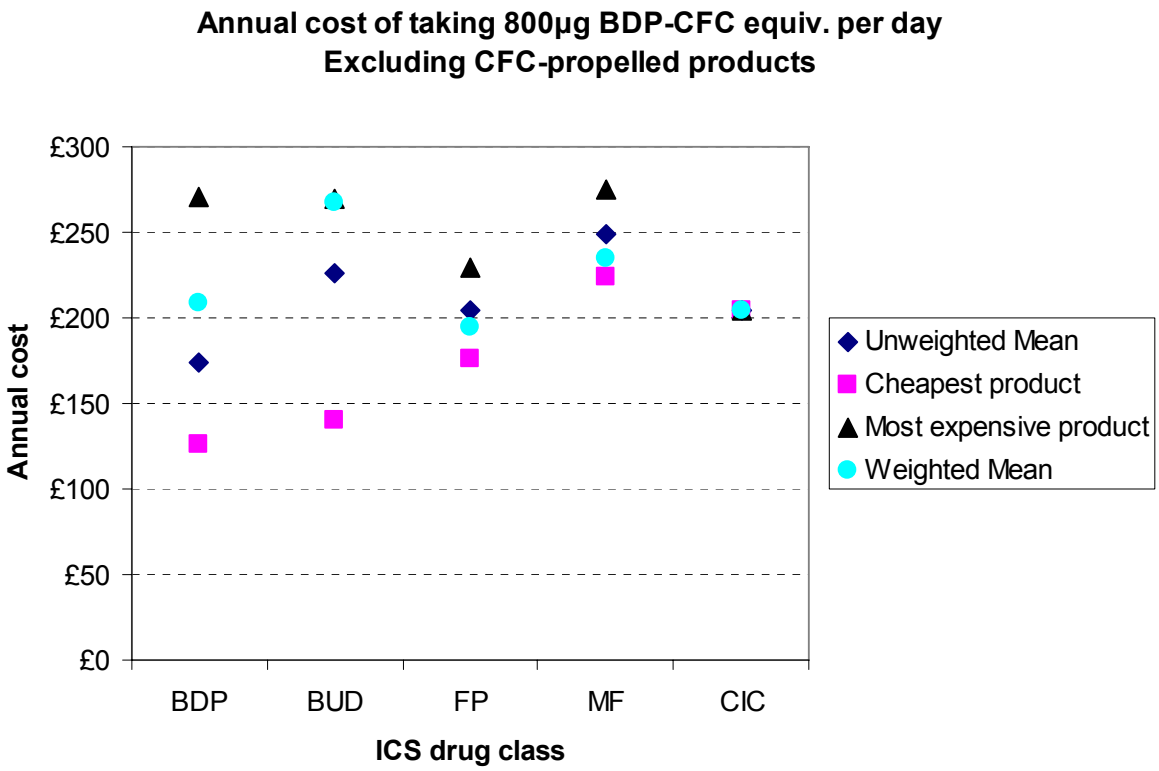
	Preparations with same inhaler and propellant type (2006 £)			All preparations of drug (2006 £)	
	pMDI with CFC	pMDI with HFA	DPI	Including CFC-propelled	Excluding CFC-propelled
BDP	59	126	248	157	208
BUD	153	N/A	268	225	268
FP	N/A	176	225	195	195
MF	N/A	N/A	235	235	235
CIC	N/A	204	N/A	204	204



Notes: Cheapest products of each drug: BDP = Becotide 200µg (200 D); BUD = Novolizer 200µg (100 D Ref.); FP = Flixotide Evohaler 250µg (120 D); MF = Asmanex Twisthaler 400µg (60 D); CIC = Alvesco 160µg (120 D).

Most expensive products of each drug: BDP = Becodisks 400µg (120 Ref.); BUD = Pulmicort Turbohaler 200µg (100 D) or 400µg (50 D); FP = Flixotide Disk 250µg (60 D Ref.); MF = Asmanex Twisthaler 400µg (30 D); CIC = Alvesco 160µg (120 D).

FIGURE 27 *Annual cost of 800µg ICS per day by drug, including all products*



Notes: Cheapest products of each drug: BDP = Qvar 100µg (200 D); BUD = Novolizer 200µg (100 D Ref.); FP = Flixotide Evohaler 250µg (120 D); MF = Asmanex Twisthaler 400µg (60 D); CIC = Alvesco 160µg (120 D).

Most expensive products of each drug: BDP = Becodisks 400µg (120 Ref.); BUD = Pulmicort Turbohaler 200µg (100 D) or 400µg (50 D); FP = Flixotide Disk 250µg (60 D Ref.); MF = Asmanex Twisthaler 400µg (30 D); CIC = Alvesco 160µg (120 D).

FIGURE 28 *Annual cost of 800µg ICS per day by drug, excluding CFC-propelled products*

6.5.3.2 Research question 2

Cost comparison: What is the cheapest ICS at Step 4 (high dose ICS)?

The results presented below were conducted on the basis that **we found no consistent evidence of differential effectiveness in trials comparing the five comparators of interest** at this dose level (see section 5.2.3).

Table 63 and *Table 64* below summarise the unweighted and weighted mean annual cost of the four ICS drugs available at these high doses, by inhaler and propellant type, when taken at 1500 or 1600µg per day (BDP-CFC equivalent). Following the tables, *Figure 29* and *Figure 30* also plots the weighted and unweighted mean annual cost, and the estimated annual cost of using the cheapest and the most expensive product for each ICS.

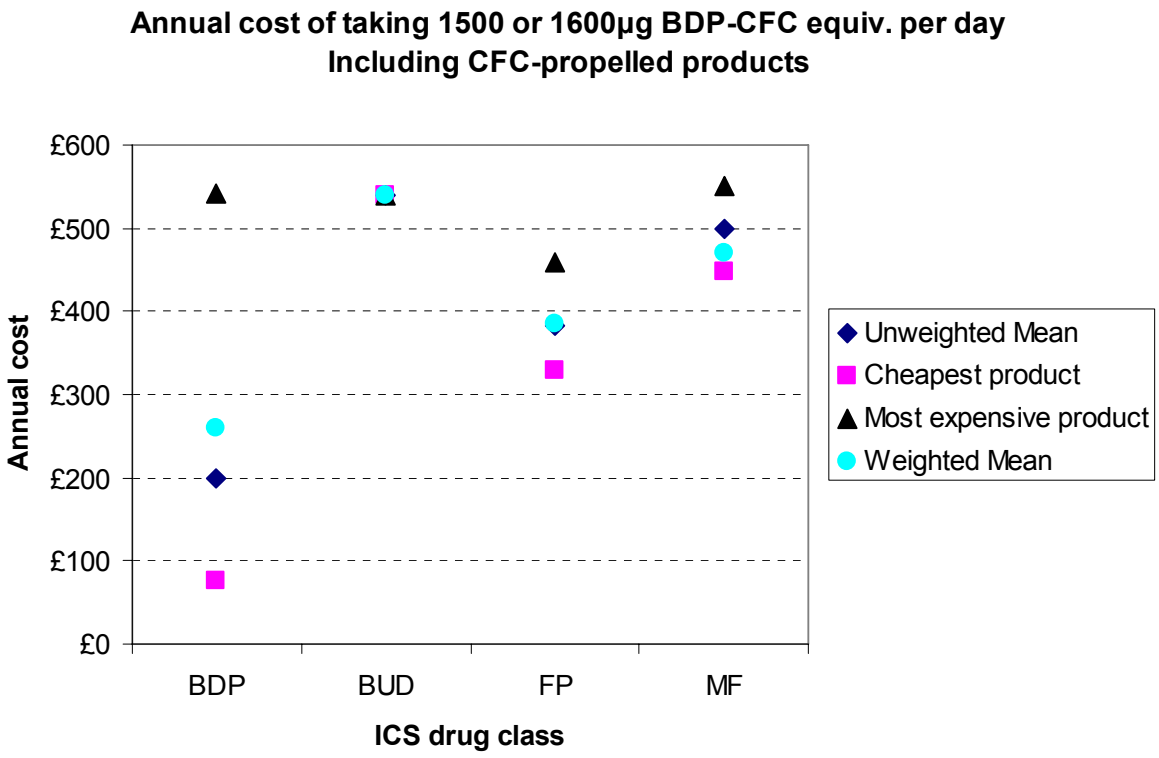
They show that, overall at this dose level, BDP appears to be the current cheapest ICS drug, costing on average £260 per year (weighted mean) or £198 per year (unweighted mean). If CFC-propelled products are excluded from the available products, BDP is still the cheapest according to the unweighted mean, but FP becomes the cheapest using the weighted mean annual cost. Excluding CFC-propelled products, and using current prices, causes a substantial increase in the weighted mean annual cost of taking BDP at this dose level, since the typically cheaper CFC-propelled products still account for over half of the product types and quantities of BDP sold. In contrast, for FP and MF no currently available products are CFC-propelled, so their exclusion does not alter the calculated mean annual cost. On average, BUD (only available as Pulmicort Turbohaler® at this high dose level) is the most expensive ICS drug according to both the unweighted and weighted mean annual costs counting all products of each ICS drug, and whether CFC-containing products are excluded or not. However, looking at the full range of costs within each ICS drug type, there is wide variation in the cost of FP, MF and especially BDP products. While the most expensive MF, BUD and BDP products are very similar in annual cost, using the cheapest CFC-free products for each drug vary from £135 per year (BDP using Asmabec Clickhaler® 250µg) to £447 (MF using Asmanex Twishaler® 400µg) or £540 (BUD using Pulmicort Turbohaler® 400 µg).

TABLE 63 *Unweighted mean annual cost of ICS by drug if on 1500 or 1600µg BDP equivalent per day*

	Preparations with same inhaler and propellant type (2006 £)			**All preparations of drug (2006 £)**	
	pMDI with CFC	**pMDI with HFA**	**DPI**	**Including CFC-propelled**	**Excluding CFC-propelled**
BDP	148	186	290	198	269
BUD	N/A	N/A	540	540	540
FP	N/A	352	391	383	383
MF	N/A	N/A	499	499	499

TABLE 64 *Weighted mean annual cost of ICS by drug if on 1500 or 1600µg BDP equivalent per day*

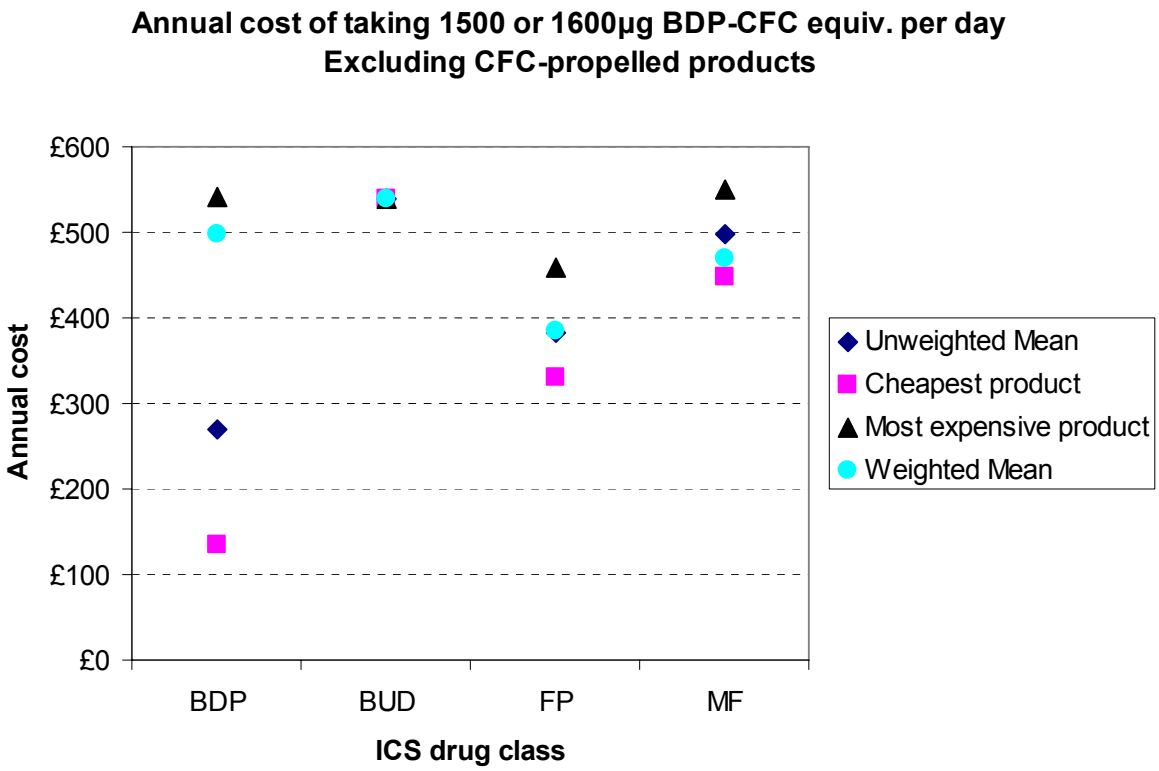
	Preparations with same inhaler and propellant type (2006 £)			All preparations of drug (2006 £)	
	pMDI with CFC	pMDI with HFA	DPI	Including CFC-propelled	Excluding CFC-propelled
BDP	139	N/A	497	260	497
BUD	N/A	N/A	540	540	540
FP	N/A	352	425	385	385
MF	N/A	N/A	469	469	469



Notes: Cheapest products of each drug: BDP = Becloforte 250µg (200 D); BUD = Pulmicort Turbohaler 400µg (50 D); FP = Flixotide Disk 250µg (60 D with device); MF = Asmanex Twisthaler 400µg (60 D).

Most expensive products of each drug: BDP = Becodisks 400µg (120 Ref.); BUD = Pulmicort Turbohaler 400µg (50 D) or 400µg (50 D); FP = Flixotide Disk 250µg (60 D Ref.); MF = Asmanex Twisthaler 400µg (30 D).

FIGURE 29 *Annual cost of 1500 or 1600µg ICS per day by drug, including all products*



Notes: Cheapest products of each drug: BDP = Asmabec Clickhaler 250µg (100 D); BUD = Pulmicort Turbohaler 400µg (50 D Ref.); FP = Flixotide Accuhaler 500µg (60 D); MF = Asmanex Twisthaler 400µg (60 D).

Most expensive products of each drug: BDP = Becodisks 400µg (120 Ref.); BUD = Pulmicort Turbohaler 400µg (50 D) or 400µg (50 D); FP = Flixotide Disk 250µg (60 D Ref.); MF = Asmanex Twisthaler 400µg (30 D).

FIGURE 30 *Annual cost of 1500 or 1600µg ICS per day by drug, excluding CFC-propelled products*

6.5.3.3 Research question 3a

Which is the more cost-effective: to increase the dose of ICS alone or to add a LABA to treatment with a lower dose of ICS? (steps 2-3 of the guidelines).

The cost consequence analysis presented below was undertaken on the basis that the review of clinical effectiveness found that ICS/LABA combination therapy was generally more effective than ICS as monotherapy when the dose ratio of ICS was 2:1. This question was also the main focus of our exploratory model-based cost-utility analyses (*Appendix 10*), and we incorporate some insights from that analysis below.

The chapter on clinical effectiveness has described and summarised the general pattern of outcome differences according to the particular ICS plus LABA drugs being compared to ICS at a higher dose. In this section, we repeat those summary tables, but additionally (a) indicate the magnitude of any measured differences in the common trial outcomes, and (b) state what the annual cost of the preventer drugs would be using the equivalent products (in the UK) to those actually used in the clinical trials.

The UK equivalent products for trialled products not available in the UK were assumed to be: Seretide Accuhaler® (for Seretide Diskus®); Symbicort Turbohaler® (for Symbicort Turbuhaler®, and for the ICS drugs: Flixotide Disk® (for Flovent® or Flixotide Diskus®). In one study, by Lalloo and colleagues,[230] the specific BUD DPI product used was not stated, so for costing purposes we assumed it would be Pulmicort Turbohaler® in the UK treatment setting).

The costs per dose for each product were obtained from the British National Formulary (issue No. 51, March 2006).[276]

Cost-consequence comparisons

There are five RCTs which compare FP/S with a higher dose of FP or BUD. Of the two trials which compared FP/S with higher dose FP only one showed a significant difference in any outcome (a +0.1L higher increase in FEV_1 from baseline); the other reported very small differences in AQLQ score change and exacerbations but did not report any tests of significance for these differences. For the higher dose comparison, the annual medication cost of FP/S combination (500µg/100µg per day) is £35 less than the higher dose of FP. In contrast, for the comparison at lower doses, the annual cost of the FP/S combination (200µg/100µg per day) is £92 higher per year. For the three trials which compare FP/S with BUD at higher dose, there seems to be a more consistent pattern of significant improvements in PEFR (morning and evening) and in symptom-free days and nights, favouring the combination inhaler. However, for these trials, the estimated annual cost of the FP/S combination varies from being £94 cheaper to £109 more expensive than the alternative of BUD at a higher dose.

There are also five trials which compare BUD/F in a combination inhaler with higher dose FP (one trial) or higher dose BUD (four trials). Again, there appears to be a reasonably

consistent pattern of significant improvements in PEFR (morning and evening), and in symptom-free days with combination therapy compared to an increased dose of ICS alone. In these trials, the annual cost of BUD/F varies from being £163 cheaper to £66 more expensive than the ICS alone at higher daily dose.

Consequences and cost of FP/SAL *vs* FP: n=2 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										Annual Cost
			Lung function			Symptoms			HRQoL	SABA	Exacerbations	Adverse events, % of patients	
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN					
1000µg vs. 500/100µg	Bergmann 12w parallel group DPI n=365	*FP*	NSD										**£481**
		FP/SAL							+0.3[†] (in AQLQ score change)		3 fewer[f] (1 vs 4)		**£446 = £35 less**
500µg vs. 200/100µg	Busse 12-24w parallel group DPI n=558	*FP*	+0.10L*** diff. in change from baseline						NSD		NSD		**£287**
		FP/SAL											**£379 = £92 more**

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies); NSD = no significant difference between trial arms; [f] indicates that results favour this trial arm but no significance testing has been reported

* P <0.05; ** P <0.01; *** P <0.001

Consequences and cost of FP/SAL *vs* BUD: n=3 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										Annual Cost
			Lung function			Symptoms			HRQoL	SABA	Exacerbations	Adverse events, % of patients	
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN					
1600µg vs. 500/100µg	Jenkins 24w parallel group DPI n=353	*BUD*						NSD			NSD	18%	**£540**
		FP/SAL	+0.09L*** diff. in mean at endpoint	+25*** diff. in mean over whole trial	+18*** diff. in mean over whole trial		+26*** median days (in 24w trial)		+0.45** (in AQLQ score change)			14%	**£446 =£94 less**
800µg vs. 200/100µg	Johansson 12w parallel group DPI n=349	*BUD*	C				C	C				38%	**£270**
		FP/SAL		+11*[a] diff. in adj. mean over whole trial	+11** diff. in adj. mean over whole trial						3 fewer[f] (7 vs 10)	38%	**£379 =£109 more**
	Zhong 6w parallel group DPI n=398	*BUD*	NSD									24%	**£270**
		FP/SAL		+23*** diff. in mean change from baseline	+13** diff. in mean change from baseline		+18%*** (diff. in day SFDs) +19%*** (diff. in 24hr SFDs)	+20%***				24%	**£379 =£109 more**

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; C = stated as comparable between trial arms, but no other data presented; NSD = no significant difference between trial arms; + indicates results favour this trial arm

f indicates that results favour this trial arm but no significance testing has been reported; a see main text

*** = P <0.001 ** = P <0.01 * = P <0.05

Consequences and cost of BUD/FF *vs* FP: 1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										Annual Cost
			Lung function			Symptoms			HRQoL	SABA	Exacerbations	Adverse events, % of patients	
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN					
500µg vs. 400/9µg	Bateman 12w parallel group DPI n=344	*FP*				NSD	NSD						**£287**
		BUD/FF	+0.11L*** diff. in geometric mean at endpoint	+20*** diff. in mean change from baseline	+17*** diff. in mean change from baseline					-0.18* diff. in mean change from baseline	12.2% points lower % of mild exacerbations		**£231 = £56 less**

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies); NSD = no significant difference between trial arms; [f] indicates that results favour this trial arm but no significance testing has been reported

* P <0.05; ** P <0.01; *** P <0.001

Consequences and cost of BUD/FF *vs* BUD: n=4 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										Annual Cost
			Lung function			Symptoms			HRQoL	SABA	Exacerbations	Adverse events, % of patients	
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN					
400µg vs. 200/9µg	Lalloo 12w parallel group DPI n=467	*BUD*	NSD									54%	**£135**
		BUD/FF		+9* diff. in mean change from baseline	+9*** diff. in mean change from baseline		+6%** (diff. in 24hr SFDs)			-0.2* diff. in change from baseline	26[f] fewer patients (136-110) having mild exacerbations	58%	**£201 = £66 more**
400µg vs. 200/9µg	O'Byrne 52w parallel group DPI n=2760	*1.BUD*	NSD 1vs.2								NSD 1vs.2	57%	**£270**
		2.BUD/FF[to]		+7*** diff. in mean over whole trial	+4*** diff. in mean over whole trial		+7%			-0.25 (fewer) puffs per day		52%	**£201 = £69 less**
		3.BUD/FF[mar]	+0.1L diff. in means over whole study	+16*** diff. in mean over whole trial	+15*** diff. in mean over whole trial		+8%			-0.45 (fewer) puffs per day	0.32*** fewer mild exacerbations per patient/year 0.16*** fewer severe exacerbations per patient/year	54%	**£201 = £69 less** (for maintenance drugs only) **or £302**, if £101 annual cost of BUD/F as reliever is added

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results										Annual Cost
			Lung function			Symptoms			HRQoL	SABA	Exacerbations	Adverse events, % of patients	
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN					
400µg vs. 200/9µg	Pohl 20w parallel group ADM DPI n=133	*BUD*	C								C	81 events	**£486**
		BUD/FF		+9[f] diff. in mean at endpoint	+7[f] diff. in mean at endpoint				+6* diff. in SF-36 score (at endpont?)			74 events	**£324 = £163 less**
800µg vs. 400/9µg	Scicchitano 52w parallel group DPI n=1890	*BUD*										NSD	**£270**
		BUD/FF[mar]	+0.1[f] diff. in mean at endpoint	+20*** diff. in mean at endpoint	+14*** diff. in mean at endpoint	-3.3% diff. in NWs	+7.5%*** diff. in 24hr SFDs				0.61*** hazard ratio for severe exacs.		**£231 = £39 less**

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; ADM = adjustable dose maintenance in which those receiving BUD had a mean of 560µg/day, metered (448µg/day delivered), and those receiving BUD/FF had a mean of 1440/43µg/day, metered (1152/35µg/day delivered); C = results stated to be comparable between treatment arms, but no other data presented; NSD = no significant difference between trial arms

[f] indicates that results favour this trial arm but no significance testing has been reported; to terbutaline only used as reliever in this arm

[mar] combination inhaler used as both maintenance and reliever medication in this arm

All outcome and cost differences for O'Byrne at al. are for BUD/FF compared with BUD. The cost of BUD/FF as a reliever medication (mean = 1 dose per day) is £101 per year, compared with terbutaline or salbutamol cost of only £5 to £25 per year.

* P <0.05; ** P <0.01; *** P <0.001

Overall, these comparison tables show that while there are some consistent statistically significant differences in clinical effectiveness, which in general favour the use of combination inhalers, they are often (but not always) cheaper than increasing the ICS dose. Even in this relatively small sample of trials, the variation in dose levels and products compared is such that the differences in annual medication costs vary widely. These comparisons reinforce one of the broad conclusions from the exploratory cost-utility analysis that, on top of small and uncertain differences in treatment effectiveness, the considerable variations in product costs within each drug type introduce so much additional uncertainty that conventional decision rules for making judgements about cost-effectiveness are almost worthless.

Also, it should be remembered that these cost-consequence comparisons are (a) strictly limited to the particular ICS versus ICS plus LABA comparators that have been included in existing trials (and they therefore overrepresent comparisons with increased FP or BUD, and include no comparisons with increased BDP or other ICS), and also (b), for decision making purposes, suffer from the same limitations as any single short-term trial-based economic evaluation.[278] Of course, they omit any potential cost savings due to any exacerbations avoided, and the value of potential quality of life gains due to having more days and nights without asthma symptoms. (Our model-based analysis has shown that the latter factor, in particular, can greatly influence cost-effectiveness estimates for this comparison.) They therefore still only offer a limited perspective on our original, broader, cost-effectiveness question.

6.5.3.4 Research question 4

Combination versus separate inhalers at Step 3

For the comparison of both combination inhalers with the same drugs delivered in separate inhalers, clinical equivalence between the treatment strategies can be assumed from the results of the clinical effectiveness analysis. The cost comparisons presented below are therefore justified on the basis that **we found no consistent evidence of differential effectiveness in trials comparing the comparators of interest** (see section 5.2.6)

As *Table 65* and *Table 66* below show, for both currently available combination products (Seretide® and Serevent®), the combination ICS-with-LABA product is almost always

cheaper than taking the same drugs in separate inhalers. For taking BUD with FF, using Symbicort via Turbohaler is always cheaper than taking Pulmicort via Turbohaler (at the same BUD dose) and taking FF separately. The estimated annual savings vary between £36 and £227 depending on the exact preparation of FF used and the daily dose of BUD required.

For taking FP with SAL, using Seretide via Accuhaler is also always cheaper than taking Flixotide Accuhaler (at the same FP dose) and SAL separately. The estimated annual savings vary from £85 (if on 200µg FP per day) and £298 (if on 1000µg FP per day). Similarly, using Seretide via Evohaler is always cheaper than taking Flixotide via Evohaler (at the same FP dose) and taking SAL separately.

Note that, as specified in our research Question 4, we have only assessed the comparative annual cost of the combination inhalers with the same ICS and the same or broadly equivalent LABA. If the combination inhalers were compared with, for example, BDP plus LABA in separate inhalers the overall result we have stated may not hold.

TABLE 65 *Annual cost of combination versus separate inhalers: BUD with FF added*

		Annual cost (£) by daily dose of BUD		
Combination or BUD	**FF**	**200µg per day**	**400µg per day**	**800µg per day**
Symbicort Turbohaler (combination product)		201	231	462
Separate inhalers: Pulmicort Turbohaler, plus:	Atimos Modulite 10.1µg	296	363	498
	Oxis 4.5µg (or 9µg)*	369	437	572
	Foradil 12µg	391	458	593
Difference in annual cost (separate less combination):				
Separate inhalers: Pulmicort Turbohaler, plus:	Atimos Modulite 10.1µg	+95	+132	+36
	Oxis 4.5µg or 9µg	+169	+206	+110
	Foradil 12µg	+190	+227	+131
*Oxis® 4.5µg and 9µg are the same price per dose.				

TABLE 66 *Annual cost of combination vs separate inhalers: FP/SAL added*

Preparation		**Annual cost (£) by daily dose of FP**		
	Taken as	**200µg per day**	**500µg per day**	**1000µg per day**
As dry powder:				
Flixotide Accuhaler	2 blisters/day	109	259	440
Serevent Accuhaler (or aerosol inhaler)#	2 blisters/day*	356	356	356
Both (total):		465	615	796
Seretide Accuhaler (FP and S combined)	2 blisters/day*	379	446	498
Difference in annual cost:		+85	+169	+298
As aerosol:				
Flixotide Evohaler	4 puffs/day	66	259	440
Serevent aerosol Inhaler	4 puffs/day*	356	356	356
Both (total):		422	615	796
Seretide Evohaler (FP and S combined)	4 puffs/day*	237	479	815
Difference in annual cost:		+185	+135	-19

* Each blister contains 50µg of SAL, and each puff contains 25µg of SAL

\# Serevent Accuhaler and aerosol inhaler are the same price per µg.

6.5.3.5 Research question 5

FP/SAL vs BUD/FF at Step 3

The clinical effectiveness review did not identify any consistent differences in effectiveness between the two combination inhalers (see section 5.2.7), and so we believe it was reasonable to assume clinical equivalence between these two treatment strategies.

Table 67 compares the cost of taking ICS with LABA in the two currently licenced combination inhalers, Seretide® and Symbicort®. In making the comparison between these products we have assumed that 400µg and 800µg (metered dose) of BUD are equivalent to 200µg and 500µg of FP, respectively, and also that 12µg (metered) of FF per day has effectiveness equivalent to 100µg of SAL per day. While this assumption partly reflects the levels of drugs used in the existing head-to-head trials of Symbicort® versus Seretide® (which compare Symbicort 800µg BUD versus Seretide 500µg FF per day), it should be

noted that all these trials involved Seretide Diskus (which is marketed as Accuhaler in the UK), rather than Seretide Accuhaler.

At the lower dose level, the cheapest combination inhaler is BUD/F for DPI (Symbicort Turbohaler® = £231 per year) but this is only slightly cheaper than FP/S as aerosol for pMDI (Seretide Evohaler® = £237 per year). At the higher dose level FP/S for DPI (Seretide Accuhaler®) is the cheapest at £446 per year, but this is only £16 cheaper than having the ICS 'equivalent' dose of BUD/F Symbicort Turbohaler®.

TABLE 67 *Annual cost of combination inhalers compared*

Combination product	**Taken as**	**400µg* BUD per day**	**800µg* BUD per day**
Symbicort Turbohaler (BUD/FF)	2 puffs/day	231	462
		200µg FP per day	**500µg FP per day**
Seretide Accuhaler (FP and S combined)	2 blisters/day	379	446
Seretide Evohaler (FP and S combined)	4 puffs/day	237	479
* metered dose			

6.6 Summary of the economic analyses

Below we summarise the economic analyses and/or cost comparisons for each the cost-effectiveness research questions (with the exact question wording revised in the light of the clinical effectiveness evidence, and the infeasibility of formally assessing cost-effectiveness for most questions).

Q1. What is the cheapest type of ICS at Step 2 of the BTS/SIGN Guidelines?

At low ICS doses at Step 2 of the Guidelines the weighted mean annual cost of taking an ICS drug at 400µg BDP-CFC (or equivalent) varies over three-fold from £53 for BUD to £170 for MF. The weighted mean annual cost of taking an ICS drug at a higher dose of 800µg BDP-CFC (or equivalent) varies from £157 for BDP to £235 for MF. At this higher dose level currently available BUD preparations cost on average £225 per year; only slightly less expensive than MF.

CFC-containing products are currently considerably cheaper than the dry powder or HFA-propelled alternatives for each drug. As a consequence, and assuming pack prices and relative market shares remain the same, when CFC-containing products are withdrawn, the weighted mean annual cost of taking BDP will increase from £62 to £90 (at a 400µg ICS/day dose level) and from £157 to £208 (at a 800µg ICS/day dose level). Consequently, amongst non-CFC-containing preparations FP is currently the cheapest ICS in terms of weighted mean annual cost, at £195 per year at the higher dose level. With the unweighted mean annual costs, there is still an increase in the cost of BDP and BUD products when CFC-containing products are excluded, but the ordering of the drugs from cheapest to most expensive is less altered.

What these weighted averages conceal, however, is very wide variations in the cost of individual preparations for each drug. This is an issue particularly for BDP, BUD and FP products. For example, currently the cheapest way of obtaining 800µg of BDP per day is with Becotide® 200µg four times daily (4.07p per dose = £59.42 per year); the most expensive way is to use Becodisks® 400µg twice daily (37.14p per dose = £271.13 per year). Similarly, for obtaining 800µg of BUD per day, the cheapest product is Novolizer® BUD 200µg taken four times daily (9.59p per dose = £140.01 per year); the most expensive products are Pulmicort Turbohaler® 200µg and 400µg (18.5p and 37p per dose = £270.10 per year).

Q2. What is the cheapest type of ICS at Step 4 of the BTS/SIGN Guidelines?

At a dose level of either 1500 or 1600µg of BDP-CFC equivalent per day, BDP appears to be the current cheapest ICS drug, based on either weighted or unweighted mean annual costs (costing £260 and £198 per year respectively). However, if CFC-propelled products are excluded FP becomes the cheapest ICS product according to our estimated means, when weighted according to current product market shares. Excluding CFC-propelled products, and using current prices, causes a substantial increase in the weighted mean annual cost of taking BDP at this dose level.

Q3a. What are the relative costs and consequences of taking ICS plus LABA in a combination inhaler, versus taking an increased dose of ICS?

Alongside evidence of some relatively consistent clinical effectiveness differences favouring combination inhalers, they can often also be cheaper than increasing the dose of ICS – at least when based on those products used in the same trials. However, we are cautious not to make any firm cost-effectiveness conclusion from these cost consequence data, since this 'result' largely depends on the specific dose-levels, and exact products compared in these trials. Furthermore, we have not factored in the other potential cost advantages that might accrue to combination inhalers if the relative reductions in exacerbation rates measured in some trials were more certain. Nor, as important, do they capture the potential quality of life impacts of reducing the proportion of days or nights with symptoms which some trials show. When we do factor in such variables however, as we have done in our exploratory cost-utility analysis (*Appendix 10*), the major uncertainty in the cost estimates remains, and the joint uncertainty surrounding the cost and effectiveness estimates available from the research literature prevents any straightforward use of conventional rules for interpreting cost-effectiveness ratios.

Q4. What is cheapest – taking ICS with LABAs in combination or separate inhalers?

Overall, taking ICS with LABAs as either of the two currently available combination products is nearly always cheaper than taking the relevant ingredient drugs in separate inhalers. Only when taking very high doses of Seretide® (1000µg FP per day costing £815 per year) would it be slightly cheaper to take the equivalent ingredient drugs in separate inhalers (taking Flixotide Evohaler® and Serevent® aerosol inhaler separately would cost £796 per year, or £19 less). For all the other assessed comparisons of equivalent drugs, using combination inhalers was between £36 and £227 cheaper per year.

Q5. Which combination inhaler is the cheapest?

This comparison crudely assumed that 400µg and 800µg of BUD are equivalent to 200µg and 500µg of FP, respectively, and also that 12µg of FF per day has effectiveness equivalent to 100µg of SAL per day. On the basis of these assumptions there is no combination inhaler which is the cheapest in all circumstances. At the lower daily dose of 400µg BUD or 200µg

FP per day, Seretide Evohaler® and Symbicort Turbohaler® are very similar in annual cost (£237 and £231), with Seretide Accuhaler® being more expensive than both of these (£379 per year). Similarly, when taking 800µg BUD or 500µg FP per day, the annual cost of taking Symbicort Turbohaler® (£462) is similar to that of either Seretide product (Accuhaler £446 and Evohaler £479 per year).

7. Factors relevant to the NHS and other parties

Asthma is one of the most common chronic conditions in the UK with a prevalence of approximately 5.2 million.[9] Therefore the economic burden of asthma in both direct and in-direct costs to the NHS is high. In 2005 expenditure on corticosteroids for respiratory conditions cost the NHS £436 million. Although this was only 15th in terms of the number of prescriptions issued, this is the third largest component of the total cost of community-dispensed drugs in England.

Estimates of the prevalence of treated asthma in adults vary somewhat according to the source used to obtain them. However, estimates from the General Practice Research Database indicate that the prevalence of adults being treated for asthma ranged from 44.5 – 89.4 per 1000 patients for men aged 15 years and over and from 52.2 – 88.0 per 1000 patients for women of the same age group. In both sexes, prevalence was highest in those aged over 65 years. Adolescents and adults with asthma place various demands on the NHS budget, ranging from the cost of prescribed asthma medications, to various levels of health service use including GP and nurse consultations, accident and emergency department visits, and hospital admissions. Each of these is associated with a varying level of cost.

7.1 ICS therapy alone

The cost comparisons presented in this review indicate there are currently considerable relative differences in the mean annual cost between the different ICS preparations, as well as large cost differences between individual products within each ICS drug. However the absolute size of these differences, of up to £200 per year, may not seem excessive. From our systematic review of clinical effectiveness these differences do not appear to be associated with any additional treatment benefit which would off-set the additional cost of the more expensive options. Therefore, unless there are other benefits associated with the more expensive products (such as ease of correct use), there may be little justification for the sometimes considerable cost differences between the five licensed comparators. There are potential cost savings to be made for the NHS if suitable patients who are currently treated

with the more expensive ICS drugs or preparations could be switched to a cheaper option. Currently the largest cost savings would be associated with switching all patients to the cheapest BDP/BUD CFC-propelled preparations available depending on the target daily dose required. However, this is not a realistic treatment strategy as CFC-propelled devices are due to be phased out in the near future, and there are additional GP consultation costs associated with a review to switch patients between treatment strategies and drugs. With the phasing out of CFC-propelled products the cost of providing ICS therapy to the NHS is likely to increase. Additional costs will be associated with switching patients who are currently on CFC-propelled formulations to new preparations and the higher costs associated with all non-CFC propelled preparations of ICS. The exact cost implications to the NHS are difficult to project, as it is likely that as CFC-propelled formulations are removed from the market, the relative market share of non-CFC formulations will change and new CFC-free products may also enter the market. In order to realise any potential cost savings it may be important to review patients ICS therapy in routine GP or nurse consultations and examine whether switches can potentially be made to cheaper preparations of the same product.

Importantly, any potential cost savings of switching patients between either ICS drugs or individual preparations might easily be off-set by the costs incurred by potentially higher exacerbation rates. The BTS/SIGN Guidelines state that patients and clinicians should choose the preparation that most suits the individual patient. This will be based not only on the preparation, but also the suitability of the device and the complexity of the treatment regimen to an individual patient. It is therefore necessary that any potential switches to cheaper preparations, should be done with the patients agreement in order that concordance rates are not diminished. This is particularly pertinent within both an adolescent age group and also in the elderly.

7.2 ICS plus LABA

There are potential direct savings to the NHS if patients using ICS and LABA in separate inhalers switch to combination ICS/LABA products delivered in the same inhaler. Taking Symbicort (BUD/FF) via Turbohaler is associated with an estimated annual saving between £36 and £227 compared to taking Pulmicort via Turbohaler and taking FF separately (the exact saving depending on the specific preparation of FF used and the daily dose of BUD required).

Taking Seretide (FP/S) via Accuhaler is associated with an estimated annual saving of between £85 (if on 200µg FP per day) and £298 (if on 1000µg FP per day) compared to taking Flixotide and Serevent via Accuhaler. Likewise, using Seretide via Evohaler is nearly always cheaper than taking Flixotide via Evohaler (at the same FP dose) and taking SAL separately.

8. Discussion

Undertaking this assessment has highlighted the difficulties in assessing intervention effects for the treatment of asthma. In the most part these are a reflection of the complex nature of the disease and the way that by necessity outcomes are defined and measured within clinical trials. In the sections below a brief summary of these issues is outlined.

8.1 Assessing the effectiveneness of interventions for asthma

Asthma is a common chronic condition with a number of definitions based on disease process, clinical symptoms and their pattern over time and response to external stimuli. Each definition defines different populations in terms of severity, the underlying pathological process and the likely disease trajectory. Asthma is also partly defined by the variation of symptoms over time, thus making the detection of changes due to interventions more difficult to identify.

In terms of outcomes of treatment for asthma, death is very uncommon and so is not an informative outcome measure for assessing the effectiveness of treatment at the levels of severity which are considred in this report. A wealth of other outcome measures that are commonly reported can broadly be divided into the categories of lung function, symptoms, acute exacerbations and use of rescue medication, but no standardised measures are used consistently in trials. Measures of lung function such as FEV_1 and morning and evening PEFR are among the most commonly reported outcomes. However, although FEV_1 is widely reported in trials, it may be expressed as absolute changes or % predicted, thus preventing clear comparisons between results of different studies. Symptoms are also widely reported, but trials do not use consistent methods for scoring symptoms or defining measures such as symptom-free days or nights. Similarly, definitions of exacerbations vary considerably. Very few trials report health related quality of life which, as well as being important in its own right, is needed to inform cost-utility analysis. Composite outcomes are also reported, but again there is no consistency across trials in the way such outcomes are defined, thus preventing clear comparisons being made across all relevant technologies.

While lung function provides the more objective assessment of response to treatment, and probably more closely reflects the underlying disease process, the clinical significance of

reported changes in lung function are not clear. Disease severity also relates to the underlying disease process, reflected in lung function and symptoms, but is most commonly defined by level of medication. Patients on substantial amounts of medication may be classified as having moderate or severe disease, but this classification will give no indication of their level of symptoms which may be well or poorly controlled.

The aim of treatment is to control symptoms and enable patients to lead as normal a life as possible, so well controlled asthma is a composite concept that varies between patients and professionals. It is dependent on any given patient's expectations for their lifestyle (e.g. being active versus sedentary and a willingness to avoid known trigger factors), as well as their acceptance of a regular treatment regimen. Each individual therefore must balance these factors to allow them to achieve an acceptable level of symptoms and medication and an acceptable lifestyle for them. Part of this balance is the extent to which patients will adhere to a medication regimen when they are symptom-free; many will adhere while they are symptomatic, but choose to reduce treatment levels once symptom-free. This step down in treatment may be appropriate in response to symptoms, but it may happen too quickly and lead to a return of symptoms or an exacerbation. Mild exacerbations may be managed either by the patient alone by increasing medication use, or be managed within a primary care setting, leading to the wide variation in definition referred to above. From the perspective of assessing cost-effectiveness, however, it is particularly important to be able to identify the health care resource use associated with more severe exacerbations. These are usually defined as those exacerbations requiring hospital admissions or attendance in emergency departments, but many non-clinical factors influence admission to hospital, particularly for both adolescents and the elderly.

Assessing differences in health care costs for the treatment of asthma is difficult, because of the difficulty in deriving a single representative cost for each drug. There are a range of alternative products, available in a range of doses and delivered by different devices for each drug. Therefore there can be a number of ways of achieving any given daily dose of a particular drug, with significant consequences for the cost of delivering that dose. In order to make any comparisons in terms of costs between the different drugs, assumptions have to be made regarding dose equivalence and the way in which the target daily dose is achieved.

A further assumption must be made regarding the context of the BTS/SIGN Guidelines for assessing intervention effects of the different comparators under consideration. Whilst the

Guidelines are well established and have been used for a number of years within the UK, it is clear that many clinical trials are not set within their context, and the treatment regimens assessed do not fit neatly into the Guideline steps. For example, a number of trials have assessed different ICS in dose ratios of 1:2 (BDP-CFC equivalent) whereby the lower dose comparator arm is within Step 2 of the Guideline, and the higher dose arm is at a dose level within Step 4. Furthermore, use of the Guideline steps for assessing intervention effects for only ICS and ICS/LABA creates an artificial boundary between the treatment choices possible within the context of this assessment, and those available in clinical practice. Within this assessment the effects of stepping up effectively steroid naïve patients directly from Step 1 (SABA use only) to Step 3 (ICS and LABA) has not been reviewed, although anecdotal evidence suggests that this does occur in clinical practice, particularly if control of nocturnal symptoms is poor. Additionally, the effects of concomitant medication use e.g. the addition of a leukotriene receptor antagonist or theophylline, for patients treated at Step 4 of the Guidelines has not been reviewed, despite the fact that most patients would not be treated on high dose ICS alone at this step.

The two other areas that have not been formally assessed in this assessment report are the issues of device type and concordance, issues which are inextricably linked. It is well recognised that a large proportion of the asthmatic population has difficulty in using particular inhaler devices. This difficulty relates particularly to pMDIs and to a lesser extent to DPIs. Both require the ability to coordinate inhalation with activation of the inhaler. However, within the context of a clinical trial only those patients who are able to use the device type being trialled effectively will be eligible for inclusion. All trial evidence of the effectiveness of inhaled treatment for asthma should therefore be considered carefully for its generalisability to the general population with asthma rather than the subgroup able to use the trial devices.

Given the probable device-related variations in both compliance with correct inhaler technique and adherence to recommended daily doses, the rate of concordance with treatment regimens is likely to be considerably higher in clinical trials than routine practice. Whilst concordance rates were not formally assessed in the clinical effectiveness review, concordance rates were around 70% to 95% in the trials where reported. This is considerably higher than the rates observed in practice, for which it is generally observed that approximately 50% of patients take the full amount of prescribed medication (see Background). This figure is likely to vary considerably depending on the level of support

patients get in primary care and from asthma specialist nurses and their ability to use their prescribed inhaler devices.

8.2 Limitations of the evidence base

There is a relatively large volume of evidence for the efficacy and safety of ICS and LABAs. Trials of these drugs have been conducted and published over decades, as new drugs have been tested and launched. They vary considerably in size, patient characteristics, treatment strategies tested, methodological quality and standards of reporting. This is to be expected given the broad remit of this assessment.

The trials identified vary in treatment duration from around six weeks to two years, with the majority lasting 12 to 24 weeks. These trials do not adequately capture the longer-term effects of ICS and LABA therapy, particularly long term adverse events and impact on bone mineral density, and growth, particularly for younger patients. Relatively few of the trials followed up patients beyond six months to a year.

It is also not clear in the trials what consititutes the minimal clinically significant change for many of the reported outcomes such as lung function, symptoms or exacerbations. Lung function probably reflects the underlying disease process more closely than symptom measures or HRQOL, while exacerbations are probably only triggered when lung function drops below a certain threshold. Hence it is likely that lung function changes may still be detectable at a point in the disease process when patients have few if any symptoms.

The wide range of possible outcome measures, most with no widely accepted and standardised method of measuring them, makes comparison across studies difficult and combining studies in a meta-analysis largely inappropriate. Trials have also been conducted for a variety of reasons and are not necessarily powered to detect superiority of one ICS over another. It is also not always clear how well blinding is maintained when drugs are delivered through different devices, although some trials report the use of placebo devices. Reporting of baseline population characteristics and outcome measures is frequently poor or selective. Additionally the patients included in many of the trials may not necessarily be representative of patients seen in routine clinical practice. Entry criteria for many of the trials generally favoured relatively younger, healthier patients without co-morbidities (e.g. cardiovascular disease, COPD), as they do in many clinical areas. Although some trials did accept

smokers, heavy smokers were often excluded. Results were rarely reported separately for smokers and extrapolation from the results of non-smokers to this group is not advised. The results of this assessment therefore may not be generalisable to older patients with other significant conditions, including advanced irreversible airways disease.

8.3 Review of clinical effectiveness

Just under 70 RCTs were included in this assessment of which approximately half have been included in Cochrane systematic reviews. This assessment therefore adds to this body of evidence, providing a systematic synthesis of these drugs within the context of a comprehensive and recognised care pathway. Below we discuss the key findings according to Steps 2 to 4 of the pathway, in the context of our five review questions.

Review question 1: Which ICS is the most-effective at low doses?

Twenty two relevant RCTs of the efficacy and safety of ICS at doses up to 800µg per day BDP/BUD or equivalent (corresponding to Step 2 of the BTS/SIGN Guidelines)[1] were identified. Within this dose range there was a high degree of variability in the doses used in the trials, ranging from 100µg to 800µg per day. There did not appear to be a particular dose that was more commonly tested than others.

Beaseline populations, where sufficiently reported, were generally appropriate for Step 2 of UK guidelines.

In general all of the ICS were associated with favourable changes across a range of outcomes. However, there were few statistically significant differences between them when evaluated in pairwise comparisons at the accepted clinically equivalent doses. The ICS can be considered generally equivalent in clinical terms, although few studies explicitly aimed to assess clinical equivalence / non-inferiority.

The BTS/SIGN Guidelines note that BDP and BUD are approximately equivalent in clinical practice.[1] Similarly, the Cochrane review of BDP and BUD[54] noted few significant differences between them. The results of the current assessment generally accord with these findings, although not all studies in the Cochrane review were included in this assessment and vice versa. In this assessment, when BUD and BDP were compared (five studies, all at a nominal

1:1 dose ratio) the only significant differences were for measures of lung function. There was a significant difference in favour of BDP in FEV_1 from a meta-analysis of two studies. However, for morning and evening PEFR there was a significant difference in favour of BUD, although this was reported in one small trial. Adverse events appeared similar.

The BTS/SIGN Guidelines also note that FP provides equal clinical activity to BDP and BUD at half the dosage.[1] This is based on a reported increased potency for FP. In the Cochrane review of FP compared to BDP or BUD,[168] the only significant differences between the drugs when administered at a 1:2 dose ratio (FP: BDP/BUD) were for FEV_1 and morning PEFR, which were in favour of FP. There were few differences between the drugs on other outcome measures, although limitations in the reported data prohibited meta-analysis of these outcomes. Results of the comparison of FP with BDP in the current assessment (comprising a sub-set of studies in the Cochrane review, plus an additional study) were similarly mixed. In general there were few significant differences between groups across outcomes. All six of the included trials compared the two at a nominal 1:2 dose ratio. However, in one trial FP was shown to be statistically more favourable on all of the efficacy measures, but in this study FP was given at a slightly higher dose ratio than 1:2, which may account for the more favourable outcomes for it. Results of the comparison of FP with BUD (five studies, all at a nominal dose ratio 1:2) were also mixed. Significant differences in favour of FP were identified for symptoms, although this was only from one trial. Meta-analysis of the proportion of patients with an adverse event was significantly in favour of BUD.

As yet there are no published Cochrane reviews of the newer ICS, specifically CIC and MF, either compared to each other or to the established corticosteroids. This assessment is therefore one of the first to systematically review their relative safety and efficacy. One of the key findings is that there is currently a limited evidence base for the newer corticosteroids, and caution is thus advised when interpreting the results of trials. Trials of CIC compared to BUD and FP were included. However, no trials of CIC versus MF were included.

Comparing CIC to BUD at a nominal dose ratio of 1:2 (CIC: BUD, both via HFA pMDI) found no significant differences. Furthermore, non-inferiority was appropriately demonstrated for measures of lung function. Caution is advised as only one trial of this comparison was included, although it was a multi-centre trial of over 400 participants.

When compared at a 1:1 dose ratio and delivered by an HFA pMDI, there were no significant differences between CIC and FP for any outcomes, as demonstrated in one study. Non-inferiority was also appropriately demonstrated for lung function. [redacted]

The BTS/SIGN Guidelines[1] note that, from the limited evidence available, MF (currently only available as a DPI) is equivalent to twice the dose of BDP (delivered by a CFC pMDI). Unfortunately, no relevant trials comparing these two drugs were identified which met the criteria for inclusion in the current assessment. However, a small number of trials were included which compared MF with BUD, and with FP.

When given at a 1:1 dose ratio (with both MF 400µg and BUD 400µg delivered by a DPI inhaler), results from one trial showed statistically significant differences in favour of MF on measures of lung function, symptom-free days, and use of rescue medication. Adverse events were comparable. However in another trial, which used double the dose of both drugs (thus on the borderline of Step 2 and Step 4 of the BTS/SIGN Guidelines care pathway) only FEV_1 was significant, suggesting that both drugs may have approached a plateau in dose response (other variables being equal). At a 1:2 dose ratio (MF : BUD, from one trial) the only statistically significant difference was for FEV_1, in favour of MF. The general finding, therefore, is that MF is statistically superior to BUD on a range of outcomes at the same nominal daily dose (under 800µg per day), but this effect is diminished when the dose of BUD is doubled. It should be noted that this study does not compare BUD and MF at the accepted clinically equivalent dose ratio.

In contrast to the comparison with BUD, there were no statistically significant differences between MF and FP at a 1:1 dose ratio. When delivered at a 1:2 dose ratio (MF : FP) there were significant differences for morning PEFR and nocturnal wakenings in favour of FP. Caution is advised in interpreting this result, as only one trial of this comparison was included, although it was a large multi-centre international trial. On the basis of this one trial, therefore, MF and FP at the same daily dose appear to be generally comparable, at least on the basis of absence of significant differences. Doubling the dose of FP appears to increase

the likelihood of FP being more favourable, a similar observation for the comparison of CIC with FP.

Review question 2: Which ICS is the most-effective at high doses?

Twenty-four relevant RCTs of the efficacy and safety of ICS at high doses in excess of 800µg per day (BDP/BUD or equivalent, corresponding to Step 4 of the BTS/SIGN Guidelines) were included. There was variability in the doses used in the trials, ranging from 800µg to 2000µg per day (ex-valve) (lower for CIC and MF). The baseline populations for the trials, where sufficiently reported, were appropriate for this step of the guidelines, in that they had previously been treated with ICS and usually other medication such as LABAs, leukotriene antagonists or theophyllines. It should be noted that, according to the guidelines, these high doses of ICS should not be prescribed on their own. Other medication should be co-prescribed. It is not always clear from the trial reporting whether this is the case in the trials reviewed here and the results should therefore only be extrapolated to the guideline context with caution.

The results of comparisons of ICS at high doses were similar to those of comparisons of ICS at low doses in finding that there were few statistically significant differences between the steroids.

For the comparison of BDP with BUD, the evidence base was relatively limited, with only two small short-term cross-over trials included. The only significant difference was for exacerbations, in favour of BUD (from one of the trials).

The comparison of FP with BDP was larger, comprising 10 RCTs of varying length, dose, design, and size. All but two of these compared the drugs at a 1:2 dose ratio (FP : BDP). Again, there were few statistically significant differences between them, consistent with our assessment of these drugs at lower doses. Where significant differences were found they were for measures of lung function and for exacerbations, as reported in one of the two studies (using a 1:1 dose ratio). All but one of the 10 RCTs compared the steroids using CFC pMDI inhalers, some with spacers. However, we did identify one additional study comparing HFA pMDI BDP to HFA pMDI FP at a nominal 1:1 dose ratio (the BDP brand being QVAR extra-fine Autohaler). Non-inferiority was demonstrated for the primary outcome, morning PEFR in the ITT, but not the PP, analysis. There were no statistically

significant differences between the treatments for the remaining outcomes. Based on these studies high doses of CFC pMDI FP appear to result in comparable control to BDP at half the dose. If using an HFA pMDI, similar doses of the two drugs can achieve comparable control. This is primarily based on absence of significant differences, and methodological limitations of the trials need to be taken into account.

For the comparison of FP and BUD, the only significant differences were for FEV_1, which favoured FP, reported in one of the six trials. This applied whether they were compared at a 1:1 or a 1:2 dose ratio. Meta-analysis of three of the trials showed no significant difference in adverse events. This was in contrast to meta-analysis of low dose FP and BUD, discussed earlier, where there was a significant difference in favour of FP. It is not clear whether this is an artefact of the dose ratios used, study methods, or whether there is another explanation.

In common with the lower dose ICS comparisons discussed earlier, there is a paucity of evidence for the newer steroids at high doses. Trials comparing CIC with FP were identified, all of which were commercial in confidence. However, comparisons with BDP, BUD, or MF were lacking.

[redacted]

There was limited evidence for the efficacy and safety of MF at high doses. When compared with FP (one study) or BUD (one study) there was little in the way of significant differences.

Review question 3: Which is more effective – an ICS or a combination inhaler containing an ICS and a LABA?

(a) ICS and LABA where the dose of the ICS is higher when used alone, compared to the dose in the combination inhaler.

For patients who are inadequately controlled on low dose ICS, the options include increasing the dose of the ICS up to the 800µg per day dose threshold for Step 3 of the guidelines, or adding in a supplemental drug treatment. The BTS/SIGN Guidelines[1] recommend a trial of an add-on therapy for such patients before increasing the ICS dose above 800µg per day. The first choice is a LABA. Other add-on therapies include leukotriene receptor agonists and theophyllines, which are outside the scope of this assessment.

In this assessment 10 trials were included where the dose of ICS was higher than the dose in the combination inhaler arm. They varied considerably in terms of length, aims, and methodological quality. Baseline populations, where reported sufficiently, appeared appropriate for this step of the guidelines in that they were not steroid naïve. Half of the studies used the FP/SAL combination inhaler, whilst the other half used the BUD/FF combination inhaler. ICS doses, when used in combination with LABAs, varied from 200µg to 800µg day for BUD, and 200µg to 500µg per day for FP. When used alone the ICS doses varied from 400µg to 1600µg per day for BUD, and from 500µg to 1000µg per day for FP. In general, the ICS dose when used alone was at approximately double the accepted clinically equivalent dose that was used in combination with the LABA.

The general finding from the trials assessed is that ICS and LABA in a combination inhaler is superior to increasing the dose of the ICS, across a range of outcomes. This applied to both of the combination inhalers evaluated in the trials. This finding accords with the BTS/SIGN Guidelines and with the results of a Cochrane review.[169] Morning and evening PEFR was significantly favourable for combination therapy in all but one trial. Combination therapy was also significantly more favourable for reducing the need for rescue medication (in terms of puffs per day) in all the trials that reported this outcome. The three trials that measured the impact on HRQOL all reported significant differences in favour of combination therapy. However, results for FEV_1 were mixed, as was the case for symptoms. The proportion of

patients experiencing adverse events appeared comparable across the trials. There were no significant differences for two trials on this outcome when pooled in a meta-analysis.

The general finding that ICS and LABA is more effective than doubling the dose of ICS extends to the use of combination inhaler being used for both maintenance and symptom relief compared to ICS alone. This was evaluated in one study[232] which compared BUD/FF to BUD.

One of the findings of the Cochrane review was that there was no significant difference between treatments in terms of reducing exacerbations requiring systemic corticosteroids. Results for exacerbations from the current assessment, comprising both mild and severe exacerbations, were mixed. In some trials there were no significant differences between treatments, in some combination therapy was significantly more effective, and in others combination therapy appeared favourable but no statistical tests were reported to clarify the role of chance in the findings.

It is important to note that the constituent ICS in the combination inhalers were not always the same as the ICS used alone, as was the case in four of the 10 studies (e.g. BUD compared to FP/SAL). However, the doses used in the ICS alone group appear similar to the accepted clinically equivalent dose of the same ICS as in the combination inhaler. For example, in a trial of 800µg per day of BUD compared to 200µg of FP/SAL, the BUD dosage is approximately double the amount that would have likely been used if the comparison had been between FP and FP/SAL, based on the potency ratio of 1:2 FP: BUD. This is likely to lessen any confounding associated with differences in dose. The results of this assessment do not appear to differ for these studies compared to those where the same ICS was used in both trial arms. While it seems intuitive that an ICS should be tested against a combination inhaler containing the same ICS, in clinical practice patients at Step 2 of the care pathway may switch from any of the five currently licensed ICS to a combination inhaler in Step 3 (e.g. moving from BDP to a combination inhaler containing FP/SAL).

As the evidence base we have assessed only considers ICS alone at approximately double the accepted clinically equivalent dose of the ICS in the combination treatment, we cannot comment on whether findings would be different if a higher dose ratio were compared.

Further, it should also be acknowledged that these findings are applicable only to DPIs as none of the studies used a pMDI to deliver the drugs. This is relevant to the FP/SAL combination inhaler which is available as both a DPI and a pMDI.

(b) ICS and LABA where the dose of the ICS is similar in both treatment arms

As discussed, the BTS/SIGN Guidelines recommend either increasing the dose of ICS or adding in a supplemental drug, such as a LABA, for patients uncontrolled on low doses of ICS. However, a body of evidence exists comparing ICS with ICS and LABA where the ICS dose is similar in both strategies. These trials were conducted to evaluate the safety and efficacy of the combination inhalers compared to standard treatment with ICS.

In this assessment nine such trials were included, six evaluating the FP/SAL combination, and four evaluating the BUD/FF combination. In all trials the same ICS was used in both comparators. As was the case with the studies discussed in the previous section, there was a great deal of variation in terms of aims, treatment duration, dose, size and methodological quality. The ICS dose varied from 200µg to 1000µg per day for FP, and 200µg to 800µg per day for BUD.

The aims of the trials varied. For example, some compared once or twice daily combination therapy with ICS alone. In one study the aim was to compare the efficacy of increasing doses of the two treatments to achieve asthma control. The characteristics of the patients also varied. In some trials patients were described as having moderate-persistent asthma. In others they were described as having mild to moderate asthma. In general patients enrolled were those whose asthma was symptomatic, or sub-optimally controlled, and treated with ICS, as appropriate for Step 2-3 of the guidelines. The results of these trials cannot therefore be extrapolated to the situation of using ICS and LABA in combination in steroid naïve patients, which is outside the context of the guidelines and not considered in this review.

The general finding was that ICS and LABA was statistically superior to ICS alone across most outcomes, as might be expected. In three of the studies, all of which evaluated the FP/SAL combination, there were no significant differences for FEV_1. There were no significant differences for nocturnal wakenings in three trials. However, for all other

outcomes the combination inhaler was superior to ICS alone. The proportion of patients experiencing adverse events appeared similar between the treatments.

These findings resonate with those of a Cochrane review which found that the addition of LABA to ICS in patients who are symptomatic on low to high doses of ICS reduced the rate of exacerbations requiring systemic steroids, improved lung function, symptoms and use of rescue medication.[170]

As was the case with the ICS and LABA compared to higher dose of ICS studies, findings are applicable only to DPIs as none of the studies used a pMDI to deliver the drugs.

Review question 4: ICS and a LABA administered in a combination inhaler compared to separate inhalers

The scope for this assessment, as set by NICE, includes the use of ICS and LABA in a combination inhaler, but not in separate inhalers. It should therefore be acknowledged that there is a wider evidence base for the use of ICS and LABA in separate inhalers compared to ICS alone, as summarised by the Cochrane Collaboration.[169;170] The scope does, however, include the use of ICS and LABA in a combination inhaler compared to the two in separate inhalers.

Six trials were included, three comparing FP and SAL combination inhaler to separate inhalers; two comparing BUD and FF combination inhaler to separate inhalers; and one comparing FP/SAL in a combination inhaler to BUD+FF in separate inhalers. The ICS doses were similar in both treatment strategies, and ranged from 200µg to 1000µg per day for FP, and 800µg per day for BUD.

There were very few statistically significant differences between the treatments across the various efficacy outcomes. This applied to comparisons involving both combination inhalers. For some outcomes (e.g. morning PEFR) non-inferiority was demonstrated. The findings of this assessment are in accord with the BTS/SIGN Guidelines, which state that there is no difference in efficacy between ICS and LABA given in combination versus separate inhalers. The two treatment modalities were similar in terms of adverse events. Meta-analysis of adverse events found no statistically significant differences in adverse events, serious

adverse events and discontinuations due to adverse events. The numbers of these events were generally small however.

Expert clinical opinion suggests that one of the advantages of combination inhalers is that the risk of patients taking LABAs on their own without ICS is reduced. When ICS and LABA are prescribed separately it is suggested that the rapid symptom relief provided by the LABA may mean that some patients are less likely to routinely take their ICS. The LABA will not have reduced the underlying inflammation and patients may be at increased risk of exacerbation. The BTS/SIGN Guidelines[1] make it clear that LABAs should not be used without ICS.

Review question 5: Combination inhaler compared to combination inhaler

Three head to head RCTs comparing the two currently available ICS and LABA combinations were included in this assessment. Daily ICS doses were 800µg for BUD, and 500µg for FP. Results were mixed, with the FP/SAL combination significantly superior on some outcomes, and BUD/FF combination superior on others. In the one trial that reported FEV_1, BUD with FF was significantly superior, as it was for symptom-free days. There were no statistically significant differences between groups in symptom scores, or HRQOL in one trial, whilst symptom scores were described as being 'comparable' between groups in another study. In two trials BUD/FF was significantly superior in terms of exacerbations, whilst in a third FP/SAL were superior. Meta-analysis found that there were no significant differences between the treatment groups in rates of adverse events, serious adverse events or withdrawals due to adverse events. Again, it should be acknowledged that all three of these studies used DPI inhalers. However, BUD/FF combination inhaler is only currently available as a DPI.

Further trials comparing the two combination inhalers may yield a more definitive answer to the question of which is more effective. Our updated literature search in October 2006 identified one such study,[279] although its methodology and findings have not formally been assessed (see *Appendix 5* for a list of other relevant studies identified by this search). Brief examination of this large multi-centre, six month trial found that both combination inhalers were associated with favourable changes across outcomes, with no significant differences between them. However, the FP/SAL combination was significantly superior in reducing the moderate/severe exacerbation rate.

8.4 Estimates of costs and exploring cost-effectiveness

It was not possible to develop an appropriate and valid cost-utility model for the treatment of asthma with an ICS, used either alone or in combination with a LABA at the appropriate steps of the BTS/SIGN Guidelines. The reasons for not reporting the full model methods and results in the main body of the report have been previously outlined in section 6.4. We therefore adopted a cautious approach to the economic analysis for this report, and present for each question either a cost comparison or a cost-consequence comparison. These two different methods of analysis were used appropriately in relation to the findings from the accompanying clinical effectiveness review. A cost comparison of the different ICS and ICS plus LABA preparations was undertaken where the clinical effectiveness review showed no consistent evidence of differential treatment effects between the comparators (research questions 1,2,4 and 5). A cost consequence comparison was undertaken where the clinical effectiveness review indicated that there were significant differences in effects between the two comparators (research question 3). Here the overall pattern of effectiveness differences identified in the systematic review were presented along side the estimated current NHS preventer medication costs for each of the comparators in the trials.

Cost comparisons

These cost comparisons have been shown in section 6.5. They relied upon a range of assumptions for arriving at each mean annual cost of taking a particular ICS or combination inhaler. In particular, they used the conventional (GINA and BTS/SIGN) dose-equivalence ratios for different ICS drugs and/or propellants, and use the 2005 community-dispensed prescription sales data for weighting the cost of different products within each drug type. For these reasons they should be viewed as a form of illustrative economic 'what if' analysis: 'If they were equally effective, what would be the likely differences in the annual cost of treatment?

ICS versus ICS

There are considerable differences in weighted mean annual cost between the different ICS, as well as large cost differences between different preparations of the same ICS. The annual cost varies six-fold between different preparations of BDP to there being no variation in the

cost of CIC as there is only one non-CFC propelled preparation currently on the market. The cost differences between different BDP preparations are smaller, however, if the (typically cheaper) CFC-propelled preparations are excluded from the analysis. At the present time at the starting low dose of 400µg/day BDP devices tend to be the cheapest, and even when CFC-propelled devices are excluded at this dose BDP still appears the cheapest. At doses of 800µg/day and 1500-1600µg/day BDP products appear to remain the cheapest available. At these doses when CFC-propelled products are excluded, then FP products tend to be the cheapest of the ICS products available. When non-CFC propelled products are considered the mean annual cost of both BDP and BUD increases, and the overall cost differences between the five ICS drugs diminishes. As there are currently no CFC-propelled products available for FP, CIC and MF, their costs remain constant. However, whilst the use of weighted averages may provide a useful measure for comparing the cost for each ICS drug with each other, they conceal the often considerable variation in costs for each preparation of the ICS drugs, and the considerable overlap in costs between the ICS. These basic results which are based on the weighted and unweighted averages are derived with a number of assumptions necessarily being made. They should therefore be viewed and interpreted with an appropriate amount of caution.

Our systematic review of the published research evidence has highlighted the fact that there is little demonstrated difference in effectiveness between the different ICS comparators under trial conditions. On this basis there appears to be little justification for the sometimes considerable cost differences between different products containing the five licensed drugs. However, other differences between the products, such as inhaler device characteristics and propellant taste, will probably influence how effectively or easily they are used.

As previously discussed, there is a reasonable percentage of the asthmatic populaton that has difficulty in using certain types of inhaler devices. Therefore given the probable device-related variations in both compliance with correct inhaler technique and adherence to recommended daily doses, the cost savings that could be realised by using the cheapest ICS via the cheapest device (a pMDI) could potentially result in an increase in other health care resource use, through an increase in exacerbations resulting from poorer control of asthma. While we cannot quantify this theoretical increase, as discussed previously, concordance with treatment in trials is around 80%, while in the general population of adolescents and adults with asthma, it may be that less than 50% take the full amount of prescribed

medication (see Background). Choosing a more expensive delivery device that the patient prefers and can easily use correctly might well improve concordance, thus minimising other health care resource use.

ICS and LABA versus ICS alone

The general findings from the clinical effectiveness review indicated that combination ICS and LABA therapy is superior to doubling the dose of ICS alone, across a range of outcomes. However, these effects are not consistent across all outcome measures. The relative annual costs associated with combination therapy versus an increased dose of ICS alone are highly variable and depend both on the dose required and the particular delivery device used. These variations in the costs of both ICS and LABA drugs mirror the observations from the cost comparisons presented for ICS drugs alone, that any generic conclusions about cost-effectiveness of each ICS drug are not possible, as they are confounded by the number and varying prices of the different products available for each drug.

ICS and LABA versus ICS and LABA

For both of the currently available combination inhalers (Seretide and Symbicort) using the combination inhaler is nearly always cheaper than taking the same drugs in separate inhalers. The cost savings associated with the use of combination inhalers vary considerably depending upon the exact preparation of the drugs used and the dose required. It can therefore be suggested that the use of combination inhalers in preference to separate inhalers would lead to with further indirect cost savings. As has previously been discussed, there are no significant differences in effectiveness between the two modes of drug delivery. The ease of using a combination inhaler, which prevents use of LABA alone without ICS, may lead to better concordance. If symptoms are better controlled, the need for rescue medications and health care consultations due to exacerbations may well be reduced.

There are no consistent cost differences between the two combination inhalers, as the relative costs depend upon both the required dose and the delivery device used. Therefore there is no combination inhaler which is the cheapest in all circumstances.

Summary of the cost comparisons

At the present time there is a large variation in the costs between the five ICS and two LABA products available. This variation is dependent upon both the ICS or ICS/LABA dose required and the preparation used. Currently, BDP-CFC propelled preparations tend to be the cheapest on the market, but there is a large variation in cost between the different BDP preparations. As CFC-propelled products are phased out, the overall cost of ICS therapy is likely to increase. When only non-CFC propelled products are considered then there is less variation in the costs between the five ICS drugs, although MOM consistently appears to be marginally more expensive than the other four ICS products. It should be noted that the use of weighted averages can provide a useful way of representing the major differences between the drugs, but they conceal the wide variations in the cost of individual products containing each drug. They will also inevitably be sensitive to year-on-year shifts in the market share or price of individual products. For this reason, we have presented both weighted and unweighted mean costs for each cost comparison.

8.5 Strengths and limitations of the assessment

8.5.1 Strengths and limitations of the systematic review of clinical effectiveness

In terms of strengths, this assessment has followed transparent and accepted methods for conducting systematic reviews. A protocol outlining the scope and methods was agreed and published early on in the process. An expert advisory group comprising clinicians specialising in respiratory medicine, general practitioners, and health economists have provided advice throughout the assessment and have commented on a draft of this report.

The effect of inhaler devices was outside the scope of the present assessment. However, in order to reduce any potential confounding in the assessment of the different comparators under consideration, only trials in which the inhaler type and propellant were the same in each of the trial arms were included in the systematic review.

In terms of limitations, it was not possible to report every outcome measure reported in each of the included trials. As discussed earlier, there are numerous ways of measuring and reporting measures of asthma control. To achieve brevity we prioritised key measures from each of the relevant outcomes. For example, of the various ways of measuring lung function

we only reported FEV_1, and morning and evening PEFR as these appeared to be the most commonly used and clinically meaningful. Consequently, in some trials the primary outcome has not been reported in this assessment if it was not a measure that had been prioritised. Furthermore, some of the outcomes that have been reported here may have been secondary outcomes that the trials were not necessarily powered to detect differences in. This should be kept in mind when interpreting the findings.

It was not always possible to conduct meta-analysis in order to provide a quantitative estimate of treatment effect. This would have provided greater statistical power to show differences. Differences between studies in length and dose meant that in many instances it was not appropriate to pool studies. In cases where pooling was appropriate poor reporting of the results of the trials prohibited quantitative synthesis (e.g. limited data available on the variance associated with effect measures). Consequently, much of the assessment of clinical effectiveness has been reported narratively. It has been challenging summarising such a large evidence base in this way.

The quality of reporting in the trial reports was poor in places. For example, the brand name for the inhaled steroids and the devices used to dispense them were not always mentioned. It was also particularly difficult to determine whether or not a combination inhaler had been used, or whether ICS and LABA had been delivered by separate inhalers. Where possible we contacted authors for further clarification, but time did not allow for this to be conducted routinely.

As discussed earlier, this assessment aimed to build upon previously published evidence syntheses of the efficacy and safety of ICS. The rationale was to reduce duplication and to ensure the project was manageable.

The Cochrane Airways group kindly made available data from their systematic reviews. We performed data extraction and quality assessment only on the trials that met our inclusion criteria that were supplemental to the Cochrane reviews. The completed data extraction and quality assessment forms for these supplemental studies are available in *Appendix 4*. For further details of the remaining studies please refer to the Cochrane reviews.[54;168-171]

8.5.2 Strengths and limitations of the economic evidence and analyses

Economic analysis has been severely restricted as we were unable to populate the cost-utility model from the relevant trial data available to assess cost-utility. Ideally, an economic evaluation in asthma should capture the quality of life and cost impacts both of different levels of control and exacerbation severity and frequency, and also be able to compare all potential treatments concurrently. To some extent therefore, all existing evaluations, including those submitted by industry sponsors to NICE, are limited. Evaluations based solely on symptom free days, for example, may not adequately capture the full spectrum of costs and disutility associated with other indicators of poor control and exacerbations. Conversely, evaluations dominantly based on exacerbations as an outcome, including the exploratory analysis carried out as part of this report, may not fully reflect differences in costs and utility associated with varying levels of 'non-exacerbation' asthma control. In the absence of established models that can (a) include all relevant technologies in a single evaluation and (b) capture the consequences of differences in all levels of control most comparisons have focussed on an analysis of the costs associated with the mean annual treatment costs for each ICS and LABA drug.

Strengths

The cost comparison approach we adopted was a pragmatic response to the lack of evidence of differential clinical effectiveness for some research questions. In the absence of a formal model-based cost-utility or cost-effectiveness analysis these comparisons clearly illustrate the wide variation in possible costs for each ICS drug, and how these vary by product type/strength, daily dose and inhaler type. Although we have chosen to show averages for each ICS, we have put them in context by showing both weighted and unweighted means and also the cheapest and most expensive product for each ICS at each dose level. With a view to other changes currently taking place in the UK market for asthma drugs, we have also generated estimates with and without CFC-propelled products included. Finally, for the comparison of combined ICS with LABA versus ICS alone, our simple cost-consequence analysis at least presents the main clinical effectiveness review findings alongside their estimated costs in a disaggregated form.

Limitations

The main limitation of our economic analyses is that they do not include a comprehensive model-based cost-utility analysis which integrates all relevant cost and effectiveness evidence relevant to the decision problems. This omission is partly due to the nature of the published trial evidence base for these decision problems, but also to do with the inherent challenges of modelling the full spectrum of asthma outcomes, from symptom control and quality of life impacts to severe exacerbations.

All of the cost comparisons discussed above have involved a number of necessary simplifying assumptions including (i) the relative doses of different ICS drugs which are currently assumed to have equivalent effectiveness (ii) the exact mix of products which would probably be used to achieve any particular daily dose level of ICS or ICS-with-LABA, and (iii) using 2005 community prescription sales as a way of producing a weighted mean annual cost for each group of drug preparations. For these reasons, and because the range of available ICS and combination products is currently undergoing considerable change (with CFC-containing products being phased out, and some new HFA-propelled BDP products recently entering the market), the conclusions should be viewed with appropriate and substantial caution.

8.6 Other considerations

As already discussed, the relevance to decision makers of trial-based evidence on the clinical effectiveness of asthma treatments is often limited by a range of factors to do with the characteristics of the patients in the trials, or the inevitably partial selection of drugs and inhaler devices that have mostly been compared. The evidence base may therefore be on comparisons between technologies that are not relevant within current clinical guidelines, focus on efficacy and safety rather than 'real-world' (e.g. adherance-diminished) effectiveness, and be conducted in patients who are specially selected to be able to comply or who are monitored more thoroughly than would be the case in routine clinical care. Furthermore, the fact that most choices between different asthma drugs involve a simultaneous choice of inhaler type (or, choice of inhaler device may effectively determine the asthma drug 'chosen'), creates further difficulties in using an evidence base which is largely aimed at comparing either drugs or devices.

In addition to these difficulties, it may be that the average effectiveness results that clinical trials mainly produce are inappropriate in another more fundamental way. Asthma drug treatment decisions are inherently reversible. Also, the drugs themselves are, in general, quite safe (certainly at the low to moderate doses with which most people are managed). This is why asthma treatment guidelines are implicitly based on an iterative approach of 'trying out' what works best in achieving symptom control for individual patients. Given such a clinical context, with the possibility of multiple reversible clinical decisions, there may be a legitimate argument for retaining the current variety in products, both in terms of drug types and inhaler devices, given acceptable variation in average effectiveness and costs. In addition to variation in people's ability and willingness to use different inhaler devices effectively, it may be that there are subtle differences in people's response to the different ICS drugs themselves (or to the addition of a LABA to an ICS) which mean that some individuals, for example, respond more to particular ICS compounds than others.

9. Conclusions

There is a vast literature on the clinical and cost-effectiveness of the five ICS used alone or in combination with a LABA for the treatment of chronic asthma in adults. Around two-thirds of the RCTs included in this review compared ICS with each other at doses within the range of steps two to four of the BTS/SIGN Guidelines. Within these steps the majority of the trials were of the three older ICS: BDP, BUD and FP. Fewer trials assessed the two newer ICS: MF or CIC.

The remaining studies assessed the effectiveness of the addition of a LABA to an ICS compared with an ICS alone, with the latter given either at the same or an increased dose to that in the combination inhaler. Further identified trials have also examined the use of ICS and LABA therapy, delivered through a combination inhaler, or through separate inhalers.

ICS *versus* ICS

From the available evidence, the clinical effectiveness and short-term safety of the five ICS when used at the accepted clinically equivalent dose ratios, at either Step 2 (low dose) or Step 4 (high dose) of the Guidelines is similar. Whilst equivalence between the comparators certainly cannot be assumed from the results, there appear to be no consistent significant differences between the comparators in effects when delivered by the same delivery device and propellant. As no cost-utility model could be used to estimate cost-effectiveness, cost comparisons were undertaken between the different ICS preparations. These showed that there are no consistent cost differences between the comparators, as the costs depend upon both the required dose and the specific product used, which includes delivery device. In general, at a typical starting dose of 400µg/day BDP devices currently tend to be the cheapest, and remain so even when CFC-propelled devices are excluded. At doses of 800µg/day and 1500-1600µg/day BDP-CFC propelled products remain the cheapest available. At these doses when CFC-propelled products are excluded, then FP is then the cheapest of the ICS products available. When CFC-free products are considered, the mean annual cost of both BDP and BUD increases, but the overall cost differences between the five ICS drugs diminishes. For FP, CIC and MF as there are currently no CFC-propelled products available. However, the use of weighted and unweighted averages to represent the

cost associated with each ICS tends to conceal the wide variations in costs between the individual preparations of each drug, and the wide overlap in costs between the drugs.

ICS *versus* ICS+LABA

The general findings from the clinical effectiveness review indicated that combination ICS and LABA therapy is superior to doubling the dose of ICS alone, across a range of outcomes. However, these effects are not consistent across all outcome measures.

Alongside evidence of some relatively consistent clinical effectiveness differences favouring combination inhalers, we have shown they are often also cheaper than doubling the dose of ICS. However, we are cautious not to make any firm cost-effectiveness conclusion from these cost consequence data, since this 'result' largely depends on the specific dose-levels, and exact products compared in these trials. Furthermore, we have not factored in the other potential cost advantages that might accrue to combination inhalers if the relative reductions in exacerbation rates measured in some trials were more certain. Nor do they capture the potential quality of life impacts of reducing the proportion of days or nights with symptoms, which some trials show. When such variables are factored in, as we have done in our exploratory cost-utility analysis (*Appendix 10*), the major uncertainty in the cost estimates remains, and the joint uncertainty surrounding the cost and effectiveness estimates available from the research literature prevents any straightforward use of conventional rules for interpreting cost-effectiveness ratios.

ICS plus LABA versus ICS plus LABA

Combination versus single inhaler devices

There were no consistent differences in the effectiveness of combination ICS plus LABA therapy delivered concurrently compared to delivery in separate inhalers. Cost comparison between the two regimens showed that taking an ICS with a LABA as either of two currently available combination products (Symbicort and Seretide) is cheaper than taking the relevant ingredient drugs in separate inhalers.

The use of single inhaler therapy not only provides a simpler treatment regimen, but may also enhance concordance with maintenance ICS therapy and reduce the likelihood of

LABAs being used without ICS. From this review there appears to be no significant clinical differences in effectiveness between the two modes of treatment delivery, and potential cost savings to the NHS with use of a combination inhaler compared with separate inhalers. Therefore, in the general context of long-term maintenance treatment, use of a combination inhaler should be preferred to prescribing the same drug ingredients in separate inhalers.

Combination versus combination inhaler devices

From the limited evidence available, the clinical effectiveness of the two combination ICS and LABA inhalers (Seretide and Symbicort) appears to be similar when used at accepted clinically equivalent dose ratios. The cost comparison that was undertaken indicated there were no consistent cost differences between the available combination inhalers, as the relative costs depend on the dose required and the specific product used. Therefore there is no combination inhaler which is the cheapest in all circumstances.

9.1 Research recommendations

Primary Research

The assessment of cost-effectiveness in this review was hampered by our inability to get any overall estimate of the relative clinical effectiveness of the five ICS. Direct comparisons of all five ICS in a single large head to head trial would provide both an estimate of any differences and a clarification of the uncertainty around the central estimates. The need for trial evidence comparing the newer ICS drugs, CIC and MF, with other ICS drugs would be particularly useful.

Future trials of treatment for chronic asthma should standardise the way in which outcome measures are defined and measured. There should be a greater focus on patient-centred outcomes such as HRQOL and symptoms. This will provide a more meaningful estimation of the impact of treatment on asthma control.

Most settings for the trials in this review are not fully specified, making it difficult to generalise them to primary care practice, where most patients in the UK are treated. In addition, the trial protocols often do not reflect the actual treatment options that patients follow in routine care. Outside trial settings, patients at steps 2-3 of the guidelines may alter their ICS dose either

under a self management plan or in consultation with their GP, effectively resulting in a variable dose of ICS over time. In order to obtain more accurate estimates of the effectiveness of ICS in a UK setting, more patients from the UK should be entered into trials and the setting fully specified in terms of methods of recruitment and level of routine care received during the trial. In addition, trials should explicitly try to capture the changes individual patients may make in their ICS dose over time.

For informing future cost-utility and cost-effectiveness analyses from a UK NHS perspective there is a need for longitudinal studies which comprehensively track the care pathways followed when people experience asthma exacerbations of different severity. The most recent studies of this kind in the UK are over ten years old, and the NHS 'service landscape' for people with urgent problems has changed considerably during the intervening years (e.g. NHS Direct, GP out-of-hours cooperatives, walk-in centres).

Research synthesis

We have noted that not all patients are treated strictly within the guidelines. One particular practice is the increasing tendency to use ICS and LABA in combination at Step 2-3 of the guidelines in steroid naïve patients. A systematic review of this treatment option would be helpful to inform future iterations of the guidelines.

Standardisation of outcome measures

The evidence base that was assessed in the current review was highly heterogeneous both in terms of the way that outcome measures had been defined and measured, but also in the level of reporting of the trial results.

Methods of reporting in trials require standardisation. In particular where statistical results are presented, means and standard deviations should be provided. This will enable such studies to be included in quantitative meta-analysis. The statistical methods of analysis should also be explicitly stated. In addition, the overall trial methods should be explicitly documented and reported with adherence to the CONSORT statement[280] standard of reporting being made a priority.

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Appendices

APPENDIX 1 – Expert advisory group

Dr Nick Adams	Consultant Physician	
Dr Alan Cade	Consultant Paediatrician	Plymouth Hospitals NHS Trust
Dr Chris Cates	Co-ordinating Editor	Cochrane Airways Review Group
Dr Tim Harrison	Consultant Physician (pharmacotherapy)	Nottingham City Hospital
Prof Stephen Holgate	MRC Clinical Professor of Immunopharmacology	Southampton General Hospital
Ms Emily Lancsar	Lecturer 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	General Practitioner	Honiton Medical Practice
Dr David Sinclair	Consultant Physician, Respiratory Medicine	Torbay District Hospital
Prof Anne Tattersfield	Emeritus Professor of Respiratory Medicine	
Prof John Warner	Professor of Child Health	Dept. 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

May 4th 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 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 a 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 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 pre-dispose 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. Whilst severe exacerbations of asthma may cause death, mortality from the condition is relatively low compared to 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 general practitioner 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, (PEFR)), 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 a week or if symptoms disturb sleep more than once a week, or if the patient has suffered exacerbations in the last two 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 & Hanburys], Beclometasone Cyclocaps [APS], Becodisks [Allen & Hanburys], Becotide [Allen & Hanburys], Easyhaler [Ranbaxy], Filair [3M], Filair Forte [3M], Qvar [3M], Pulvinal Beclometasone Dipropionate [Trinity])
- budesonide (Budesonide Cyclocaps [APS], Novolizer [Viatris], Pulmicort [AstraZeneca])

- ciclesonide (Alvesco [Altana])
- fluticasone propionate (Flixotide [Allen & Hanburys])
- mometasone furoate (Asmanex [Schering-Plough])

Beclometasone dipropionate, budesonide and fluticasone propionate have been used for some time, whilst ciclesonide and mometasone are relatively new. There are a variety of delivery systems including pressurised metered-dose inhalers (pMDI), breath-activated pMDIs, dry powered 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 (mcg) twice daily for budesonide and beclometasone dipropionate; 100–250mcg twice daily for fluticasone propionate; 200–400 mcg per day for mometasone furoate, and 160 mcg daily for ciclesonide (British National Formulary, 50)[P5]. The BTS recommends titrating to the lowest dose at which effective control is maintained. In adults this can be up to 800 mcg per 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 IC does not adequately control symptoms there are a number of potential treatment options. One is to continue with the IC but to increase the dose to the higher end of the recommended range (e.g. up to 800 mcg). 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 micrograms (mcg) twice daily. This can be titrated up to 500/50 mcg twice daily. Correspondingly, a typical dose of budesonide/formoterol is 80/4.5 mcg twice daily, titrated up to 320/9 mcg 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 mcg 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 IC dose should be increased up to the higher end of the dose range (e.g. up to 800mcg 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. 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 four 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 pre-requisite 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 sub-groups, in terms of disease severity, age, and smokers/non-smokers. Concordance according to different patient sub-groups 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, PEFR)
  - 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];[P8];[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 a 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 to 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 (2005)[P12], and Drummond and colleagues (1997)[P13]. For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues, 2004)[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 Personal Social Services 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* fully reflect these various factors 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 either 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 National Health Services and Personal Social Services. 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 2nd 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) 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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P4 BTS/SIGN. British Guideline on the Management of Asthma. Thorax 58[(Supplement 1)], i1-i-94. 2003.

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P7 Adams N, Bestall JM, Jones PW. Inhaled beclomethasone versus budesonide for chronic asthma. [Review] [47 refs]. Cochrane Database of Systematic Reviews 2002;(1):CD003530.

P8 Adams N, Bestall JM, Lasserson TJ, Jones PW. Inhaled fluticasone versus inhaled beclomethasone or inhaled budesonide for chronic asthma in adults and children.[update of Cochrane Database Syst Rev. 2004;(2):CD002310; PMID: 15106173]. [Review] [104 refs]. Cochrane Database of Systematic Reviews 2005;(2):CD002310.

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P10 Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma [Cochrane review]. Cochrane Database of Systematic Reviews 2005 Issue 4. Chichester (UK): John Wiley & Sons, Ltd; 2005.

P11 NHS Centre for Reviews and Dissemination. Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for those Carrying Out or Commissioning Reviews. CRD Report Number 4 (2nd Edition). 2001. York, York Publishing Services Ltd.

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P15 National Institute for Clinical Excellence. Guide to the Methods of Technology Appraisal. 2004. London, National Institute for Clinical Excellence.

APPENDIX 3 – Systematic reviews: Search strategies

Clinical effectiveness search strategy: Corticosteroids in asthma

Databases 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(R) <1966 – 2006 Run on 15/02/2006; update search run on 26/09/06

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

Search strategy 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(R) <1966 to March Week 1 2006>

Searched 09/03/2006; Update search 6/10/2006

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(R) 1966-to May Week 1 2006>. searched 11/5/2006; update search run on 6/10/06

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.
Database: Ovid MEDLINE(R) <1966 to May Week 3 2006>; searched 26-05-06

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(R) <1966 to July Week 4 2006> Searched 02/08/2006

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 ID: [249] **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 AstraZeneca (manufacturers of BUD+FORM)	**Group A:** *n* = 219 Drug(s): BUD + FORM Dose: 320 + 9µg b.i.d. (adjustable to 160-640µg BUD + 4.5-18µg FORM b.i.d. *in open extension period* [mo2-7]) Delivery: DPI Duration: 1mth (double-blind) + 6mo (open-label) **Group B:** *n* = 215 Drug(s): BUD + FORM Dose: 320 + 9µg b.i.d. Delivery: DPI Duration: 1mth (double-blind) + 6mo (open-label) **Group C:** *n* = 224 Drug(s): FP+S Dose: 250µg FP + 50µg S b.i.d. Delivery: DPI Duration: 1mth (double-blind) + 6mths (open-label) **Run-in period:** Duration: 10-14d ICS: any LABA: not allowed Relief: terbutaline sulphate or salbutamol **Additional treatment allowed:** ▪ Relief: terbutaline sulphate or salbutamol ▪ Other: none (inhaled cromones, leukotriene modifiers, additional β_2-agonists,	**Number randomised:** 658 **Sample attrition/dropout:** *n*=83 (25 for AEs; 18 ineligible; 6 lost to follow-up; 34 other) **Inclusion criteria:** ▪ At study entry: ▫ age ≥12 ▫ history of asthma for ≥6 mths ▫ FEV_1 ≥50% predicted ▫ maintained on ICS for ≥3mths, with stable dosage of 500-1200µg in prev. 1mo ▪ During last 7d of run-in: ▫ total asthma symptom score ≥1 on 4d ▫ PEFR 50-85% of post-bronchodilatory PEFR ▫ compliant **Exclusion criteria:** ▪ respiratory tract infection within previous 1mo ▪ smoking history ≥10 pack-years ▪ systemic steroids in previous 1mo **Baseline characteristics:** ▪ Male : Female = 299:359 ▪ Mean age (range) = 46 (12-85) ▪ Median duration of asthma (range) = 12-13yr* (0-73) ▪ 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: l (range) = 2.73 (0.98-6.11); % predicted (range) = 84% (45-156%) ▪ Mean PEFR after bronchodilator, l/min (range) = 467 (167-951) ▪ Reliever use, occasions/day (range) = 1.8 (0-12.5) ▪ Reliever-free days (range) = 27% (0-100%) * range of values across groups	**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 ≤2d ▫ ≤2d with reliever use ▫ ≤4 reliever uses ▫ AM PEFR ≥80% of predicted every day **Secondary measures:** ▪ am & pm PEFR ▪ 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 ▫ AM PEFR ≥80% of predicted every day ▪ exacerbations (oral steroids for ≥3d, ER visits and/or hospitalisation) **Method of assessing outcomes:** ▪ Daily patient diaries: ▫ PEFR (AM & PM) ▫ symptoms, effects and extra medication ▪ Spirometry (study entry; post run-in; after 1mo blinded Rx; after 6mo open extension)

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
	xanthines, β-blockers and inhaled anticholinergics explicitly disallowed)		**Length of follow-up:** none beyond 7mo study period

RESULTS

Outcomes	Group A (*n*=219)	Group B (*n*=215)	Group C (*n*=224)	*p*-value
FEV_1				
AM PEFR, mean change, baseline to mo7 – l/min:	27.5[a]	34[a]	35[a]	NS[b,c,d]
Symptom-free days				
Nocturnal awakenings – (%): mean difference (95%CI)	12.5%[a]	19.5%[a] 4.7%[b] (0.3,9.2%)[b]	16%[a]	<0.05[b]
Acute exacerbations – *n*: rate (*n*/mths) rate reduction (95%CI)	35[a] 0.024	50[a] 0.036 32.0%[b] (-4.8,55.9%;)[b]	59[a] 0.041 39.7%[c] (8.3,60.3%)[c]	NS[b,d]; 0.018[c]
Systemic corticosteroids, ≥3d courses of oral steroids – *n*:	33[a]	46[a]	52[a]	
Use of reliever, mean times/day: mean difference (95%CI)	0.58[a]	0.94[a] 0.30[b] (0.12,0.48)[b]	0.80[a] 0.23[c] (0.05,0.41)[c]	<0.01[b]; <0.05[c]
Mortality				
QoL				
Adverse events – *n* (%): Any Serious Oral candidiasis Dysphonia Headache Discontinuation due to AEs	 124 (57%) 8 (4%) (1%) (1%) (3%) 27 (12%)	 124 (58%) 11 (5%) (2%) (1%) (2%) 31 (14%)	 147 (66%) 5 (2%) (3%) (7%) (4%) 25 (11%)	 0.847[b,f]; 0.064[c,f]; 0.095[e,f] 0.490[b,f]; 0.412[c,f]; 0.130[e,f] 0.446[b,g]; 0.175[c,g]; 0.545[e,g] 1.000[b,g]; 0.001[c,g]; 0.001[e,g] 0.544[b,g]; 0.800[c,g]; 0.261[e,g] 0.574[b,f]; 0.768[c,f]; 0.320[e,f]
Other: Well controlled asthma weeks (wk32)	49%[a]	66%[a]	56%[a]	

[a] values estimated from graphs
[b] Group A *v*. Group B
[c] Group A *v*. Group C
[d] reported as "no significant difference" in text, but no *p*-values provided
[e] Group B *v*. 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)*

RESULTS

Outcomes	Group A (*n*=219)	Group B (*n*=215)	Group C (*n*=224)	*p*-value

Comments

- Odds ratios (95% CI) for well controlled asthma weeks:
  - over entire treatment period: Group B *v*. Group C = 1.289 (0.981, 1.694; *p*=NS)
  - over open extension phase (mo2-7): Group A *v*. Group B = 1.335 (1.001, 1.783; *p*=0.049); Group A *v*. Group C = 1.048 (0.791, 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 1yr, Group A *v*. Group C = 4.9
- PM PEFR was significantly lower in Group A. Mean differences – l/min (95% CI): Group A *v*. Group B = 9.6 (1.8, 17.5; $p<0.05$); Group A *v*. Group C = 8.4 (0.7, 16.1; $p<0.05$)
- FEV_1 only reported for initial 4-wk treatment period.
- In Group A during adjustable dosage phase (mo2-7): 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 7d.
- For use of reliever and nocturnal awakenings, mean differences (reported in text) correspond poorly with apparent difference in mean values (shown in figures) (?ANOVA artefact; ?different time-periods).

METHODOLOGICAL COMMENTS

- **Allocation to treatment groups:** block randomisation according to schedule computer-generated by a third party
- **Blinding:** double-blind, double-dummy for initial 1mo; 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 was 0.67 (i.e. an increase from 40% to 48.5%)
- **Attrition/drop-out:** 4 patients were excluded from analysis for primary endpoint (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. PEFR) and subjective (e.g. symptom scores) measures. Only physician-assessed efficacy variable (FEV_1) is only reported for initial 4-wk 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 AstraZeneca (manufacturers of BUD+FORM)

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 intention to treat analysis?	adequate
9. Were withdrawals and dropouts 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

Thirty pages, containing the data extraction tables of four trials submitted by Altana and designated "commercial in confidence", have been deleted.

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [234] **Author:** Aubier *et al* **Year:** 1999 **Country:** not specified; investigators are from France, Germany and 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 + S (combination) + placebo Dose: 500µg FP + 50µg S BD Delivery: 2 separate DPIs (FP+S & placebo) Duration: 28 weeks **Group B:** *n* = 171 Drug(s): FP + S (concurrent) Dose: 500µg FP + 50µg S BD Delivery: 2 separate DPIs (FP & S) Duration: 28 weeks **Group C:** *n* = 165 Drug(s): FP + placebo Dose: 500µg FP BD Delivery: 2 separate DPIs (FP & placebo) Duration: 28 weeks **Run-in period:** Duration: 2 wk 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/dropout:** *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 12wk before run-in ▪ treated with BDP or BUD 1500-2000µg/day or FP 750-1000µg/day for 4wk 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 PEFR >50% and <85% of maximum PEFR 15min after inhaled salbutamol 400µg ▫ FEV_1 50-100% of predicted value **Baseline characteristics:** ▪ Male : Female = 269:234 ▪ Mean age (range) = 48 (12-79) ▪ Smoking history: current = 71 (14%); ex-smoker = 195 (39%); never smoked = 237 (47%) ▪ Duration of asthma (yr): <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 PEFR during run-in Wk2 (1/min) = 352	**Primary measure:** mean morning PEFR during wks 1-12 **Secondary measures:** ▪ evening PEFR ▪ symptom-free days & nights ▪ days & nights when "rescue" salbutamol was not required ▪ FEV_1 (absolute and predicted) ▪ serum cortisol levels & 24-hr urinary cortisol excretion (assessed in a subset of 318 patients) ▪ adverse events ▪ compliance **Method of assessing outcomes:** ▪ Clinic assessments in wks -2, 0, 2, 4, 12, 20, 28 and 28+2 ▪ daily diary card, recording ▫ (wks -2 to 12) morning and evening PEFR (highest reading of 3) ▫ (wks -2 to 28) changes in concomitant medication and AEs ▪ at assessments in wks 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-wk treatment period + follow-up visit at wk 28+2

RESULTS

Outcomes	Group A (*n*=167)	Group B (*n*=171)	Group C (*n*=165)	*p*-value
FEV_1, mean change from baseline to wk 28 – l:	0.25[d]	0.15[d]	0.18[d]	0.454[b]; 0.061[c]
PEFR, mean[a] change from baseline – l/min (SE):				
AM: wks 9-12	38 (3.9)	36 (3.8)	22 (4.0)	0.771[b]; 0.003[c]
AM: wks 1-12	35 (3.1)	33 (3.1)	15 (3.1)	0.535[b]; <0.001[c]
PM: wks 9-12	31 (3.8)	26 (3.7)	13 (3.9)	0.27[b]; <0.001[c]
PM: wks 1-12:	29 (3.1)	23 (3.0)	9 (3.1)	0.16[b]; <0.001[c]
Symptom-free days – mean % (wks 1-12)	38[d]	38[d]	28[d]	NS[b,e]
Symptom-free nights – mean % (wks 1-12)	58[d]	55[d]	51[d]	NS[b,e]
Acute exacerbations				
Use of systemic corticosteroids				
Mortality				
QoL				
Patients experiencing adverse events – 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 (<l%)	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 (<l%)	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 *v*. Group B
[c] Group A *v*. 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 wks 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+S combination and FP+S 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:

METHODOLOGICAL COMMENTS

- Mean PEFR and FEV_1 were adjusted according to ANCOVA, with baseline data as a covariate.
- Equivalence of Group A *v*. Group B was based on 90% CI (unstratified Wilcoxon Rank Sum) for mean difference in AM PEFR between groups (Δ = 15 l/min).
- Superiority of Group A *v*. 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 adverse events 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

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 intention to treat analysis?	adequate
9. Were withdrawals and dropouts 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 ID: [244] **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/S + placebo Dose: 100/50µg b.i.d. + placebo b.i.d. Delivery: S/F combination via one Diskus inhaler + placebo via another Diskus inhaler Duration: 12wks **Group B:** *n* = 123 Drug(s): FP + S Dose: 100 + 50µg b.i.d. Delivery: concurrent therapy via separate Diskus inhalers Duration: 12 wks **Run-in period:** Duration: 2 wks ICS: continued to take their ICs Relief: any bronchodilator therapy was replaced by salbutamol via a Diskhaler inhaler or a pressurised metered-dose inhaler **Additional treatment allowed:** ▪ Relief: salbutamol in the form of a pressurised metered-dose inhaler for symptomatic use. ▪ Other: unknown	**Number randomised:** 244 **Sample attrition/dropout:** ▪ 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 adverse event: 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 adverse events resulting in treatment withdrawal. **Sample crossovers:** NA **Inclusion criteria:** ▪ Age ≥12yrs with symptomatic asthma ▪ History of documented reversible airways obstruction and receiving BDP or BUD 400-500µg/day or FP 200-250µg/day for ≥4 wks prior to the start of treatment. ▪ Have recorded a symptom score* totalling ≥2 on at least 3 of the last 7 consecutive days during the run-in period ▪ Have a mean morning PEFR (calculated from the last 7 days of the run-in period) between 50 + 85% of their PEFR measured 15min after administration of salbutamol 400µg at the start of treatment. * Daytime: 0 = no symptoms during the day, 5 = symptoms so severe that they are affected work/school and normal daily activity. Night-time: 0 = no symptoms during the night, 4 = symptoms so severe the patient did not sleep. **Exclusion criteria:** ▪ Receiving (or having received in the 4 wks prior to the start of treatment) either salmeterol or any other inhaled LABA ▪ A lower respiratory tract infection within 4 wks of the run-in period ▪ Taking oral, depot or parenteral corticosteroids within 4 wks of the run-	**Primary measure:** Mean am PEFR **Secondary measures:** ▪ PEFR pm ▪ FEV_1 ▪ Use of rescue salbutamol ▪ Day & night-time symptom score **Method of assessing outcomes:** ▪ Clinician visits at 2, 4, 8, and 12 wks after the start of treatment, and 2 wks after cessation of treatment. Not to take their medication on the morning of, and to avoid taking rescue medication within 6hr of, and clinic visit. ▪ FEV_1 (3 measurements and the highest one was recorded) ▪ Adverse events reported spontaneously by the patient or as a result of non-suggestive questioning by the clinician were recorded ▪ Systolic and diastolic blood pressure and pulse rate ▪ Oropharynx examined for any clinical evidence of candidiasis ▪ Fasting blood sample taken between 8am to 10am at the beginning and end of the treatment for biochemical and haematological analysis and the measurement of morning serum cortisol level

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		in period, or ▪ Taking two or more courses of oral depot or parenteral corticosteroids within 12 wks of the run-in period ▪ An acute exacerbation of reversible airways obstruction that required hospitalisation within 12 wks of the run-in period ▪ A smoking history of 10 pack yrs (i.e. 10 cigarettes/day for 20 yrs or 20 cigarettes/day for 10 yrs or 40 cigarettes/day for 5 yrs) **Baseline characteristics:** ▪ Age: mean (range) = 33 (12-78) ▪ Male : Female = 104/140 ▪ Smoking history ▫ Current = 19 ▫ Ex-smoker = 46 ▫ Never = 179 ▪ Mean PEFR (L/min) predicted ▫ Morning = 366.5 ▫ Evening = 378.5 ▪ Mean FEV_1 (L), % 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% symptom-free days, mean (no. of patients) = 4 ▪ >75% symptom-free nights, 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	▪ Patient's record ▪ PEFR am & pm (3 measurements with the highest value recorded) ▪ Use of rescue salbutamol ▪ Day & night-time symptom score **Length of follow-up:** 14 wks

RESULTS

Outcomes	Group A (*n*=121)	Group B (*n*=123)	*p*-value
FEV_1 [a]:			
adjusted mean change at wk 12 (L)	0.20	0.17	NR
adjusted mean change from baseline at wk 12 (% predicted)	6	6	NA
PEFR:			
▪ Adjusted change in mean morning PEFR (L/min)			
▪ Week 1			
▪ Week 2	34	30	0.374
▪ Week 3	36	33	0.610
▪ Week 4	41	31	0.061
▪ Week 5-8	41	31	0.051
▪ Week 9-12	44	33	0.049
▪ Week 1-12	47	39	0.220
▪ Adjusted change in mean evening PEFR (L/min)	42	33	0.098
▪ Week 1	30	27	0.561
▪ Week 2	32	29	0.587
▪ Week 3	35	31	0.429
▪ Week 4	36	28	0.135
▪ Week 5-8	37	30	0.177
▪ Week 9-12	39	34	0.393
▪ Week 1-12	36	30	0.241
>75% symptom-free days, [No. of patients (%)]	48 (40)	52 (43)	
>75% symptom-free nights, [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/days phonia	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 wk 2, 4, 6, 8, and 10 can be roughly estimated from the 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.

METHODOLOGICAL COMMENTS

- **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 PEFR and FEV1 values were analysed using analysis of covariance, 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 intention-to-treat basis.

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 and 1 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 intention to treat analysis?	Adequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [235] **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/S Dose: ▪ Phase I: dose 100/50, 250/50, or 500/50µg b.i.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 wks ***Group B*:** *n* = 550 Drug(s): FP Dose: ▪ Phase I: dose 100, 250, or 500µg b.i.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 wks **Stratum 2** (≤ 500µg BDP or equivalent daily) ***Group A:*** *n* = 585 Drug(s): FP/S Dose: ▪ Phase I: dose 100/50, 250/50, or 500/50µg, b.i.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 wks ***Group B:*** *n* = 578 Drug(s): FP Dose: ▪ Phase I: dose 100, 250, or 500µg b.i.d., step-up until total control or the highest dose was reached	**Number randomised:** 3421 **Sample attrition/dropout:** 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 & hospital clinics ▪ Aged ≥12 <80 yrs ▪ At least a 6mths history of asthma ▪ Reversibility: an increase in FEV_1 ≥ 15% (and ≥200ml) after inhalation of short-acting $ß_2$-agonists documented within the previous 6mths or as assessed during run-in ▪ A smoking history of <10 pack-yrs ▪ No use of long-acting inhaled or oral $ß_2$-agonists within the previous 2 wks **Exclusion criteria:** ▪ Having well-controlled asthma on ≥ 3 of the 4 wks during run-in **Baseline characteristics:** ▪ Mean age (range) = 40 (9-83) ▪ Male : Female (%) = 42 : 58 ▪ Mean atopy (%) = 58 ▪ Mean pre-bronchodilator FEV_1, L/min = 2.4 ▪ Mean prebronchodilator FEV_1 % predicted = 77 ▪ Mean am PEFR, L/min = 345.83 ▪ Mean am PEFR %	**Primary measure:** Proportion of patients who achieved well-controlled asthma with FP/S v. FP during phase I **Secondary measures:** ▪ Cumulative proportion of patients achieving control in phase II ▪ Dose of ICs & time to achievement of the first well-controlled asthma wk ▪ Proportion of patients & dose to achieve totally controlled asthma ▪ Time to achieve the first totally controlled wk ▪ Asthma quality of life (using AQLQ) ▪ Exacerbation rates (requiring oral corticosteroids, hospitalizations or information or emergency visits) ▪ Morning pre-dose FEV_1 ▪ Adverse events **Method of assessing outcomes:** ▪ Clinic visit at wks 12, 24, 36, and 52; control assessed over an 8-wk period before each clinic visit. ▪ No other details reported **Length of follow-up:** 52 wks

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
	▪ Phase II: continued on the final dose in phase I until the end of the trial Delivery: dry powder inhalers Duration: 52 wks **Stratum 3** (>500 to ≤ 1000µg BDP or equivalent daily) ***Group A*:** *n* = 576 Drug(s): FP/S Dose: ▪ Phase I: dose 100/50, 250/50, or 500/50µg, b.i.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 wks ***Group B*:** *n* = 579 Drug(s): FP Dose: ▪ Phase I: dose 100, 250, or 500µg b.i.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 wks **Run-in period:** Duration: 4 wks ICS: continued on their usual dose (if any) Relief: NR **Additional treatment allowed:** ▪ Relief: NR ▪ Other: NR	predicted = 76.67 ▪ Rescue medication, mean occasions/day = 1.8 ▪ Mean daily symptom score* = 1.8 ▪ Night-time awakenings, mean occasions/night = 0.5 ▪ Mean exacerbation rate [§] = 0.53 ▪ Duration of asthma (% patients): ▪ 6mths – <1yr = 3.67 ▪ ≥1 -<10 yrs = 38 ▪ ≥10 yrs = 58.33 ▪ Smoking status (% patients): ▪ Current smoker = 7.83 ▪ Former smoker = 14.50 * 0 - none, 5-severe. [§] Documented episodes of hospitalization and /or course of oral steroids or antibiotics for the treatment of an exacerbation of asthma during the past 12mths	

RESULTS

Outcomes	Group A (*n*=)	Group B (*n*=)	*p*-value
FEV_1: *see additional table*			
PEFR:			
Symptom-free days			

RESULTS

Outcomes	Group A (*n*=)	Group B (*n*=)	*p*-value
Nocturnal awakenings			
Acute exacerbations [a]			
Use of systemic corticosteroids			
Use of reliever medication			
Mortality			
QoL: *see additional table*			
Adverse events – n (%): [b]			
Other: *see additional table*			

[a] mean rate of exacerbations requiring either oral steroids or hospitalization/emergency visit per patient per yr over wks 1-52: can be roughly estimated from figure 3 in the paper.

[b] serious adverse events during the 1 yrs period were 4% in S/F and 3% in FP arm. Overall incidence of drug-related adverse events was 10% in each group. No statistical differences between treatments at wk 52 (p = 0.318, 95% CI 0.92, 1.31)

METHODOLOGICAL COMMENTS

- **Allocation to treatment groups:** randomization 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, 2.552) for group A v. 2.52 (95% CI 2.448, 2.592) for group B, in stratum 2 was 2.42 (95% CI 2.352, 2.488) for group A v. 2.38 (95% CI 2.314, 2.446) for group B, and in stratum 3 was 2.28 (95% CI 2.212, 2.348) for group A v. 2.33 (95% CI 2.264, 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 1was 4.4 (95% CI 4.283, 4.517) for Group A v. 4.5 (95% CI 4.382, 4.618) for group B, in stratum 2 was 4.7 (95% CI 4.583, 4.817) for group A v 4.5 (95% CI 4.445, 4.555) for group B, and in stratum 3 was identical for group A and group B. However, there no detail on how this sub-group of which this data was 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 analyzed using the log-rank test, stratified by country. FEV_1, AQLQ and cortisol were analyzed using analysis of covariance adjusted as for the primary end point with baseline covariate. Cortisol data was log transformed prior to analysis. Exacerbation rates were analyzed over the 1-yr 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 un-assessable patients.
- **Attrition/drop-out:** withdrawals at phase I = 377 (11%), at phase II from baseline = 526 (15%). The study was analyzed on an intention-to-treat basis by individual strata; the intention-to-treat 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 6ths before screening. ▪ **Conflict of interests:** study supported by GlaxoSmithKline R & D Limited

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 intention to treat analysis?	Adequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

Outcomes	**Stratum 1**		**Stratum 2**		**Stratum 3**		
	Grp A (*n*=533)	**Grp B (*n*=531)**	**Grp A (*n*=572)**	**Grp B (*n*=564)**	**Grp A (*n*=561)**	**Grp B (*n*=555)**	**P value**
FEV_1: % predicted (SD) Phase I: adjusted mean change (SE) Grp A minus Grp B, (SE)* Phase II: adjusted mean change (SE) Grp A minus Grp B, (SE)*	76 (18.14) 0.45 (0.02) 0.14 (0.03) 0.52 (0.02) 0.17 (0.03)	79 (18.83) 0.31 (0.02) 0.34 (0.02)	78 (18.17) 0.35 (0.02) 0.13 (0.02) 0.37 (0.02) 0.13 (0.02)	77 (18.34) 0.22 (0.02) 0.24 (0.02)	75 (18.55) 0.29 (0.02) 0.12 (0.02) 0.32 (0.02) 0.14 (0.03)	76 (17.44) 0.17 (0.02) 0.18 (0.02)	P < 0.001*
	Grp A (*n*=282)	**Grp B (*n*=275)**	**Grp A (*n*=339)**	**Grp B (*n*=331)**	**Grp A (*n*=346)**	**Grp B (*n*=345)**	
Mean overall AQLQ score § Phase I: adjusted mean change (SE) Grp A minus Grp B, (SE)* Phase II: adjusted mean change (SE)	1.5 (0.1) 0.2 (0.1) 1.6 (0.1) 0.1 (0.1)	1.3 (0.1) 1.4 (0.1)	1.3 (0.1) 0.3 (0.1) 1.3 (0.1) 0.2 (0.1)	1.0 (0.1) 1.2 (0.1)	1.1 (0.1) 0.2 (0.1) 1.2 (0.1) 0.2 (0.1)	0.8 (0.1) (0.1)	

Grp A minus Grp B, (SE)*							
Proportion of patients who achieved near-maximal mean overall AQLQ scores at wk52- %	62	62	64	53	57	45	

* Group A vs Group B
§ Obtained at selected sites. No detail on how the subgroup was defined.

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [197] **Author:** Bousquet *et al* **Year:** 2000 **Country:** 17 countries **Study design:** Randomized, evaluator-blind, active-controlled, multi-centre **Number of centres:** 57 **Funding:** Schering Plough research institute	**Group A:** *n* = 185 Drug(s): MF+ placebo Dose: 100µg b.i.d. Delivery: DPI Duration: 12 wks **Group B:** *n* = 176 Drug(s): MF+ placebo Dose: 200µg b.i.d. Delivery: DPI Duration: 12 wks **Group C:** *n* = 188 Drug(s): MF+ placebo Dose: 400µg b.i.d. Delivery: DPI Duration: 12 wks **Group D:** *n* = 181 Drug(s): BUD Dose: 400µg b.i.d. Delivery: Pulmicort Turbuhaler Duration: 12 wks **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/dropout:** 101 (14%) **Sample crossovers:** Not reported **Inclusion criteria:** ▪ Age ≥12yrs ▪ History of asthma for ≥6mo ▪ 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% & absolute volume increase of at least 200ml within 30 min after 2 inhalations of salbutamol. ▪ Non smoker or had stopped smoking ≥ 6mths 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 6mths prior to screening, unless on a stable maintenance schedule ▪ Methotrexate, cyclosporine or gold within 3mths ▪ Systemic steroids or another investigational drug in the month prior to screening ▪ Daily Nebulised ß$_2$ adrenergic agonists >1mg ▪ Any LABA <2wks prior to screening ▪ Ventilator support in the past 5yrs ▪ Hospitalization for asthma in the last 3mths ▪ >12 puffs./day of salbutamol on any ≥2 occasions in the past 6mths ▪ Clinical evidence of significant pulmonary disease other than	**Primary measure:** change from baseline to endpoint in FEV_1 **Secondary measures:** ▪ FVC ▪ PEFR ▪ Symptom scores ▪ Nocturnal awakenings requiring salbutamol use as rescue medication ▪ Daily salbutamol use ▪ Physician evaluation of response to therapy ▪ Adverse event **Method of assessing outcomes:** ▪ Daily patient diaries: ▫ PEFR (am & pm) (highest of 3 efforts) ▫ Salbutamol use ▫ Asthma symptoms ▫ Number of night-time awakenings requiring salbutamol use ▫ Adverse events ▫ Use of study drug and concomitant medications ▪ Treatment visits after 1, 2, 3, 4, 8, & 12wks of treatment: ▫ Pulmonary function (FEV_1 and FVC) by spirometry ▫ Oropharyngeal exam for the presence of candidiasis, reviewed diary cards, & 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) & compliance in the use of rescue medication (objective assessment of doses used & review of the patient's diary

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		asthma ▪ History or glaucoma and/or posterior sub-capsular cataracts ▪ Increase of decrease in FEV_1 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 wks 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) ▪ Male : Female = 315: 415 ▪ White: African: Hispanic: Asia: other = 555:9:160:5:1 ▪ Mean weight (kg) = 71.5 (range 34-144) ▪ Smoking history – n (%): never 510 (70), not in past 6mths 216 (30) ▪ Mean duration of asthma yrs (range) = 15.75 (1-64) ▪ Mean FEV1(% 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 grp) ▪ Theophylline use (Yes/No - n) = 19/163 ▪ Salbutamol use (µg/day) = 262.25	data reports) **Length of follow-up:** 12 wks

RESULTS

Outcomes*	Group A (*n*=185)	Group B (*n*=176)	Group C (*n*=188)	Group D (*n*=181)	*p*-value
FEV_1, L:	0.10±0.03	0.016±0.03	0.16±0.03	0.06±0.03	<0.05 [ab]
PEFR: (am, L/min) change from baseline to endpoint ± SE	18.20±5.3	37.84±5.4	37.3±5.2	24.75±5.3	<0.05 [ab]
Symptom-free days					
Nocturnal awakenings: change from baseline	-0.06	-0.09	-0.16	-0.07	

RESULTS

Outcomes*	Group A (*n*=185)	Group B (*n*=176)	Group C (*n*=188)	Group D (*n*=181)	*p*-value
to endpoint					
Acute exacerbations					
Use of systemic corticosteroids					
Use of reliever medication: change of salbutamol use in µg/day from baseline to endpoint	-45.8	-90.66	-72.13	-33.90	<0.05 [a]
Mortality					
QoL					
Adverse events – n (%): · Dysphonia (n) · Oral candidiasis (n)	 8 4	 5 6	 9 4	 4 3	
Physician-evaluated response to therapy: change from baseline to endpoint	2.43	2.33	2.25	2.53	<0.05 [ab]
Patient self report-mean score of wheezing am	-0.07	-0.17	-0.27	-0.10	<0.05 [bd]
Patient self report-mean score of difficulty breathing am	-0.01	-0.20	-0.24	-0.14	<0.05 [d]
Patient self report-mean score of Cough am	-0.10	-0.16	-0.19	-0.19	

* Values are presented as change from baseline to endpoint (the last treatment visit) (± SE)

[a] Group B vs Group D

[b] Group C vs Group D

[c] Group B vs Group A

[d] Group C vs Group A

Comments

- The incidence of adverse events judged by investigators to be related to treatment was similar for all treatment groups (17-20%). Serious adverse events 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 wk 12.

METHODOLOGICAL COMMENTS

- **Allocation to treatment groups:** Randomization 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 randomized 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 analyzed 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 analyzed 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.

METHODOLOGICAL COMMENTS

- **Attrition/drop-out:** 101/730 patients (14%) did not complete the treatment: 15% in MF-DPI 100µg group, 10% and 18% in MF-DPI 200µg and 400µg group, and 14% in BUD group, respectively. The analyses of efficacy and safety were based on all the randomized patients who received at least one dose of study mediation and who had post-baseline data (intention-to treat 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 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 intention to treat analysis?	Reported
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [198] **Author:** Buhl *et al* **Year:** 2005 **Country:** Multinational **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: 160µg ex-actuator dose q.d. in the evening Delivery: HFA metered dose inhaler Duration: 12 wks **Group B:FP** *n* = 263 Drug(s): FP Dose: 88µg ex-actuator dose b.i.d. Delivery: HFA metered dose inhaler Duration: 12 wks **Run-in period:** Duration: 1 to 4 wks ICS: None Relief: Salbutamol (100µg/puff) **Additional treatment allowed:** ▪ Relief: Not stated but presumably salbutamol (100µg/puff) ▪ Other:	**Number randomised:** 529 **Sample attrition/dropout:** *n* = 45 (8.5%). 24 for CIC; 21 for FP. **Sample crossovers:** n/a **Inclusion criteria:** ▪ 12-75 yrs of age ▪ Diagnosis of asthma according to American Thoracic Society guidelines for at least 6mths ▪ Maintained on a constant dose of ICS up to 500µg/d 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 hrs + a decrease in FEV_1 ≥10% after ICS withdrawal ▪ All patients had to demonstrate a reversibility of FEV_1 ≥ 15% after inhaling 200-400µg of salbutamol, or have shown a diurnal PEFR fluctuation of at least 15% during the baseline period **Exclusion criteria:** ▪ Required systemic steroids within 4 wks of the baseline period or more than 3 times during the last 6 mths ▪ An asthma exacerbation, lower respiratory tract infection or hospitalisation for asthma 4 wks before baseline entry ▪ Other relevant lung diseases, such as COPD ▪ Smoking history of ≥ 10 pack-yrs **Baseline characteristics:** ▪ Intention to treat population ▪ The treatment groups were balanced with regard to prior use of ICS and other asthma medications ▪ Median (yrs) age (range): CIC 41 (12-74), FP 38 (12-74) ▪ F:M %: CIC 61/39, FP 54/46 ▪ Mean FEV_1, L (SD): CIC 2.383 (0.61), FP 2.44 (0.73) ▪ Mean FEV_1, % predicted (range): CIC 75 (51-108), FP 75 (48-92)	**Primary measure:** Change in FEV_1 from baseline to end of treatment **Co-primary measures:** Change in FVC Change in am PEFR **Secondary measures:** ▪ Mean $FEF_{25\%-75\%}$ ▪ PEFR pm ▪ 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, & mean $FEF_{25-75\%}$ were recorded at baseline and at wks 1, 2, 4, 8, and 12. AM & PM PEFR (mini-Wright peak flow meters) and use of rescue medication were recorded daily in patient diaries The day & 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 & may have been devised specifically for the study. Adverse events experienced by a patient or observed by an investigator were recorded at each study visit

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		▪ 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, L (SD): CIC 3.183 (0.91), FP 3.312 (0.98) ▪ Morning PEF (diary), L/min (SD) CIC 358 (6), FP 369 (7)	**Length of follow-up:** 12 wks

FEV1 – forced expiratory flow in 1 second, PEFR – peak expiratory flow, FVC – forced vital capacity, $FEF_{25\%-75\%}$ - mean forced expiratory flow between 25% to 75% of vital capacity, q.d.– once a day, b.i.d. – twice a day
No further information was provided on the methods used to assess outcomes or on treatment protocols/rescue medication.

RESULTS

Outcomes	Intention to treat			Per Protocol		
	CIC (*n*=266)	FP (n=263)	p-value	CIC (*n*=230)	FP (n=221)	*p*-value
FEV_1, L:						
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, 0.066)		0.801	-0.03 (-0.113, 0.053)		0.477
Morning PEFR, L/min:						
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 (-13,7)		0.582	-8 (-18, 3)		0.162
FVC, L						
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, 0.115)		0.486	0.008 (-0.082, 0.099)		0.857
Use of rescue medication (not clearly defined in text)						
Baseline, median	1.43	1.71		1.43	1.86	
Change†	-1.0	-1.21		-0.9	-1.21	
Change vs FP point estimate (95%CI)†	0.14 (-0.0, 0.43)		0.13	0.29 (0.0, 0.57)		0.053
% of symptom free days* (median)	58%	65%	Not reported			
% of nights without	100%	100%	Not reported			

RESULTS

Outcomes	Intention to treat			Per Protocol		
	CIC (*n*=266)	FP (n=263)	p-value	CIC (*n*=230)	FP (n=221)	*p*-value
nocturnal awakenings* (median)			Not reported			
Total asthma symptom score						
Baseline, median	1.48	1.57		1.55	1.5	
Change†	-0.75	-0.86		-0.78	-0.82	
Change vs FP point estimate (95%CI)†	0.07 (-0.11,0.29)		0.387	0.0 (-0.14, 0.26)		0.778
Daytime symptom score						
Baseline, median	0.86	1.0		0.93	1.0	
Change†	-0.43	-0.5		-0.44	-0.5	
Change vs FP point estimate (95%CI)†	0.0 (-0.0, 0.14)		0.317	0.0 (-0.14, 0.14)		0.722
Night-time symptom score						
Baseline, median	0.5	0.5		0.5	0.5	
Change†	-0.29	-0.33		-0.27	-0.29	
Change vs FP point estimate (95%CI)†	0.0 (0.0, 0.1)		0.53	0.0 (0.0, 0.1)		0.520
Mortality	0	0				
Adverse events, 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
*estimated by reviewer from graph
†Hodges-Lehman point estimate (N.B. the differences presented are not simple subtractions)

RESULTS

Outcomes	Intention to treat			Per Protocol		
	CIC (*n*=266)	FP (n=263)	p-value	CIC (*n*=230)	FP (n=221)	*p*-value

Comments

The per protocol 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 intention to treat group. It is also unclear how many were included in the per protocol analysis or if they were all excluded for protocol violations etc.

The change from baseline for each treatment group for FEV_1, FVC, morning PEFR, rescue medication, and symptom scores were significant ($p<0.0001$).

Incomplete data was presented in the text for evening PEFR and FEF_{25-75}. Evening PEFR 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 0.601L/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 hrs of administration in the ciclesonide and fluticasone groups ($p<0.0001$). Morning PEFR 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 per-protocol analysis, based on valid cases, and an intention to treat analysis, based on the full analysis set, was 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 PEFR were -0.2L, -0.2L and -25L/min 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 analysis of covariance, 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% CI 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 nonparametric 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 endpoint for which statistical significance was observed to morning and evening PEFR, sum of asthma symptom scores, and use of rescue medication.

Sample size/power calculation: Based on a between-treatment difference of at most 0.05L and a standard deviation of 0.425L for the FEV_1 changes, a sample size of 170 per protocol (230 intention to treat) patients per treatment group was required to provide a power of 90% to demonstrate non-inferiority.

Attrition/drop-out: Forty-five patients discontinued participation in the study prematurely. Twenty-four patients in the CIC group dropped out – 6 due to adverse events, 4 due to lack of efficacy and 14 for other medical and non-medical reasons. Twenty-one patients in the FP group dropped out – 3 due to adverse events and the remaining 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 intention to treat analysis?	Adequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [245] **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/S Dose: 250/50µg b.i.d. Delivery: Diskus inhaler (Seretide) + placebo Duration: 28 wks **Group B:** *n* = 191 Drug(s): FP + S Dose: 250 + 50µg b.i.d. Delivery: Diskus DPI inhaler Duration: 28 wks **Run-in period:** Duration: 2 wks continuing ICS: BDP or BUD 800-1200µg or FP 400-600µg q.d. Relief: salbutamol **Additional treatment allowed:** ▪ Relief: salbutamol ▪ Other: ▪ **Trial aim:** to determine whether grps A and B are clinically equivalent. Secondary aim to assess safety of grp A over 28 wk treatment period.	**Number randomised:** 371 randomised patients **Sample attrition/dropout:** 36 were withdrawn: 20 (11%) from Grp A, 16 (8%) from Grp B (p=ns). Most common reason for withdrawal was adverse events (see results); lost to follow-up (n=6); non compliance (n=2), violation entry criteria (n=2) **Sample crossovers:** None reported **Inclusion/exclusion criteria:** ▪ Aged ≥ 12 yrs with symptomatic asthma despite inhaled corticosteroids. ▪ Documented clinical history of reversible airways obstruction ▪ Treatment with BDP, BUD (both 800-1200µg/day) or FP (400-600µg/day) for ≥ 4 weeks before. ▪ Symptom score (day + night-time) totalling ≥ 2 on ≥ 4 of the last 7 consecutive days of run-in ▪ Mean PEFR (from last 7 days of run-in) of 50%-85% of PEFR measured 15 mins after 400µg salbutamol at the start of treatment ▪ Exclusion criteria: ▪ Treatment with salmeterol or other long-acting β_2-agonist in 4 wks before recruitment; lower respiratory tract infection or treatment with corticosteroids (oral, depot, parenteral) within 4 wks of run-in; treatment with 2 or more courses of oral, depot or parenteral corticosteroids within 12 wks of run-in; acute exacerbations of reversible airways obstruction requiring hospitalisation within 12 wks of run-in; smoking history of 10 pack-yrs or greater. **Baseline characteristics:** ▪ Sex, n (%) F/M: Grp A 88 (49)/92 (51); Grp B 109 (57)/82 (43) ▪ Mean (yrs) age (range): Grp A 42.8 (13-73); Grp B 41.4 (15-75) ▪ Smoking history, n (%): Grp A Current 27 (15), Ex 53 (29), Never 100 (56); Grp B Current 25 (13), Ex 69 (36), Never 97 (51) ▪ Mean baseline PEFR, L/min (%	**Primary measure:** PEFR (am & pm) **Secondary measures:** ▪ FEV ▪ Use of salbutamol ▪ Day & night-time symptom score ▪ Compliance ▪ Adverse events **Method of assessing outcomes:** PEFR (mini-Wright peak flow meter) best of three recorded in diary card. FEV: highest value of at least 3 maximal & reproducible efforts. Rescue salbutamol Day & night-time symptom score in daily record card (daytime score ranged from 0-5 from no symptoms to severe to affect work/school. Night-time score ranged from 0-4 from no symptoms to so severe no sleep) Compliance: number of doses used divided by expected use. **Length of follow-up:** 30 wks (efficacy measurements recorded for first 12 wks of study only). Patients assessed at start of run in and treatment periods, and at 2, 4, 8, 12, 20, & 28 wks after randomisation and two wks after cessation of double blind treatment.

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		predicted), n (%): Grp A morning 398 (84), evening 415(88); Grp B morning 391 (85), evening 415 (89) ▪ Mean baseline FEV_1 (L) (% predicted): Grp A 2.51 (75); Group B 2.55 (77) ▪ Use of concurrent asthma medication, n (%): Grp A methylxanthines 7 (4), ipratropium bromide 2 (1); Grp B methylxanthines 6 (3), Ipratropium bromide 1 (<1)	

RESULTS

Outcomes	Group A (*n*=180)	Group B (*n*=191)	*p*-value
PEFR: mean morning adjusted changes from baseline, L/min, 12 wks [?average of measurements]	43	36	See next row
PEFR: difference in mean morning change from baseline, L/min between Grp A and Grp B, 12 wks	-6, (90% CI -13 to 0) within equivalence definition of 15L/min. The 95% CI (-14, 2) also within the equivalence definition.		
PEFR: mean morning predicted adjusted mean change from baseline, 12 wks	9%	7%	See next row
PEFR; mean morning treatment difference in predicted score between Group A and Group B, 12 wks	-2% (90% CI -3 to 0%) p=0.052		
PEFR: mean evening adjusted changes from baseline, L/min, 9-12 wks/1-12 wks	36 35	26 25	See next row
PEFR: difference in mean evening change from baseline, L/min between Group A and Group B, 9-12 wks/1-12 wks	-10 L/min (90% CI -17 to -3 L/min) p=0.020 -10 L/min (90% CI -16 to -4 L/min) p=0.008		
PEFR: mean evening predicted adjusted mean change from baseline, 9-12 wks/1-12 wks	8% 7%	5% 5%	See next row
PEFR; mean evening treatment difference in predicted score between Group A and Group B, 9-12 wks/1-12 wks	-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/min, 28 wks	0.26	0.24	See next row
FEV_1: treatment difference	-0.02 (90% CI -0.09 to 0.05)		
Symptom-free days, change from baseline in proportion with median zero score, n (%)	Baseline 1(1) 12 wks 63(35)	Baseline 4(2) 12 wks 61(32)	
Symptom-free night times, change from baseline in proportion with median zero score, n (%)	Baseline 61(34) 12 wks 111(62)	Baseline 58(30) 12 wks 101(53)	
For both median daytime and night-time symptom scores, there were no significant differences between the treatment groups.			
Percentage patients with ≥75% symptom-free days, n (%)	Baseline 1(1) 12 wks 39(22)	Baseline 1(1) 12 wks 29 (15)	See next row
Median difference between Grp A and Grp B	0% (90% CI -4 to 0%)		
Percentage patients with ≥75% symptom-free night, n(%)	Baseline 41(23) 12 wks 86(48)	Baseline 39(20) 12 wks 80 (42)	See next row
Median difference between Grp A and Grp B	-3% (90% CI -9 to 0%)		
Acute exacerbations			

RESULTS

Outcomes	**Group A (*n*=180)**	**Group B (*n*=191)**	***p*-value**
Use of systemic corticosteroids			
Did not require salbutamol on ≥75% of days, n (%) Baseline: During first 12 wks:	 10(6) 72 (40)	 21(11) 64 (34)	 See next row
Median difference between group A and Group B	-4%, 90% CI -11 to 0%		
Did not require salbutamol on ≥75% of nights, n (%) Baseline: During treatment period:	 85 (47) 125 (69)	 90 (47) 118 (62)	 See next row
Median difference between Grp A and Grp B	-3%, 90% CI -6 to 0%		
Mortality			
QoL			
Drug related Adverse events – n (%) over 28 wk period (≥ 2% frequency): Headaches Candidiasis: Mouth/throat Candidiasis: non-specific site Hoarseness or dysphonia Throat irritation Upper respiratory tract infection Asthma Palpitations Tremors Dizziness Chest symptoms	 9(5%) 8(4%) 3(2%) 7(4%) 5(3%) 4(2%) 4(2%) 4(2%) 4(2%) 3(2%) 3(2%)	 10(5%) 7(4%) 1(<1%) 7(4%) 5(3%) 3(2%) 3(2%) 2(1%) 1(<1%) 1(<1%) 0	
Patients reporting adverse events, n (%)	160 (89)	164 (86)	
Withdrawals due to adverse events, n (%)	12 (7)	9 (5)	
Compliance (mean medication use expressed as a % of expected use) wks 1-12/wks 1-28	96%/95%	95%/94%	Not reported

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 Grp 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 intention to treat 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 PEFR. *Apriority* equivalence was regarded as a 90% CI within ± 15 L/min (ref 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 (800-1200µg/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 Glaxo Wellcome 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 intention to treat analysis?	Inadequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [196] **Author:** Corren *et al* **Year:** 2003 **Country:** USA **Study design:** Randomised, multi-centre, double-blind, double-dummy, placebo- & 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 wks **Group B:** *n* = 104 Drug(s): MF* Dose: 440µg (metered dose, delivering approximately 320µg ex-mouthpiece) q.d. Delivery: DPI Duration: 8 wk **Group C:** *n* = 106 Drug(s): BUD Dose: 400µg q.d. Delivery: DPI Duration: 8 wks **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 wks before screening. ▪ Other: no ▪ * mometasone furoate ▪	**Number randomised:** 262 **Sample attrition/dropout:** 19% **Sample crossovers:** NA **Inclusion criteria:** ▪ Age ≥12 yrs ▪ A history of asthma for ≥ 6 mths ▪ Daily use ICS for ≥30 days & stable ICS regimen within recommended dose ranges for 2 wks prior screening (Flunisolide 1000-2000µg/day, BUD 400-800µg/day; triamcinolone acetonide 600-1600µg/day; BDP 252-840µg/day, and FP 200-500µg/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 ≥200ml at screening or within the past 12mths **Exclusion criteria:** ▪ Required oral CIS treatment for more than a total of 14 days during the 6mths immediately prior screening ▪ Required a burst of systemic steroids within 1mth prior screening ▪ Treatment with leukotriene modifiers within 2 wk prior screening ▪ Treatment with methotrexate, cyclosporine, gold, or other immunosuppressive agents within the past 3mths ▪ Emergency hospital treatment for asthma twice in the previous 6mths ▪ Hospitalised for an asthma exacerbation within the prev. 3mths ▪ Required ventilatory support for asthma within the prev. 5 yrs ▪ Other respiratory or clinically significant disease other than asthma	**Primary measure:** ▪ FEV_1 ▪ PEFR (am & pm) **Secondary measures:** ▪ $FEF_{25\%-75\%}$ ▪ FCV ▪ Asthma symptoms ▪ Albuterol use ▪ Nocturnal awakenings ▪ Physician-evaluated response-to-therapy scores and compliance ▪ % of asthma symptom free days* ▪ Adverse events * Defined as a day where both the total am & pm scores (rating wheezing, difficulty breathing) were zero **Method of assessing outcomes:** ▪ Visits during treatment on day 1 (baseline) and wks 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: ▫ PEFR (am & pm) ▫ Nebulised $ß_2$-adrenergic agonists treatment ▫ Number of albuterol inhalations ▫ Asthma symptoms ▫ Number of nocturnal awakenings requiring

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		▪ Smokers within the prev. 6mths or demonstrated a clinical condition requiring daily use of nebulised ß$_2$-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 yrs ▪ Sex (m/f) = 96/165 ▪ Caucasian: black: other = 233:16:12 ▪ Mean weight (lb) = 171.67 ▪ Mean duration of asthma = 19.67 yr ▪ Mean (least square mean)% predicted FEV_1 = 73.37	albuterol ▫ Adverse events ▫ Daily use & time of use of study medication ▫ Concomitant medication **Length of follow-up:** 8 wks

RESULTS

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

[a] least squares mean change from baseline at endpoint from two-way ANOVA
[b] group B vs group C
[c] 'there was no differences among groups in overall incidence of adverse events'
Outcome in terms of asthma symptoms: wheezing score (am & pm), difficulty breathing score (am & pm), and total asthma score (am & pm) are available in table 4 in the paper.

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, 2.45) for Grp B v. 2.48 (95% CI 2.36, 2.60) for Grp C. Similarly, PEFR (pm) was higher in Grp C – 401.22 (95% CI 383.31, 419.13) compared to Grp B – 375.03 (95% CI 353.84, 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 significant 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

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 intention to treat analysis?	Partial
9. Were withdrawals and dropouts 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 ID: [180] **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: 200µg q.i.d. Delivery: DPI (Pulvinal) Duration: 8 wks **Group B:** *n* = 16 Drug(s) BUD Dose: 200µg q.i.d. Delivery: DPI (Turbuhaler) Duration: 8 wks **Run-in period:** Duration: 2 wks before randomisation ICS: 2 wks wash-out; however, all had treatment with BDP MDI 1000µg for previous 8 wks. 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 & completed the study period"; unreported drop-outs may have occurred) **Sample attrition/dropout:** no withdrawals reported **Inclusion criteria:** ▪ Age 18-65 yrs ▪ Clinical diagnosis of moderate persistent Asthma ▪ Treated with 1000µg BDP MDI at constant daily dose for prev. 8 wks ▪ stability of lung function (*i.e.* diurnal variation of PEFR <20%) in prev. 4 wks ▪ 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 properly fill in the diary cards ▪ Providing of written informed consent **Exclusion criteria:** ▪ Evidence of symptomatic infective exacerbation in the previous 4 wks ▪ Likelihood of exposure to allergens or sensitising agents for the total study period ▪ History of clinically significant cardiac, renal, neurologic, 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%) ▪ 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 ▪ PEFR (% predicted ± SD) = BDP 72.7	**Primary measure:** not specified **Secondary measures:** ▪ FEV_1 (absolute and predicted) ▪ FVC ▪ PEFR (am & pm) ▪ $FEF_{25-75\%}$ ▪ $MEF_{50\%}$ ▪ Rescue salbutamol consumption ▪ Incidence of bronchospasm attacks ▪ Symptoms ▪ Adverse events ▪ Serum ECP ▪ AM serum cortisol ▪ Standing heart rate ▪ BP **Method of assessing outcomes:** ▪ Clinic assessments at wks -2, 0, 2, 4, 6, & 8: ▫ FEV_1 (highest reading of 3), FVC, PEFR, $FEF_{25-75\%}$, MEF_{50} ▫ adverse effects reported ▪ Daily diary card, recording ▫ AM & PM PEFR (highest of 3) ▫ rescue salbutamol consumption ▫ bronchospasm attacks ▫ symptoms (patient-rated scores for wheezing at rest, wheezing after exercise, coughing attacks at rest, coughing attacks after exercise and chest tightness) ▪ At wks 0, 4 & 8 ▫ serum ECP ▪ At wks 0 & 8 ▫ morning serum cortisol ▫ standing heart rate ▫ systolic and diastolic blood pressure **Length of follow-up:** 8 wks

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		± 21.5, BUD 70.6 ± 14.8	

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]
wk 2	2.67 ± 0.8	1.99 ± 0.5	<0.05[b]; NS[a,c]
wk 4	2.68 ± 0.7	2.08 ± 0.6	<0.05[b]; NS[a,c]
wk 6	2.71 ± 0.8	2.15 ± 0.5	<0.05[b,c]; NS[a]
wk 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	
wk 4	78.9 ± 9.8	73.8 ± 18.6	
wk 8	79.2 ± 10.3	75.6 ± 19.7	
PEFR – l/min ± SD			
Baseline	5.80 ± 1.9	5.01 ± 1.4	NS[a]
wk 2	7.04 ± 2.0	5.28 ± 1.7	NS[a,b,c]
wk 4	6.88 ± 1.5	5.53 ± 1.9	NS[a,b,c]
wk 6	7.07 ± 1.9	5.32 ± 1.5	<0.05 [b]; NS[a,c]
wk 8	7.49 ± 1.6	5.88 ± 2.0	<0.05 [b]; NS[a,c]
Morning PEFR – l/min ± SD			
Baseline	400 ± 115[d]	360 ± 90[d]	NS[a]
wk 2	435 ± 100[d]	365 ± 90[d]	NS[a,b,c]
wk 4	440 ± 80[d]	380 ± 90[d]	NS[a,b,c]
wk 6	460 ± 80[d]	385 ± 90[d]	<0.05[b,c]; NS[a,c]
wk 8	470 ± 85[d]	400 ± 95[d]	<0.05[b]; NS[a,c]
Evening PEFR – l/min ± SD			
Baseline	425 ± 95[d]	375 ± 80[d]	NS[a]
wk 2	445 ± 85[d]	385 ± 90[d]	NS[a,b,c]
wk 4	455 ± 75[d]	395 ± 90[d]	NS[a,b,c]
wk 6	465 ± 80[d]	400 ± 80[d]	<0.05[c]; NS[a,b]
wk 8	490 ± 90[d]	410 ± 60[d]	<0.05[c]; NS[a,b]
Symptom free days			
Nocturnal awakenings			
Acute exacerbations			
Use of reliever medication, number of puffs/day			
Baseline	2.3 ± 0.3	2.3 ± 0.3	NS[a]
wk 2	2.1 ± 0.3	2.2 ± 0.4	NS[a,b,c]
wk 4	1.6 ± 0.3	2.3 ± 0.5	NS[a,b,c]
wk 6	1.1 ± 0.3	1.8 ± 0.5	NS[a,b,c]
wk 8	0.7 ± 0.3	1.6 ± 0.5	<0.05[b]; NS[a,c]
Use of systemic corticosteroids			
Mortality			
QoL			

RESULTS

Outcomes	Group A (BDP) (*n*=16)	Group B (BUD) (*n*=16)	*p*-value
Adverse events – n (%):	none	none	see comments
Other			
Bronchospasm attacks in 24hrs – number ± SE			
baseline	1.1 ± 0.3	1.1 ± 0.3	NS[a]
wk 2	0.9 ± 0.2	1.1 ± 0.3	NS[a,b,c]
wk 4	0.8 ± 0.3	1.0 ± 0.3	NS[a,b,c]
wk 6	0.8 ± 0.3	0.9 ± 0.3	NS[a,b,c]
wk 8	0.3 ± 0.1	0.8 ± 0.3	<0.05[b]; NS[a,c]

[a] Group A *v*. Group B
[b] Group A *v*. baseline
[c] Group B *v*. baseline
[d] estimated from graph by reviewer

Comments
- Point data for morning PEFR and evening PEFR 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 wk 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).
- Three patients in Grp A and 2 patients in Grp B had upper airways infection thought to be unrelated to treatment.
- No significant variations within or between groups were reported in heart rate, 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, sECP, 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, sECP, 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.
  - Chi-square test to compare the distribution of adverse events
  - 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 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: n/a ▪ **Conflict of interests:** not reported; 1 author is from Chiesi (Italian manufacturers of BDP)

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 intention to treat analysis?	not reported
9. Were withdrawals and dropouts completely described?	n/a

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 ID: [247] **Author:** Fitzgerald *et al* **Year:** 2005 **Country:** 15 countries (Australia, Austria, Belgium, Bulgaria, Macedonia, Canada, Estonia, Finland, Germany, Ireland, Latvia, 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/S + placebo Dose: 250/50µg b.i.d. Delivery: FP/S via DISKUS & placebo via Turbuhaler DPI Duration: 52 wks **Group B:** *n* = 344 Drug(s): BUD/FORM+ placebo Dose: 400/12µg b.i.d. (adjustable within range 200µg BUD/6µg FORM q.d. to 800µg BUD/24 µg FORM b.i.d. *after wk 4*) Delivery: 2 separate BUD/FORM via Turbuhaler & placebo via DISKUS DPI Duration: 52 wks **Run-in period:** Duration: 2 wks before randomisation ICS: continued "to take their current asthma medication" Relief: as needed salbutamol **Additional treatment allowed:** Relief: inhaled salbutamol only 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.	**Number randomised:** 706 **Sample attrition/dropout:** *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 adverse events; 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 yrs and <70 yrs ▪ Documented clinical history of asthma ▪ FEV_1 60-90% predicted ▪ Treated with any ICS at dose equivalent to 200 to 500µg/day BDP combined with a LABA, or an ICE alone at a dose equivalent to >500 to 1000µg/day BDP for ≥12wk before enrolment ▪ Ability to use peak flow meter and correctly record values on diary card At the end of the 2-wk 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 1mth 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 **Baseline characteristics:** ▪ Male : Female = SAL/FP 140:204, FOR/BUD 128:216 ▪ Mean age (years ± SD) = SAL/FP 46 ± 14, FOR/BUD 44 ± 14 ▪ Smoking history: not reported ▪ Duration of asthma ≥10 years	**Primary measure:** Mean % of symptom-free days (over 24hr 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 PEFR ▪ % well controlled asthma wks ▪ 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 PEFR <70% of the mean of the last 7 days in wks 1-4 for >2 consecutive days ▪ Adverse events ▪ Compliance **Method of assessing outcomes:** ▪ Clinic visits at baseline, wks 0, 4, 16, 28, 40, and 52 recording ▫ FEV_1 ▫ adverse effects ▪ daily diary card, recording ▫ asthma symptom score for prev. 24hr ▫ number of nocturnal awakenings due to asthma ▫ number of occasions of salbutamol use during previous 24hrs ▫ NO. of Turbuhaler inhals. in prev. 24hr ▫ PEFR (highest reading of 3)

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		(number and %) = SAL/FP 197 (57%), FOR/BUD 200 (58%) ▪ FEV1, (absolute value l ± SD) = SAL/FP 2.53 ± 0.80, FOR/BUD 2.52 ± 0.70 ▪ FEV_1, (% predicted ± SD) = SAL/FP 82 ± 21, FOR/BUD 81 ± 13 ▪ Morning PEF (l/min ± SD) = SAL/FP 357 ± 103, FOR/BUD 362 ± 100 ▪ Daily asthma symptom score (mean ± SD) = SAL/FP 1.9 ± 0.6, FOR/BUD 1.9 ± 0.5	▪ Compliance (deemed compliant if actual number of doses taken was ± 30% of the expected number) **Length of follow-up:** 52 wks + follow-up visit at wk 52+ 2

RESULTS

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

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

RESULTS

Outcomes	Group A (*n*=344)	Group B (*n*=344)	*p*-value

Comments

The proportion of patients who were compliant with each device was similar in the 2 treatment arms: with the Diskus, 80.8% of the SAL/FP group and 82.6% of the FOR/BUD group were compliant; with the Turbuhaler, 66.9% of the SAL/FP group and 68.3% of the FOR/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 intention to treat analysis (*18 participants were randomised but excluded from ITT population due to absent efficacy data and/or took no study medication*)
  - Percentage of symptom free days 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 PEFR 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 anticipated 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% 2-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+S

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 & secondary outcomes: adequate FEV_1: unknown
5. Was the care provider blinded?	unknown

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
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 intention to treat analysis?	adequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [184] **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: 400µg b.i.d. Delivery: DPI (Easyhaler) Duration: 8 wks **Group B:** *n* = 79 Drug(s): BUD Dose: 400µg b.i.d. Delivery: DPI (Turbohaler) Duration: 8 wks **Run-in period:** Duration: 2 wk s prior randomisation ICS: continued treatment with either BDP or BUD 800-1000µg q.d. Relief: not reported **Additional treatment allowed:** ▪ Relief: salbutamol 100µg MDI rescue medication permitted p.r.n. ▪ Other: 1 wk course of oral steroid permitted if asthma deteriorated	**Number randomised:** 79 **Sample attrition/dropout:** *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:** 8wks BDP followed by 8wks BUD 8wks BUD followed by 8wks BDP **Inclusion/exclusion criteria:** ▪ Age >18 yrs ▪ Stable bronchial asthma controlled by daily use of BDP or BUD inhalation aerosols during previous 4 mths ▪ No prev. experience with Easyhaler or Turbuhaler MDPIs ▪ No respiratory infection or asthma exacerbation during prev. 8 wks ▪ No oral steroids during prev. 8 wks **Baseline characteristics:** ▪ Male : Female = BDP 21:18, BUD 18:22 ▪ Mean (yrs) age (± SD) = BDP 51 ± 16, BUD 50 ± 14 ▪ Smoking history: not reported ▪ Duration of asthma (yrs ± SD):BDP 9.4 ± 7.7, BUD 11.4 ± 10.6 ▪ History of atopy = BDP 38.5%, BUD 42.5% ▪ FEV1, (absolute value l ± SD) = BDP 2.31 ± 0.84, BUD 2.37 ± 0.60 ▪ FEV_1, (% predicted ± SD) = BDP 75 ± 18, BUD 78 ± 18 ▪ Morning PEF (l/min ± SD) = BDP 365 ± 110, BUD 346 ± 115 ▪ Evening PEF (l/min ± 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:** PEFR (am) **Secondary measures:** ▪ FEV_1 (absolute) ▪ PEFR (pm) ▪ FVC ▪ Diurnal variation in PEFR ▪ Day & night-time asthma symptom scores ▪ Patient-rated treatment efficacy scores ▪ Patient-rated acceptability of device ▪ Salbutamol inhals.per day ▪ Serum cortisol levels ▪ Adverse events **Method of assessing outcomes:** ▪ Follow-up visits before crossover (wks 9-10) and last follow-up visit (wks 17-18) are primary time points for evaluation of efficacy ▫ FEV1, FVC ▫ patient-rated treatment efficacy on VAS scale ▫ patient's assessment of device acceptability on VAS scale ▫ serum cortisol ▪ Daily patient diary recording: ▫ am & pm PEFR (highest reading of 3) ▫ number of salbutamol inhalations per day ▫ severity scores for asthma symptoms (dyspnoea, wheezing and cough) during day and night ▫ adverse events **Length of follow-up:** 2 wks run-in period plus two 8 wks treatment periods = 18 wks

RESULTS

Outcomes	BDP (*n*=79)	BUD (*n*=79)	95% CI for treatment difference; *p*-value
FEV_1 – l:			
treatment period	2.47	2.39	0.01, 0.17; *p*=NS[a]
AM PEFR – l/min			
treatment period	372	372	-8.3, 4.8; *p*=NS[a]; *p*=0.01[b]
PM PEFR – l/min			
treatment period	382	381	-7.0, 7.1; *p*=NS[a]
Symptom-free days			
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 adverse events – n (%):	2	1	
Cough	1	1	
Dysphonia	1		
Oropharyngeal mucosal irritation	8	9	

[a] Group A *v.* 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 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 patientwise percentage scores (sum score of period of interest divided by theoretical maximum score for that period).
  - Patients' assessment of devices using VAS scale was analysed using Wilcoxon's signed rank test.
  - Analysis was intention to treat.
- **Sample size/power calculation:** designed to enrol 58 patients per treatment group to detect (with 90% power; $\alpha = 0.05$) a difference between groups of 30 l/min in AM PEFR (assuming mean of 450 l/min & SD 70 l/min).
- 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

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 intention to treat analysis?	adequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [201] **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: 1000µg b.i.d. Delivery: MDI + spacer Duration: 6 wks **Group B:** *n* = 15 Drug(s): BUD Dose: 1000µg b.i.d. Delivery: MDI + spacer Duration: 6 wks **Run-in period:** Duration: 1 wk ICS: none specified Relief: none specified **Additional treatment allowed:** Relief: salbutamol as needed Other: none specified	**Number randomised:** 15 **Sample attrition/dropout:** *n*=2 ("One patient opted out of study during second drug phase and other during the first drug phase") **Sample crossovers:** 6 wks BDP, washout of 1 wk followed by 6 wks BUD; or 6 wks BUD, washout 1 wk followed by 6 wks BDP **Inclusion/exclusion criteria:** ▪ Age 14-45 ▪ Newly diagnosed patients with asthma (diagnosis based on history of recurrent cough & wheezing & documentation of >12% and 200ml increase in FEV_1:FVC after inhalation of 200µg 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 (9AM) µg/100ml ▪ Serum cortisol (4pm) µg/100ml ▪ 24h urinary steroids mg/24h ▪ FVC (L) ▪ FEV1 (L) **Method of assessing outcomes:** ▪ Patient diary for recording ▫ symptoms ▫ drugs ▪ Beginning and end of treatment periods ▫ samples of blood (9AM and 4PM) and urine (24hr) for cortisol ▫ spirometry (FVC, FEV_1) **Length of follow-up:** None beyond two 6 wks periods

RESULTS

Outcomes	Grp A BDP (*n*=15)	Grp B BUD (*n*=15)	*p*-value
FEV_1 – L (SD) Baseline wk 6	 1.86 (0.88) 2.44 (0.76)	 2.14 (0.79) 2.69 (0.82)	 $p<0.05^{b,c}$
FVC (L) Baseline wk 6	 2.89 (0.80) 3.18 (0.72)	 3.04 (0.87) 3.71 (0.62)	 $p<0.05^{c}$; NS^{b}
Serum cortisol 9AM µg/100ml Baseline wk 6	 19.27 (4.41) 19.67 (4.10)	 19.63 (3.58) 18.78 (3.26)	 $NS^{b,c}$
Serum cortisol 4PM µg/100ml Baseline wk 6	 12.46 (2.95) 12.42 (2.73)	 12.53 (2.03) 11.57 (2.35)	 $NS^{b,c}$
24hr urinary steroids mg/24h Baseline wk 6	 16.20 (4.92) 15.80 (3.73)	 15.63 (4.02) 15.49 (3.19)	 $NS^{b,c}$

RESULTS

Outcomes	Grp A BDP (*n*=15)	Grp B BUD (*n*=15)	*p*-value

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

Comments

- Study included ten healthy subjects of either sex, age range 18-35 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 PEFR; 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. Dropouts excluded from data analyses.

GENERAL COMMENTS

- **Generalisability:** limited to young patients (<45)
- **Outcome measures:** appropriate and objective
- Inter-centre variability: n/a
- 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?	n/a
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 intention to treat analysis?	inadequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [237] **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: 250µg b.i.d. Delivery: DPI Diskus Duration: 52 wks **Group B: SFC** *n* = 27 Drug(s): FP/SAL Dose: 250/50µg b.i.d. Delivery: DPI Diskus Duration: 52 wks **Run-in period:** Duration: 4 wks ICS: FP 250µg b.i.d. Relief: Not stated whether the Salbutamol 200µg rescue med. also applied to run-in period **Additional treatment allowed:** ▪ Relief: ▪ Salbutamol 200µg Other: None stated ▪ Objective was to investigate whether adding salmeterol to fluticasone has a prolonged effect on the bronchial inflammatory process in asthma	**Number randomised:** 54 **Sample attrition/dropout:** *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 yrs ▪ $FEV_1 \geq 70\%$ of predicted value after maximal bronchodilation ▪ Sensitization to cat, dust mite and/or grass pollen allergens ▪ Bronchial hyperresponsiveness to histamine, PC_{20} histamine ≤ 8.0 mg/ml at end of run-in period ▪ Clinically stable disease without exacerbations within 3 mths requiring oral steroids and/or antibiotics prior to entry into study ▪ No changes to asthma medication during 4 wks prior to entry ▪ Ability to use Diskus inhaler and perform reproducible lung function tests **Exclusion criteria:** ▪ Comorbidity likely to interfere with the study (undefined) ▪ Lower respiratory tract infection or use of antibiotics during 4 wks before study entry ▪ Use of the following during the study: theophylline, sodium cromoglycate, nedocromil sodium or antileukotrienes; or antibiotics 4 wks prior to study ▪ Current smokers, or regular smokers within 6 mths before study entry, or a smoking history of > 10 pack-yrs ▪ Pregnant or lactating females ▪ Inability to follow therapy instructions ▪ Participation in another clinical trial within 4 wks prior to the study **Baseline characteristics:** ▪ Median (yrs) age (range): FP: 32 (19-57), SFC: 32 (21-59)	**Primary measure:** Sputum eosinophil numbers and eosinophilic cationic protein concentrations **Secondary measures:** ▪ Neutrophil-related sputum parameters ▪ Respiratory membrane permeability ▪ FEV1 ▪ 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: ▫ PEFR ▫ Rescue medicine use ▫ Symptom scores ▪ Measurement of FEV_1 (spirometry), allergy responsiveness & biochemical parameters in clinic visits **Length of follow-up:** None beyond the 52 wks treatment period

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		▪ % M:F: FP: 30:70, SFC: 37:63 ▪ Median (range) ICS use before study (µg/day): FP: 593 (200-1200), SFC: 619 (200-1000) ▪ FEV_1 (% predicted) at start of run-in, geo mean (± SD): FP: 89.9 (14), SFC: 88.8 (± 18) ▪ FEV_1 (% predicted) at end of run-in, geo mean (± SD): FP: 92.6 (16), SFC: 93.1 (16.1) ▪ Mean (± SD) morning PEF (l/min) at end of run-in: FP: 422 (102), SFC: 418 (102) ▪ Mean (± SD) evening PEF (l/min) at end of run-in: FP: 435 (110), SFC: 431 (106) ▪ Mean (± SD) morning symptom score at end of run-in: FP: 0.2 (0.3), SFC: 0.3 (0.5) ▪ Mean (± SD) evening symptom score at end of run-in: FP: 0.6 (0.6), SFC: 0.6 (0.7) ▪ 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) ▪ Geo mean (± SD) PC20 histamine at start of run-in (mg/ml): FP: 0.14 (0.16), SFC: 0.5 (1.5) ▪ Geo mean (± SD) PC20 histamine at end of run-in (mg/ml): FP: 1.0 (1.5), SFC: 1.6 (1.3) Notes: Morning and evening symptom scores use scales 0-4 and 0-5 respectively but no further details given	

RESULTS

Outcomes	FP (*n*=27)	SFC (*n*=27)	*p*-value
Mean (± SE) morning PEF (l/min) at mth 12	From chart [a]	From chart [a]	Not given
Mean short-acting β_2 agonist use (puffs/day) at mth 12	From chart [b]	From chart [b]	Not given
	Mean (SE) difference SFC – FP over the 1-yr study period [c]		
Morning PEF (l/min)	29 (9)		$p < 0.001$
Evening PEF (l/min)	36 (9)		$p < 0.001$
Morning symptom score (scale 0-4)	-0.1 (0.1)		$p = 0.02$
Evening symptom score (scale 0-5)	-0.2 (0.1)		$p = 0.01$
Short-acting β_2 agonist use (puffs/day)	-0.9 (0.3)		$p < 0.001$

RESULTS

Outcomes	FP (*n*=27)	SFC (*n*=27)	*p*-value
FEV_1 (% predicted)	2.7 (1.5)		$p = 0.07$
Mortality	Not reported		
QoL	Not reported		
Adverse events – n (%): None reported (apart from one drop-out due to worsening asthma)			
Other			

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

Comments
- For PEFR and short-acting β_2 agonist use, data are available also for mths 0, 1, 3, 6, 9, and 11 (in Fig. 2).
- Results have been extracted for the relevant outcomes only.
- Difference between FP and SFC in mean morning PEF over the whole treatment period was significant ($p < 0.01$).
- Difference between FP and SFC 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 SFC (results not shown).

METHODOLOGICAL COMMENTS

- **Allocation to treatment groups:** No details of the randomization 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 SFC 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 α=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

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 endpoints (various biochemical and allergen-inducible markers). Only a small proportion of the results concerns objective and appropriate clinically relevant endpoints (PEFR, 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 intention to treat analysis?	Inadequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [242] **Author:** Kuna *et al* **Year:** 2006 **Country:** eight 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 + FORM Dose: 160/9µg 2 puffs q.d. (181/10.2µg ex valve) Delivery: Turbuhaler® Duration: 12 wks **Group B:** *n* = 207 Drug(s): BUD + FORM Dose: 160/9µg* b.i.d. (181/10.2µg ex valve) Delivery: Turbuhaler® Duration: 12 wks **Group C:** *n* = 207 Drug(s): BUD Dose: 200µg pm q.d.* Delivery: Turbuhaler® Duration: 12 wks **Run-in period:** Duration: 2 wks ICS: BUD 100µg b.i.d. Relief: None stated **Additional treatment allowed:** ▪ Relief: Terbutaline sulfate or another preferred short-acting β_2-agonist (dose not stated) ▪ Other: None stated ▪ * BUD/ FORMOTEROL doses reported as ex-actuator, single BUD dose reported as ex-valve	**Number randomised:** 617 but 1 patient did not receive any study medication → 616 in ITT population **Sample attrition/dropout:** *n* = 61 (10%), comprising 26 due to asthma deterioration, 10 due to other adverse events, and 25 for other reasons. **Sample crossovers:** None **Inclusion criteria:** ▪ Men or women aged: ≥ 18 yrs ▪ Asthma of minimum duration 6 mths, not optimally controlled despite a daily dose of 200-500µg 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 sulphate 1mg or salbutamol 0.4mg **Exclusion criteria:** ▪ Use of any systemic corticosteroids within the prev. 30 days ▪ Seasonal asthma (defined as asthma exacerbated by seasonal increases in aeroallergens) ▪ Respiratory infection in the 4 wks prior study entry ▪ Severe cardiovascular or any other significant disease ▪ Used β-blocker therapy (including eye drops) ▪ History of heavy smoking (≥ 10 pack-yrs) ▪ 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: Grp1 1/day (*n*=202), Grp2 2/day (*n*=207), Grp3 (*n*=207) ▪ Mean (yrs) age (range): Grp 1 45.8 (18-80), Grp 243.9 (19-80), Grp3 45.1 (18-78) ▪ % M:F: Grp1 40:60, Grp2 38:62, Grp3 44:56	**Primary measure:** Mean change AM PEFR from baseline to end of 12-wk treatment **Secondary measures:** PM PEFR, asthma symptoms, use of reliever, nocturnal waking, FEV_1 **Method of assessing outcomes:** Patient diary cards recording: ▪ AM & PM PEFR 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 ▪ Adverse events (any) ▪ 76 (38%) of patients on 1/day BUD + FORMOTEROL ▪ 78 (38%) of patients on 2/day BUD + FORMOTEROL ▪ 74 (36%) of BUD patients ▪ Serious adverse events ▪ (not related to treatment) ▪ 2 patients on 1/day ▪ BUD + FORMOTEROL ▪ 1 patient on 2/day BUD + FORMOTEROL ▪ 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

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		▪ Asthma (yrs) duration (range): Grp1 11.5 (1-63), Grp2 12.2 (0-50), Grp 3 10.6 (1-58) ▪ ICS dose µg /day (range): Grp1 363 (200-500), Grp2 371 (200-500), Grp3 368 (200-500) ▪ FEV_1 at baseline (litres): Grp1 2.36, Grp2 2.32, Grp3 2.36 ▪ FEV_1 % of predicted norm (range): Grp1 79.3 (37-115), Grp2 77.9 (23-123), Grp3 78.3 (38-119) ▪ Reversibility of FEV_1 (%) upon inhalation of terbutaline sulphate 1mg or salbutamol 0.4mg (range): Grp1 23.5 (12-91), Grp2 23.4 (12-75), Grp3 23.2 (12-95) ▪ Morning PEF l/min (range): Grp1 356 (115-684), Grp2 351 (173-692), Grp3 358 (98-740) ▪ Evening PEF l/min (range): Grp1 366 (112-670), Grp2 362 (181-738), Grp3 371 (112-753) ▪ % nocturnal waking due to asthma: Grp1 15.8, Grp2 (0-100), Grp3 17.9 ▪ % symptom-free days: Grp1 37.8, Grp2 36.1, Grp3 38.1 ▪ % asthma control days: Grp1 33.9, Grp2 32.5, Grp3 35.1	12 weeks into randomized treatment. Adverse events also assessed at clinic visits by interviewer questioning patients and if reported spontaneously by patient ▪ Patient records to obtain composite measures: ▪ Symptom-free days (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 wks reported

RESULTS

Outcomes (mean values)	SYMBICORT once daily (*n*=202)	SYMBICORT twice daily (*n*= 207)	BUD (*n*=207)	*p*-value
Mean (95% CL) morning PEF change from baseline (l/min)	23.4 (18.1, 28.6)		5.5 (0.3, 10.6)	$p < 0.001$
		24.1 (19.0, 29.2)	5.5 (0.3, 10.6)	$p < 0.001$
Mean (95% CL) evening PEF change from baseline (l/min)	9.6 (4.4, 14.8)		-1.7 (-6.8, 3.5)	$p < 0.01$
		18.3 (13.2, 23.4)	-1.7 (-6.8, 3.5)	$p < 0.001$
Mean (95% CL) % of symptom-free days	50.0 (46.0, 54.0)		43.4 (39.4, 47.3)	$p < 0.05$
		50.3 (46.3, 54.3)	43.4 (39.4, 47.3)	$p < 0.05$
Mean (95% CL) % of nocturnal awakenings	11.3 (9.0, 13.6)		12.0 (9.8, 14.3)	ns
		9.9 (7.7, 12.2)	12.0 (9.8, 14.3)	ns
Mean (95% CL) % of reliever-free days	61.8 (58.1, 65.4)		55.5 (52.0, 59.1)	$p < 0.05$
		66.3 (62.7, 69.9)	55.5 (52.0, 59.1)	$p < 0.001$
Mean (95% CL) % of asthma control (asthma-free) days	47.3 (43.4, 51.3)		40.0 (36.2, 43.9)	$p < 0.01$
		47.3 (43.4, 51.1)	40.0 (36.2, 43.9)	$p < 0.01$
Mean FEV_1 change from baseline (litres): [a]	0.08		-0.01	$p < 0.05$

RESULTS				
Outcomes (mean values)	**SYMBICORT once daily** (*n*=202)	**SYMBICORT twice daily** (*n*= 207)	**BUD** (*n*=207)	***p*-value**
		0.12	-0.01	$p < 0.05$
Use of systemic corticosteroids				
Mortality				
QoL				
Adverse events – no. of patients (%): (most frequently-reported endpoints)				
All adverse events	76 (38%)	78 (38%)	74 (36%)	*p*-values not given for adverse events
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 adverse events (no. of patients) (see comments)	2	1	4	
Other				

[a] Calculated from baseline and 12-week FEV_1 values given in the text
ns: not statistically significant ($p \geq 0.05$)

Comments

- Once and twice daily SYMBICORT resulted in significantly (about 7%) more asthma control days (26 days per year) compared to BUD ($p < 0.01$; from text)
- Increase in evening PEFR differed significantly ($p < 0.05$) between the two SYMBICORT cohorts
- Adverse events 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 randomization 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.
- **Method of data analysis:** Analyses were performed on the ITT population, defined (by inference) as all the randomized patients that entered the treatment phase of the study who received at least some study medication. 95% CI 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% CI were derived do not appear to have been checked for normality. Percentages of symptom-free days, reliever-

METHODOLOGICAL COMMENTS

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 a 18 l/min difference in PEFR between treatments at α=0.05, assuming a SD of 50 l/min
- **Attrition/drop-out:** 61/616 randomized and treated patients withdrew from the study:
  - 26 asthma deterioration (10, 5, 11 for once-day SYMBICORT, twice-day SYMBICORT, BUD respectively)
  - 10 due to other (unspecified) adverse events (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-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 wks) 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 intention to treat analysis?	Adequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [238] **Author:** Lundback *et al* **Year:** 2006 **Country:** Sweden **Study design:** double-blind, parallel-group, RCT **Number of centres:** one **Funding:** GlaxoSmithKline plc.	**Group A: SFC** *n* = 95 Drug(s): FP/SAL Dose: FP/S 250/50µg b.i.d. Delivery: Diskus™ inhaler Duration: 52 wks **Group B: FP** *n* = 92 Drug(s): FP Dose: 250µg b.i.d. Delivery: Diskus™ inhaler Duration: 52 wks **Group C: Salmeterol** *n* = 95 Drug(s): Salmeterol Dose: 50µg b.i.d. Delivery: Diskus™ inhaler Duration: 52 wks **NB**: *Only Groups A and B are of interest.* **Run-in period:** Duration: 2 mths ICS: 1-mth pre-run-in period on 'previous therapy', and 1-mth run-in period where daily ICS dose was reduced to a max of BUD 400µg q.d. or equivalent Relief: not reported **Additional treatment allowed:** ▪ Relief: salbutamol DPI (0.2mg) or salbutamol MDI (0.1mg) ▪ Other: none	**Number randomised:** 282 **Sample attrition/dropout:** *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 didn't want to continue; 1 personal reasons) **Sample crossovers:** n/a **Inclusion criteria:** ▪ Aged 18-70 yrs ▪ Mild-moderate persistent asthma, with symptoms at least twice/wk ▪ AHR demonstrated by methacholine challenge with PC_{20}<8mg/ml[a] ▪ diurnal variation in PEFR of ≥20% on >3 days during last 14 days of run-in ≥30% difference between highest + 2nd lowest PEFR reading during any 7 days in run-in period ▪ reversible increase of ≥15% in FEV_1 or PEFR after 0.8mg salbutamol inhalation **Exclusion criteria:** ▪ Daily doses of ICS ≥1200µg ▪ ≥1 life-threatening exacerbations requiring hospitalisation during previous 12mths ▪ Hypersensitive to β-agonists or ICS ▪ pregnant or lactating ▪ Respiratory tract infection during the 4 wks prior to run-in **Baseline characteristics:** ▪ Mean age (yrs): SFC 39.9, FP 39.1 ▪ Male : Female (%): SFC 34:66, FP 42:58 ▪ Proportion with asthma >10yrs (%): SFC 58, FP 58 ▪ Smokers (%): SFC 14, FP 12 ▪ Weight (kg): SFC 72.9, FP 75.3 ▪ Height (cm): SFC 168.8, FP 169.7 ▪ FEV_1 % predicted (%): SFC 92.1, FP 93 ▪ Mean methacholine PC_{20} (mg/ml): SFC 0.5, FP 0.6 ▪ Methacholine PC_{20} <8mg/ml[a] (%): SFC 97.8, FP 97.8 ▪ + reversibility test[b] (%): SFC 22.1, FP 17.4	**Primary measure:** No of pts requiring an increase in study medication **Secondary measures:** ▪ no of pts experiencing ≥2 exacerbations[e] ▪ morning PEFR ▪ PEFR diurnal variation ▪ FEV_1 ▪ FVC ▪ AHR[d] ▪ Day & night-time symptom scores ▪ rescue medication use ▪ adverse events **Method of assessing outcomes:** ▪ Patient diary cards (used for 7 days prior to randomisation and for 14 days prior to each clinic visit): ▫ PEF (am and pm) ▫ asthma symptom scores ▫ rescue medication use ▫ adverse events ▪ Clinic assessments at baseline, 1, 3, 6, 9 & 12 mths after randomisation: ▫ lung function (FEV_1 & FVC) ▫ AHR (at baseline & after 12mths) ▫ physician recording of adverse events **Length of follow-up:** none beyond 12 mths treatment period (there was a 2-yr open-label follow-up period, but results are not reported in this paper)

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		▪ PEF- variability (%): SFC 16.8, FP 17.4 ▪ Previous medication (%): SABA: SFC 93, FP 95; LABA: SFC 20, FP 22; CS: SFC 73, FP 62; other[c]: SFC 5, FP 3	

[a]conc. 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]AHR – airway hyper-responsiveness. [e]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/d for ≥2 consecutive days, or an increase of ≥2 doses/d in regular inhaled medication (study medication or additional ICS) for ≥2 d by the patient's own decision, or ≥2 d when asthma symptoms presented the patient's work or normal activities. If rescue medication was insufficient, exacerbations were treated with oral prednisolone (25mg) for 5 d. A total of 192 pts (68%) had previously received ICS (the median dosage was BUD 500µg/d or equivalent).

RESULTS

Outcomes	SFC (*n*=95)	FP (*n*=92)	*p*-value
No. requiring increase in study medication, *n* (%)	10 (10.5%)	32 (34.8%)	*p*<0.001
Morning PEF[†] (l/min)	38	21	diff +16.9, *p*<0.01
PEF diurnal variation[†]	-2.5	-1.6	diff -0.9, *p*=ns
FEV_1[†] (l)	0.09	0.02	diff +0.07, *p*=ns
FVC[†] (l)	0.07	0.05	diff +0.01, *p*=ns
Improvement in AHR after 12mths (mean[†] methacholine PC_{20}) (mg/ml)	1.8	1.1	*p*<0.05
≥2 acute exacerbations (%)	4.2%	17.4%	*p*<0.01
Median proportion of symptom-free days (%)	66.7%	67.9%	
Median symptom-free nights (%)	100%	100%	
Median proportion of rescue medication-free days (short acting B_2 agonists) (%)	85.7%	85.7%	
Median proportion of rescue medication-free nights (short acting B_2 agonists) (%)	100%	100%	
Use of systemic corticosteroids			
Mortality			
QoL			
Adverse events* – n (%): any RTI[‡] musculoskeletal pain gastroenteritis hoarseness/dysphonia sinusitis headaches	 92 (97%) 70 (74%) 9 (9%) 11 (12%) 10 (11%) 8 (8%) 2 (2%)	 88 (96%) 72 (78%) 11 (12%) 5 (5%) 8 (9%) 5 (5%) 6 (7%)	not reported

RESULTS

Outcomes	SFC (*n*=95)	FP (*n*=92)	*p*-value
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			

†Mean change from baseline, adjusted for baseline value, stratum, age and sex; *most frequently occurring (≥5%) adverse events; ‡upper respiratory tract infections plus viral respiratory infections; ns = not significant

Comments
- Results have been presented for SFC 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 12mths, or in the case of 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.
- **Method of data analysis:** analyses were performed on ITT population defined as all patients who were randomised to treatment and received at least one dose of study medication. The pairwise chi-square test was used to compare proportions, the analysis of covariance 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 wks 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 (SFC vs FP or salmeterol) 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%) SFC; 5 (5%) FP). 2% in SFC group and 2% in FP group withdrew due to adverse events. 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 12mth treatment period, or if they had any 2 of the following during the 2wks prior to the 12mth clinic visit: night symptoms requiring rescue medication >twice; daily symptoms requiring rescue medication >every other day; diurnal variability of mean morning PEFR ≥20% on >4days; a reduction in PEFR of ≥15%; or a decrease in clinic FEV_1 ≥10%. Patients randomised to salmeterol were transferred to SFC (50µg/250µg), patients on FP (250µg) had their dose increased to FP 500µg, and patients on SFC (50µg/250µg) were given SFC (50µg/500µg). Patients who needed an increase in study medication as a result of an exacerbation during the 12mth treatment period stopped the blinded phase of the study and continued in the study on an open-label basis.

GENERAL COMMENTS
▪ **Generalisability:** patients would appear to be clinically representative of patients with mild-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 intention to treat analysis?	adequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [189] **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: 400µg (200µg b.i.d.) Delivery: MDI+ spacer Duration: 12 mths **Group B: BDP800** *n* = 21 Drug: BDP Dose: 800µg (400µg b.i.d.) Delivery: MDI +spacer Duration: 12 mths **Group C: FP750** *n* = 13 Drug: FP Dose: 750µg (375µg b.i.d.) Delivery: MDI +spacer Duration: 12 mths **Group D: BDP1500** *n* = 13 Drug: BDP Dose: 1,500µg (750µg b.i.d.) Delivery: MDI +spacer Duration: 12 mths **Run-in period:** Duration: 4 wks ICS: BDP 800µg or 1,500µg q.d. depending on the dose of ICS use prior to entry Relief: salbutamol as required; most pts 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	**Number randomised:** 69 **Sample attrition/dropout:** n=4 (6%) (adverse event 1, non-compliance 1, no reason specified 2) **Sample crossovers:** n/a **Inclusion criteria:** ▪ Mild to moderate asthma ▪ aged 20-55 yrs for men; aged 20-45 yrs for women (pre-menopausal) ▪ 6 mths prior use of ICS (400-1,600µg /q.d.) **Exclusion criteria:** ▪ A change in regular asthma med. (other than ICS) treatment with antibiotics for infections of upper or lower respiratory tract ▪ Hospital admission during prev. 4 wks ▪ Treatment with systemic corticosteroids during previous 8 wks ▪ >3 short courses of oral steroids or depot corticosteroids in previous 12 mths ▪ Excessively overweight or underweight[a] ▪ Immobilisation ▪ Fractures occurring in 6 mths 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 mths preceding start of study ▪ Treatment with any medication likely to influence bone metabolism **Baseline characteristics:** ▪ Mean age (yrs): 38 to 40 across groups ▪ Male: Female, n (%): 46:23 (67-33%) ▪ Caucasian, n (%): 66 (96%) ▪ Mean height, (cm): 170-174 across grps ▪ Mean weight, (kg): 64-75 across grps ▪ Mean baseline % predicted FEV_1: 75.0-90.2 across grps ▪ Mean baseline % predicted PEFR: 78.4-97.8 across grps	**Primary measure:** Bone mineral density (BMD) of the distal radius **Secondary measures:** ▪ Cortisol ▪ Biochemical markers of bone metabolism[b] ▪ Lung function: PEFR and FEV_1 ▪ Adverse events **Method of assessing outcomes:** ▪ Clinic visits at start and end of run-in and every 2 mths through treatment period: ▫ BMD (at 0, 6 & 12 mths) by pQCT[c] and DXA[c] ▫ cortisol by chemoluminescence immunoassay ▫ bone markers by, radioimmunoassay, enzyme immunoassay and HPLC using blood/urine samples ▫ FEV_1 at each clinic visit ▫ adverse events at each clinic visit ▪ Diary cards before taking study medication, daily during last 2 wks of run-in and during the 2 wks preceding each clinic visit: ▫ PEF a.m. and p.m. using mini-Wright peak flow meter **Length of follow-up:** 12 mths treatment period + additional follow-up visit 2wks after completing of

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
	treatment with low and high doses of inhaled FP and BDP over 1yr on bone mass and metabolism.	▪ Duration of asthma, n: <12 yrs: 2; ≥12 yrs: 67 ▪ History of smoking, n (%): never 36 (52%); ex-smoker 23 (33%); current smoker 10 (14%)	study

[a]not defined; [b]markers of bone metabolism - serum osteocalcin (OC), alkaline phosphatise (bone specific), pro-collagen type 1 carboxy terminal propeptide (P1CP), creatinine, calcium, carboxy terminal cross linked telopeptide of type I collagen (ICTP); [c]pQCT – peripheral quantitative computed tomography of radius and tibia, evaluating trabecular, total (integral) and compact bone; DXA – dual energy x-ray absorptiometry of lumbar spine, evaluating a mixture of cortical and trabecular bone.

RESULTS

Outcomes	FP400 (*n*=22)	BDP 800 (*n*=21)	FP750 (*n*=13)	BDP 1500 (*n*=13)	*p*-value
PEFR:					
FEV_1:					
Symptom-free days					
Nocturnal awakenings					
Acute exacerbations, n (%)[†]	0	1 (5%)	2 (15%)	1 (8%)	*p*=ns
Use of systemic corticosteroids					
Mortality					
QoL					
Adverse events – n (%): hoarseness/dysphonia allergic skin reactions oral candidiasis rash/skin eruptions	 1 (5%) 0 0 0	 1 (5%) 0 0 0	 1 (8%) 0 0 0	 0 0 0 0	
Other: Mean serum cortisol concentration (nmol/l)* Baseline n coefficient of variation (%) 12 mths n coefficient of variation (%)	 466 22 29 532 21 41	 474 21 35 486 19 50	 424 13 59 299 12 122	 370 13 54 406 12 41	

[†]requiring a short course of oral corticosteroids; *reference range is 138-635

RESULTS

Outcomes	FP400 (*n*=22)	BDP 800 (*n*=21)	FP750 (*n*=13)	BDP 1500 (*n*=13)	*p*-value

Comments

Bone mineral density

- 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 12mths. Overall, compared with baseline values, there was no loss of trabecular or integral bone in the radius or tibia in any pts over the 12mths. Some negative changes were recorded in the median bone density of compact bone of the radius (FP750 pts) and tibia (BDP800 and FP750 pts), 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 mths (*p*=0.048) in pts 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 mths, nor was there any difference at 12 mths 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 mths.

Bone markers

- With the exception of the bone re-sorption 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 mths treatment. In the low dose comparison group, a statistically significant difference in the change from baseline in osteocalcin at 12 mths (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 re-sorption marker ICTP at 6 mths (p=0.031) suggested greater bone re-sorption 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 mths study showed that the patients were well controlled on all treatments. Mean values either remained similar or tended to increase slightly above baseline values.

Adverse events

- 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 AE.
- All geometric mean cortisol values remained within the normal range throughout the 12 mths study period.

METHODOLOGICAL COMMENTS

- **Allocation to treatment groups:** randomisation methods not specified. Allocation to treatment groups depended on whether patients were in the low dose 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 re medications. All scans were performed under blinded conditions.
- **Comparability of treatment groups:** states that the demographic and baseline characteristics were well-

METHODOLOGICAL COMMENTS

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 pts each.
- **Attrition/drop-out:** 4 pts (6%) (1 from each group) withdrew from the study: adverse event (n=1, BDP1500), non-compliance (n=1, BDP800), no reason specified (n=1 FP400, n=1 FP750).

GENERAL COMMENTS

- **Generalisability:** includes patients with mild-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 intention to treat analysis?	inadequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [194] **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 AM + placebo PM Dose: 200µg q.d. (≈160µg ex-actuator) Delivery: HFA-MDI Duration: 12wks **Group B:** *n* = 131 Drug(s): CIC PM + placebo AM Dose: 200µg q.d. (≈160µg ex-actuator) Delivery: HFA-MDI Duration: 12wks **Group C:** *n* = 134 Drug(s): BUD Dose: 200µg b.i.d. Delivery: HFA-MDI Duration: 12wks **Run-in period:** Duration: 2-2.5wks ICS: BUD 200µg b.i.d. Relief: inhaled salbutamol (100µg/puff) **Additional treatment allowed:** Relief: inhaled salbutamol (100µg/puff) Other: 1 other concomitant medication (inc. LABA, oral β_2-agonist, leukotriene antagonist, theophylline, inhaled disodium cromoglycate, nedocromil) **Trial aim:** to assess the non-inferiority of Group B *v.* Group C	**Number randomised:** 405 **Sample attrition/dropout:** *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 ▫ persistent asthma for ≥6 mths ▫ constant dose of BDP (≤500µg/d), FP (200-250µg/d), BUD (400µg/d) or equivalent ICS for previous ≥4wk ▫ FEV_1 ≥70% predicted ≥4hr after last rescue medication and 24hr after withholding other medication ▪ After run-in: ▫ *stable asthma*, defined as · no fluctuation ≥20% in diurnal PEFR, no need for >4 puffs/day of rescue medication & no night symptom score ≥2 on any consecutive 2 of prev. 10d · no need for oral steroids · FEV_1 >69% predicted ≥4hr after last rescue medication and 24hr after withholding all medication except BUD ▪ Either after run-in or during last yr: ▫ FEV_1 reversibility ≥12% after 200-400µg salbutamol or ▫ positive hyperresponsiveness test (PC20) **Exclusion criteria:** ▪ Any prior use of systemic steroids ▪ Exacerbation/hospitalisation in prev. 4 wks ▪ COPD ▪ Disease states contraindicating ICS ▪ Smoking history of ≥10 pack-yrs ▪ Pregnancy or breastfeeding ▪ Abnormal laboratory values **Baseline characteristics:** ▪ Male : Female = 213:190 ▪ Median (yrs) age (range) = 29-32 (18-69)* ▪ Median weight, kg = 55-57* ▪ Smoking history = 380 (94%) non-smokers, 23 (6%) ex-smokers ▪ ICS pre-treated = 356 (88%) ▪ Concomitant medication before entry, n (%): LABA = 105 (26%); xanthines = 62 (15%); ICS+LABA = 54 (13%); antihistamines = 37 (9%); nasal corticosteroids = 24 (6%)	**Primary measure:** Change in FEV_1 at the end of treatment **Secondary measures:** ▪ Difference in FEV_1 betw. randomisation & study visits ▪ FVC ▪ PEFR ▪ Diurnal PEFR fluctuation ▪ Asthma symptom scores ▪ Rescue medication use ▪ Adverse events **Method of assessing outcomes:** ▪ Clinic assessments at baseline and wks 0, 2, 4, 8, and 12: ▫ FEV_1, FVC and PEFR (highest reading of 3; ≥4hr after last use of salbutamol and ≥24hr 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 PEFR readings AM & PM ▫ symptom scores ▫ rescue medication use **Length of follow-up:** None beyond 12-wk treatment period

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		▪ Mean FEV_1, l = 2.2-2.3* ▪ Mean FEV_1, % predicted = 92-94* ▪ 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)* ▪ Mean morning PEF, l/min = 318.1-324.8* ▪ PEFR fluctuation, %(range) = 6.9-7.3(0-34)* ▪ * range of values across all 3 arms	

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:				
difference – l (95%CI)	-0.036 (-0.120,0.045)[c]	0.022 (-0.061,0.105)[d]		0.383[c]; 0.598[d]
p-value (baseline *v.* wk 12)	0.001	NS[e]	0.035	
PEFR, mean[b] change from baseline:				
AM – l/min (95%CI)	-5.7	8.0	-1.3	NS[c,e]; NS[d,e]
difference, AM – l/min (95%CI)	-4.4 (-16.4,7.5)[c]	9.3 (-2.8,21.5)[d]		0.464[c]; 0.131[d]
difference, PM – l/min (95%CI)	-1.1 (-12.4,10.3)[c]	4.0 (-7.5,15.5)[d]		0.855[c]; 0.490[d]
Symptom-free days – %	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				
Adverse events – *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]
URTIs	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 *v.* Group C
[d] Group B *v.* 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)

RESULTS

Outcomes	Group A (n=139[a])	Group B (n=131)	Group C (n=133[a])	p-value

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 PEFR fluctuation were maintained versus baseline, with no significant differences between the treatment groups.
- No oropharyngeal adverse effects 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 L).
  - 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.
  - FVC (Δ = -0.20 L) and PEF (Δ = -25 L/min) 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 symptom-free days, days free of rescue medication, days free of nocturnal awakening, and control of asthma symptoms as perceived by patients (ie, no symptoms and no rescue medication use) analysed by Mann-Whitney U tests.
  - Primary and secondary efficacy end points evaluated by analysis of covariance.
- **Sample size/power calculation:** designed to have 90% power to establish the non-inferiority of Group B *v*. 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

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
4. Were outcome assessors blinded to the treatment allocation?	adequate for Group A *v.* Group B; inadequate for Group C (open label)
5. Was the care provider blinded?	adequate for Group A *v.* Group B; inadequate for Group C (open label)
6. Was the patient blinded?	adequate for Group A *v.* 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 intention to treat analysis?	partial
9. Were withdrawals and dropouts 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 ID: [232] **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/FORM Dose: 80/4.5µg b.i.d. 80/4.5µg as needed Delivery: Turbuhaler Duration: 52 wks **Group B:** *n* = 909 Drug(s): BUD/FORM Dose: 80/4.5µg b.i.d. + terbutaline 0.4mg as needed Delivery: Turbuhaler Duration: 52 wks **Group C:** *n* = 926 Drug(s): BUD Dose: 320µg b.i.d. + terbutaline 0.4mg as needed Delivery: Turbuhaler Duration: 52 wks **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 (30mg/day)	**Number randomised:** 2760 Sample attrition/dropout: *n* = 412 (67 adverse events; 111 eligibility criteria not fulfilled; 47 lost to follow-up; 187 other) **Sample crossovers:** NR **Inclusion/exclusion criteria:** **Inclusion criteria:** ▪ Age ≥4 ▪ 1 ≥ exacerbations in previous yr ▪ ICS 400-1000µg/day in previous yr ▪ Constant dose of ICS ≥ 3 mths ▪ 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 Rx10 ≥ inhalations reliever medication on any one day ▪ Additional exacerbations **Baseline characteristics:** ▪ Mean age (range) = 36 (4-79) ▪ Male : Female = 1231:1529 ▪ 4-11 yrs, n (%): 341 (12%) ▪ Mean duration of asthma = 9 yrs (range:0-69) ▪ FEV1 (L): 2.12 (range: 0.62-4.50) ▪ FEV1 (% predicted): 73 (range: 43-108) ▪ FEV1 reversibility: 21% (range: 2%-89%) ▪ ICS dose at entry (µg/day): 598-620* ▪ LABA use at entry (n): 250-258 (28%) ‡ ▪ 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) ▪ Symptom free days (%): 23.5 (range: 0.0-100) ▪ Reliever free days (%): 8.4 (range: 0.0-100) ▪ Asthma control days (%): 5.6	**Primary measure:** Time to first severe exacerbation (defined as hospitalization emergency room treatment; oral steroid treatment (or an increase in ICS and/or other additional treatment for children aged 4-11 years) or AM PEFR<= 70% of baseline on 2 consecutive days). **Secondary measures:** ▪ PEFR (am & pm) ▪ FEV_1 ▪ Time to first mild exacerbation (defined as AM PEFR<= 80% of baseline, ≥2 reliever inhalations/day above baseline or awakenings caused by asthma). ▪ Asthma symptom scores (day/night) ▪ Rescue medication use (day/night) ▪ Symptom free days ▪ Rescue medication free days ▪ Asthma control days ▪ Nocturnal awakenings ▪ Mild exacerbation days ▪ Adverse events **Method of assessing outcomes:** ▪ Clinic assessments at beginning and end of run-in and 1, 3, 6, 9, & 12mths ▫ PEFR (am & pm) mini-Wright PEFR meter ▪ FEV_1 (spirometry at clinic visits) ▪ Daily patient diaries (symptoms, awakenings, effects and extra medication) ▪ Electrocardiogram, AM plasma cortisol, vital signs (at clinic visits)

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		(range: 0.0-90) ▪ Awakenings (% of nights): 20.9 (range: 0.0-100) ▪ * values=combination of metered and delivered doses ▪ ‡ includes combinations of ICS/LABA and LABA	**Length of follow-up:** none beyond 12 mths treatment period

RESULTS

Outcomes	Group A (*n*=925)	Group B (*n*=909)	Group C (*n*=926)	*p*-value
FEV_1, mean[a] over 12 mths treatment period	2.51	2.43	2.41	<0.001[b]; <0.001[c]; 0.09[d]
PEFR (L/min), mean[a] over 12 mths treatment period AM: PM:	355 360	346 349	339 345	<0.001[b]; <0.001[c]; <0.001[d] <0.001[b]; <0.001[c]; <0.001[d]
Symptom-free days (%) mean[a] over 12 mths treatment period	54	53	46	0.52[b]; <0.001[c]; <0.001[d]
Nocturnal awakenings, (% of nights) mean[a] over 12 mths treatment period	9	12	12	<0.001[b]; <0.001[c]; 0.60[d]
Severe exacerbations including PEFR falls: patients with event (%)[e] Severe exacerbations resulting in medical intervention: patients with event (%)[e]	16 11	27 21	28 19	<0.001[b]; <0.001[c]; 0.74[d] <0.001[b]; <0.001[c]; 0.37[d]
Use of reliever (puffs/day) mean over 12mths Use of reliever (puffs/night) mean over 12mths	0.73 0.28	0.84 0.37	1.03 0.43	<0.001[b]; <0.001[c]; <0.001[d] <0.001[b]; <0.001[c]; 0.003[d]
Use of systemic corticosteroids (courses per patient) Children (4-11 yrs) Adults (12-80 yrs)	0.05 0.19	0.30 0.42	0.38 0.25	NR
Mortality				
QoL				
1or more adverse events – n (%): 1or more serious adverse events - n (%)	496 (54%) 46 (5%)	475 (52%) 62 (7%)	528 (57%) 48 (5%)	0.58[b]; 0.99[c] ; 0.03[d]
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	9 (1%)	6 (1%)	10 (1%)	0.61[b]; 0.82[c]; 0.45[d]
Dysphonia	11 (1%)	13 (1%)	12 (1%)	0.69[b]; 0.84[c]; 0.84[d]

RESULTS

Outcomes	Group A (*n*=925)	Group B (*n*=909)	Group C (*n*=926)	*p*-value
Discontinuation due to respiratory events	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 *v*. Group B
[c] Group A *v*. Group C
[d] Group B *v* Group C
[e] p values based on the instantaneous risk of experiencing at least one severe exacerbation (Cox proportional hazard 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/FORM maintenance + relief group (Group A) compared with the BUD/FORM + SABA (Group B) and BUD + SABA groups (Group C); HR = 0.50 (95% CI: 0.40, 0.64) and 0.55 (95% CI: 0.43, 0.70) respectively.
- The RR of severe exacerbation requiring medical management was reduced by 53% for BUD/FORM maintenance + relief compared with BUD/FORM + SABA; HR=0.47 (95% CI: 0.39, 0.57) and by 46% compared with BUD + SABA; HR=0.54 (95% CI: 0.44, 0.66) The effect of using BUD/FORM 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 electrocardiogram, haematology, clinical chemistry, or urinalysis were observed between the treatment groups or over time.

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 analyses 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 number of severe exacerbations were compared using a Poisson regression model, with adjustments for over-dispersion. Secondary efficacy endpoints were evaluated by analysis of co-variance, with the baseline value as covariate and the mean daily data over the 12-mth treatment period as the treatment mean. All hypothesis testing was two-sided, with p values of less than 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 adverse events 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 endpoint and safety was 2753, with LOCF for missing

METHODOLOGICAL COMMENTS
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 ANOVA model ▪ **Conflict of interests:** study support and one author's 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 intention to treat analysis?	partial
9. Were withdrawals and dropouts completely described?	partial

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http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [200] **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: 100µg b.i.d. Delivery: DPI Duration: 12 wks **Group B:** *n* = 182 Drug(s): MF Dose: 200µg b.i.d. Delivery: DPI Duration: 12 wks **Group C:** *n* = 184 Drug(s): MF Dose: 400µg b.i.d. Delivery: DPI Duration: 12 wks **Group D:** *n* = 184 Drug(s): FP Dose: 250µg b.i.d. Delivery: DPI Diskhaler Duration: 12 wks **Run-in period:** Duration: 1-2wk 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/dropout:** *n* = 102 (1 before receiving and study Rx; 4% due to treatment failure) **Inclusion criteria:** ▪ Age ≥12 ▪ History of asthma for ≥6 mths ▪ 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 ≥200ml within 30min of albuterol×2 **Exclusion criteria:** ▪ Smoking within previous 6mo ▪ Methotrexate, cyclosporine or gold Rx in previous 3 mths ▪ Oral steroids >14d in previous 6 mths ▪ Systemic steroids or investigational Rx in previous 1 mth ▪ >1mg q.d. nebulised BA / any LABA ▪ immunotherapy, unless on a stable maintenance schedule ▪ Inpatient hospitalisation for asthma in previous 3 mths ▪ Intubation for asthma in previous 5yrs ▪ ≥2 emergency hospital treatments in previous 6 mths ▪ Between screening and baseline: ▫ FEV_1 increase/decrease ≥20% ▫ >12 inhalations of albuterol on any 2 consecutive days ▪ Respiratory tract infection within previous 2 wks ▪ Pregnant, breastfeeding or pre-menarcheal women ▪ Significant oral candidiasis ▪ Other clinically significant disease ▪ Abnormal laboratory values **Baseline characteristics:** ▪ Mean (yrs) age (range) = 41 (12-79) ▪ Male : Female = 295:437 ▪ White:black:other = 555:4:173 ▪ Mean duration of asthma = 15yr ▪ Mean FEV_1 (% predicted) = 75% ▪ Previous ICS – *n* (%) @ mean dose, µg: BDP = 362 (49%) @ 614; BUD = 230	**Primary measure:** Mean change in FEV_1 from baseline to endpoint **Secondary measures:** ▪ PEFR ▪ $FEF_{25-75\%}$ ▪ FVC ▪ Asthma symptom scores ▪ Rescue medication use ▪ Nocturnal awakenings ▪ Physician evaluation ▪ Adverse events **Method of assessing outcomes:** ▪ Clinic assessments at screening, baseline, day 4 & wks 1, 2, 4, 8, & 12: ▫ spirometry (highest readings of 3) ▫ oropharyngeal examination ▪ Daily patient diaries: ▫ PEFR (AM & PM) (highest readings of 3) ▫ symptoms, effects and extra medication **Length of follow-up:** None beyond 12-wk treatment period

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		(31%) @ 623; flunisolide = 34 (5%) @ 774; FP = 103 (14%) @ 462; triamcinolone acetonide = 1 (0%) @ 149	

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 – l ± SE:	0.07±0.04	0.16±0.04	0.19±0.04	0.16±0.04	0.02[b]; NS[c,d,e]
PEFR, mean[a] change from baseline to last evaluable visit – l/min (SE):	15±5	29±6	30±5	32±5	≤0.05[b,d,e]
Symptom-free days					
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 – µ/day	-13.23	-94.84	-38.10	-52.06	*p*<0.01[d]; NS[c,b,e]
Use of systemic corticosteroids					
Mortality					
QoL					
Adverse events – *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 *v*. Group C [primary efficacy comparison]
[c] reported as "no significant difference" in text, but no *p*-values provided
[d] Group A *v*. Group B
[e] Group A *v*. Group D
[f] Group B *v*. Group C
[g] Group B *v*. Group D
[h] Group C *v*. 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*

RESULTS

Outcomes	Group A (*n*=182)	Group B (*n*=182)	Group C (*n*=184)	Group D (*n*=184)	*p*-value

Comments

- Results of PEFR (PM) "similar" to those of PEFR (AM).
- Symptom measures: improvements in all groups compared to baseline in AM wheezing and AM & PM coughing. Breathing difficulty (AM) scores were significantly better with FP (Group D) compared to lower-dose MF (Groups A & B) ($p \leq 0.05$) but not Group C.
- Physician-evaluated improvement was significantly higher in Groups B, C & D compared to 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 & 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 l (95%CI 2.43, 2.63) for Group A *v.* 2.38 l (95%CI 2.28, 2.48) for Group C. Similarly, PEFR was higher in Group A – 383 l/min (95%CI 365, 401) – compared to Group C – 362 l/min (95%CI 344, 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.
- **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 endpoint in any pairwise 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 & D discontinued treatment. Reasons for discontinuations are incompletely reported: 7%, 4%, 3% & 4% of Groups A, B, C & D, respectively, withdrew because of treatment failure; 5%, 3%, 5% & 4% of Groups A, B, C & 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 analyses used centre as a covariate
- **Conflict of interests:** study support 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

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
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 intention to treat analysis?	adequate
9. Were withdrawals and dropouts 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 ID: [231] **Author:** Pohl *et al* **Year:** 2005 **Country:** Austria **Study design:** **D**ouble-blind, parallel-group, RCT **Number of centres:** 16 across Austria **Funding:** AstraZeneca	**Group A: ICS[1]** *n* = 68 Drug(s): BUD Dose: 320µg 2 puffs b.i.d first 4 wks, then ADM[3] Delivery: Pulmicort® Turbuhaler® Duration: 20 wks **Group B: ICS/LABA[2]** *n* = 65 Drug(s): BUD/FORM Dose: 160/4.5µg 2 puffs b.i.d., first 4 wks, then ADM[3] Delivery: Symbicort® Turbuhaler® Duration: 20 wks **Run-in period:** not reported **Additional treatment allowed:** ▪ Relief: Terbutaline (Bricanyl® Turbuhaler®) (0.4mg[b]) 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 & October 2002 **Sample attrition/dropout:** n=7 (5%) (5 for Grp1& 2 for Grp2) due to no efficacy measurement on treatment – eliminated from the ITT population n=24 (19%) of ITT population (15 for Grp1 & 9 for Grp2) withdrew after week 2 **Sample crossovers:** n/a **Inclusion criteria:** ▪ Aged ≥ 19yrs ▪ With asthma indicated by FEV_1 of a short-acting bronchodilator of ≥ 15% or 200ml within 1mth 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 wks prior to study entry ▪ URTIs in the 6wks 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 (yrs) age (range): Grp1=45 (20-82), Grp2=45 (20-80) ▪ Male : Female (%): Grp1 59:41, Grp2 48:52 ▪ Median (range) asthma duration (yrs): Grp1= 4.5 (0-30), Grp2=10 (0-35) ▪ Documented smoking habit,	**Primary measure:** No. of patients per treatment grp who experienced ≥1 treatment failure[4] **Secondary measures:** ▪ HRQL ▪ Patient & physician ▪ treatment satisfaction ▪ Dose of medication ▪ % of days on which ▪ patients required reliever ▪ medication ▪ FEV_1 ▪ PEFR **Method of assessing outcomes:** ▪ Medial Outcomes Study ▪ Short-Form (36-item) for HRQL Health Survey (SF-36) ▪ Patient & physician assessment with treatment satisfaction measured wk 20 using visual analogue scale[5] ▪ Daily patient diaries ▫ PEFR (am & pm) ▫ 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, & 20 wks **Length of follow-up:** None beyond 20 wks treatment period

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		n(%): Grp1=21 (33), Grp2=24 (38) ▪ Previous ICS treatment, n(%): Grp1=40 (63), Grp2=40 (63) ▪ Mean (range) FEV_1 % predicted: Grp1=65 (39-85), Grp2=67 (35-88)	

RESULTS

Outcomes	Group A – ICS 320µg (*n*=63)		Group B – ICS/LABA 160/45µg (*n*=63)		*p*-value
PEFR morning: mean (l/min) change from baseline	398		407		
PEFR evening: mean (l/min) change from baseline	404		411		
FEV_1 : mean (l) change from baseline	0.37		0.36		
Mean number of inhalations per day of ICS	3.4(1072µg dose)		3.1(494µg dose)		$p = 0.024$
Symptom-free days	Not reported		Not reported		
Nocturnal Awakenings	Not reported		Not reported		
Exacerbations during last 12 weeks, n (%)	1 (1)		2 (3)		
Median inhalations per day (ICS dose) [b]	3.6 (1152µg)		2.8 (448µg)		
Use of rescue medication, mean % of days used	17.4		16.2		$p = 0.040$
Use of systemic corticosteroids, n (%)[c]	2 (3)		5 (8)		
Mortality	Not reported		Not reported		
HRQL (means): SF-36	Wk0	Wk20	Wk0	Wk20	
Physical functioning	80.7	87.2	77.6	85.9	$p = 0.0.25$[d]
Physical role functioning	75.0	81.3	73.8	88.5	not reported
Bodily pain	82.0	88.4	78.8	89.6	not reported
General functioning	64.8	69.3	61.7	68.7	not reported
Vitality	56.9	66.4	55.4	63.4	not reported
Social functioning	86.2	92.7	87.6	93.7	not reported
Emotional role functioning	85.2	83.4	86.0	90.5	$p = 0.035$[e]
Mental health	70.0	78.0	71.3	73.5	not reported
Satisfaction with treatment (VAS scores - mm)					
Patient assessment	75.6		85.4		$p = 0.013$
Physician assessment	71.1		83.6		$p = 0.001$
Number of adverse events	81		74		
Other					

[1]=Inhaled Corticosteroids; [2]=: Inhaled Corticosteroids/Long-lasing β_2-agonist. [3]=Fixed starting dosage was for first 4 wks only, then dose was adjusted to 2-4 inhalations daily during wks 5-8, and 1-4 inhalations daily during wks 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. [4]=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. [5]=VAS 0-100mm (0mm=not satisfying & 100mm= very satisfying). ADM = Adjustable Maintenance Dosing

RESULTS

Outcomes	Group A – ICS 320µg (*n*=63)	Group B – ICS/LABA 160/45µg (*n*=63)	*p*-value

Comments

- [a]: all used nebulised β_2-agonist.
- [b]: reported group difference of approximately 700 µg (61%) in the ICS dose.
- [c]: Grp1 were treated with oral steroids; Grp2 used nebulised β_2-agonists.
- [d]: for 6 units; [e]: for 12.1 units – no explanations given for units.
- For patients with diary assessments on at least 5 clinic visits, a total of 36/47 (77%) patients in Grp2 & 25/42 (60%) patients in Grp1 stepped down their medication during the study.
- 75% of Grp2 patients used reliever for symptom relief less than 1 day per wk, 50% of Grp2 patients were reliever-free on 99% of the days in the study, compared with 96% of study days being reliever-free for 50% of Grp1 patients.
- Although patients in Grp2 used reliever medication on a significantly lower percentage of day, is was reported that there were no difference between the two treatment grps in the percentage of days on which patients used reliever medication for symptom relief.
- There were no treatment-related serious adverse events.
- 20 adverse events 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 Grp1; 3 cases each of myalgia and nervousness, and 1 instance each of heart disorder, dyspnea, rhinitis, pruritis, and taste alterations in Grp2.
- 3 patients reported serious adverse events in connection with hospitalisation (1 accident, 1 planned cardiac examination in Grp2 & 1 evaluation of hypertension in Grp1).

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 (Grp1 = 4.5 yrs, Grp2 = 10 yrs, 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 & 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 & demographic characteristics & all efficacy & safety endpoints 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, & PEFR were compared using the Mann-Whitney *U*-test. Differences between baseline scores & values at wk 20 used for analysis. No standard deviation or CI given.
- **Sample size/power calculation:** assuming that the incidence of treatment failure (primary endpoint) with ICS is 25%, a sample size of 80 patients per grp 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 & the study was not powered to test the hypotheses for the primary efficacy endpoint.
- **Attrition/drop-out**: n=133, 7 (5%) drop-out due to no efficacy measurement on treatment (Grp1 1%, Grp2 4%). ITT population n=126, 24 (19%) withdrew wk2 (Grp1 n=15 (12%), Grp2 n=9 (7%). Of these 11 (9%)

METHODOLOGICAL COMMENTS

were lost to follow-up, 4 (3%) withdrew owing to an adverse event (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 investigators discretion. The study used an adjustable maintenance dosing regime, adjusting the starting dosage after 4 wks to 2-4 inhalations daily for ICS (max 640µg) during wks 5-8 and 1-4 inhalations daily (max 1280µg) during wks 9-20. ICS/LABA higher-dose Budesonide only (max 320 µg).

GENERAL COMMENTS

- **Generalisability:** patients would appear to be clinically representative of patients with mild-moderate asthma.
- **Outcome measures:** appropriate & 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 intention to treat analysis?	Inadequate
9. Were withdrawals and dropouts 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 ID: [243] **Author:** Ringdall *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: 250/50µg b.i.d. Delivery: Diskus (Seretide) + 2 placebo DPI Turbuhalers Duration: 12wks **Group B:** *n* = 216 Drug(s): BUD/FORM Dose: 800/12µg b.i.d. Delivery: DPI Turbuhalers + 2 placebo Diskus Duration: 12 wks **Run-in period:** Duration: 2 wks 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/dropout:** 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 1000-1600µg/day of BUD, BDP or flunisolide, or 500-800µg/day FP ▪ Reversibility was defined as an increase in forced expiratory volume in one second of ≥15% from baseline, 15 min after inhaling 400µg 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 wks before visit 1, or any LABAs in the 2 wks before visit 1 Had a recent history of upper or lower RTI ▪ Smokers with a history of 10 pack-yrs or more or had an acute asthma exacerbation within 1 mth before visit 1. **Baseline characteristics:** Mean (yrs) age (±SD): SAL/FP 46.5 (14.0), FORM + BUD 48.1 (13.9) Male % (±SD): SAL/FP 84 (40), FORM + BUD 105 (49) PEFR am L/min: SAL/FP 349 (101), FORM + BUD 348 (101) PEFR pm L/min: SAL/FP 368 (103), FORM + BUD 367 (103) FEV_1 L: SAL/FP 2.18 (0.62), FORM +	**Primary measure:** Mean PEFR am **Secondary measures:** ▪ PEFR am & pm & at other timepoints ▪ PEFR % diurnal variation, ▪ Clinical FEV_1, rate ▪ Severity of exacerbations ▪ Day & night-time symptom scores ▪ Night-time awakenings ▪ Use of rescue salbutamol, ▪ Withdrawals from study ▪ Asthma-related health-care resource utilisation (Norwegian health-care system and costs, not data extracted), ▪ Adverse events. **Method of assessing outcomes:** ▪ Diary record cards for daily PEFR and asthma symptom score. ▪ Daily PEFR best of three before taking any rescue medication. ▪ Mean PEFR calculated over the 12 wks 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 1-6 with 1: no symptoms to 6: symptoms so severe that could not go to work/ perform normal activities. Night symptom score range from 1-5 with 1: no symptoms during the night to 5: symptoms so severe that I did not sleep

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		BUD 2.20 (0.63) FEV % predicted: SAL/FP 69.2 (10.7), FORM + BUD 69.0 (10.1) FEV % reversibility: SAL/FP 26.0 (14.1), FORM + BUD 25.0 (11.5) *Mean inhaled steroid dose (µg/day)* FP: SAL/FP 549 (88), FORM + BUD 546 (81); BDP: SAL/FP1165 (66), FORM + BUD 1124 (66); BUD: SAL/ FP1404 (45), FORM + BUD 1409 (64); Flunisolide: SAL/ FP 1214 (7), FORM + BUD 1167 (3) ▪	at all) ▪ Adverse events defined as any untoward medical occurrence irrespective of causality. All classified by investigator as serious or non-serious, & the cause assessed as unrelated, unlikely, possibly, probably, or almost certainly related to study drugs. **Length of follow-up:** 12 wks 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/min change from baseline:	43	47	Not reported
PEF (per protocol population) L/min change baseline:	N=157 43	N=167 41	Difference -3.2L/min (95% CI -15.0, 8.6, p=0.593)
Median % diurnal variation PEF	N=187 Baseline 7.8 Endpoint 4.7	N=192 Baseline 8 Endpoint 5.1	Difference -0.3, 95% CI -1.0, 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, 0.07, p=0.796
Symptom-free days (was an outcome but data not reported)†			
Nights without awakenings, % median of nights (proportions for each treatment estimated from figure)	80	60	Difference 4.9, 95% CI 0.0, 12.0, p=0.02†
Nights without symptoms, % median (proportions for each treatment estimated from figure)	85	72	Difference 2.7, 95% CI 0.0, 8.4, p=0.04†
Nights with a symptom score <2 median (proportions for each treatment estimated from figure)	98	97	Difference 0.0, 95% CI 0.0, 1.2, p=0.03†
Acute exacerbations (total number during treatment)	129	206	
No. of mild exacerbations (estimated from graph)	105	175	

RESULTS			
Outcomes	**Group A (*n*=212)**	**Group B (*n*=216)**	***p*-value**
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, & severe) per patient per 84 days of treatment	N=211 0.472	N=215 0.735	Ratio: 0.64, 95% CI 0.51, 0.80, p<0.001*
*corresponding to a 31% risk reduction † discrepancy between difference as reported in the paper, and estimated by reviewers from the graph.			
Use of systemic corticosteroids			
Mortality			
QoL			
Adverse events – total n (%): Of these: Upper respiratory tract infection	91 (43) 26 (12)	78 (36) 18 (8)	
A/E causing 1% or more patients to withdraw (asthma resurgence/loss of control)	1 (<1%)	6 (3%)	
Possible drug related adverse events Of these: oral candidiasis Hoarseness/dysphonia Throat irritation Worsening asthma control Tremors Tachycardia Muscle cramps and spasms	18 1 6 4 0 0 3 0	23 9 2 1 4 3 0 3	
Serious adverse events	2	3	
Mean exposure to study treatments, days (SD)*	79 (17.6)	79 (17.8)	
*almost 90% of patients were exposed for 77 days (11 wks) or above.			
Number of asthma-related hospital/GP visits for patients with moderate-to-severe asthma: Accident and Emergency visits hospital days on general ward Outpatient visits GP home visits GP clinic visits GP telephone contacts	 1 7 6 15 12 13	 1 18 17 7 11 11	
Exacerbation definitions: Mild – a deterioration in asthma requiring an increase in relief medication use, which the investigator deemed clinically relevant, or PEF_{am} >20% below baseline (mean of last 10 days of run-in) for ≥2 consecutive days, or >3 additional reliever inhalations per 24-h period with respect to baseline for ≥2 consecutive days, or awakening at night due to asthma for ≥2 consecutive days. Moderate – PEF_{am} >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.			

RESULTS

Outcomes	Group A (*n*=212)	Group B (*n*=216)	*p*-value

Comments
†Patients in both groups showed similar improvements in day time symptoms with no significant differences (no data reported)
Similar use of salbutamol in both groups with no significant differences noted.
Data for PEFR pm not reported but authors report that it followed a similar pattern to PEFR am over 12 wks.

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 to 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 FORM+BUD group. No statistical significance value reported.
- **Method of data analysis:** Analysis based on intention-to-treat population. For mean PEFR am the analysis also repeated on per-protocol population. For PEFR variables ANCOVA used adjusted for age, sex, county 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 FORM and BUD. This was defined as the lower limit of the 95% confidence interval for the difference in mean PEFR am over wk 12 being -15L/min or above. Assuming a residual standard deviation of 50 L/min for PEFR am 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.

GENERAL COMMENTS

- **Generalisability:** patients with moderate to severe asthma, on daily ICS dose 1,000-1,600µg/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

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
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 intention to treat analysis?	Inadequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [246] **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 mths extension study in a sub-set of centres (in Sweden, n= 321 patients). As this sub-set only represents a proportion of those originally randomised results have not been extracted.	**Group A:** *n* = 390 Drug(s): BUD/FORM. Dose: 320/9µg b.i.d. Delivery: DPI Turbuhaler (Symbicort) Duration: 6 mths **Group B:** *n* = 196 Drug(s): BUD + Formoterol Dose: 320 + 9µg b.i.d. Delivery: DPI (Pulmicort & Oxis Turbuhaler) Duration: 6 mths **Run-in period:** Not reported **Additional treatment allowed:** ▪ Relief: terbutaline sulphate (0.25mg/dose) or alternative short acting β_2-agonist. ▪ Other: Oral corticosteroids for exacerbations, on max 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 cromones 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/dropout:** 47 (8%) discontinuations, 26 (6.6%) in Grp A, and 21 (10.7%) in Grp B. **Sample crossovers:** None reported **Inclusion criteria:** ▪ Age: ≥18 yrs ▪ Perennial asthma (min duration 6 mths) ▪ FEV_1 ≥50% predicted normal ▪ Requiring treatment with an ICS (400-1200µg) ▪ 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) = 45.0 (18-81) ▪ Time since asthma diagnosis, yrs (range) = 15.0 (1-67) ▪ Smokers/ ex-smokers, n = 74/159 ▪ ICS, µg/day (range) = 709 (400-1600) ▪ FEV_1 litre (range) = 2.85 (0.9-5.5) ▪ FEV_1 % predicted normal (range) 94.5 (37-155) ▪ FVC litre (range) = 3.79 (1.3 - 6.5) ▪ Mean ACQ score† = 1.5 to 1.6 (range 0 – 4) across groups. ▪ Mean overall mini-AQLQ score¶ = 5.3 to 5.4 (range 2 – 7) across groups.	**Primary measure:** Adverse events **Secondary measures:** FEV_1 FVC Exacerbations HRQL/Symptoms **Method of assessing outcomes:** ▪ Patients assessed in clinic at four visits: Visit 1 at baseline, visits 2 at 4wks, visits 3 at 13 wks, visits 4 at 26 wks). ▪ Information on adverse events collected at each visit via questionnaire. ▪ Blood & urine samples taken at visits 1 (baseline), 3 and 4. ▪ Electrocardiography (ECG), pulse rate, BP pressure performed at visits, 1, 3 and 4. ▪ Spirometry (FEV/FVC) performed at all visits. ▪ HRQOL& asthma control assessed at all visits. ▪ HRQOL measured using the mini asthma quality of life questionnaire (miniAQLQ)¶ ▪ Control (symptoms, reliever medication & lung function) measured by the self-administered Asthma control questionnaire (ACQ)†. **Length of follow-up:** Lung function, miniAQLQ & ACQ analysed as change from baseline (visit 1) to average of values at visits 3 & 4

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES

¶MiniAQLQ, Mini asthma quality of life questionnaire, consisted of 15 items related to 4 domains: symptoms, activity limitations, emotional function and environmental stimuli; †ACQ, asthma control questionnaire, contained 7 items: 5 items about asthma-related symptoms, one item on reliever mediation usage and one item on lung function, all relating to preceding week.

RESULTS

Outcomes	Group A (*n*=389)	Group B (*n*=196)	*p*-value
PEFR:			
FEV_1 litres : (Mean change from baseline to visits 3-4)*	0.14	0.17	
FVC litres : (Mean change from baseline to visits 3-4)*	0.09	0.10	
Symptom-free days			
Nocturnal awakenings			
Symptoms: ACQ score, mean change from baseline† (95% CI)	-0.50 (-0.50 to -0.42)	-0.46 (-0.57 to -0.35)	ns
Acute exacerbations – mean dose of oral corticosteroids (mg/study day)[a]	1.1[b]	1.3	
Acute exacerbations – withdrawals due to asthma (%)	2.3[b]	3.1	
Use of systemic corticosteroids (%)	15[b]	14	
Mortality			
QoL – mean change from baseline in overall miniAQLQ¶ score (95% CI)	0.48 (0.39 to 0.57)	0.45 (0.33 to 0.56)	ns
Adverse events‡ – n (%):	77	69	
Serious adverse events n (%)	13 (3.3)	5 (2.6)	
Discontinuations due to adverse events	11	9	
Discontinuations due to deterioration in asthma	7	5	
Adverse events (%), 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 adverse events (%)			
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
*Converted by reviewer from % increase from baseline into mean increase in litres. FEV_1: Grp A based on a 5% increase, Group B based on a 6% increase. FVC: both groups based on a 2.5% increase.
†Scored on a scale from 0 to 7, where 0 = high levels of asthma control.

RESULTS

Outcomes	Group A (*n*=389)	Group B (*n*=196)	*p*-value

[¶]Scored on a scale from 0 to 7 where 0 = severe asthma problems.
[‡]One patient in Group A did not receive any medication and was excluded from the safety analysis.
[a]Dose equivalent ratio was 20/3 for prednisolone to BDP and 5/4 for prednisolone to methylprednisolone
[b]n=390 for Group A

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 mths 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 to 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 reduced by 30% in each treatment group.
- Adverse events:
  - After adjustment for differences in total treatment exposure, the number of adverse events was similar (0.009 vs 0.008 per treatment day in Group A and Group B respectively).
  - All serious adverse events 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 adverse events.

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:** Intention to treat, 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 analysis of variance 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 analysis of variance 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 to 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 per 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 intention to treat analysis?	Adequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [233] **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+FORM)	**Group A:** *n* = 947 Drug(s): BUD + Formoterol Dose: 320*+ 9µg† q.d. Delivery: DPI ▪ Relief: ≤10 extra puffs /day of BUD+ FORM p.r.n. Duration: 52 wks **Group B:** *n* = 943 Drug(s): BUD Dose: 320µg* b.i.d. Delivery: DPI ▪ Relief: ≤10 puffs / day of terbutaline DPI 0.4mg‡ p.r.n. Duration: 52 wks **Run-in period:** Duration: 2wks ICS: any Relief: terbutaline DPI 0.4mg‡ p.r.n. **Additional treatment allowed:** ▪ Relief: [see above] ▪ Other: severe exacerbations treated with oral prednisolone 30mg/d for 10d; no details of any allowable additional maintenance treatment ▪ * delivered dose; metered dose = 400µg ▪ † delivered dose; metered dose = 12µg ▪ ‡ delivered dose; metered dose =	**Number randomised:** 1890 **Sample attrition/dropout:** *n* = 317 (62 AEs; 72 ineligible; 32 lost to follow-up; 151 other) **Inclusion criteria:** ▪ At study entry: ▫ age 12-80 ▫ history of asthma for ≥6 mths ▫ ≥1 clinically important exacerbation in previous 2-12mo ▫ maintained on ICS at a dosage of 400-1600µg for ≥3 mths, with stable dosage in previous 30d ▫ FEV_1 50%-90% predicted ▫ FEV_1 reversibility after 1mg inhaled terbutaline ≥12% (& ≥200ml for aged ≥18) ▪ After run-in: ▫ symptomatic, moderate-to-severe asthma **Exclusion criteria:** ▪ systemic steroids or inhaled cromones in previous 30d ▪ ≥3 courses of systemic steroids in previous 6 mths ▪ cardiovascular disease or other significant disorder ▪ respiratory tract infection affecting asthma within previous 1mth ▪ smokers with history ≥10 pack-yrs ▪ >10 puffs of reliever on any day of run-in **Baseline characteristics:** *mean (range) except where specified* ▪ Male : Female = 798:1092 ▪ Age – yr = 43 (11-80) ▪ Median duration of asthma – yr (range) = 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) ▪ Symptom-free days = 10% (0-100%) ▪ Asthma control days = 8% (0-100%)	**Primary measure:** Time to first severe exacerbation = ER visit ▪ hospitalisation need for systemic steroids ▪ AM PEFR ≤70% of baseline on 2 consecutive days **Secondary measures:** ▪ Severe exacerbations Requiring medical Intervention ▪ Mild exacerbation days = ▫ nocturnal awakening; ▫ AM PEFR ≤80% of baseline; and/or ▫ ≥2 puffs / 24h reliever more than at baseline ▪ Mild exacerbations (= 2 mild exacerbation days of same type consecutively) ▪ PEFR (am & pm) ▪ Symptom scores (day, night-time & total) ▪ Nocturnal awakenings ▪ Symptom-free days (= 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) ▪ adverse events **Method of assessing outcomes:** ▪ Daily patient diaries: ▫ PEFR (am & pm) ▫ symptoms, effects and use of medication ▪ Spirometry (baseline; clinic visits 3-7 [frequency not specified]) ▪ AEs reported spontaneously and assessed at clinic visits (inc. some biochemistry & ECGs) **Length of follow-up:**

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
	0.5mg		none beyond 1yr study period

RESULTS

Outcomes	Group A (*n*=947)	Group B (*n*=943)	Comparisons	*p*-value
FEV_1, mean throughout study – l :	2.54	2.45	MD: 0.10 (0.071, 0.130)[a]	<0.001
PEFR,				
AM – l/min (range):	372.1 (100-751)	348.5 (93-805)	MD: 20.3 (17, 24)[a]	<0.001
PM – l/min (range):	369.6 (99-720)	354.7 (91-808)	MD: 14 (10, 18)[a]	<0.001
Symptom-free days – % (range):	41.7 (0-100)	34 (0-100)	MD: 7.5 (5, 10)[a]	<0.001
Nocturnal awakenings – % (range):	9.4 (0-100)	13.0 (0-100)	MD: -3.3 (-4.8,-1.7)[a]	<0.001
Acute exacerbations:				
patients with events – *n* (%):	170 (18%)	259 (27%)	HR: 0.61 (0.50, 0.74)	<0.001
patients with events requiring medical interventions – *n* (%):	137 (14%)	212 (22%)	HR: 0.61 (0.49, 0.75)	<0.001
events – *n*:	331	546		
hospitalisation / ER – *n*:	15	25		
systemic steroid courses – *n*:	182	324		
PEFR falls – *n*:	134	197		
events requiring medical interventions – *n*:	197	349		
Use of systemic corticosteroids, treatment days – *n*:	1,776	3,177		
Use of reliever medication,				
rescue-free days – % (range):	59.8% (0-100%)	47.2% (0-100%)	MD: 11.0% (8%, 14%)[a]	<0.001
days with >2 puffs – %:	12%	21%		
days with >4 puffs – %:	3%	6%		
Mortality				
QoL				
Adverse events – *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%, 11%)[a]	<0.001
mean daily ICS dose – µg/d:	466	640		

MD = mean difference; HR = hazard ratio

[a] mean differences calculated by ANOVA model

[b] two-tailed Fisher's exact test, *calculated by reviewer*

RESULTS

Outcomes	Group A (*n*=947)	Group B (*n*=943)	Comparisons	*p*-value

Comments

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

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: AM (placebo or BUD); PM (BUD+FORM or BUD); prn (BUD+FORM 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 Groups 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 and 2 authors from AstraZeneca (manufacturers of BUD+FORM).

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

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
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 intention to treat analysis?	reported
9. Were withdrawals and dropouts 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 ID: [248] **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/FORM Dose: 160/4.5µg 2 puffs b.i.d. - titrated up or down to improve control*, plus additional inhalations for relief as needed Delivery: DPI Turbuhaler(Symbicort) Duration: 52 wks **Group B:** *n* = 1076 Drug(s): FP/SAL Dose: 250/50µg b.i.d. - titrated up or down to improve control*, plus salbutamol for relief Delivery: DPI Diskus (Seretide) Duration: 52 wks **Run-in period:** Duration: 2 wks 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 budesonide/formoterol for maintenance plus as needed medication, with fluticasone/salmeterol plus salbutamol as rescue medication	**Number randomised:** 2143 **Sample attrition/dropout: 269 (13%) discontinued (Grp A n=119; Grp B n=150).** ▪ Eligibility criteria violation: 83 (Grp A n=37; Grp B n=46) ▪ Adverse events: 34 (Grp A n=13; Grp B n=21) ▪ Lost to follow-up 34 (Grp A n=15; Grp B n=19) ▪ Miscellaneous reasons: n=118 (Grp A n=54, Grp B n=64) **Sample crossovers:** none reported **Inclusion criteria:** ▫ Outpatients aged ≥ 12 years with a diagnosis of asthma (American Thoracic Society) for ≥ 6 mths ▫ ≥ 500µg /day^{-1} of budesonide or fluticasone (or ≥ 1000µg of another ICS, e.g. BDP) for at least 1 mth before study entry ▫ Pre-terbutaline FEV_1 40-90% predicted ▫ At least 1 severe exacerbation > 2 wks but ≤ 12 mths before study entry ▪ At randomisation: ▫ use of as needed medication on ≥4 of the last 7 days of run-in **Exclusion criteria:** Use of budesonide/formoterol or fluticasone/salmeterol during last 3 mths **Baseline characteristics, Mean (range) unless stated:** Male : Female – 880: 1263 Age – 45 (range 12-84) Asthma duration – 12-13 yrs (range 0-75) across groups Pre-terbutaline FEV_1 % predicted – 73 (range 28 to 115 across groups) FEV_1 reversibility – 13 ICS dose (µg/day) at entry – 881 to 888 (range 50 to 3000) across groups Baseline ICS: budesonide n=1318 (62%); fluticasone n=525 (24%); beclometasone n=300 (14%) Inhaled LABA use at study entry: n(%) 811 (38)	**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 & post terbutaline FEV_1 ▪ As-needed medication use ▪ Symptoms (Asthma Control Questionnaire ACQ-5) ▪ HRQOL (Asthma Quality of Life Questionnaire AQLA(S)) ▪ Adverse events ▪ Severe exacerbations excluding unscheduled visits, not resulting in hospital admission/ER, 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 mths (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. ▪ Adverse events were recorded spontaneously and at visits 2 - 6.

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		Reliever use inhalations $24h^{-1}$: 2.6 to 2.7 (range 0.2 to 33.7) across groups Overall ACQ-5 score**: 1.86 to 1.87 (range 0.00 to 5.20) across groups ▪ Overall AQLQ(S)*** score: 4.95 to 4.97 (1.19 to 7.00) across groups ▪ Use ≤ 4 puffs of as-needed medication $week^{-1}$ % of patients: 5	**Length of follow-up:** 12 mths

***Treatment (further details):** From wk 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 160/4.5µg 4 inhalations per day^{-1} to 2 inhalations per day^{-1}. In Group B downwards titration from 250/50µg b.i.d. to 100/50 µg b.i.d. was allowed. In this group physicians could step up to 500/50 µg b.i.d.
** Five questions scored on a scale of 0-6, where 0 = no symptoms
*** 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.

RESULTS

Outcomes	Group A (*n*=1067)*	Group B (*n*=1076)*	*p*-value
PEFR:			
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
Symptom-free days			
Symptom-free nights			
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†
Severe exacerbations - total number of events¶	255	330	<0.01
Severe exacerbations - rate events per $patient^{-1}$ $–yr^{-1}$	0.24	0.31	0.0025‡
Severe exacerbations excluding unscheduled clinic visit - patients with an event n (%)	132 (12)	167 (16)	0.025†
Severe exacerbations excluding unscheduled clinic visit - rate events per $patient^{-1}$ $–yr^{-1}$	0.19	0.23	0.023‡
Severe exacerbations - number of unscheduled visits¶	40	60	
Severe exacerbations – number of hospitalisations/Emergency room visits¶	45	50	
Severe exacerbations due to ER visits/hospitalisations – patients with an event, n (%)	31 (3)	46 (4)	0.18†
Severe exacerbations due to ER visits/hospitalisations rate events per $patient^{-1}$ $–yr^{-1}$	0.04	0.05	0.38‡
Severe exacerbations – number of courses of oral corticosteroids¶	170	220	
Use of rescue medication in last 2 wks of study (max of 4 inhalations per $week^{-1}$) %	76	66	

RESULTS

Outcomes	Group A (*n*=1067)*	Group B (*n*=1076)*	*p*-value
Use of rescue medication in last 2 wks of study¶ (>4 inhalations per week^{-1}) % ¶	24	34	
Mortality	0	2§	
QoL: mean adjusted change in overall AQLQ(S) score from baseline	0.60	0.57	0.51
Serious adverse events – n (%):	80	88	

* 2,143 patients were randomised and a total of 2,135 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 n's for the groups presented here are as randomised.
† = p value based on the instantaneous risk of experiencing at least one severe exacerbation (Cox proportional hazards model).
‡ = p-values based on relative rate analysis (Poisson regression).
¶ = estimated from graph by reviewer
§ = 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 9-44%, p=0.0025)
- The risk of a severe exacerbation was 25% lower in Group A (95% CI 7-39%, p=0.0076).
- The risk of a severe exacerbation excluding unscheduled visits was 23% lower in Group A (95% CI 3-39%, 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 (1,980 vs 2,978 respectively)
- Mean as-needed use inhalations per day^{-1} 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^{-1} (defined as low use) was higher in Group A compared with Group B (odds ratio 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 adverse events that were considered by the investigator to be causally related to study medication.
- Authors report that 55 patients discontinued the study due to adverse events (27 in Group A vs 28 in Group B). This is discrepant with other figures reporting that 34 patients discontinued due to adverse events (13 in Group A, and 21 in Group B).
- Average daily microgram ICS dose was similar between the two groups over the treatment period, Group A = 562µg (maintenance) + 91µg (as-needed) vs Group B 583µg (maintenance only). Corresponding values expressed as beclometasone dipropionate (BDP) doses were 1,019µg/day^{-1} (Group A maintenance and as needed) vs 116µg/day^{-1} (Group B maintenance only).
- Approximately 40% of Group B patients received the maximum dose (100/1,000 µg/day^{-1}) 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 640/18µg/day^{-1} to 320/9µg/day^{-1} (4 vs 2 maintenance inhalations per day^{-1}) and 31% completed the study on this dose.

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 does of the combinations to be titrated up or down.

METHODOLOGICAL COMMENTS

- **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 intention to treat but data from eight patients randomised unavailable. Time to first severe exacerbation compared between groups using a long rank test/ Cox proportional hazards model. Rate of severe exacerbation per patient^{-1} per year^{-1} 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 1,000^{-1} 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, Grp A n=119 (11%); Grp 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 intention to treat analysis?	Inadequate
9. Were withdrawals and dropouts 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)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: [226] **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 + 50µg b.i.d. Delivery: DPI (Accuhaler®) Duration: 6 wks **Group B:** *n* = 187(ITT); 175(PP) Drug(s): BUD Dose: 400µg b.i.d. Delivery: MDI (Turbuhaler®) Duration: 6 wks **Run-in period:** Duration: 2 wks ICS: continued treatment with routine ICS Relief: salbutamol **Additional treatment allowed:** Relief: salbutamol Other: not reported	**Number randomised:** 398 **Sample attrition/dropout:** ▪ 6 patients failed to fulfil eligibility criteria ▪ 38 patients not evaluable ▫ adverse events: 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 & 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 ▪ Per protocol (PP) population = 354 **Sample crossovers:** none reported **Inclusion criteria:** ▪ At entry: ▫ age 18-70 ▫ documented history of asthma, currently receiving BUD or BDP at a total daily dose ≤500µg/day for prev. ≥4 weeks ▪ Symptom score (day & night) ≥2 on 4/last 7 days of run-in period ▪ Reversibility: ▫ ≥15% reversibility & 200mL elevation in FEV_1 after inhalation of β_2-agonist (salbutamol 400µg) 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 6mo prior to visit 1 ▪ 50% ≤FEV_1 ≤85% of predicted at visit 2/2a (bronchodilators withheld prev. ≥4hr) ▪ Ability to understand & complete diary record card, use a mini-Wright peak flow meter & record PEFR correctly **Exclusion criteria:** ▪ Use of systemic corticosteroids within 4wk, antileukotriene agents within 2wk, inhaled LABAs or oral β_2-agonists within 1wk of visit 1 ▪ change of asthma medication within 2wk of study entry ▪ Upper/lower RTI infections, acute exacerbation of asthma necessitating hospitalisation, or ▪ having used any investigational drugs within 4 wks of entry	**Primary measure:** mean AM PEFR **Secondary measures:** ▪ PM PEFR ▪ use of rescue medication ▪ day- and night-time asthma symptoms scores ▪ FEV_1 ▪ adverse events **Method of assessing outcomes:** ▪ Daily patient diary: ▫ AM & PM PEFR (highest of 3) ▫ use of rescue medication ▫ symptom scores ▫ adverse events ▫ concomitant medication use ▪ Visit 1 (wk -2): ▫ medical history ▫ physical & oropharyngeal examinations ▫ vital signs ▫ lung function (FEV_1) ▪ Visit 2/2a* (wk 0): ▫ FEV_1 ▪ Visits 3&4 (wks 3&6): ▫ "routine assessments" ▫ FEV_1 ▫ compliance evaluation ▪ Visit 5 (wk 6+1): ▫ clinic assessment for safety purposes **Length of follow-up:** 6 wks treatment period + follow-up at wk 6 + 1 for safety purposes * visit 2a = re-evaluation 3 days after visit 2 for participants

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		▪ FEV_1 ≤50% or ≥85% of predicted at visit 2/2a ▪ unduly troubling symptoms ▪ Any serious uncontrolled disease (inc. 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 **Baseline characteristics (ITT population):** **Group A (n=199)** ▪ Age [mean(range)]: 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 (L): 1.91 ▪ Mean morning PEFR (L/min): 272 ▪ Mean evening PEFR (L/min): 278 ▪ Mean daytime symptom score (0-5): 1.62 ▪ Mean night-time symptom score (0-5): 1.20 ▪ Symptom-free days (%): 13.39 ▪ Symptom-free nights (%): 25.68 ▪ Symptom-free days (24hour periods) (%): 7.0% ▪ Rescue medication (mean no. 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)]: 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 (L): 1.90 ▪ Mean morning PEFR (L/min): 273 ▪ Mean evening PEFR (L/min): 275 ▪ Mean daytime symptom score (0-5): 1.65 ▪ Mean night-time symptom score (0-5): 1.25 ▪ Symptom-free days (%): 13.48 ▪ Symptom-free nights (%): 21.29 ▪ Symptom-free days (24hour periods) (%): 9.0% ▪ Rescue medication (mean no. puffs/day): 1.34 ▪ Rescue medication-free days [N(%)]: 20(28)	who did not initially meet randomisation criteria

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		▪ Rescue medication-free days [N(%)]: 20(28) ▪ % Rescue medication-free daytime period (%): 26.9% ▪ % Rescue medication-free night-time period (%): 32.2%	

RESULTS

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

RESULTS

Outcomes (ITT population)	Group A (*n*= 199)	Group B (*n*=187)	*p*-value

[d] 1 - symptom-free nights
[e] most commonly reported adverse events: pharyngitis, oedema, rash, palpitations, headache
[f] most commonly reported adverse events: 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 per-protocol population (n=179(A), n=175(B))

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 PEFR compared between groups using ANCOVA, allowing for effects as a result of baseline PEFR, centre, gender, age & treatment group. For secondary efficacy variables, time was substituted for baseline value.
  - % symptom-free days & nights 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 PEFR 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 15L/min with 95% confidence (treatment with S/FP was defined as superior to treatment with budesonide if the lower limit of the 95% CI for the treatment difference was >0L/min, and assuming a max SD of 40L/min).
- 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 & 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

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
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 intention to treat analysis?	Adequate
9. Were withdrawals and dropouts 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)
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. *Journal of Allergy & Clinical Immunology* 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. *Respiratory Medicine* 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. *Journal of 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 mug of fluticasone propionate/salmeterol. *Journal of Allergy & Clinical Immunology* 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. *Clinical Therapeutics* 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. *Respiratory Medicine* 2006;100:1651-6.

Systematic reviews

Kaliner MA. Pharmacologic characteristics and adrenal suppression with newer inhaled corticosteroids: A comparison of ciclesonide and fluticasone propionate. *Clinical Therapeutics* 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, May 21 26, 2004, Orlando* 2004;A37.

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

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; May 20 25; San Diego, California* 2005;B35.

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]. *Journal of Allergy & Clinical Immunology* 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; May 20 25; San Diego, California* 2005;B35.

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

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

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

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; May 20 25; San Diego, California* 2005;B35.

APPENDIX 7 – Systematic review of economic evaluations: Additional tables

TABLE A7.1 *Relevant published economic evaluations of corticosteroids for asthma in adults: Study designs*[a]

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Andersson *et al*, 2001[253]	CEA/ trial (FACET,Pauwels RA *et al*. 1997[282])	UK, Spain, etc. 9 countries (without Sweden). Setting NR.	Moderate, persistent symptoms. Age 17-80yrs	• 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 & a severe exacerbation 2. From expert opinion survey	1. Mild/severe exacerbations 2. Episode-free days 3. symptom-free days	One-way & 2 threshold analysis

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

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Booth *et al*, 1995[254]	CEA/ trial (Langdon and Capsey. 1994[191])	UK, conducted in 57 general practices in the UK.	Asthma patients. Age 18 to 70yrs. (oral steroids naïve during the previous 6 weeks)	• FP 400 • BUD 800	Not reported (but implicit: UK NHS)	8 weeks. No discounting	1. Study medication 2. Relief medication 3. Medication used to treat "causally related adverse events"	Cost per successfully treated week (successful treatment: an increase of ≥5% of predicted PEF)	One-way, varying the level of improvement in PEF

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Briggs *et al,* 2006[b255]	CEA & CUA/ trial & model	44 countries. Patients were from General practice & hospital clinics[c]	Uncontrolled asthma. Age ≥12yrs and < 80yrs	**For strata 1 & 2** • FP/S: 200/100, 500/100, or 1000/100 • FP 200, 500, or 1000; **For stratum 3** • FP/S: 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/N 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

[b] The study had two phases. Phase I: dose-escalation in a case they filed to achieve total control in at least 7 wks of an 8 wk 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 6ms prior to screening for study entry and then they were randomised from the 3 strata to receive either FS or F ----- Stratum1: no ICs; Stratum 2: ≤ 500µg BDP daily or equivalent. Stratum 3: from 500µg to ≤1000µg BDP daily or equivalent.

[c] Information from the GOAL study by Bateman et al, 2004; 170 (8):836-844[235]

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Ericsson *et al*, 2006[283]	CEA/ trial (Bateman *et al*. 2003[229])	37 centres in 6 countries (4 in Europe). Setting NR	Persistent asthma. Age ≥18yrs	• 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: ○ Hospitalization (general medicine and ICU) ○ Emergency room visits ○ Physician visits ○ Nurse visits ○ House call ○ Phone calls ○ Pharmacy contacts 3. Work days lost	Episode-free days	One-way (only for 2 variables)

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Johansson *et al*, 2006[257]	CEA/ trial (Vogelmeier *et al*. 2005[248])	16 (6 Asian, 10 European, countries including UK. Setting NR	Adults and adolescents ≥ 12yrs previously used ICS	• BUD/FF: 800/24, plus additional inhalations as needed • PF+S: 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' confidence intervals estimated for base care ICER)

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Johansson et al, 1999[284] (nb. dual publication of 1 of 3 comparisons in Lundback 1999[260])	CEA/ trial (Edwards *et al*,1998[285], and Nathan *et al*, 1999[286])	North American effectiveness & resource use data, Setting NR	Adults and adolescents with asthma	• FP/S: 200/100 • FP 200	Swedish healthcare system	12 weeks. No discounting	1. Hospital contacts: emergency room visits, inpatient days 2. General practitioner contacts: clinic visits 3. Medication: study drug, relief medications, and concurrent drugs	1. Successfully treated weeks %, 2. Episode-free days %, 3. Symptom-free days %	One-way and two-way
Jönsson *et al*, 2004[287d]	CEA/ trial (OPTIMA, O'Byrne *et al*, 2004[288])	17 countries (15 in Europe). Setting NR.	Mild-to moderate persistent asthma. Aged ≥12 yrs	• BUD 200 • BUD/FF: 200/12 • BUD 400 • BUD/FF: 400/12	Swedish health care payer and society	12 months. No discounting	1. Healthcare: days in hospital, visits to health professionals 2. Medication use (study, reliever, & other) 3. Days off work due to asthma	1. Symptom-free days, 2. Severe exacerbations	Applying unit cost (prices) from the UK and Spain to entire patient population

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

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Lundbäck *et al*, 1999[260]	CEA/ 3 trials (Edward et al. 1998[285]; Nathan *et al*, 1999[286], Pieters *et al*, 1998[289], and White *et al*, 1999[290])	North American (FP=200 or 500), and European (FP=1000). Setting NR.	Adult and adolescent patients with asthma	• FP/S 200/100 vs. FP 200 • FP/S 500/100 vs. FP 500 • FP+S 1000+100 separate inhalers vs. FP 1000	Swedish healthcare system	12 week. 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. Symptom-free days %	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

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Lundbäck *et al*, 2000[291]	CEA/ trial (Jenkins *et al*, 2000[224])	44 centres in 10 countries including 8 in Europe.[e] Setting NR	Age ≥12yrs; moderate to severe asthma, symptomatic on current doses of inhaled CIS (BDP or BUD 800-1200, or FP 400-800 µg/day)	• FP/S: 500/100 • BUD 1600	Swedish healthcare system	24 weeks. No discounting	1. Direct health care cost (hospital contacts and general practitioner contacts) 2. Drug costs	1. Successfully treated weeks %, 2. Episode-free days %, 3. Symptom-free days %	One-way and two-way. Varied the criterion fro successfully treated week in 1% increments. Best/worst case scenario for symptom and episode-free days

[e] Data from the supplement of the trial by Jenkins et al, 2000; 94:715-723[224]

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Marchetti *et al*, 2004[261]	CUA/ model	Italy Setting NR	Adults with moderate or severe persistent asthma	*For moderate* • BDP 1000 • BDP-extrafine 400 • FP 400 • BUD 800 *For severe* • BDP 1500 • BDP-extrafine 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. Health care services: • GP visit • Hospital ○ day hospital ○ ED visit including hospitalization, complicated diagnosis DRG, and discharged from ED ○ peneumologist 2. Increased asthma 3. Related medication	QALE (quality-adjusted life expectancy)	By varying the unit cost for ICS, and transition rates
Palmqvist *et al*, 1999[262] (nb. dual publication of 1 of 3 comparisons in Lundback 1999[260])	CEA/ trial (White *et al*, 1999[290])	North American. Setting NR	Adults and adolescents with moderate to severe asthma	• FP/S: 500/100 • FP 500	Swedish healthcare system	12 weeks. No discounting	1. Hospital contacts: emergency room visits, inpatient days 2. General practitioner contacts: clinic visits 3. Medication costs: study drug, relief medications, and concurrent drugs	1. Successfully treated weeks %, 2. Episode-free days %, 3. Symptom-free days %	One-way and two-way

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Pieters *et al*, 1999[263] (nb. dual publication of 1 of 3 comparisons in Lundback 1999[260])	CEA/ trial (Pieters *et al*, 1998[289])	Patients were from centres in France, Germany and The Netherlands. Setting NR	Corticosteroid-dependent asthma. Age not reported	• FP+S: 1000+100, separate inhalers • FP 1000	Swedish healthcare	12 weeks. No discounting	1. Hospital contacts: accident & emergency visits, intensive care unit days, inpatient days, and outpatient visits 2. General practitioner 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. Symptom-free days %	One-way

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Price and Briggs, 2002[264]	CEA/ trail (Kavuru et al, 2000[236]) & model	42 centres in the US.[f] Setting NR	Adults and adolescents (≥12yrs) with symptomatic asthma	• FP/S: 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	Probabilistic sensitivity analysis
Steinmetz *et al*, 1998[265]	CEA/ trial (Steinmetz and Trautmann, 1996[292])	45 ambulatory or out-patient centres in Germany	Corticosteroid-naïve patients with moderate asthma. Age between 17-70yrs	• 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 adverse event related to asthma or its treatment, office-based physician visits, and hospitalisations	1. Number of successfully treated patients (with ≥10% improvement in PEFR) 2. % symptom-free days (24hr period without day- or night-time asthma symptoms)	One-way

[f] Data from supplement of the trial by Kavuru et al. J ALLERGY CLIN IMMUNOL, 2000; 105: 1108-16

Author, year	Analysis type/base	Country, setting	Population	Comparators/ comparisons	Perspective	Time horizon, discounting	Costs included	Outcomes	Sensitivity analyses
Venables *et al*, 1996[266]	CMA/ trial (Venables *et al*, 1996[293])	UK in general practice	Symptomatic asthmatics; age 18-70yrs inclusive (Steroid- free or receiving ≤200 µg/day ICS)	• BUD 400 qd • BUD 200 bid • FP 400 qd	Implicit NHS perspective	8 weeks. No discounting	Drug cost: study medication, relief medication, medication for causally related adverse events	Cost effective ratio of : 1. % symptom free days 2. % days on which patients achieved a ≥5% improvement from baseline in predicted AM PEF	Two-way and one-way

TABLE A7.2 *Relevant model-based economic evaluations of corticosteroids for asthma in adults: Decision model design and key assumptions*

Author, Year	Model structure	Sources of probabilities	Sources of utilities	Sources of costs	Model validation
Marchetti *et al*, 2004[261]	Markov model	• Transition probabilities from six published RCTs: Price D, et al, 2002; Fireman P, et al, 2001; Worth H, et al, 2001; Aubier M, et al, 2001; Reichel W, et al, 2001; and Fairfax A, et al, 2001 • Exacerbations: Hoskins G, et al, 2000 • Local adverse effects 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 R, et al, 2001 • ED for an exacerbation: assumed • Retail prices: www.sanita.it (accessed Sep 2004) • Working days lost: Ungar WJ, 2000 • Time off paid work: Banca d'Italia, 2000 • Overall number of unproductive days: assumed	None described
Price and Briggs, 2002[264]	Markov model	The trial by Kavuru et al, 2000; 105:1108-16	The trial by Kavuru et al, 2000; 105:1108-16[236]	• Medication costs: the Monthly Index of Medical Specialities of November 2000. • Costs associated with the primary and secondary exacerbation health states: the paper by Hoskins G et al, 1998; 12:193-8. • The hospital and community health service (HCHS) inflation index (by Netten A et al, 1998.)	None described

TABLE A7.3 *Relevant published economic evaluations of corticosteroids for asthma in adults: Results*[a]

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Andersson *et al*, 2001[253]	BUD 200	BUD+FF: 200+24, separate inhalers	Total direct costs: • UK: 191 Euro • Sweden: -549 Euro • Spain: -28 Euro	Average per-patient-year Number of symptom-free days: 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 symptom-free days • UK: 4.67 Euro • Sweden: not relevant (dominate) • Spain: not relevant (dominate)
	BUD 800	BUD+FF: 800+24, separate inhalers	Total direct costs: • UK: 271 Euro, p<0.001 • Sweden: -286 Euro • Spain: 103 Euro	Average per-patient-year: Number of symptom-free days: 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 symptom-free days • UK: 6.60 Euro • Sweden: not relevant (dominate) • Spain: 2.51 Euro
Booth *et al*, 1995[254]	BUD 800	FP 400	*Total average cost per patient per week: £ 0.97*	*Proportion of successfully treated weeks: +11.9%*	*ICER= £ 8.15*

[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 otherwise specified. *Results in Italic were calculated by the reviewer.*

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Briggs *et al*, 2006[255]	• FP 200 • FP 500 • FP 1000	• FP/S: 200/100 • FP/S: 500/100 • FP/S: 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 £13700 (95%CI 11000, 18300) Stratum 2: cost-per QALY gained £11000 (95%CI 8600, 14600)
	• FP 500 • FP 1000	• FP/S: 500/100 • FP/S: 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, 10700)
Ericsson *et al*, 2006[283]	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, 25.9), p<0.001 • Change in evening PEF (l/min): 17.2 (95%CI 11.2, 23.2) , p<0.001 • % change in FEV_1 (l): 4.7 (95%CI 2.0, 7.4) , p<0.001 • Change in reliever medication (inhalations/day): 0.18 (95%CI -0.35, -0.01), p=0.04 • Patients with one or more mild exacerbations (%): -12.3 (95%CI -22.2, -2.17), p=0.017 • Patients with one or more severe exacerbations (%): not statistically significant	BUD/FF was dominant
Johansson *et al*, 2006[257]	BUD/FF: 800/24, +as needed	PF+S: 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[284]	FP 200	FP/S: 200/100	*Total direct costs per patient per day: SEK 6.4 (0.78 US$)*	• *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, 215.6) • Cost per symptom-free day: SEK 44.5 • Cost per episode-free day: SEK 46.9

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Jönsson et al, 2004[287]	BUD 200	BUD 400	*Total healthcare costs /patient /year: £594* *Total costs per patient per year: £1313*	*Symptom free days %: +3.59* *Number of SFD 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 /patient /year: 1747* *Total costs per patient per year: £1538*	*Symptom free days %: +5.09* *Number of SFD per year: 18* *Severe exacerbations avoided per year: -0.25*	*SFDs: Dominated (extended dominance)* *Exacerbations: Dominated (extended dominance)*
	BUD 200	BUD+FF: 400+12, separate inhalers	*Total healthcare costs per patient per year: 2186* *Total costs per patient per year: 1513*	*Symptom free days %: 6.24* *Number of SFD 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]	*Symptom free days %: 1.5,* p=0.55 *Number of SFD 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]	*Symptom free days %: 2.65,* p= 0.28 *Number of SFD 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*

[b] From the societal perspective there were no statistically 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).

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
	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]	*Symptom free days (%): 1.15* *Number of SFD per year: 5* *Severe exacerbations avoided per year: 0.29*	*SFDs: Dominated (extended dominance)* *Exacerbations: Dominated (extended dominance)*

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Lundbäck *et al*, 1999[260]	FP 200[c]	FP/S: 200/100[c]	*SEK 6 (read from Fig. 4)*	Change in percentage of successfully treated weeks: +32% Change in percentage of symptom-free days: +9% Change in percentage of episode-free days: +8%	Cost per successfully treated week: SEK 133.4 (95%CI 89.4, 215.6) Cost per symptom-free day: SEK 44.5 Cost per episode-free day: SEK 46.9
	FP 500[d]	FP/S: 500/100[d]	SEK 0.7	Change in percentage of successfully treated weeks: +38% Change in percentage of symptom-free days: +18% Change in percentage of episode-free days: +19%	Cost per successfully treated week: SEK 12.6 (95%CI -82.2, 93.1) Cost per symptom-free day: SEK 3.9 (95%CI -27.8, 37.2) Cost per episode-free day: SEK 3.9 (-25.4, 35.9)
	FP 1000[e]	FP+S: 1000+100, separate inhalers[e]	SEK 6.6	Change in percentage of successfully treated weeks: +25% Change in percentage of symptom-free days: +10% Change in percentage of episode-free days: +5%	Cost per successfully treated week: 192.1 (95%CI 58.3, 436.7) Cost per symptom-free day: SEK 66.8 (95%CI 17.5, 318.2) Cost per episode-free day: SEK 120

[c] This comparison also published separately as Johansson *et al*, 1999

[d] This comparison also published separately as Palmqvist *et al*. 1999

[e] This comparison also published separately as Pieters *et al*. 1998

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Lundbäck *et al*, 2000[291]	BUD 1600	FP/S: 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 symptom-free days: +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 symptom-free day: SEK 9.2

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Marchetti *et al*, 2004[261]	**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-ext 400	47.00	QALE: -1.74	BDP-ext is dominated
	BUD 800	BDP-ext 400	28.00	QALE: -1.23	BDP-ext 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-ext 800	56.00	QALE: -0.50	BDP-ext is dominated
	BUD 1600	BDP-ext 800	67.00	QALE: -0.98	BDP-ext is dominated
	BUD 1600	*FP 1000*	*11.00*	*QALE: -0.48*	*FP is dominated*
	National Service 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-ext 400	34.00	QALE: -1.74	BDP-ext is dominated
	BUD 800	BDP-ext 400	20.00	QALE: -1.23	BDP-ext 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-ext 800	48.00	QALE: -0.50	BDP-ext is dominated
	BUD 1600	BDP-ext 800	52.00	QALE: -0.98	BDP-ext is dominated
	BUD 1600	*FP 1000*	*4.00*	*QALE: -0.48*	*FP is dominated*

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Palmquist *et al*, 1999[262]	FP 500	FP/S: 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 symptom-free days: +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, 93.1) • Cost per episode-fee day: SEK 3.9 (95%CI -25.4, 35.9) • Cost per symptom free day: SEK 3.9 (95%CI -27.8, 37.2)
Pieters *et al*, 1999[f263]	FP 1000	FP+S: 1000+100, separate inhalers	*Total non-drug resource costs: 2.4 SEK* *Total direct costs/patient/day: 6.6 SEK (0.8 US$)*	(Read from figure 1 in the paper) • *Proportion of successfully treated weeks: 23.9%,* p=0.001 • *Proportions of symptom-free days: 9.8%,* p=0.012 • *Proportions of episode-free days: 5.4%,* p=0.068	• Cost per successfully treated week: 192.1SEK (95%CI 58.3, 436.7) • Cost per symptom-free day: 66.8SEK (95%CI 17.5, 318.2) • Cost per episode-free day: 120SEK (no significant difference)
Price and Briggs, 2002[264]	FP 200	FP/S: 200/100	*Mean weekly direct asthma management costs: £3.94*	*% successfully controlled weeks/patient: 19*	• Average incremental cost per successfully controlled week with FP/S: £20.83 (95%CI -£65 (FP/S dominant) to £113)

[f] Cost data was of over 12-week period. 'Successfully treated week' was defined as a week with a mean improvement in AM PEFR OF ≥ 5% of the baseline predicted value. Bothe symptom-free day and episode-free day refers to 24-hour period.

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Steinmetz *et al*, 1998[265]	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 AM PEFR L/min) =+5%* • *Symptom-free days (%): +6%*	FP is dominant (cheaper and more effective than BUD)

Author, Year	From treatment	To treatment	Incremental cost	Incremental effects	ICER (not discounted)
Venables *et al*, 1996[266]	BUD 400 qd	FP 200 bid	*0.46* £/day (P<0.001)	• *Percentage symptom-free days: 5%* (not significant) • *Percentage days with ≥5% PEF improvement: 3%* (not significant)	• Cost per symptom-free day: £*9.2* • Cost per successfully treated day: £*15.33*
	BUD 200 bid	FP 200 bid	*0.44* £/day (P<0.001)	• *Percentage symptom-free days: 9%* (not significant) • *Percentage days with ≥5% PEF improvement: 9%* (not significant)	• Cost per symptom-free day: £*4.89* • Cost/successfully treated day: £*4.89*

APPENDIX 8 – Review of existing economic models of asthma

Despite the large number of clinical trials identified in the current review (section 5), there are very few studies reporting methods for the modelling of asthma and its treatment for the purposes of cost-effectiveness analysis. 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.[255;261;294;295] A short summary of each of the four identified studies is presented here.

The Asthma Policy Model

Paltiel and colleagues (2001)[294] 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, HRQL (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 (see *Table A8.1* below). 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 A8.1 *Dimensions defining health states used in the Asthma Policy Model*

Dimensions:	**Categories:**
Disease status	chronic/stable, acute/hospital, dead
Lung function impairment	mild or moderate; based on FEV_1% predicted, where > 80% = mild, 60% to 80% = moderate
Prior hospitalisation	none, one, more than one
Age*	18 to 35-years, over 35-years
Death (cause)	asthma-related, other

*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 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 is published in abstract format only (Neumann and colleagues, 2000)[296] with no substantive information provided to support the derivation of the functional relationship presented.

In the model presented costs are estimated (1998 USA $) from published data (2 USA studies) on resource use. Health care management costs are based on medications,

consultations, and laboratory tests. Acute event costs were estimated for non emergency department (ED) urgent care visits ($63), ED visits ($242), and hospitalisations ($3,200).

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, 4.5 acute episodes per person (over 10-years). Cost-effectiveness summary measures are presented for cost per QALY and cost per additional symptom-free day. The study reported by Paltiel and colleagues acknowledges financial support from AstraZeneca.

12-week patient level model presented by Price & Briggs (2002)

Price and Briggs (2002)[255] 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 (Kavuru and colleagues, 2000).[269] 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 x 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 (Hoskins and colleagues, 1998).[297] Event costs (2000 UK£) per week were reported as £1,815-£1821 for hospital managed exacerbations, and £95 to £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 authors).

Asthma utility model by Marchetti and colleagues (2004)

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 (Revicki and colleagues, 1998).[295] It is a Markov type model with seven utility states (U1 to 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 cost utility analysis, from the perspective of the Italian NHS and the Italian societal perspective.

The time horizon for the model was 2 months (base-line analysis). Transitition probabilities between the seven health states were derived using data on percentage of symptom free days/nights from published RCTs. Data on % of symptom free days/nights was converted into an ASUI score, and transitition probabilities derived. The frequency of exacerbation events was informed by published studies. Resource use and cost estimates were informed by expert opinion (9 clinical experts). Affiliation of the authorship included pharmaceutical company representation (Chiesi Farmacutici, Italy).

Model for severe asthma, DeWilde and colleagues (2006)

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 life-time 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 current 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,[255] whilst 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),[295] which involves specific trial data for that measure of asthma control. The Asthma Policy Model (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 USA 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 to potentially provide health state values for specific asthma health states.[28;255;255;296;298-312]

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 (Briggs and colleagues, 2006,[255] and DeWilde and colleagues,[312] level of FEV_1 % predicted (Neumann and colleagues, 2000)[296] or used a multi-attribute system to characterise symptoms and control measures (Chiou and colleagues, 2005).[308] These four studies and the health state values presented are outlined in the following section.

Neumann and colleagues (2000)[296] 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 (2001),[294] 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 A9.1* below.

TABLE A9.1 *Health state values for asthma presented by Neumann and colleagues (2000)*

FEV1%	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

Key: SG=standard gamble, TTO=time trade-off, RS=rating scale, HUI3=health utility index mark 3, ASUI=asthma symptom utility index

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 (2001),[294] where TTO (health state value) = 0.521+ (0.003958 x 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 (2005)[308] 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 (3-levels), emotion (2-levels) and activity (2-levels). The study presents values elicited using the VAS and the 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 5 health states were valued using the SG technique, and therefore a power function was used to transform the VAS values to a 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 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 (2006)[255] present cost-effectiveness analysis relevant to an economic evaluation undertaken alongside the GOAL trial.[235] 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 this 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 emergency department 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 colleagues (2006)[312] 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, for CSS n=5. Dewilde and colleagues discuss a range of possible utility values for the 'day to day asthma' state. The health state values for this state following treatment (standard therapy) were (i) a mean of 0.669 (n=169) when data were mapped indirectly from AQLQ values, or (ii) 0.784 (n=166) when using data from a direct utility study (Yang and colleagues, 2006; unpublished discussion paper).

Industry submissions to NICE from GSK and AZ have presented cost utility analyses, and have discussed the estimation of health state values for asthma. Both submissions refer to the sparse evidence base available on health state values for asthma. The GSK submission uses data from the study by Briggs et al (2006) referred to above (for both adults and children).

[redacted]

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 HRQL (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 (2006)[255] report a difference (increment) of 0.104 between asthma health states of 'total control' and 'not well controlled'. Neumann and colleagues (2000)[296] indicate an increment/decrement of 0.14 – 0.17 between well controlled (80 FEV1% predicted) and poorly controlled (<60 FEV1% predicted), based on the valuation techniques of either SG, TTO or RS. This difference is much smaller when comparing those with FEV1% predicted of >80 with those in a range 60-

80. Dewilde and colleagues (2006)[312] present estimates that suggest a difference of around 0.10 to 0.22 for the health states of 'daily symptoms' and 'clinically significant non-severe exacerbation'; however this latter state may not map directly to a definition of poor control. Values presented by Chiou and colleagues (2005)[308] indicate a decrement of between 0.07 and 0.13 for health states that may reflect poor control, compared to 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 also report a comparable decrement of 0.216 for an exacerbation (defined as deterioration in asthma requiring treatment with an oral corticosteroid, an emergency department visit, or hospitalisation). Dewilde and colleagues (2006) use utility data that reflects a difference of 0.246 between non-severe exacerbation and severe exacerbation.

APPENDIX 10 – The PenTAG asthma model

A10.1 Methods

A10.1.1 Model structure

A Markov state transition model for asthma treatment was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). *Figure A10.1* below presents an influence diagram of the model structure showing the five represented states as described below.

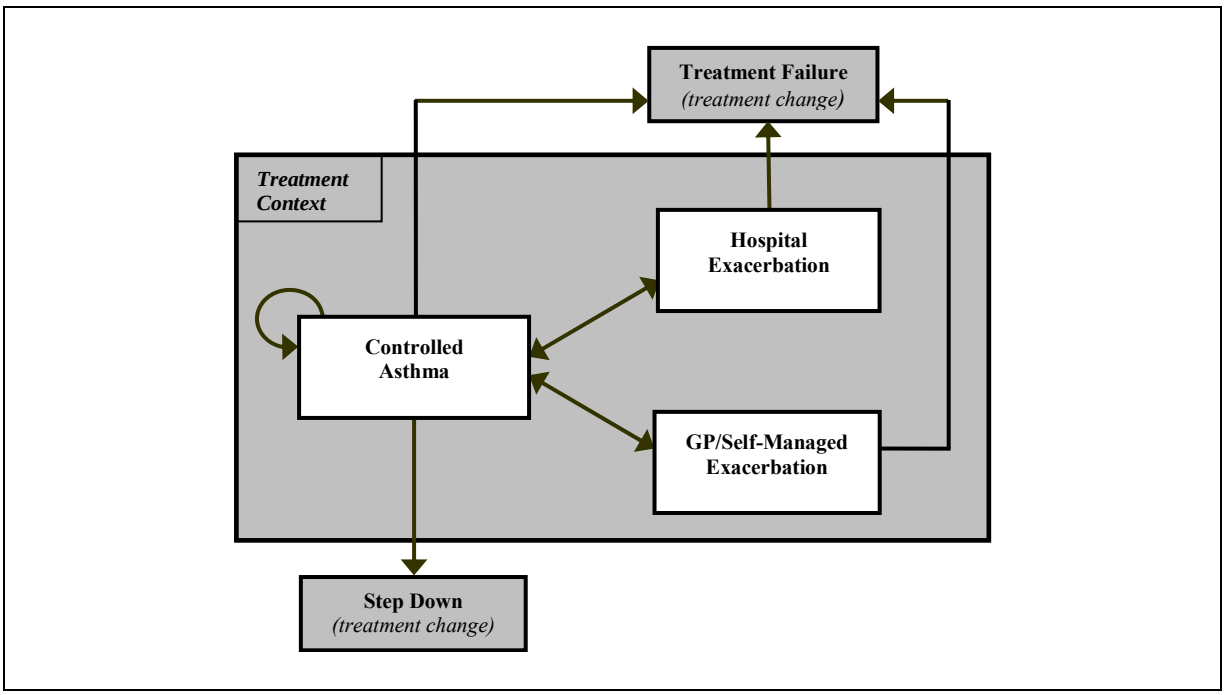


FIGURE A10.1 *Influence Diagram showing the generic model framework*

1. **Controlled Asthma (CA) :** patients who are undergoing the prescribed treatment regimen who do not experience any exacerbations during the modelled cycle.

2. **GP/Self-Managed Exacerbations (GX) :** 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 (HX):** a cycle in which a patient experiences an exacerbation which requires either attendance at an Accident and Emergency Department (A&E) or in-patient 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 (TF):** 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 guidelines. 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 (SD):** 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 guidelines. This is an 'absorbing state' in the model and is assigned an aggregate value for cost and utility.

A10.1.2 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 National Health Service & 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, probabilistic sensitivity analyses (PSA) provide the most meaningful outputs. Summary findings from the PSA are reported below for each investigated research question using scatter plots of Incremental Cost-effectiveness Ratio and Cost-Effectiveness Acceptability Curves.

A10.2 Results

A10.2.1 Research question 3a(i) – BUD/FF *versus* ICS only

A10.2.1.1 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 (see below). 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, Exeter, and the Southampton University Hospital, Southampton, supplemented by expert advice where no other data were available.

TABLE A10.1 *Model inputs (BUD/FF v higher-dose ICS): Costs (£/cycle)*

	CENTRAL ESTS		*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*

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

Utility values for the defined health states were obtained from the 2006 study by Dewilde and colleagues,[312] since they more closely matched our defined health states than other

studies containing utility estimates by health state or lung function (e.g. Paltiel et al. 2001,[294] or Briggs et al. 2006[255]). 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.

TABLE A10.2 *Model inputs (BUD/FF v higher-dose ICS): Utility values*

State	ICS ONLY & 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*

Probabilistic sampling for utilities in the PSA used beta distributions using the standard error above. 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 vs higher dose BUD (O'Byrne *et al*. 2005,[232] Rabe *et al*. 2006,[313] and Scicchitano et al. 2004[233]). 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[229-232;313] (again using weighted averages based on patient-weeks).

TABLE A10.3 *Model inputs (BUD/FF v higher-dose ICS): Transition probabilities*

	CENTRAL ESTS		*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 M Exac	0.00590	0.00419	*0.000131*	*0.001397*
Control to Hospital Exac	0.00061	0.00050	*0.000184*	*0.000162*
GP/SM Exac. To Trmt Change	0.4	0.2	*0.114798*	*0.102043*
Hosp. Exac. To Trmt Change	0.75	0.3	*0.127553*	*0.076532*
Controlled State To Trmt Change	0.00044	0.00027	*0.000088*	*0.000052*
Prop. 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 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.

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

A10.2.1.2 Simulation outputs

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

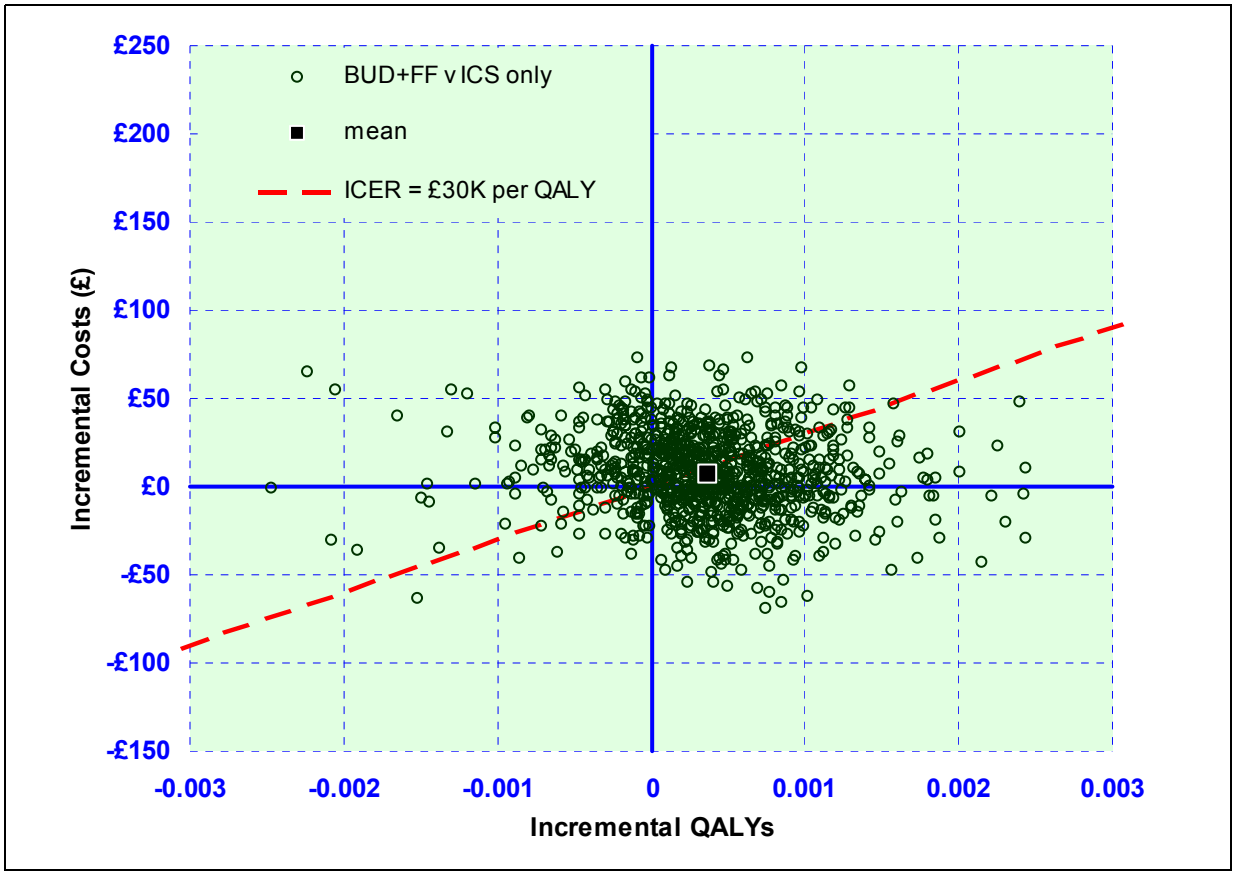
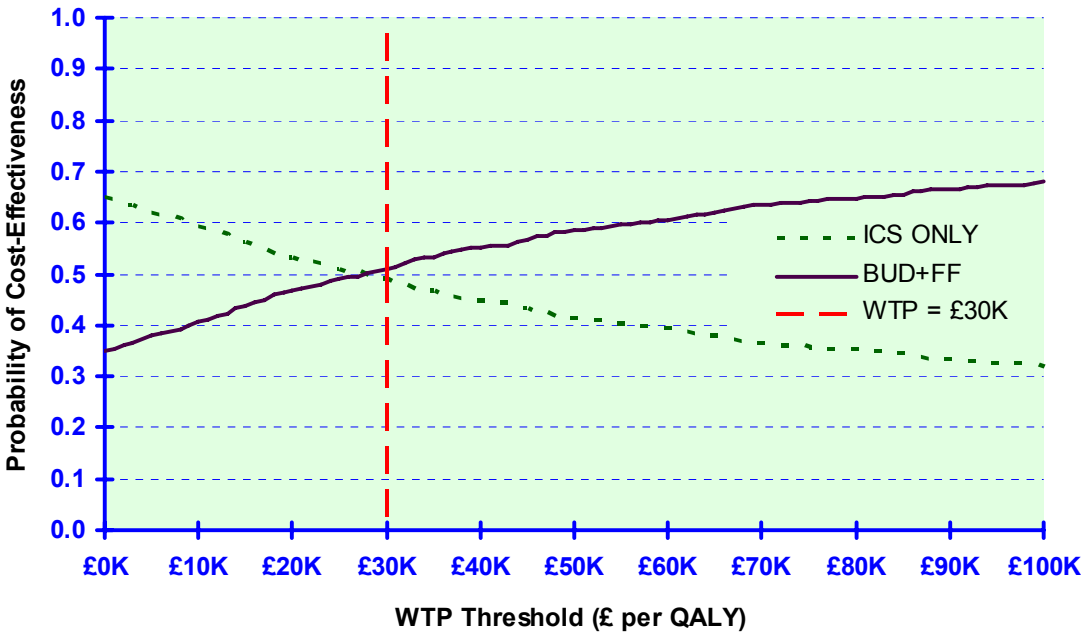


FIGURE A10.2 *BUD/FF v higher-dose ICS: Probabilistic cost-effectiveness plane scatter plot*
showing incremental cost-effectiveness of BUD/FF v higher dose ICS in 1,000 Monte Carlo simulations

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 Cost-Effectiveness Acceptability Curve (*CEAC*) is plotted below and shows the probability that BUD/FF is cost-effective for a range of WTP thresholds. This shows that there is a greater than 50% probability that BUD/FF is cost-effective at WTP threshold less that £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%. These uncertainty in these results is reflected in a different way in the variable results of the previously presented trial-specific cost-consequence analyses.



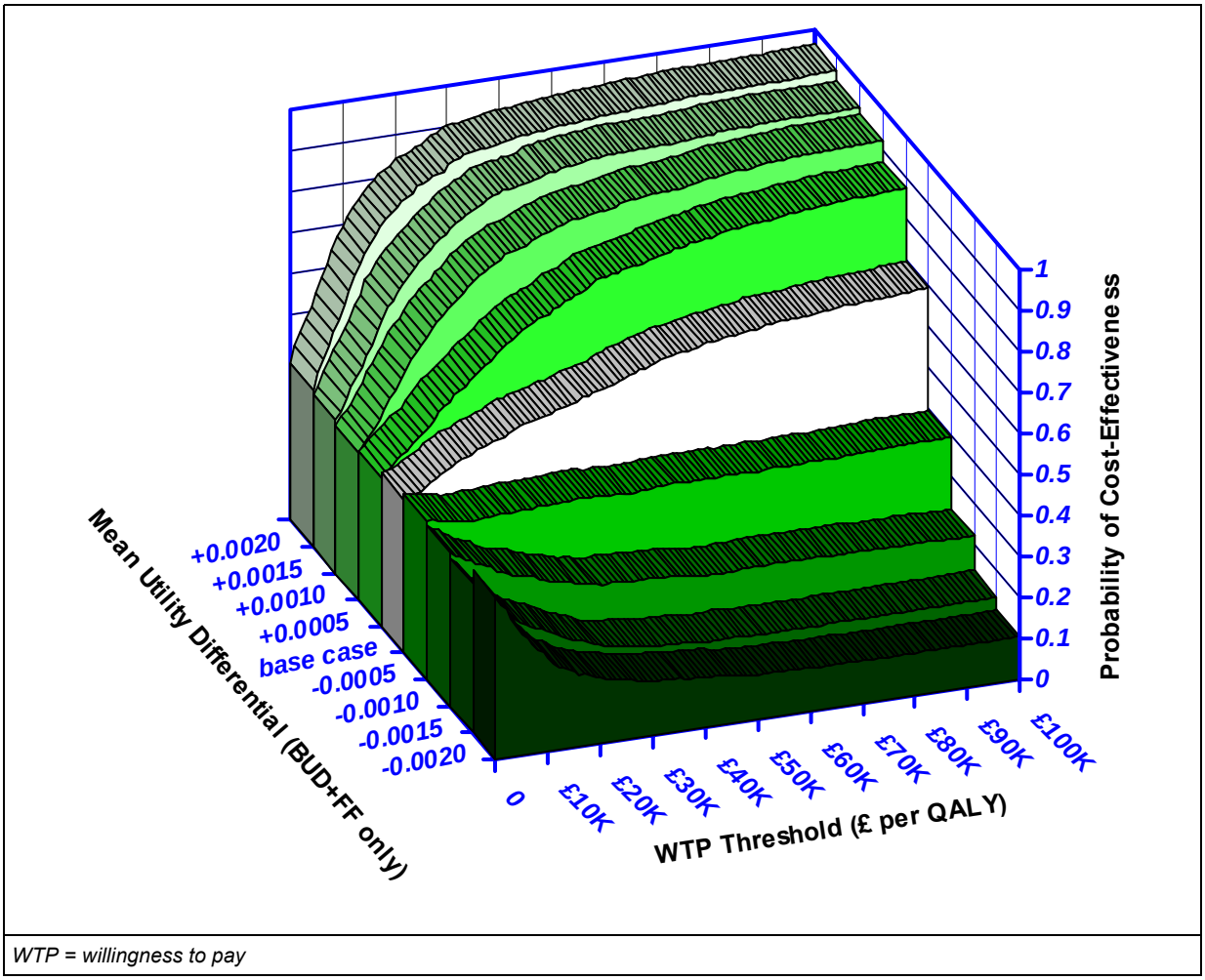
WTP = willingness to pay

FIGURE A10.3 *BUD/FF v higher-dose ICS: Cost-Effectiveness Acceptability Curve*

showing probability that BUD/FF is cost-effective, when compared to higher-dose ICS, at willingness-to-pay thresholds of up to £100,000 per QALY gained; based on simulation output for 1,000 Monte Carlo simulations

A10.2.1.3 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 1,000 trials). The resulting CEACs are presented in a three-dimensional array in *Figure A10.4* (the base case CEAC – no inter-arm variation – is given by the central curve).



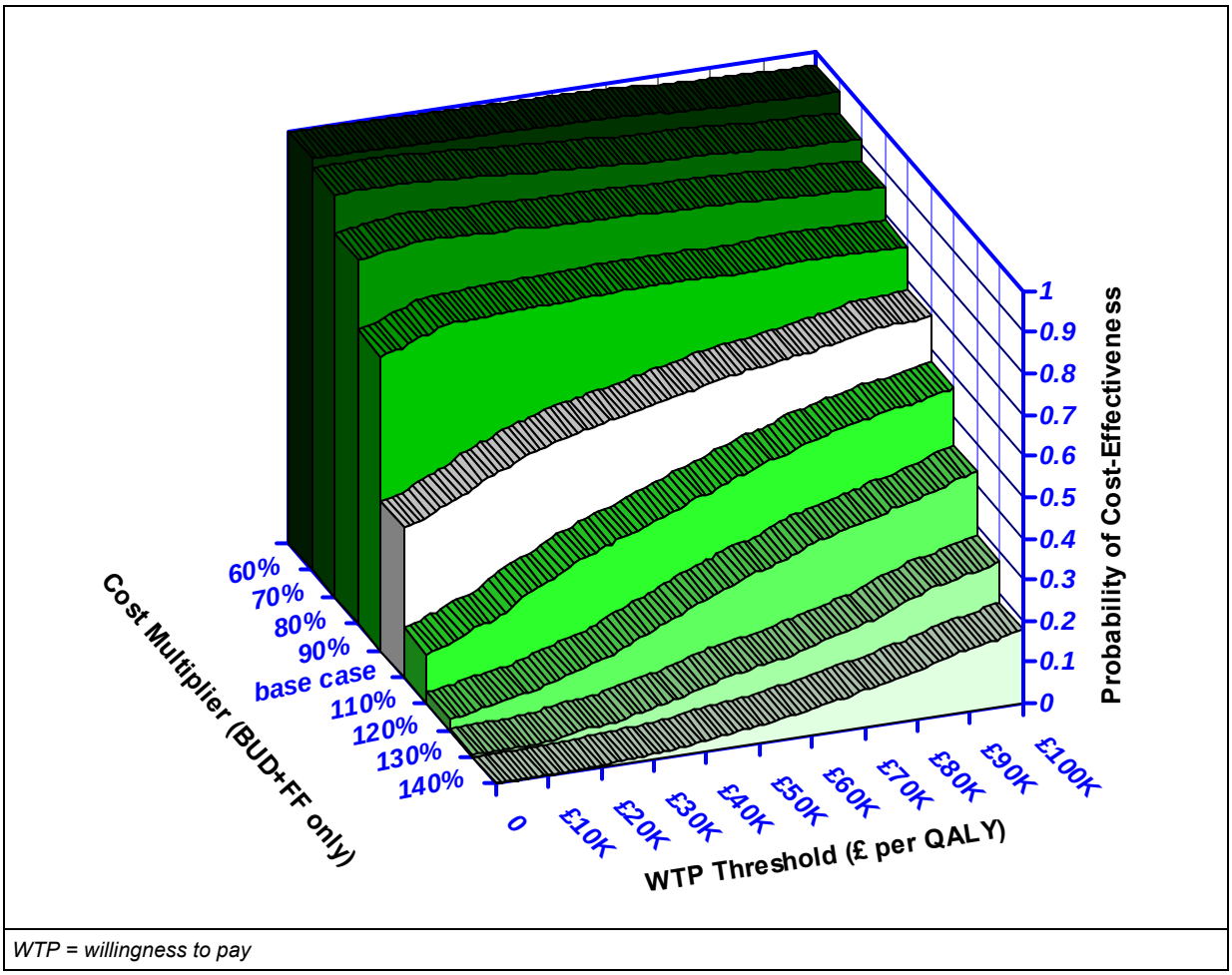
WTP = willingness to pay

FIGURE A10.4 *BUD/FF v higher-dose ICS: Cost-Effectiveness Acceptability Array (utility differential)* showing 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 1,000 Monte Carlo simulations per 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 illustrates the potentially major impact of quality-of-life improvements for asthma patients in periods without exacerbations.

A10.2.1.4 Probabilistic analysis of costs in the Controlled Asthma state

The effect of changes to costs in the Controlled Asthma state for FP/S were 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 A10.5.*



WTP = willingness to pay

FIGURE A10.5 *BUD/FF v higher-dose ICS: Cost-Effectiveness Acceptability Array (cost differential)*
showing impact of cost differential on probability of cost-effectiveness; based on 1,000 Monte Carlo simulations per curve

A10.2.2 Research question 3a(ii) – FP/S *versus* ICS only

A10.2.2.1 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/S products and doses used in the trials from which the effectiveness transition probabilities were obtained (see below).

TABLE A10.4 *Model inputs (FP/S v higher-dose ICS): Costs (£/cycle)*

	CENTRAL ESTS		*LOWER LIMIT*		*UPPER LIMIT*	
State	**ICS ONLY**	**FP/S**	*ICS ONLY*	*FP/S*	*ICS ONLY*	*FP/S*
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 Exac.	26.91	27.23	*21.65*	*22.61*	*32.16*	*31.86*
Hospital managed Exac.	1134.11	1134.44	*373.63*	*373.96*	*1894.59*	*1894.92*

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

Utility values for health states in this comparison were obtained from the cost-effectiveness study by Dewilde and colleagues[312] (as for BUD/FF versus higher dose ICS).

TABLE A10.5 *Model inputs (FP/S v higher-dose ICS): Utility values*

State	**ICS ONLY & FP/S**	*STANDARD ERROR*
Step Down	0.78	*0.00877*
Controlled Asthma state	0.78	*0.00877*
GP or Self-Managed Exacerbation	0.57	*0.07753*
Hospital-managed Exacerbation	0.33	*0.14579*

Probabilistic sampling for utilities in the PSA used beta distributions using the standard error above. 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.[222-226;314;315] Transition probabilities from the controlled to the two exacerbation states therefore had to be based on the adverse event data reported by GlaxoSmithKline in four trials of FP/S versus higher dose BUD or FP (study summaries in the GSK online trial register for: Batemen *et al*. 2006;[314] Bergmann *et al*.

2004;[223] Jenkins *et al*. 2003,[224] and; Johannson *et al*. 2001[225]), supplemented by data presented in an analysis by Matz and colleagues.[316;317] 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[222;224;226] (again using weighted averages based on patient-weeks).

TABLE A10.6 *Model inputs (FP/S v higher-dose ICS): Transition probabilities*

	CENTRAL ESTS		***STANDARD ERROR***	
Description	**ICS ONLY**	**FP/S**	***ICS ONLY***	**FP/S**
Control to Step down	0.00203	0.002026	*0.001287*	*0.001287*
Control to GP/Self M Exac	0.00713	0.003786	*0.000858*	*0.000616*
Control to Hospital Exac	0.000196	0.000555	*0.000174*	*0.000256*
GP/SM Exac. to Trmt Change	0.4	0.2	*0.114798*	*0.102043*
Hosp. Exac. to Trmt Change	0.75	0.3	*0.127553*	*0.076532*
Controlled State to Trmt Change	0.00191	0.00112	*0.000405*	*0.000312*
Prop. change on failure of FP/S to ICS only[a]	-	0.15000	-	*0.063777*

[a] Patients who have treatment failure in the FP/S arm of the model are either changed to a regimen based on the ICS only treatment or to regimen based on a higher dose of FP/S. 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/S.

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

A10.2.2.2 Simulation outputs

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

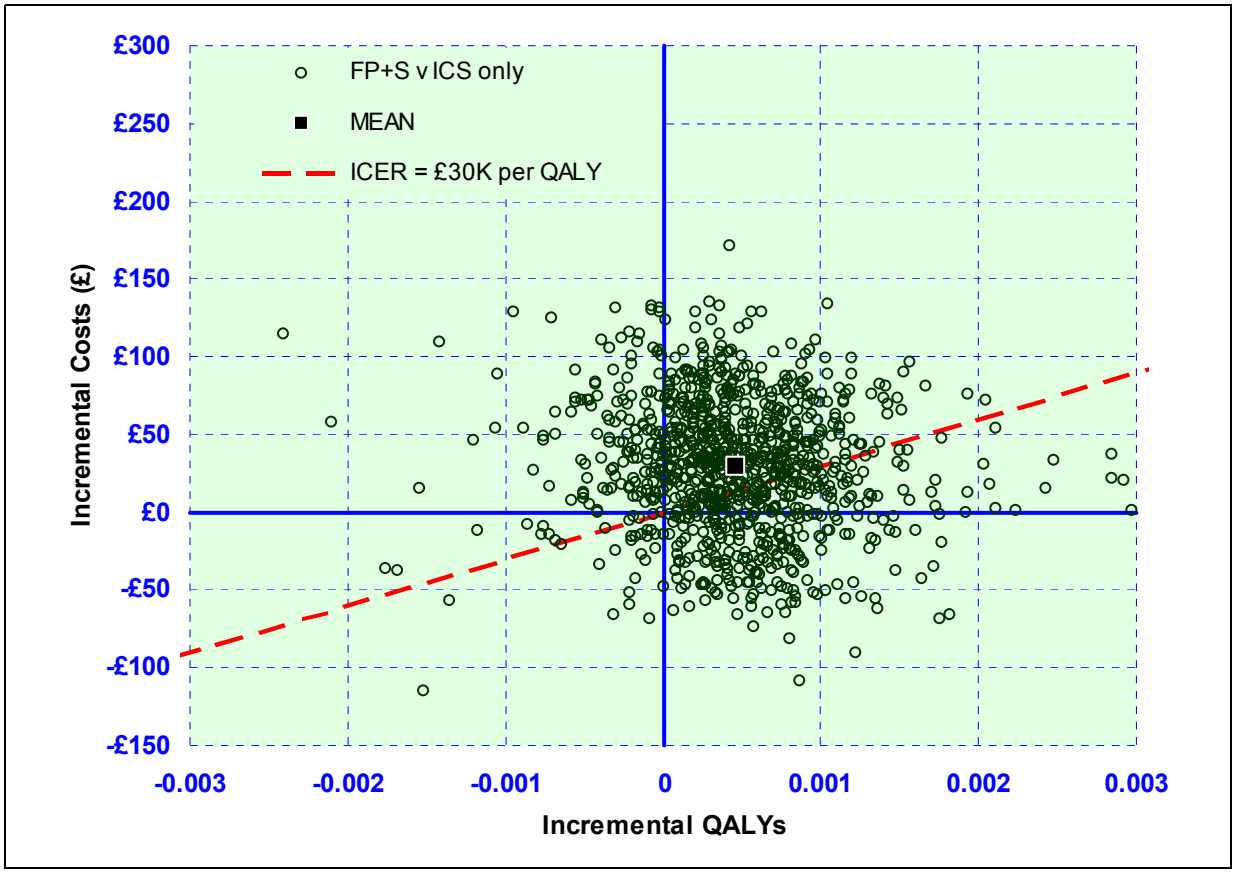
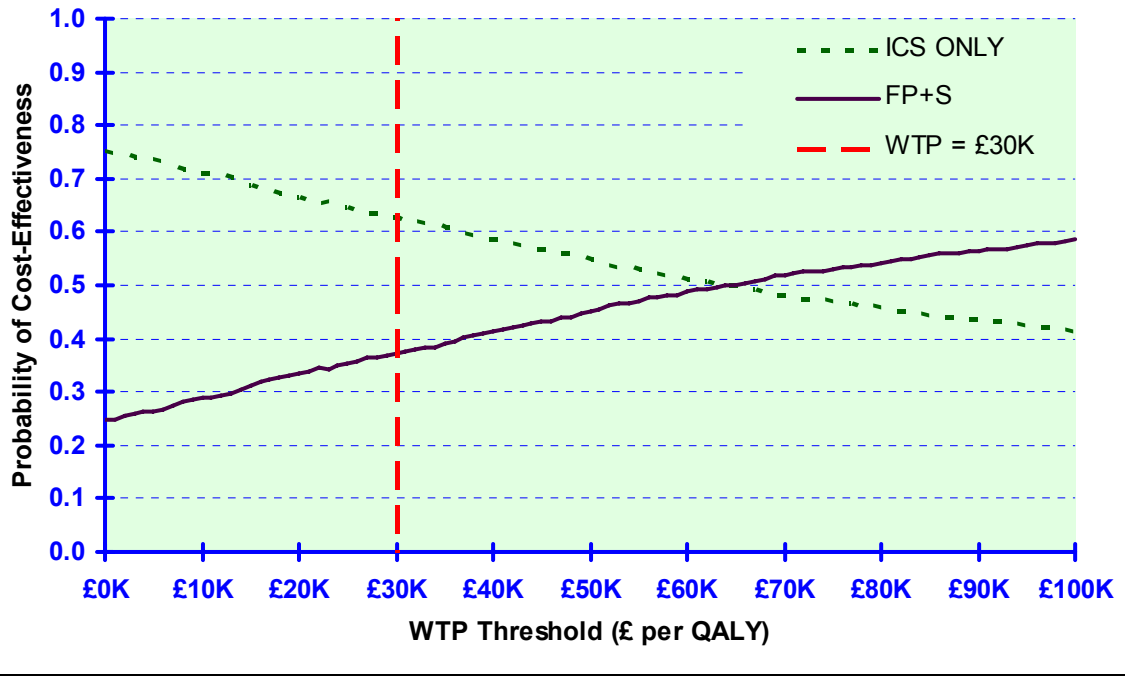


FIGURE A10.6 *FP/S v higher-dose ICS: Probabilistic cost-effectiveness plane scatter plot*

showing incremental cost-effectiveness of FP/S *v*. higher-dose ICS in 1,000 Monte Carlo simulations

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/S arm against its ICS only comparator, but also a small extra annual cost of FP/S.

The CEAC below charts the probability that FP/S 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 a 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.



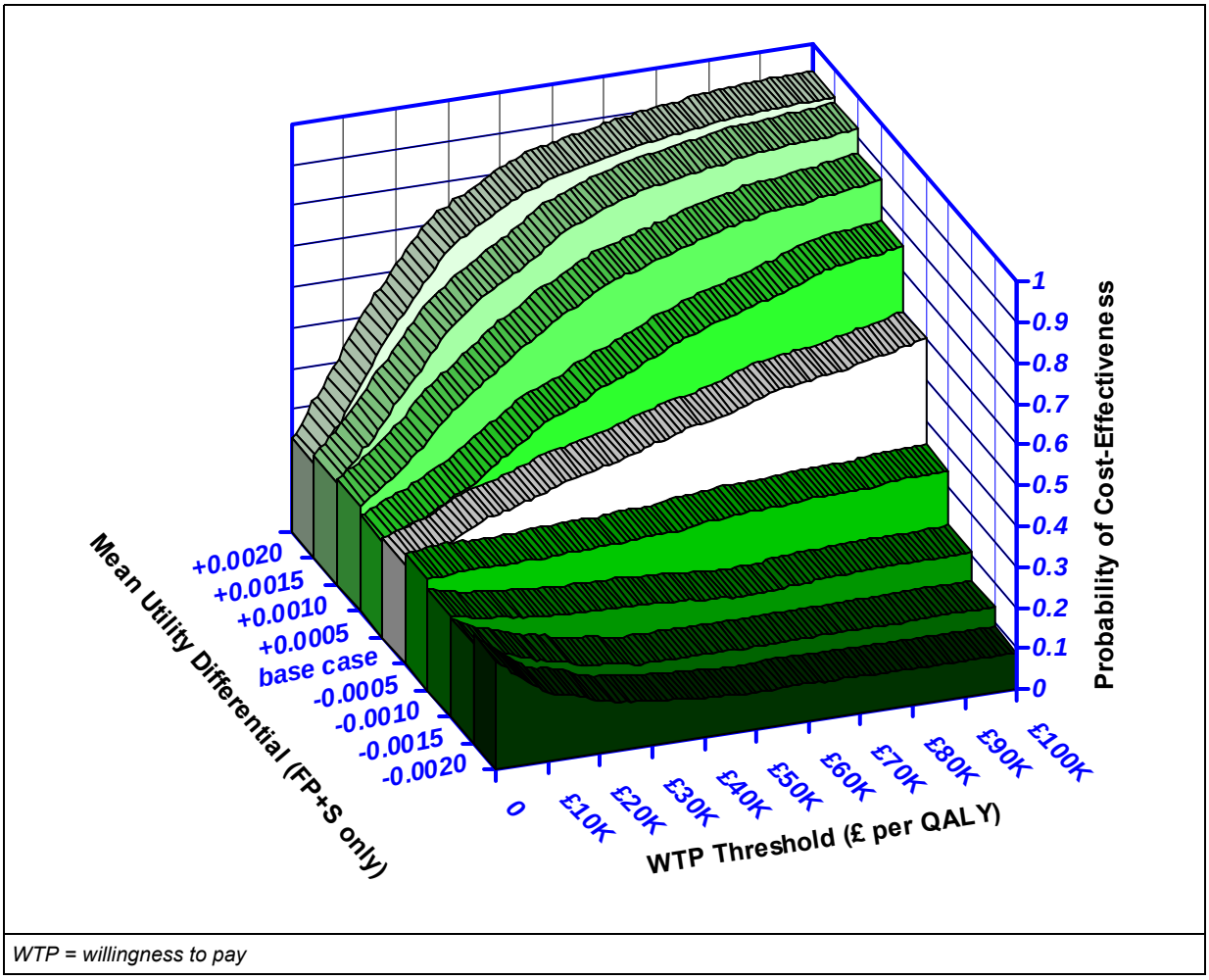
WTP = willingness to pay

FIGURE A10.7 *FP/S v higher-dose ICS: Cost-Effectiveness Acceptability Curve*

showing probability that FP/S is cost-effective, when compared to higher-dose ICS, at willingness-to-pay thresholds of up to £100,000 per QALY gained; based on simulation output for 1,000 Monte Carlo simulations

A10.2.2.3 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/S. This analysis generated the array of CEACs shown in *Figure A10.8.*



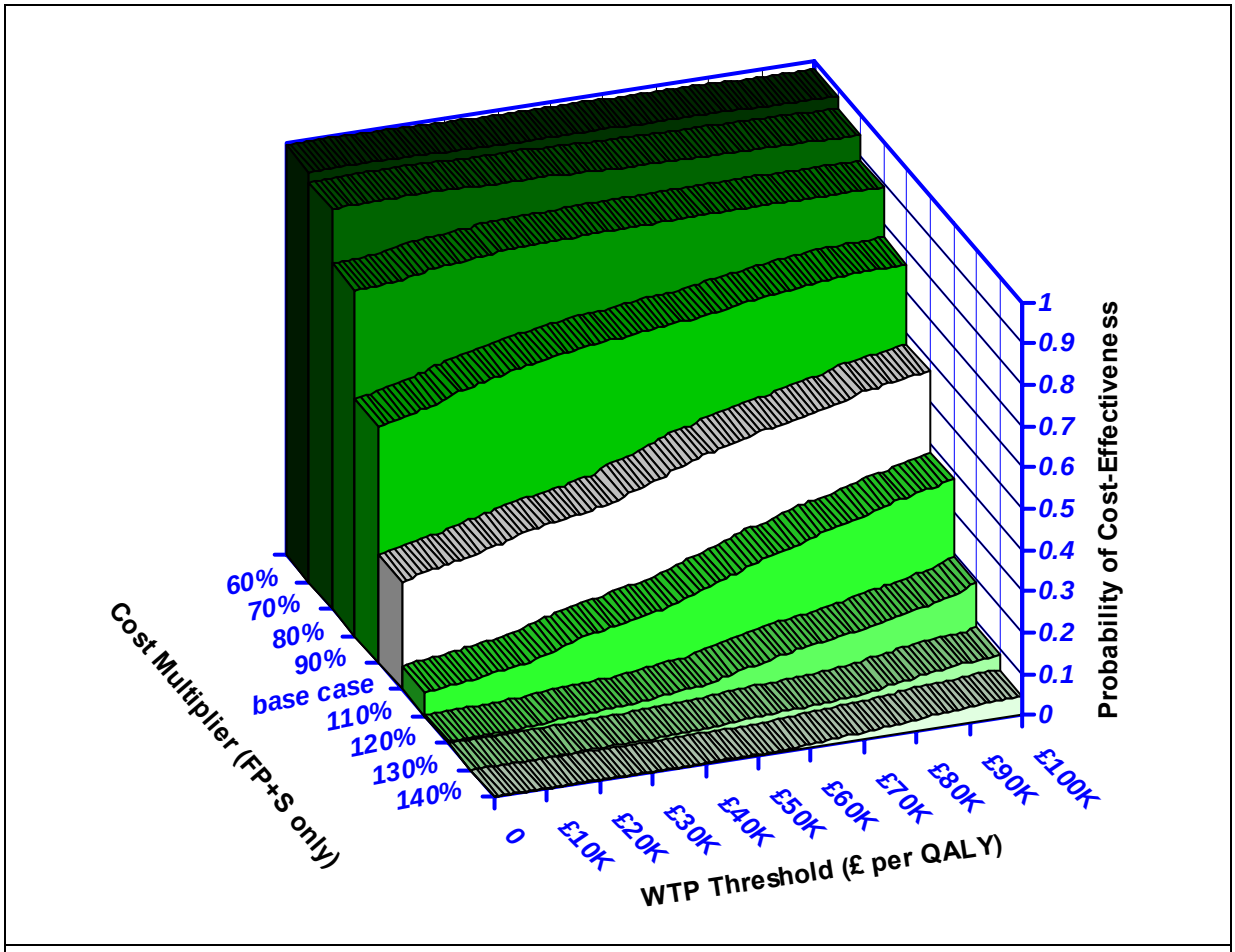
WTP = willingness to pay

FIGURE A10.8 *FP/S v higher-dose ICS: Cost-Effectiveness Acceptability Array (utility differential)*
showing 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 1,000 Monte Carlo simulations per curve

This analysis shows that relatively small alterations to utility values in one arm of the model will affect cost-effectiveness outputs quite dramatically. In the CEAC representing a maximum utility differential of 0.002 (mean 0.001), the probability that FP/S provides the better value for money, when compared to ICS only, exceeds 50% at a WTP of £30,000 per QALY. A utility increment sampled in the range 0-0.004 for FP/S increases the same probability to around 68%. This means that, if FP/S 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.

A10.2.2.4 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/S. 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 A10.9*.



WTP = willingness to pay

FIGURE A10.9 *FP/S v higher-dose ICS: Cost-Effectiveness Acceptability Array (cost differential)*
showing impact of cost differential on probability of cost-effectiveness; based on 1,000 Monte Carlo simulations per curve

A10.2.3 Research question 5 - FP/S *versus* BUD/FF

A10.2.3.1 Model inputs

TABLE A10.7 *Model inputs (FP/S v BUD/FF): Costs (£/cycle)*

	CENTRAL ESTS		*LOWER LIMIT*		*UPPER LIMIT*	
State	**BUD/FF**	**FP/S**	***BUD/FF***	***FP/S***	***BUD/FF***	***FP/S***
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*

Probabilistic sampling for costs in the PSA used triangular distributions using the lower and upper limits as specified above

TABLE A10.8 *Model inputs (FP/S v BUD/FF): Utility values*

State	**BUD/FF & FP/S**	***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*

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

TABLE A10.9 *Model inputs (FP/S v BUD/FF): Transition probabilities*

	CENTRAL ESTS		***STANDARD ERROR***	
Description	**BUD/FF**	**FP/S**	***BUD/FF***	***FP/S***
Control to Step down	0.000986	0.000986	*0.000418*	*0.000418*
Control to GP/Self M Exac	0.00458	0.00455	*0.000131*	*0.001397*
Control to Hospital Exac	0.00054	0.00066	*0.000184*	*0.000162*
GP/SM Exac. To Trmt Change	0.2	0.2	*0.102*	*0.102*
Hosp. Exac. To Trmt Change	0.3	0.3	*0.0765*	*0.0765*
Controlled State To Trmt Change	0.0001	0.00021	*0.00004*	*0.00005*

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

A10.2.3.2 Simulation outputs

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

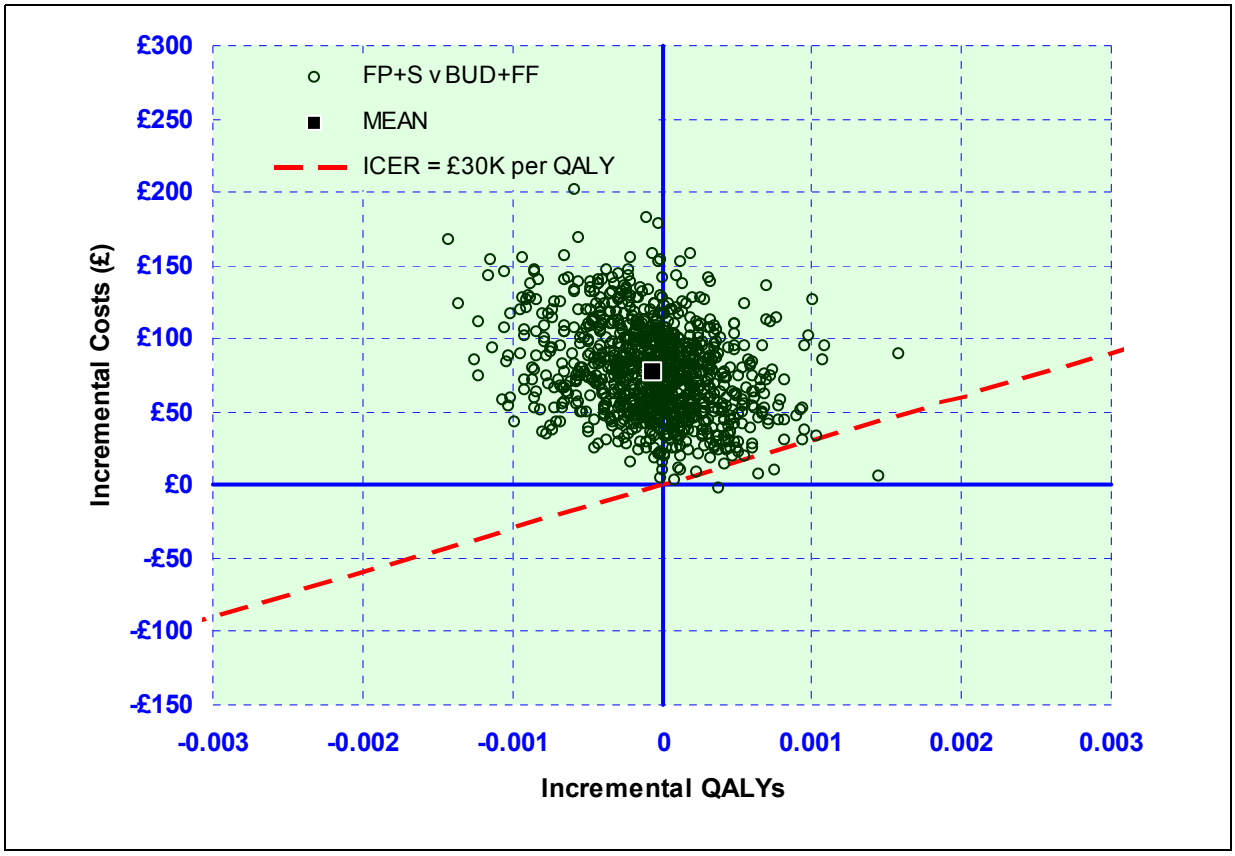
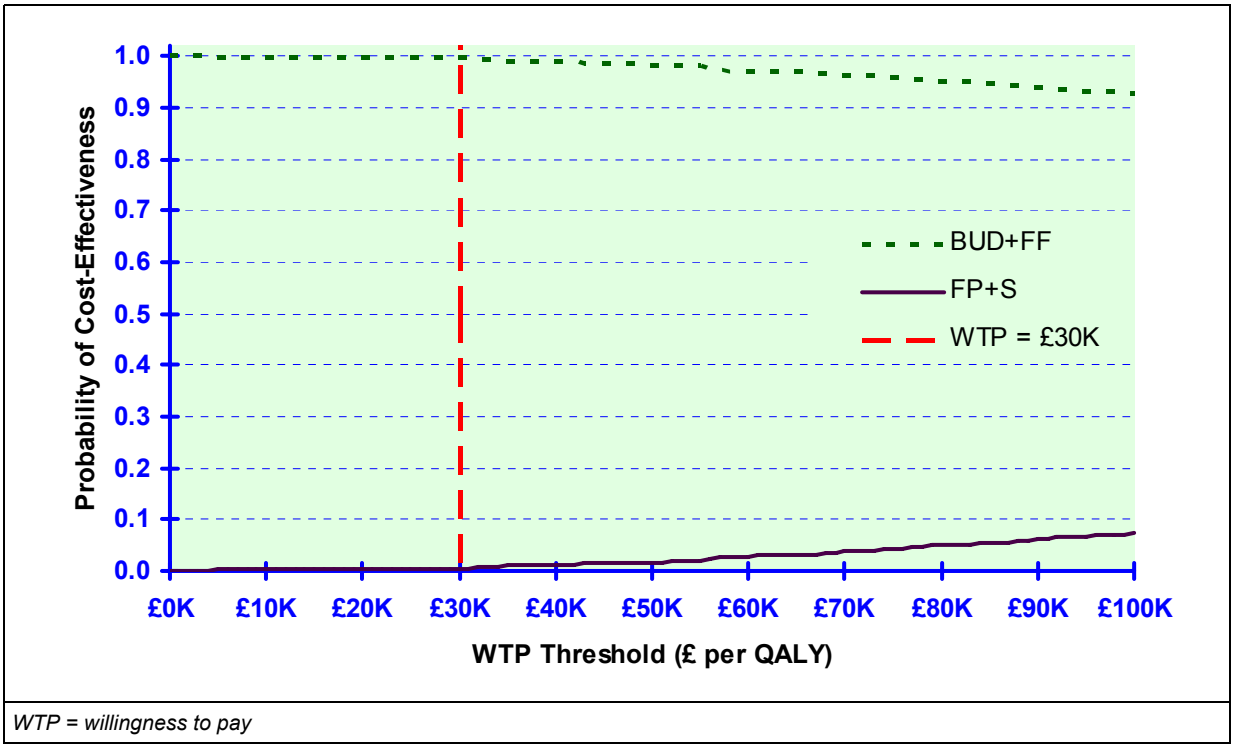


FIGURE A10.10 *FP/S v BUD/FF: Probabilistic cost-effectiveness plane scatter plot*
showing incremental cost-effectiveness of FP/S *v.* BUD/FF in 1,000 Monte Carlo simulations

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 below. This charts the probability that FP/S will be found to be cost-effective for a range of WTP thresholds.



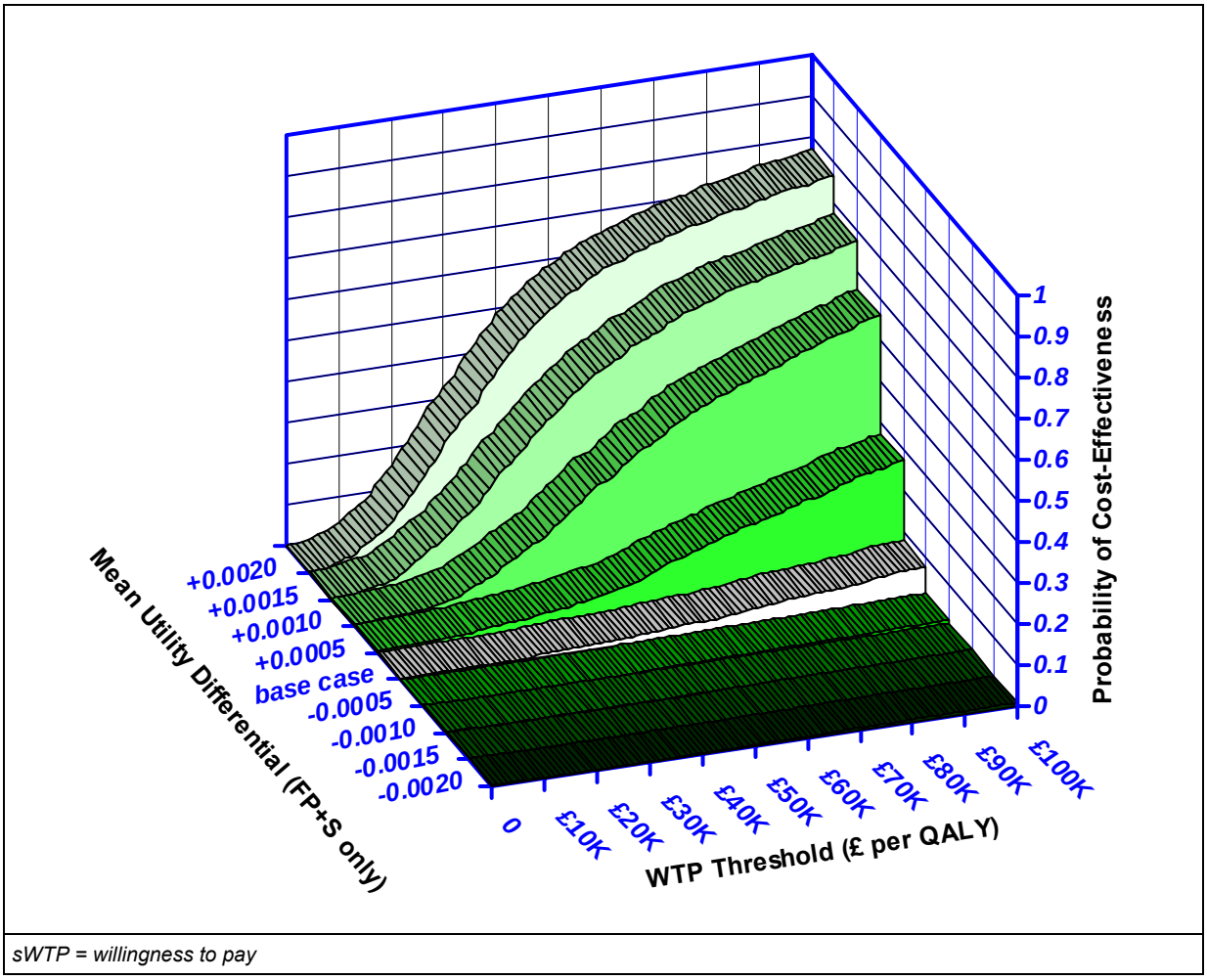
WTP = willingness to pay

FIGURE A10.11 *FP/S v BUD/FF: Cost-Effectiveness Acceptability Curve*

showing probability that FP/S is cost-effective, when compared to BUD-FF, at willingness-to-pay thresholds of up to £100,000 per QALY gained; based on simulation output for 1,000 Monte Carlo simulations

A10.2.3.3 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/S. This analysis generated the array of CEACs shown in *Figure A10.12*. This analysis confirms the importance of this variable in determining the cost-effectiveness of an intervention in this context.



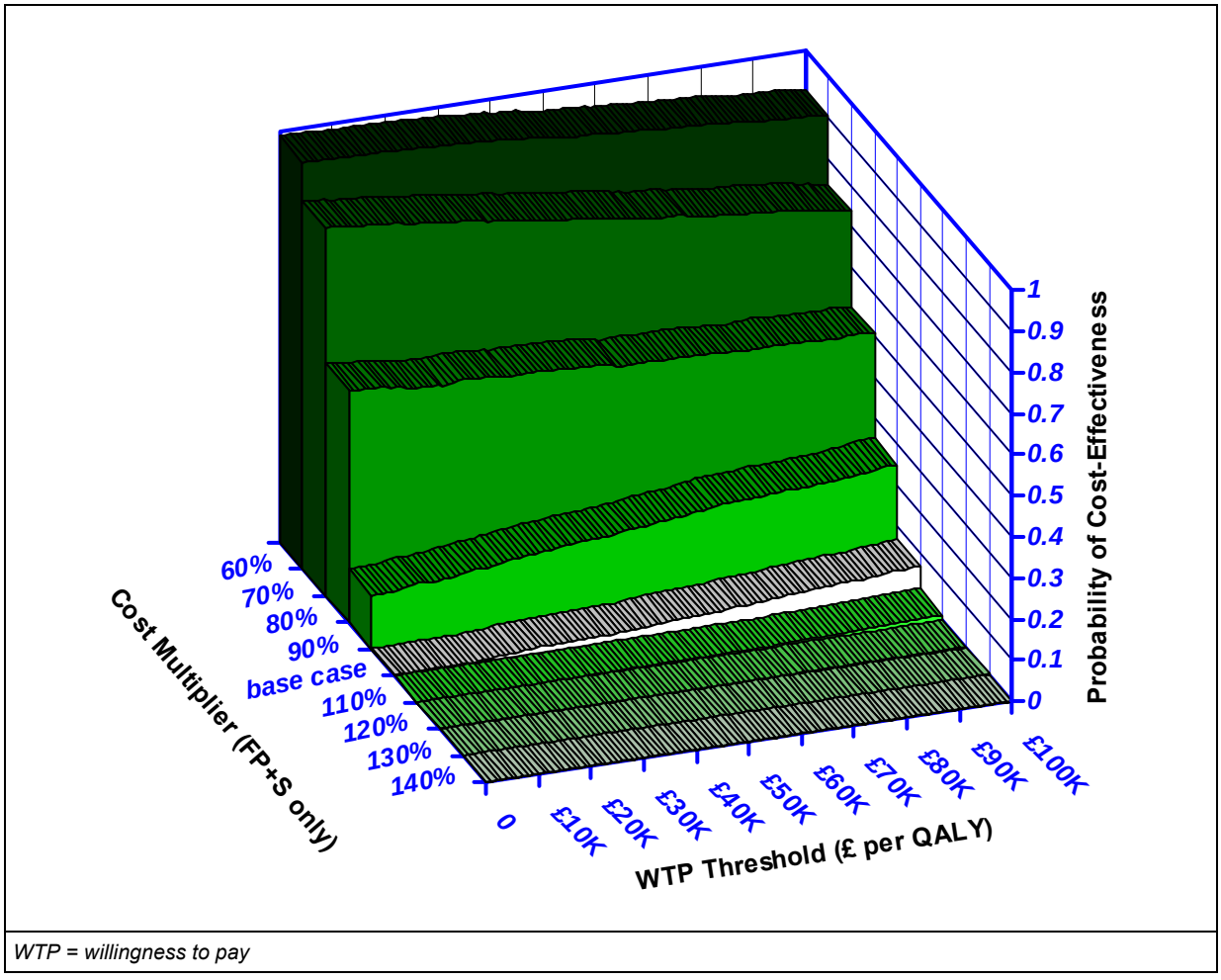
sWTP = willingness to pay

FIGURE A10.12 *FP/S v BUD/FF: Cost-Effectiveness Acceptability Array (utility differential)*

showing 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 1,000 Monte Carlo simulations per curve

A10.2.3.4 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/S. 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 A10.13*.



WTP = willingness to pay

FIGURE A10.13 *FP/S v BUD/FF: Cost-Effectiveness Acceptability Array (utility differential)*

showing 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 1,000 Monte Carlo simulations per curve

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

A10.3 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 one year model time horizon, are pre-dominant 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 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 quite 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.