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

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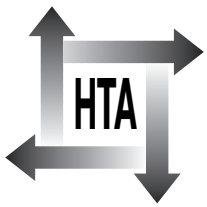

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NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/30/01. The protocol was agreed in April 2006. The assessment report began editorial review in April 2007 and was accepted for publication in July 2007. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

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

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Objectives: To assess the clinical and cost-effectiveness of inhaled corticosteroids (ICS) alone and ICS used in combination with a long-acting beta$_2$ agonist (LABA) in the treatment of chronic asthma in adults and children aged over 12 years.

Data sources: Major electronic bibliographic databases, e.g. MEDLINE and EMBASE, were searched up to February/March 2006 (and updated again in October 2006).

Review methods: A systematic review of clinical and cost-effectiveness studies was conducted. Cost comparison and cost-consequence analyses were performed where appropriate.

Results: The assessment of clinical effectiveness was based on the 67 randomised controlled trials selected from the 5175 reports identified through the systematic literature search. The most frequently reported relevant outcomes were lung function, symptoms, use of rescue medication and adverse events. The trials varied considerably. In the trials that compared low-dose ICS versus ICS and high-dose ICS versus ICS, there were few significant differences in clinical effectiveness, although a few of the trials had assessed non-inferiority between the comparators rather than superiority. At doses of 400, 800 and 'high-level' doses of 1500 or 1600 μg/day, beclometasone dipropionate (BDP) appears to be the current cheapest ICS product both with the inclusion and exclusion of chlorofluorocarbon (CFC)-propelled products. A significant treatment benefit for combination ICS/LABA therapy across a range of outcomes compared with ICS alone was identified [when the ICS was double the accepted clinically equivalent dose of the ICS in the combination inhaler, and dry powder inhalers (DPIS) were used to deliver the drugs]. When a formoterol fumarate (FF)/salmeterol (SAL) combination inhaler and a budesonide (BUD)/FF combination inhaler were each compared with their constituent drugs delivered in separate inhalers, there were very few statistically significant differences between the treatments across the various efficacy outcomes and the rate of adverse events. Combination inhalers were more often cheaper than doubling the dose of ICS alone. However, the costs were highly variable and dependent on 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. The BUD/FF combination varied from being £163 cheaper to £66 more expensive than the higher dose of either BUD or FP. When the combination inhalers were compared to each other, the results were mixed, with the FP/SAL combination significantly superior on some outcomes and the BUD/FF combination superior on others; however, meta-analysis showed that there were no significant differences between the two treatments in the rate of adverse events. Taking an ICS with a LABA as either of the two currently available combination products, FP/SAL and BUD/FF, is usually cheaper than taking the relevant

constituent drugs in separate inhalers. At very high doses of BUD (1600 μg/day), however, the BUD/FF combination inhaler can be up to £156 more expensive than having the same drugs in separate inhalers. In terms of the relative costs associated with taking one of the combination inhalers, at low dose (400 μg BUD or 200 μg FP/day) the cheapest combination inhaler is FP/SAL as a pressurised metered dose inhaler (pMDI) (Seretide Evohaler). However, this is only slightly cheaper than using BUD/FF as a DPI (Symbicort Turbohaler). At higher dose levels (800 μg BUD or 500 μg FP/day) FP/SAL as either pMDI aerosol (Seretide Evohaler) or a DPI (Seretide Accuhaler) is the cheapest combination product available, but again only slightly cheaper than the DPI BUD/FF combination (Symbicort Turbohaler). It should be highlighted, however, that the three head-to-head trials that compared the effects of FP/SAL with BUD/FF used the FP/SAL DPI combination inhaler, Seretide Accuhaler.

Conclusions: The evidence indicates that there are few 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 and tend to remain so as the daily ICS dose required increases. There is evidence that the addition of a LABA to an ICS is potentially more clinically effective than 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 on the dose required and the particular preparations used. For the combination therapies of ICS/LABA there are potential cost savings with the use of combination inhalers compared with separate inhalers, with few differences between the two treatment strategies in terms of effects. The only exception to this cost saving is with BUD/FF at doses higher than 1200 μg/day, where separate inhaler devices can become equivalent to or cheaper than combination inhalers. Neither of the two combination inhalers (FP/SAL or BUD/FF) is consistently superior in terms of treatment effect. A comparison of the costs associated with each combination therapy indicates that at low dose FP/SAL delivered via a pMDI is currently the cheapest combination inhaler but only marginally cheaper than BUD/FF delivered as a DPI. At higher doses, both the FP/SAL combination inhalers (PMDI and DPI) are marginally cheaper than BUD/FF (DPI). Future trials of treatment for chronic asthma should standardise the way in which outcome measures are defined and measured, with a greater focus on patient-centred outcomes. For informing future cost–utility and cost-effectiveness analyses from a UK NHS perspective, there is a need for longitudinal studies that comprehensively track the care pathways followed when people experience asthma exacerbations of different severity. Further research synthesis, quantifying the adverse effects of the different ICS, is required for treatment choices by patients and clinicians to be fully informed.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Chlorofluorocarbon (CFC) A propellant used in pressured metered dose inhalers. Currently being replaced by hydrofluoroalkane (HFA) propellants.

Cortisol A corticosteroid hormone that is involved in the response to stress; it increases blood pressure and blood sugar levels and suppresses the immune system.

***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.

***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.

Forced expiratory volume (FEV_1) The volume of air exhaled in 1 second of forced blowing into a spirometer.

Forced vital capacity (FVC) The total amount of air that a person can forcibly blow out after full inspiration, measured in litres.

Hydrofluoroalkane (HFA) A propellant used in pressured metered dose inhalers. Replacement for chlorofluorocarbon (CFC) propellants.

Hypothalamic–pituitary–adrenal axis (HPA axis) 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.

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.

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.

Peak expiratory flow rate The maximum rate at which air is expired from the lungs when blowing into a peak flow meter or spirometer.

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.

List of abbreviations

A&E	Accident and Emergency
ACQ-5	Asthma Control Questionnaire
ACTH	adrenocorticotropic hormone
AE	adverse event
AMD	adjustable maintenance dose
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APM	Asthma Policy Model
AQLQ	Asthma Quality of Life Questionnaire
ASUI	Asthma Symptom Utility Index
AZ	AstraZeneca
b.d.	twice a day
BDP	beclometasone dipropionate
BMD	bone mineral density
BNF	British National Formulary
BTS	British Thoracic Society
BUD	budesonide
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CFC	chlorofluorocarbon
CI	confidence interval
CIC	ciclesonide
CMA	cost minimisation analysis
COPD	chronic obstructive pulmonary disease
CRD	Centre for Reviews and Dissemination
CS	clinically significant
CSS	clinically significant severe
CUA	cost–utility analysis
DES-CIC	desisobutyryl-ciclesonide
DPI	dry powder inhaler
ED	emergency department
EMEA	European Agency for the Evaluation of Medicinal Products
ER	emergency room
FD	fixed dose
FDA	Food and Drug Administration
$FEF_{25–75\%}$	forced expiratory flow between 25 and 75% of vital capacity
FEV_1	forced expiratory volume in 1 second
FF	formoterol fumarate
FP	fluticasone propionate
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GOAL	Gaining Optimal Asthma Control
GSK	GlaxoSmithKline
HFA	hydrofluoroalkane
HPA	hypothalamic–pituitary–adrenal
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid (e.g. budesonide)
IQR	interquartile range
ITT	intention-to-treat
LABA	long-acting $beta_2$ agonist (e.g. salmeterol or formoterol)
MDI	metered-dose inhaler
MEF	maximal expiratory flow
MF	mometasone furoate

continued

List of abbreviations *continued*

MHRA	Medicines and Health Care Products Regulatory Agency
NICE	National Institute for Health and Clinical Excellence
NS	not significant
NSD	no statistically significant difference
NW	nocturnal wakings
OCS	oral corticosteroids
OR	odds ratio
PC	plasma cortisol
PCA	prescribing cost analysis
PEF	peak expiratory flow rate
pMDI	pressurised metered-dose inhaler
PP	per protocol
pQCT	peripheral quantitative computed tomography
PSA	probabilistic sensitivity analysis
PSC	posterior subcapsular cataract
PSS	Personal Social Services
QALY	quality-adjusted life-year
QCT	quantitative computed tomography
q.d.	four times a day
RCT	randomised controlled trial
RR	relative risk
SABA	short-acting beta$_2$ agonist (e.g. salbutamol or terbutaline)
SAL	salmeterol
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SF-36	Short Form questionnaire with 36 Items
SFD	symptom-free day
SFN	symptom-free night
SG	standard gamble
SIGN	Scottish Intercollegiate Guidelines Network
SMART	Salmeteral Multicenter Asthma Research Trial
SMART	Symbicort Maintenance and Reliever Therapy
SMD	standardised mean difference
SNS	Salmeterol Nationwide Surveillance
SR	slow release
SS	symptom score
ST	standard therapy
TCM	total cortisol metabolites
TTO	time trade-off
VAS	visual analogue scale
WMD	weighted mean difference
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Current asthma management

Various strategies are used in the prevention and management of asthma. Pharmacological management includes, among other drugs, inhaled corticosteroids (ICS) and short- and long-acting beta$_2$ agonists (SABAs/LABAs). Both ICS and LABAs are inhaled controller medications that need to be taken on a long-term daily basis for maximum symptom control. Medication delivery can be via a number of different types of inhaler device; these differ in the efficiency with which they deliver the drug to the lower respiratory tract.

There are currently five ICS available as licensed preparations for the treatment of asthma: 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).

Objectives

The objectives of this health technology assessment are:

- to identify, appraise and synthesise, where appropriate, the current evidence base on the clinical effectiveness and cost-effectiveness of ICS alone and ICS used in combination with a LABA in the treatment of chronic asthma in adults and children aged over 12 years
- to identify the costs associated with the different treatments
- 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.

Methods

The assessment was conducted within the context of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) Guideline on the management of asthma.

A literature search was conducted on a number of electronic bibliographic databases (e.g. MEDLINE, Cochrane CENTRAL and EMBASE) up to February/March 2006 (and updated again in October 2006).

Only trials testing different drugs using the same inhaler device/propellant were included. Therefore trials testing, for example, BDP via a pressurised metered dose inhaler (pMDI) versus BUD via a dry powder inhaler (DPI) were excluded, as were trials testing, for example, BDP via hydrofluoroalkane (HFA)-propelled pMDI versus BUD via chlorofluorocarbon (CFC)-propelled pMDI. The scope of the review was to consider the effectiveness of the inhaled steroids, as opposed to their delivery devices. Some clinical trials were specifically designed to evaluate device effects using clinically inequivalent doses. These were therefore excluded to reduce the likelihood of confounding.

A flexible framework was used to allow different types of economic analyses and a cost comparison or a cost–consequence comparison was conducted.

Results

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, seven were systematic reviews, and 10 were post-2004 conference abstracts.

The 67 trials varied considerably. While there is a comparatively large evidence base for the more established ICS (BDP, BUD, FP) compared with the newer ICS (MF and CIC), it was not possible to perform pair-wise comparisons for all the five comparators due to a lack of direct head-to-head RCTs. In many cases quantitative meta-analysis was not appropriate or feasible.

The most frequently reported relevant outcomes were lung function, symptoms, use of rescue medication and adverse events. Exacerbations and health-related quality of life were reported less frequently, and differences in the ways in which these were defined between the individual trials meant that few comparisons could be made.

Low-dose ICS versus ICS

Twenty-two RCTs were identified that compared the five ICS at low doses (400–800 μg BDP/day or equivalent). In general, all the ICS were associated with favourable changes from baseline to end-point across efficacy outcomes. Overall, there is little evidence to reject the hypothesis that there is no significant difference in clinical effectiveness between the different ICS, although a few of the trials had assessed non-inferiority between the comparators rather than superiority. A summary of results is given below:

- BDP versus BUD (five RCTs): there were few statistically significant differences between the comparators on a range of outcomes assessed across the five trials. One trial showed a significant difference in terms of morning and evening PEF in favour of BUD, but no difference in measures of forced expiratory volume in 1 second (FEV_1). A further trial showed a significant difference in favour of BDP on a measure of FEV_1. Only one trial reported on adverse events.
- FP versus BDP (six RCTs): five trials reported no statistically significant differences between FP and BDP across the outcomes assessed. One further trial showed a treatment benefit in favour of FP compared with BDP across a number of outcomes.
- FP versus BUD (five RCTs): four trials showed no statistically significant differences between FP and BUD. In a further trial, symptom measures favoured treatment with FP, but no differences on measures on lung function were observed. Meta-analysis of two trials showed BUD to be associated with significantly fewer adverse events than FP.
- CIC versus BUD (one RCT): no significant differences across measures of lung function, symptoms or exacerbation rates were observed between the comparators. Non-inferiority in terms of lung function measures was demonstrated for CIC.
- MF versus BUD (two RCTs): at a nominally equivalent dose ratio of 1:2 (MF, BUD), there was a statistically significant difference in favour of MF for the outcome of FEV_1. No significant differences were shown for the other lung function outcomes or symptoms. At a dose ratio of 1:1 there was a significant treatment benefit in favour of MF on both measures of lung function and symptoms. Adverse event rates were comparable between the two treatment arms.
- CIC versus FP (two RCTs): at nominally equivalent dose ratios of 1:1 there were no statistically significant differences between the comparators on measures of lung function, symptoms, use of rescue medication or number of exacerbations. Non-inferiority was demonstrated for lung function.
- MF versus FP (one RCT): at accepted levels of dose equivalence there were no significant differences between the comparators. At a 1:2 dose ratio (MF, FP) there were statistically significant differences in favour of FP on lung function measures and nocturnal awakenings.

No trials were identified that directly compared either BDP with MF or BDP with CIC.

High-dose ICS versus ICS

Twenty-four trials that compared ICS with ICS at high doses (800–2000 μg BDP/day or equivalent) were included. As with low-dose ICS versus ICS, there were few differences between the ICS where statistical tests had been reported. Again, some of the trials had assessed non-inferiority between the comparators. A summary of results is given below:

- BDP versus BUD (two RCTs): there were no statistically significant differences between the comparators on measures of lung function. The only statistically significant difference was for the number of exacerbations in favour of BUD.
- FP versus BDP (10 RCTs): in seven trials there were no statistically significant differences between the comparators on any of the outcome measures assessed. One trial showed significant differences in favour of FP for lung function measures and the number of exacerbations. No significant differences were observed for symptom measures. Treatment with FP was favoured in one trial for the outcome of HRQoL, whereas symptom scores were significantly lower with BDP treatment in another. There were no further significant differences, however, on any other outcome measure assessed. Across the 10 trials adverse event rates were comparable.
- HFA BDP versus HFA FP (one RCT): no statistically significant differences on measures of lung function and symptoms were shown. Non-inferiority was demonstrated for lung function measures in an intention-to-treat analysis, but not in a per-protocol analysis.
- FP versus BUD (six RCTs): there was a treatment benefit in favour of FP on some measures of lung function in two trials. Four trials showed no statistically significant differences between the comparators across a range of different outcomes. A meta-analysis of three trials showed no significant differences in the number of adverse events.
- MF versus BUD (one RCT): a treatment benefit in favour of MF on a measure of FEV_1 was

observed. There were no further significant differences between the comparators.
- CIC versus FP (three RCTs): data are commercial in confidence.
- MF versus FP (one RCT): there were no statistically significant differences on any outcome measure between the two comparators.

No trials were identified that directly compared either BDP with either MF or CIC, BUD with CIC or MF with CIC.

ICS versus ICS/LABA

Ten RCTs evaluated the effectiveness of combination ICS/LABA therapy (FP/SAL or BUD/FF) versus a higher dose of ICS alone. Half of the trials used the FP/SAL combination inhaler and the other half used the BUD/FF combination inhaler. ICS doses, when used in combination with LABAs, varied from 200 to 800 µg/day for BUD and from 200 to 500 µg/day for FP. When used alone the ICS doses varied from 400 to 1600 µg/day for BUD and from 500 to 1000 µg/day for FP. Overall, the ICS dose when used alone was at approximately double the accepted clinically equivalent dose that was used in the combination with the LABA.

The general findings indicated a significant treatment benefit for combination therapy across a range of outcomes compared with ICS alone, when the ICS was double the accepted clinically equivalent dose of the ICS in the combination inhaler. This applied to both of the combination inhalers. However, it should be highlighted that these findings are only applicable to DPIs.

An additional nine trials assessed the effects of adding a LABA to a similar dose of ICS in each of the trial arms. Six evaluated the FP/SAL combination and three the BUD/FF combination. In all the trials a similar ICS dose was used in both 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 were assessed in three and two RCTs, respectively. An additional trial compared the FP/SAL combination inhaler against BUD + FF in separate inhalers. The ICS doses were similar in both treatment modalities, and ranged from 200 to 1000 µg/day for FP and 800 µg for BUD. There were very few statistically significant differences between the treatments across the various efficacy outcomes and the rate of adverse events. Non-inferiority was demonstrated for some outcomes. 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. Daily ICS doses were 800 µg for BUD and 500 µg for FP. All were delivered via a DPI rather than a pMDI. The results were mixed, with the FP/SAL combination significantly superior on some outcomes and the BUD/FF combination superior on others. Meta-analysis showed that there were no significant differences between the two treatments in the rate of adverse events.

Economic analyses

Low-dose ICS versus ICS

At doses of 400 µg/day, BDP–CFC-propelled devices appear to be the current cheapest ICS, and remain so but at a higher annual cost if CFC-propelled products are excluded from the analysis. Excluding CFC-propelled products at this dose level diminishes the overall cost differences between the five ICS, with CIC products only marginally more expensive than BDP–CFC-free devices. At this dose FP and MF are consistently the two most expensive drugs, at almost two to three times the annual cost of taking BDP.

At the maximum low dose of 800 µg/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.

High-dose ICS versus ICS

At a dose level of 1500–1600 µg/day, BDP–CFC-propelled products appear to be the current cheapest ICS available, and remain so if CFC-propelled products are excluded from the analysis. Excluding CFC-propelled products and using current prices cause a substantial increase in the weighted mean annual cost of taking BDP at this dose level. On average, BUD (only available as one preparation at this high dose level) is the most expensive ICS drug, whether CFC-containing products are excluded or not.

ICS versus ICS/LABA

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 on 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. The BUD/FF combination varied from being £163 cheaper to £66 more expensive than the higher dose of either BUD or FP.

ICS/LABA versus ICS/LABA

Taking an ICS with a LABA as either of the two currently available combination products, FP/SAL and BUD/FF, is usually cheaper than taking the relevant constituent drugs in separate inhalers. At very high doses of BUD (1600 µg/day), however, the BUD/FF combination inhaler can be up to £156 more expensive than having the same drugs in separate inhalers. In terms of the relative costs associated with taking one of the combination inhalers, at low dose (400 µg BUD or 200 µg FP/day) the cheapest combination inhaler is FP/SAL as a pMDI (Seretide Evohaler). However, this is only slightly cheaper than using BUD/FF as a DPI (Symbicort Turbohaler). At higher dose levels (800 µg BUD or 500 µg FP/day) FP/SAL as either pMDI aerosol (Seretide Evohaler) or a DPI (Seretide Accuhaler) is the cheapest combination product available, but again only slightly cheaper than the DPI BUD/FF combination (Symbicort Turbohaler). It should be highlighted, however, that the three head-to-head trials that compared the effects of FP/SAL with BUD/FF used the FP/SAL DPI combination inhaler, Seretide Accuhaler. The relative effectiveness of the Seretide Evohaler as a pMDI compared with the Symbicort Turbohaler can therefore not be commented on.

Conclusions

The evidence reviewed indicates that there are few 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 and to remain so as the daily ICS dose required increases. The exclusion of CFC-propelled products may increase the mean annual cost of both BDP and BUD, but should have no effect 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 although the use of weighted averages to calculate these costs can provide a useful way of representing the major differences between the drugs, these often conceal the wide variations in the costs 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 than 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 and ICS monotherapy are highly variable and dependent on the dose required and the particular preparations used. For the combination therapies of ICS/LABA there are potential cost savings with the use of combination inhalers compared with separate inhalers, with few differences between the two treatment strategies in terms of effects. The only exception to this cost saving is with BUD/FF at doses higher than 1200 µg/day, where separate inhaler devices can become equivalent to or cheaper than combination inhalers. The evidence regarding the relative effects of the two combination inhalers available is mixed. Neither of the two combination inhalers (FP/SAL or BUD/FF) is consistently superior in terms of treatment effect. A comparison of the costs associated with each combination therapy indicates that at low dose FP/SAL delivered via a pMDI is currently the cheapest combination inhaler. However, this is only marginally cheaper than BUD/FF delivered as a DPI. At higher doses, both the FP/SAL combination inhalers (PMDI and DPI) are marginally cheaper than BUD/FF (DPI).

Recommendations for further research

Future trials of treatment for chronic asthma should standardise the way in which outcome measures are defined and measured, with a greater focus on patient-centred outcomes such as HRQoL and symptoms. There is also a need for longitudinal studies that comprehensively track the care pathways followed when people experience asthma exacerbations of different severity. Further research synthesis, quantifying the adverse effects of the different ICS, is required for treatment choices by patients and clinicians to be fully informed.

Chapter 1
Background

Natural history of asthma

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. Asthma 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]

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 (PEF) and forced expiratory volume in 1 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 PEF 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]

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 British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) Guideline on the Management of Asthma described in more detail in the section 'Asthma management in the UK' (p. 6). 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*

Step	Symptoms/day	Symptoms/night	PEF or FEV_1	PEF variability (%)
STEP 1 Intermittent	<once a week Asymptomatic and normal PEF between exacerbations	<2 times per month	⩾80	<20
STEP 2 Mild persistent	>once per week but <once per day Exacerbations may affect activity	>2 times per month	⩾80	20–30
STEP 3 Moderate persistent	Daily Exacerbations affect activity	>once per 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 1 and 2 of the BTS/SIGN Guideline (*Figure 1*).[3] This is particularly so for people between the ages of 16 and 45 years, with more patients treated at Step 3 in the younger and older populations.

Asthma exacerbations

There is no generally accepted definition of an exacerbation, although it can be regarded as "a sustained worsening of the individual's condition from the stable state and beyond normal day-to-day variations in symptoms, that is acute in onset and necessitates a change in regular medication".[4] Asthma exacerbations are characterised by a progressive increase in shortness of breath, cough, wheeze or chest tightness or a combination of these symptoms, accompanied by a decrease in PEF. Exacerbations can be triggered by a variety of stimuli, including allergens, viral infections, pollutants and drugs. Exacerbations are variable in severity and frequency both between individuals and within the same individual over time, and appropriate treatment will reflect both the severity and the frequency of exacerbations. Minor exacerbations may be treated by the individual using high doses of inhaled short-acting $beta_2$ agonists (SABAs) or an increased dose of inhaled corticosteroid (ICS), although sometimes a short course of systemic corticosteroids or other treatments are also needed.[1] More severe exacerbations, although less common, can potentially be life-threatening, and may require hospitalisation, treatment and monitoring until symptoms have stabilised.

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. The updated 2006 GINA also provides a classification of levels of asthma control that can be used as a basis for ongoing treatment decisions (*Table 2*).

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

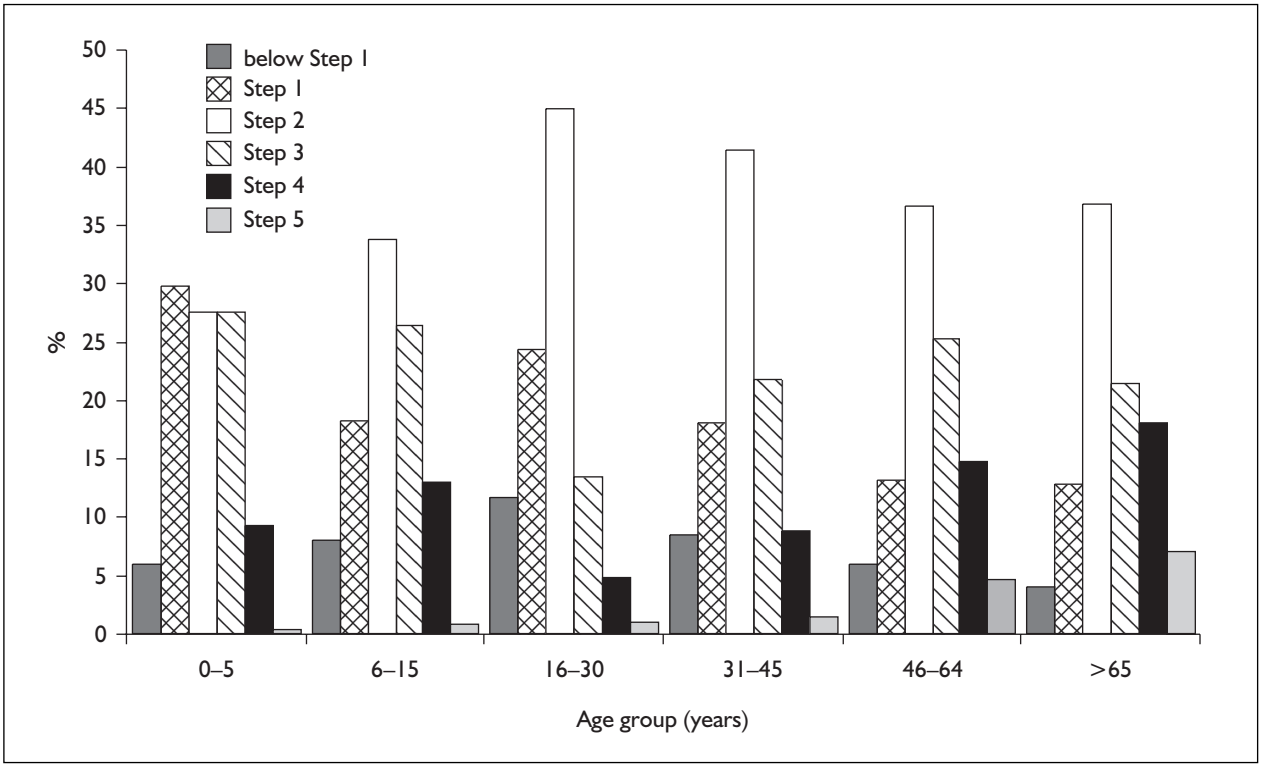

FIGURE 1 *Percentage of individuals at each step of the BTS/SIGN Guideline by age group. From a cross-sectional study performed by Neville and colleagues in 1994–5.*[3]

TABLE 2 *GINA classification of levels of asthma control*

Characteristic	Controlled (all the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less per week)	More than twice per week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue medication	None (twice or less per week)	More than twice per week	
Exacerbations	None	<80% of predicted personal best (if known)	

Source: Global Initiative for Asthma.[5]

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.[6–8] The rate of decline is generally greater in people with asthma than in the general population,[9] possibly as a result of deterioration in potentially reversible disease or the development of persistent obstruction following airway remodelling.[10] 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).

Epidemiology of asthma

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.[11] 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.[12]

The 1998 figures from the General Practice Research Database with a sampling frame of 211 general practices in England and Wales indicated that the prevalence of treated asthma in men aged 15 years and over ranged from 44.5 to 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.[13] As treatment in the UK is strongly influenced by the BTS/SIGN Guidelines (see the section 'Asthma management in the UK', p. 6), it may also be useful to consider asthma prevalence in terms of the treatment steps in the guidelines.

Mortality

Asthma deaths are rare; there were 1266 reported deaths due to asthma in 2004 (*Figure 3*). Most of these (70%) were in people over the age of 65 years; 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: (1) disease severity, (2) medical care factors both prior to and during the fatal episode, (3) health behaviour such as reduced concordance with prescribed medication, poor inhaler technique and reduced contact with primary care services and (4) adverse psychosocial factors. Therefore, a proportion of deaths due to asthma are preventable, especially in those under the age of 65 years.[14–18]

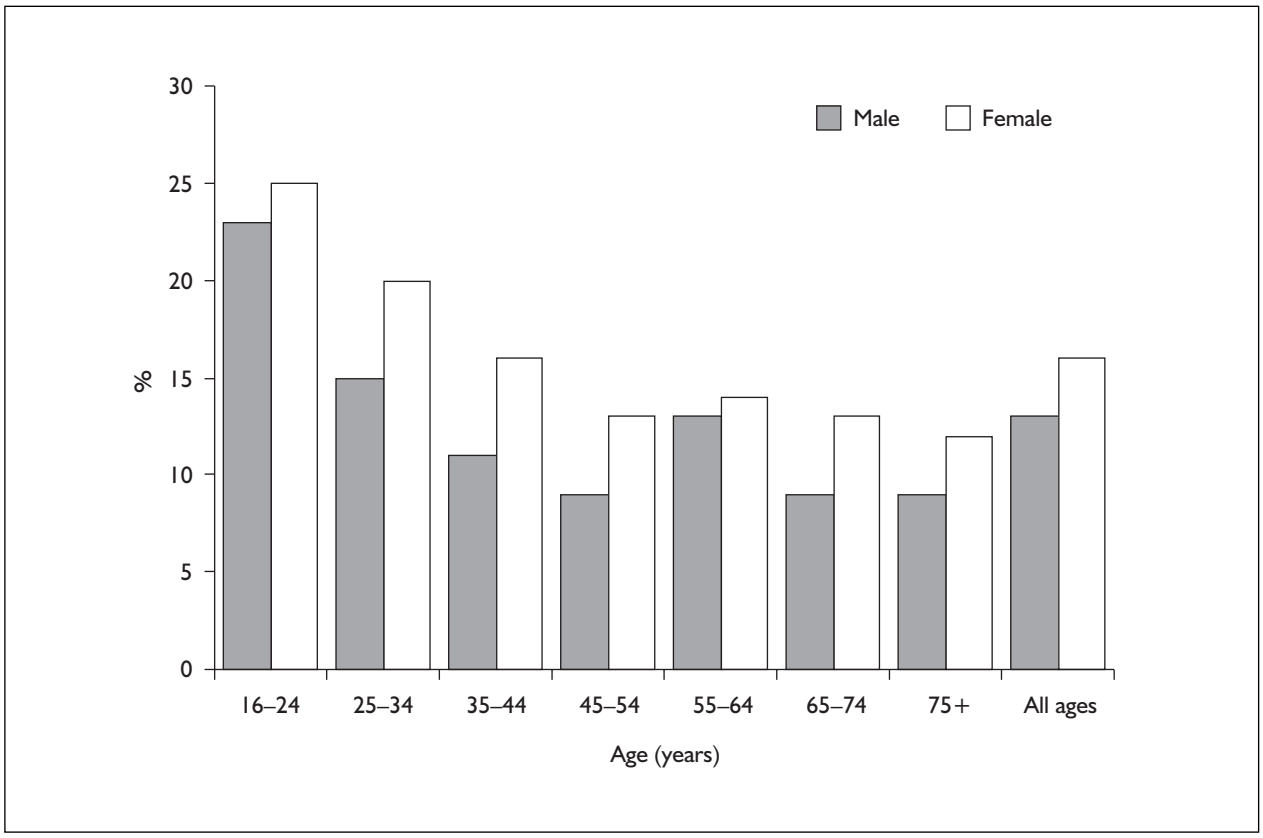

FIGURE 2 *Percentage of men and women with a lifetime doctor-diagnosis of asthma, 2001. Source: Health Survey for England 2001.*[12]

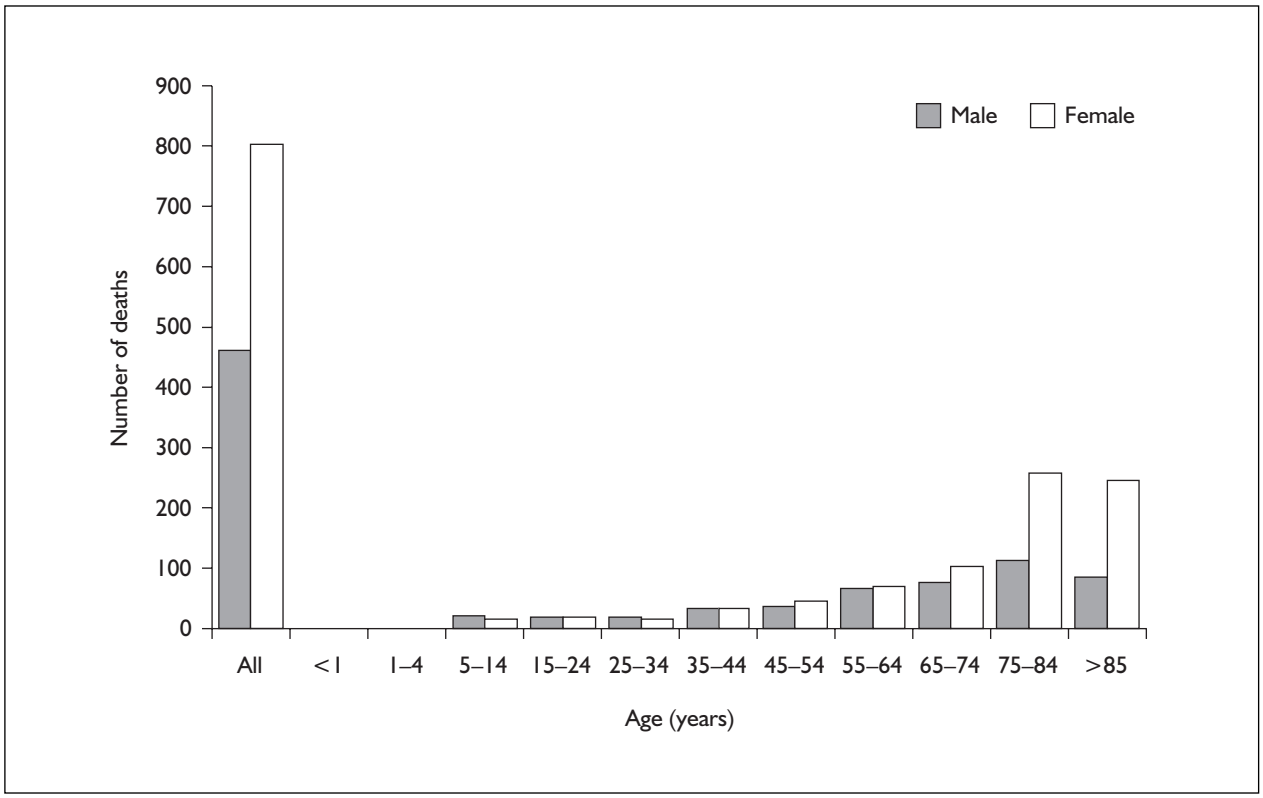

FIGURE 3 *Asthma deaths by age and sex, registrations in 2004. Source: Office of National Statistics.*[19]

Impact of asthma on health-related quality of life

Health-related quality of life (HRQoL) 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 HRQoL measurement is to assess the impact asthma has on a person's daily functioning and emotional well-being.[20] Studies indicate that patients with asthma have impaired HRQoL, and that morbidity as expressed by HRQoL in patients with asthma is substantial.[21]

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 HRQoL. It should not be assumed that meeting clinical treatment goals will necessarily be meaningful to patients, in terms of improvements in HRQoL.[22]

There is 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),[23] the Mini Asthma Quality of Life Questionnaire (Mini AQLQ),[24] the Living With Asthma Questionnaire (LWAQ),[25] the St George's Respiratory Questionnaire (SGRQ)[26] and the Asthma Bother Profile (ABP).[27] The most commonly used instrument in adults is the AQLQ, which was developed by Juniper and colleagues in the early 1990s.[23] 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 seven-point scale (higher score indicates less impairment) based on an individual's recall of their condition over the previous 2 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 HRQoL.[28]

The advantage of using disease-specific measures of HRQoL 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 with 36 Items (SF-36),[29] the Nottingham Health Profile (NHP),[30] the Sickness Impact Profile (SIP)[31] and the EuroQol instrument (EQ-5D),[32] 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 HRQoL.[33,34] Moy and colleagues retrospectively examined data from two completed clinical trials, which included individuals with mild asthma and moderate to severe asthma.[33] Using the AQLQ, they reported that lung function alone was not an independent predictor of HRQoL. Asthma severity, defined by the combination of lung function, symptoms, and reliever medication use, was correlated with HRQoL, although these parameters accounted for less than half of the variation in HRQoL.[33] 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 HRQoL is not fully accounted for by objective measures such as lung function.[34]

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.[35] 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 HRQoL 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, while recognising that individual measures such as lung function may be poor predictors of HRQoL, presented 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.[22] The study suggests that if individuals achieve guideline-based composite control they will achieve larger improvements in HRQoL 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 HRQoL improvements. Nishiyama and colleagues also reported a significant relationship between lung function and HRQoL in individuals with well-controlled asthma.[36] In this study, although correlations between physiological measures and HRQoL were weak to moderate, maintaining PEF above 80% of the predicted value was significantly associated with better HRQoL.

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 Chapter 4.

Current service provision

Asthma management in the UK

As stated previously, the management of asthma in the UK is largely based on the BTS/SIGN Guideline developed by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines 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 and Emergency Medicine using SIGN methodology adapted for UK-wide utilisation. The Guideline recommends strategies for non-pharmacological management of both 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.

At **Step 1** (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 2** (introduction of regular preventer therapy) is indicated if an individual has had exacerbations of asthma in the last 2 years, is using inhaled SABAs three times per week or more or is symptomatic three times per week or more, or waking on one occasion per week. There is no exact threshold at which movement to Step 2 should be considered as it varies between individuals. The recommended preventer therapy at Step 2 is an ICS at a starting dose of 400 µg/day [beclometasone dipropionate (BDP) equivalent; given as 200 µg twice daily]. This dose can then be titrated to the lowest dose at which effective control of asthma is maintained. **Step 3** 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 long-acting beta$_2$ agonist (LABA), although other agents can be used, such as leukotriene receptor antagonists, theophyllines and slow-release beta$_2$ agonist tablets. If asthma control remains suboptimal after the addition of a LABA, the dose of ICS may be increased to 800 µg/day (BDP equivalent) with or without the LABA. If asthma control still remains suboptimal, despite treatment with 800 µg/day of ICS, other agents should be trialled before moving to Step 4. In **Step 4**, if control remains inadequate on 800 µg/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 2000 µg/day, adding in a leukotriene antagonist, adding in a theophylline preparation or adding in a slow-release beta$_2$ agonist tablet. In **Step 5**, 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 go back to Step 4 (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, GPs are encouraged to perform annual reviews on all registered individuals with asthma within their practice.[37] Figures for England for 2004–5 suggest that most practices are achieving the targets for asthma set out within the framework (91% of the total points achievable were awarded).[38]

Discussions with clinicians both locally and nationally suggest that although the Guideline forms the basis of most pharmacological treatment of asthma in the UK, there is some variation from these recommendations in practice.

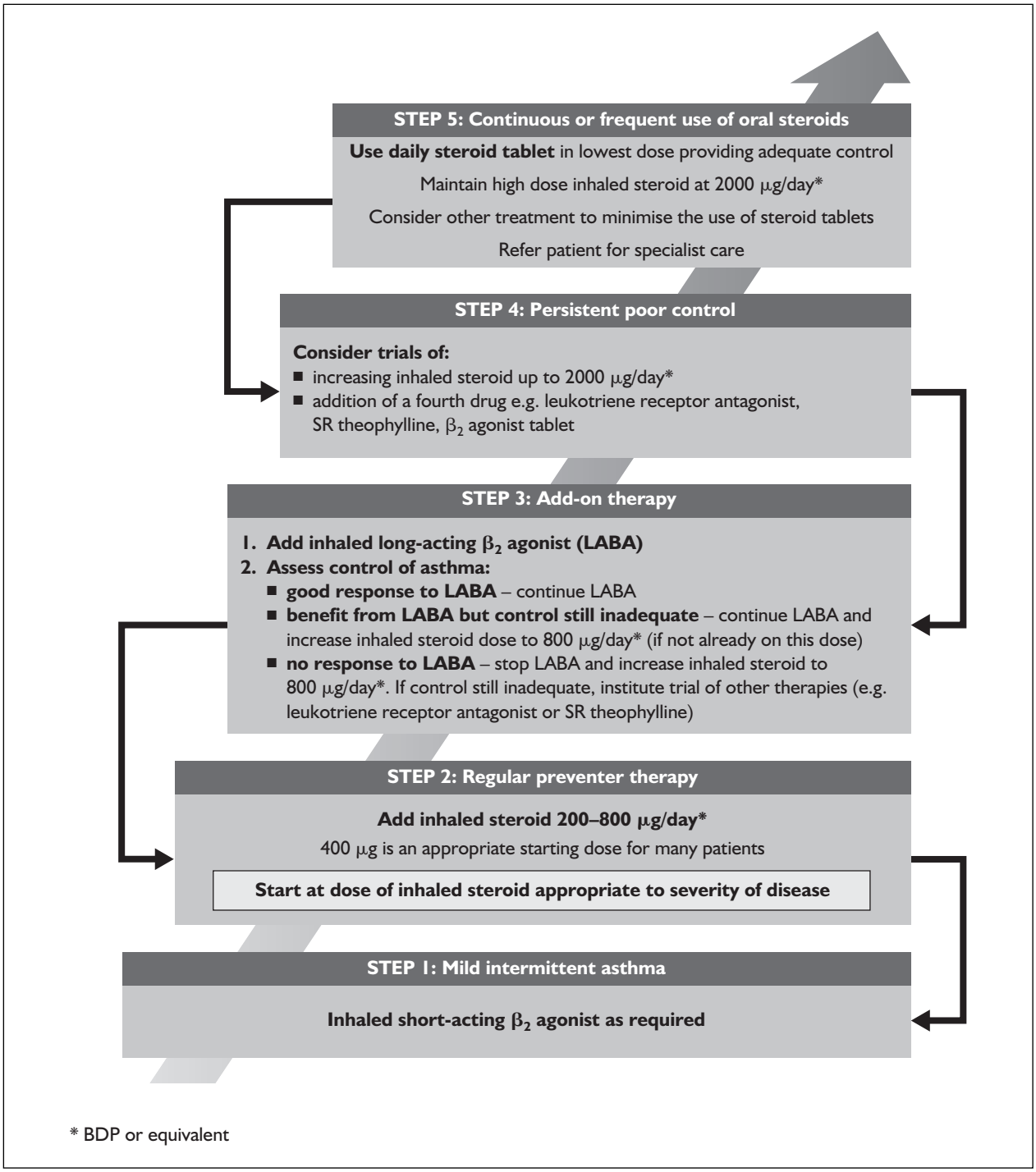

FIGURE 4 *Summary of stepwise asthma management in adults. Source: BTS/SIGN Guideline.*[1]

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 over 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.

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 healthcare resources, days off work or school and improvements in nocturnal asthma symptoms[39] and to protect against death from asthma.[40] 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.[41–43] Plans based on symptom scores and on measurements of PEF have both been found to be effective.[44] 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.[45] Action plans that incorporate an individual's personal experience of their disease are likely to be more successful.[46]

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. Anxiety surrounding the risk of adverse events (AEs) with ICS may also affect concordance. A systematic review conducted in 2000 by Cochrane and colleagues identified 10 studies that reported concordance with ICS measured using electronic devices contained within the inhaler device.[47] All but one of these studies was conducted in adults. Overall, patients took the recommended doses of medication on 20–73% of days. Average concordance, measured as the ratio of doses taken to doses prescribed, ranged from 63% to 92%.[47] Concordance measured in these studies is likely to be better than that seen in the community, since patients were aware that their concordance 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 10-year study period found that only 42% of individuals obtained a repeat prescription for ICS within the expected timeframe of the preceding prescription.[48] 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.[49] Some education programmes have been shown to improve concordance in adults and may also play a role in improving concordance within families.[50]

Description of technology under assessment

ICS

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 metered-dose inhalers (MDIs) with chlorofluorocarbon (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)], dry powder inhalers (DPIs) [Asmabec Clickhaler (Celltech), Becodisks (Allen and 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, AZ)] and non-proprietary formulations [Novolizer (Meda)], DPIs [Pulmicort Turbohaler (AZ)] and hard capsule powder inhalers [BUD Cyclocaps (APS)].
- **Fluticasone propionate (FP)** is available in MDIs with non-CFC propellants [Flixotide Evohaler (Allen and Hanburys)] and in DPIs [Flixotide Accuhaler, Flixotide Diskhaler (Allen and Hanburys)].
- **Ciclesonide (CIC)** is available in MDIs with non-CFC propellants [Alvesco (Altana)].
- **Mometasone furoate (MF)** is available in DPIs [Asmanex Twisthaler (Schering-Plough)].

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.

MDIs 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 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.[51] Use of a spacer device in conjunction with an MDI can also alter patterns of lung deposition[52] and increase the total proportion of actuator dose delivered to the lower airways.

DPIs require less coordination by an individual in order to achieve correct inhaler technique. However, lung deposition is flow dependent, requiring a forceful, deep inhalation to trigger the device correctly. The higher the flow rate, the smaller is the particle size and the better the lung deposition.[53]

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 healthcare 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.

Inhaler technique

The ability to use an inhaler correctly 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 such as 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).[47] Physicians assessed inhaler technique as 'good' in between 5 and 86% of patients. Coordination of MDI activation with onset of inspiration was cited as a particular task which individuals found difficult (17–68% of individuals were unable to do this in this set of studies).[47] In several studies, education greatly improved technique, but the amount of improvement was variable (from 6 to 46% in one study[54]).

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.[55–57] The anti-inflammatory effects may take from 1 to 3 weeks to become apparent[58] 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 on both asthma severity at baseline and the outcome measure used to assess treatment effect.[58,59] Those with severe asthma when ICS treatment is started may take longer to achieve maximal treatment effect than those with mild asthma.[58] The efficacy of ICS therapy for asthma depends on the agent being delivered in the correct dose (see the section 'Concordance', p. 8) to the correct site within the airways (see the previous section). ICS are often referred to by individuals with asthma as 'preventers'.

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 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.[60] The 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 3*).

Two of the currently available ICS (BDP and CIC) are prodrugs, that is, a pharmacologically inactive compound which is activated by esterases found only in the lungs.[60]

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 the next section). 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 3*). 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[61–67] (*Table 3*).

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.[61–67] Only the unbound fraction is pharmacologically active. All currently available ICS are cleared by the liver.

Adverse events

AEs 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 AEs as a result of therapy with ICS. Anecdotally, some clinicians appear to be very aware of the risk of systemic AEs, whereas others are reassured by the low frequency at which they are encountered in practice.

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

- **Dysphonia** is reasonably common in individuals using ICS.[68] Although the exact mechanism of dysphonia is unknown, it is thought to be related to vocal cord inflammation.[69] 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 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 4–13% of adult ICS users and 1% of children.[70,71] Its prevalence is positively correlated with total daily dose and with dosing frequency.[72,73] 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

TABLE 3 *Pharmacodynamic and pharmacokinetic characteristics of currently available ICS*

ICS	RRA	Oral bioavailability (%)	Pulmonary bioavailability (%) (device)	Comments	Ref.
BDP	53	15–20	55–60 (HFA–MDI)		61
17-BMP	1345	26	36 (CFC–MDI)	Active metabolite of BDP	61
BUD	935	11	18 (CFC–MDI)		62,63
FP	1800	<1	17 (DPI) 26 (CFC–MDI) 29 (HFA–MDI)		64,65
CIC	12	<1	–		66
Des-CIC	1200	<1	52 (HFA–MDI)	Active metabolite of CIC	66
MF	2300	<1	11 (DPI)		65,67

17-BMP, 17-BDP monopropionate; CFC–MDI, metered dose inhaler with CFC propellants; Des-CIC, desisobutyryl-ciclesonide; HFA–MDI, metered dose inhaler with HFA propellants; RRA, relative receptor affinity.

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 AEs 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 pretreatment with a bronchodilator, use of a spacer device, use of a slow inhalation technique or a change to a dry powder formulation.[68]

Systemic AEs occur as a result of the amount of drug that reaches systemic circulation by absorption through the lungs or the gastrointestinal system. As previously outlined, this is influenced by the pharmacokinetics of the ICS, the site of deposition and inter-individual characteristics that may influence the risk of systemic AEs. Accurate assessment of systemic AEs associated with ICS use is often confounded by the concomitant use of other steroid preparations, such as oral or nasal ICS.[72,74,75] The most commonly occurring systemic AEs 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.[75–77] In general, studies have indicated that HPA axis suppression is associated with the use of doses exceeding the equivalent of 1500 µg/day of BDP or BUD in adults (the equivalent of 400 µg/day of BDP or BUD in children). The effect appears to be more marked with BDP than with BUD.[78–82] Dose-ranging studies in adults and children indicate that single doses of FP exhibit three-fold greater adrenal suppression than BUD, on a microgram equivalent basis.[83] One RCT compared the effects of FP 1500 µg/day and BUD 1600 µg/day with placebo in both healthy participants and participants with moderately severe asthma over a 7-day duration.[84] 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. The 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.

Cases of adrenal crisis associated with ICS use have also been documented in the literature.[85,86] A survey of the frequency of adrenal crisis associated with ICS use[85] 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 500–2000 µg/day, 30 (91%) 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.[78,79]

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.[78,79]

One of the major concerns of long-term ICS use is the potential for AEs 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 reabsorption, causing secondary hyperparathyroidism. A number of studies have assessed the effects of high-dose ICS use on markers of serum osteoclastin and urinary hydroxyproline.[87,88] These studies have shown mixed results, with some demonstrating decreased bone formation and increased bone reabsorption in a dose-dependent manner,[87,88] whereas others have shown no effects on plasma osteoclastin concentrations at doses of BDP and BUD as high as 2000 µg/day.[89] 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.[90,91] In relation to bone density, there is limited evidence from two studies that high-dose ICS use for a duration of 3 years was associated with an 18% reduction in lumbar spine density[91] and a reduction in both lumbar spine and femoral neck density.[92] 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 876 µg/day over a 6-year period indicated that there was a negative association between cumulative steroid dose and bone mineral density (BMD) at the lumbar spine, femoral neck, Ward's triangle and trochanter, both before and after the adjustment for the effects of age and sex.[93] A doubling of the dose of ICS was associated with a decrease in BMD at the lumbar spine of 0.16 standard deviation (SD) [95% confidence interval (CI) 0.04 to 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 nor 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 BMD 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.[94]

Three further studies conducted in children have shown that doses of BDP and BUD up to 800 µg/day did not affect bone density,[95,96] and the lumbar spine density of children receiving BDP 300–400 µg/day for 6 months was not different from that of the control group.[97] 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**.[98,99] One study showed that skin thickness measured by an ultrasound scan was significantly reduced by 15–19% in patients on BDP 1000–2250 µg/day compared with controls.[98] In addition, the prevalence of bruising was significantly higher at 48% in this patient population compared with 12% in the control population.[98] 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.[99] 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.[99] The presence of skin bruising can be considered a visible marker of the AEs 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.[100] 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.[101,102] 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.[101] 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.[103–105] 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 to 1.9) for posterior subcapsular, 1.5 (95% CI 1.2 to 1.9) for nuclear and 1.1 (95% CI 0.9 to 1.3) for cortical cataracts.[106] The relative prevalence ratio of posterior subcapsular cataracts for a lifetime dose of BDP of >2000 µg/day was 5.5 (95% CI 2.3 to 13.0).[106]

There have also been case reports suggesting that ICS use may be associated with the development of **ocular hypertension or open-angle glaucoma**.[107,108] 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

3 months or more were at a small, significantly increased risk, with an odds ratio (OR) of 1.44 (95% CI 1.10 to 2.06).[109]

LABAs

Products available

There are currently two LABAs licensed for use in adults in England and Wales:

- **Salmeterol** (SAL) is available in MDIs with non-CFC propellants [Serevent (Allen and Hanburys)] and in DPIs [Accuhaler (Allen and Hanburys) and Diskhaler (Allen and 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 (AZ) 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 (AZ)].
- **FP combined with SAL** (FP/SAL) is available in MDIs with non-CFC propellants [Seretide Evohaler (Allen and Hanburys)] and DPIs [Seretide Accuhaler (Allen and Hanburys)].

Mechanism of action of LABAs

LABAs produce sustained bronchodilation (relaxation of the airways), improving airflow in and out of the lungs. In contrast to SABAs (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.

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.[110] 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) for both systemic side-effects seen in healthy volunteers[111,112] and bronchodilator effects seen in people with asthma.[113] 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.[114] FF is more lipophilic than SAL and has a much higher degree of intrinsic agonist activity.[115] In addition to bronchodilator effects, LABAs also provide protection from a number of stimuli causing bronchial hyper-responsiveness, such as methacholine, cold air, exercise, hyperventilation and histamine.[116] Despite some indication of anti-inflammatory activity in laboratory experiments, neither SAL nor FF has been shown to have anti-inflammatory effects in patients with asthma,[117,118] although preliminary evidence suggests that LABAs might have some mild anti-inflammatory effects when given in combination with ICS (see the section 'Combination inhalers', p. 15) as a result of inadvertent potentiation of the effects of the ICS.[119] The main AEs of LABAs relate to their systemic activity (see the next section). Both drugs are relatively well tolerated at recommended doses but their therapeutic window is fairly narrow.[111]

Adverse events

Most AEs 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, AEs such as tachycardia, increase in the QTc interval, hypokalaemia, hyperglycaemia and tremor are minimal in most individuals.[116] 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.[111]

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.[120–125] Although 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.[115] Tolerance to the bronchoprotective effects of LABAs against bronchoconstrictor stimuli such as methacholine challenge or exercise has been demonstrated in clinical studies.[126–129] Although bronchoconstrictor challenges are considered to be a surrogate for conditions during an asthma exacerbation, whether these laboratory-conducted studies are relevant to the everyday 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.[115,130]

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.[131] Two post-marketing surveillance studies have therefore assessed the safety of SAL and salbutamol versus either each other or placebo,[132,133] and the US Food and Drug Administration (FDA) has assessed data from three clinical trials[134,135] submitted in support of the approval of Foradil Aerolizer for marketing in the USA for reports of serious asthma exacerbations.[136]

Salmeterol Nationwide Surveillance study (SNS)

The SNS study conducted in the UK in 1990–1, randomised 25,180 patients with asthma who were considered to require regular bronchodilator treatment.[132] Patients were randomised to receive either SAL 50 µg twice daily (n = 16,787) or salbutamol 200 µg four times daily (n = 8393) 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 AEs was similar in both groups (1.19% versus 1.15%, respectively), but a significantly lower rate of severe, non-fatal asthma-related AEs was observed in the SAL group compared with the salbutamol group (9.9% versus 1.6%, respectively). The incidence of the combined trial end-point 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).[132]

Salmeterol Multicenter Asthma Research Trial (SMART)

SMART was a randomised, placebo-controlled study that compared the effects of adding SAL or placebo to usual asthma therapy.[133] Patients were randomised to receive either SAL 42 µg twice daily via an MDI or placebo twice daily for 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 three) in patients receiving SAL compared with placebo. Further *post hoc* analysis showed that compared with placebo, a higher rate of asthma-related deaths occurred in the SAL group in both white (0.01% versus 0.07%) and African American (0.04% versus 0.31%) patients. 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.[133]

Combined FF trials

Data from three pivotal randomised, placebo-controlled, double-blind trials submitted to the FDA by Novartis Pharmaceuticals in support of the approval of Foradil Aerolizer for marketing in the USA have been assessed for reports of serious asthma exacerbations.[134,135] Two of the trials were conducted in adults and one in a paediatric population. The two 12-week trials that were conducted in adults compared the effects of FF 12 µg twice daily or 24 µg twice daily with either albuterol 180 µg four times daily or placebo. Both the 12 and 24 µg twice daily doses of FF were significantly more beneficial in terms of improvement in the primary end-point of FEV_1 at the 12-week follow-up. Neither of the trials showed a statistically significant benefit for FF 24 µg twice daily compared with FF 12 µg twice daily. However, the rate of serious asthma exacerbations was higher in the FF 24 µg twice daily dose group compared with the groups receiving placebo or albuterol or the group randomised to 12 µg twice daily of FF. In the two 12-week trials in adults/adolescents, nine patients in the FF 24 µg 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 1 year, 11 patients in the FF 24 µg twice daily group had a serious non-fatal asthma exacerbation compared with eight patients in the FF 12 µg 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, no significant excess in mortality or the rate of severe exacerbations is generally observed. However, the majority of these trials were relatively short-term and are usually not powered to detect relatively rare AEs. In contrast, post-marketing surveillance studies have shown mixed results regarding an increased risk of either severe AEs or mortality with LABA use. The results of the SNS[132] indicated that there were fewer severe non-fatal AEs with the use of SAL compared with salbutamol, and there were no significant differences in the mortality rates between the groups. In contrast, the results of SMART[133] showed that there was a significantly higher rate of respiratory and asthma-related deaths in the SAL group compared with the placebo group. No difference in the primary composite outcome was observed between the groups. Likewise, the three trials that assessed the use of FF indicated that there is an excess risk of severe exacerbation associated with higher doses of FF (24 µg twice daily,) compared with either lower doses of FF (12 µg 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.

Combination inhalers

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.[137–139] 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.[140–142]

There are no apparent differences in systemic pharmacodynamics or pharmacokinetics when inhaled FP and SAL are given separately or in combination.[143]

Economic aspects of asthma

The research literature on economic aspects of asthma is large and diverse. Although it is dominated by economic evaluations comparing the cost-effectiveness of alternative treatments for asthma, it also includes 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 (1) give a broad overview of those economic aspects of asthma that have been identified in the research literature, focusing especially on studies conducted in the UK and/or focusing on asthma in adults, and (2) 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 characterise best the decision problem and model structure. It is not, therefore, intended to be totally comprehensive in terms of either the economic issues covered or the research literature included on each issue.

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 and Emergency (A&E) 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 healthcare costs of service use.[144] They sometimes also show the dominant role of people with severe asthma in generating the bulk of asthma-related healthcare costs.

Gupta and colleagues have published the most recent well-conducted cost-of-illness study of asthma in the UK.[145] Overall, they estimated that the cost to the NHS of asthma in 2000 was £754 million, of which 78.8% (£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 healthcare use.[144] Of the NHS 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 *Asthma in Wales today*) suggest that this cost to the NHS has increased to £889 million annually.[146] In a different study, cited in the same Asthma UK report, difficult-to-control asthma was estimated to cost the NHS £680 million per year.

Other data in the study by Gupta and colleagues suggest that, compared with children, adults (aged 15 years and over) contribute proportionately less to both the primary care and secondary care NHS costs (*Table 4*). These data also suggest that among adults there is one hospital admission for asthma for every 13–15 GP consultations (for asthma), whereas among children there is an asthma-related hospital admission for every eight GP consultations.

The Prescriptions Cost Analysis database[147] details the number and cost of all prescriptions dispensed in the community in England. Listing of drug classes (by 317 BNF subparagraphs) 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 angiotensin-converting enzyme inhibitors, antipsychotic 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*).

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 (pMDIs)]. This omission may be particularly important in younger age groups.

Cost to individuals with asthma, their carers and society

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 years and under), pregnant mothers (until 1 year after

TABLE 4 *GP consultations and hospital admissions for asthma in the UK*

Age group (years)	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 2000–1
0–14	46	292
15–44	25	84
45+	21	83

Source: Gupta and colleagues.[145]

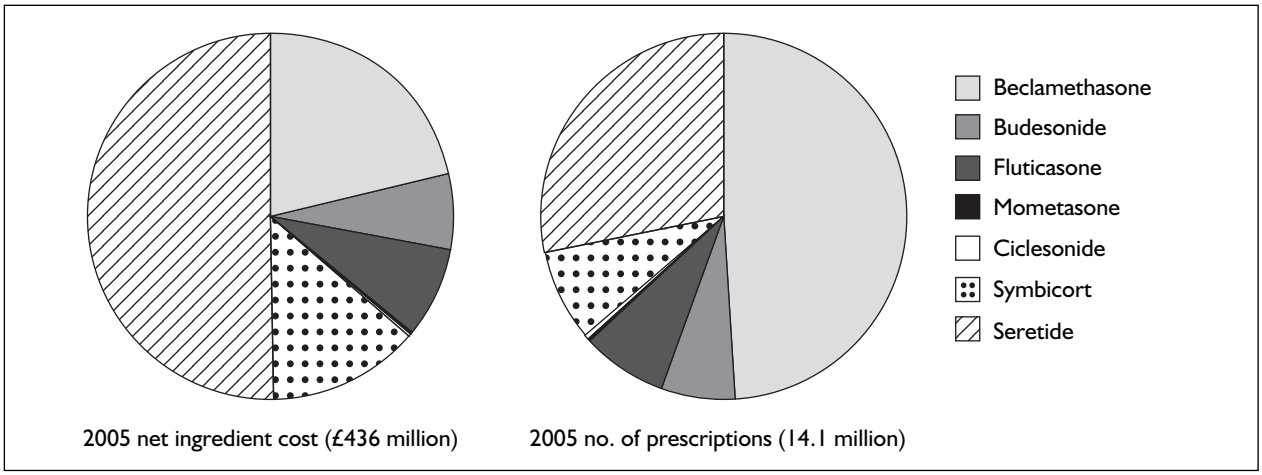

FIGURE 5 *Number and cost of community-dispensed prescriptions for ICS in England 2005. Source: NHS Health and Social Care Information Centre.*[147]

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-dependent diabetes or epilepsy, are exempt from all NHS prescription charges, but asthma is not one of these exempt conditions.[148] Across the UK, approximately 50% of individuals are eligible to pay prescription charges, but only 13% of prescriptions dispensed actually incur a charge.[148]

Patient charges for medicines may also play a part in non-concordance with recommended treatment. Although 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 one-third of these people had long-term conditions.[148] 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 USA, respectively).[149]

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 consumables include nebulisers, inhalers and peak flow meters.[150] 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.[151]

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.[144] 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 or 7 million, corresponding to an estimated 50% and 90%, respectively, of all asthma costs.[152,153]

Other time costs to individuals and carers include healthy time lost (either work or leisure), the time that individuals put into the process of receiving healthcare and the time that carers put into caring for friends and relatives with asthma.[154] 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.

Healthcare 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 healthcare costs seems strong in a range of health systems.[155,156]

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$1336, US$2407 and US$6393, respectively.[157] 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 2633 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%.[158] Since asthma exacerbations are known to be a key driver of asthma-related healthcare costs (see below), this can be regarded as further evidence of a relationship between asthma severity and costs. However, a US-based study of 2378 people with severe and difficult-to-treat asthma found no association between FEV_1 and the level of healthcare use.[159]

Healthcare resource use and level of symptom control

Although much asthma medication is prescribed as prophylactic therapy, and some asthma-related healthcare 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.[150]

Vollmer and colleagues, in a prospective US-based study, found that those with three or four control problems experienced rates of acute care episodes that were 3.5 times higher (95% CI: 2.9 to 4.3) than those for people with no reported control problems at the beginning of the study year.[160] Interestingly, they also noted that poor asthma control predicted higher levels of both acute and routine healthcare 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.

Exacerbations and healthcare 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 healthcare consultations. They are also the likely cause of the more expensive types of asthma-related healthcare 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 1 year, those who experienced an attack incurred over three times as much healthcare cost as those who did not (£381 versus £108; 1997 NHS costs).[161] Further breakdown of these costs showed that most of this difference was due to hospital stays (£169 versus £7, over the year) and medication costs (£129 versus £75). *Figure 6* shows how the proportion of people with asthma admitted to hospital in each age group is broadly related to the proportion experiencing asthma attacks.

A recent international comparative study 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.[162] Overall, a negative relationship was found between falling admissions and increased use of respiratory drugs in nine 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

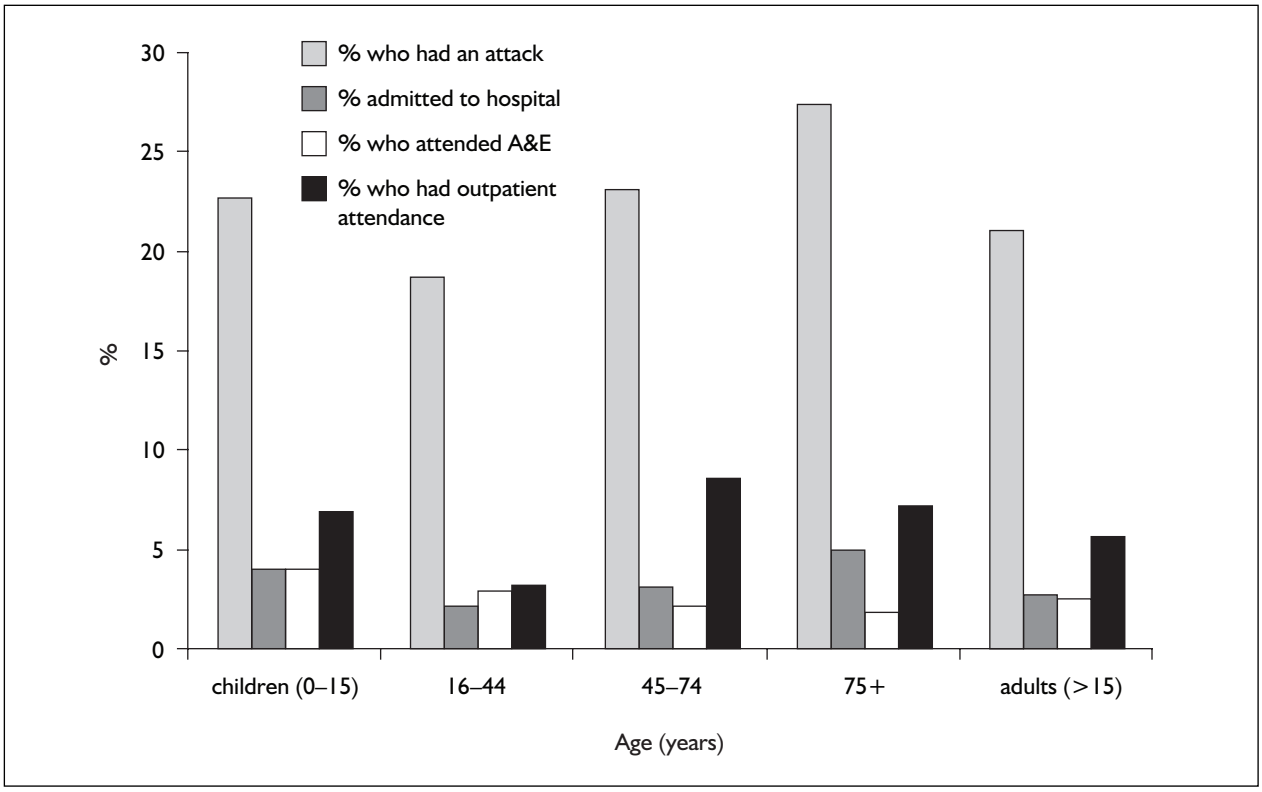

FIGURE 6 *Annual incidence of asthma attacks and usage of secondary care in the UK, by age group. Source: Hoskins and colleagues.*[161]

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.[163]

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, A&E departments), or provide emergency care and advice in their own right. It is 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.

Healthcare 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)[164,165]
- age of adults (with older age groups incurring higher costs)[165]
- 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 versus GPs, availability and use of telephone advice lines)[165,166]
- HRQoL.[160,165,167]

Summary points of the economic impact of asthma

- Asthma has considerable economic impacts beyond the resources used in providing healthcare. These impacts comprise lost days of work by asthma sufferers and their families, and lost days of school among children.
- Of the costs incurred for providing healthcare 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 healthcare resources than the separate effects added). People with difficult-to-control asthma may be another subgroup which generate more healthcare costs, but they have been less studied.
- Although 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 10 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 healthcare, and perhaps also altered the balance of self-care and formal care. In addition, the cost and cost-effectiveness of allergen avoidance strategies to reduce asthma symptoms have not been studied.
- There are some dynamic inter-relationships 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 healthcare 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.

Chapter 2
Decision problems

Aims and objectives

Assessment aim

The 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

The objectives were as follows:

- 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.

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 the device on the dose of corticosteroid delivered to the airways and, by extension, the effect of the 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 Guideline[1] is the context in which the decision problem is set, outlined in the section 'Asthma management in the UK' (p. 6). Using the steps in the Guideline, the following specific research questions were identified:

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

The relevant population for which this intervention should be considered is asthmatics who have been treated at Step 1 or Step 2 of the Guideline [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 (800–2000 µg BDP/day or equivalent), which is the most clinically and cost-effective of the five ICS? (Step 4 of the Guideline)

The relevant population for which this intervention should be considered is asthmatics who have been treated at Steps 2–3 of the Guideline (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 into 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 Guideline)
(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 Guideline)

The relevant population for which this intervention should be considered is asthmatics who have been treated at Step 2 of the Guideline (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 Guideline 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. Although this treatment strategy is not in line with that advocated in the BTS/SIGN Guideline, 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:

(a) FP and SAL in a combination inhaler or given in separate inhalers?
(b) 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 Guideline)

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

Within the context of the BTS/SIGN Guideline, it is generally accepted that the following are clinically equivalent doses: BDP 400 µg, BUD 400 µg, FP 200 µg, CIC 200 µg and MF 200 µg. Studies which compare these drugs at these drug ratios, delivered through the same device, are therefore 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, PEF)
- symptoms [e.g. nocturnal waking, morning cough, symptom-free days (SFDs) and symptom-free nights (SFNs), 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)
- AEs
- HRQoL
- mortality.

Although there is some evidence of the minimally perceived change in PEF 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.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

A peer-reviewed protocol was published in May 2006 on the website of the National Institute for Health and Clinical Excellence (NICE) and circulated among the consultees, outlining the agreed scope and methodology for this assessment.[168] This was based on the scope of the appraisal as published by NICE.[169]

The scope proposed that the assessment be conducted within the context of the stepwise approach as advocated by the BTS/SIGN Guideline on the management of chronic asthma.[1] As far as possible, the contents of this Guideline 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 that 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,[56,170–173] although in places their aims and inclusion criteria vary from those of the current assessment. Where possible, we have adopted the rigorous methods employed in those reviews, and added to the data presented in them.

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, DARE, the Health Technology Assessment (HTA) Database and Cochrane Database of Systematic Reviews were conducted to identify systematic reviews of the long-term AEs associated with either ICS use alone or in combination with a LABA. For the full search strategy and search dates, see 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 prespecified inclusion and exclusion criteria (see the next section).

Inclusion and exclusion criteria

The inclusion and exclusion criteria were specified *a priori* based on the scope issued by NICE,[169] as agreed in the published protocol.[168]

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, but those using nebulisers were excluded.

To be included, the treatment had to last for longer than 4 weeks.

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,[174] BDP[175] and FP[176] 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 versus pMDI or HFA pMDI versus CFC pMDI). The role of delivery device has been assessed by a published systematic review.[177,178] 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.
- Trials reporting comparisons between ICS and placebo were sought and included in order potentially to support economic modelling (e.g. model parameters). Details of these studies are not reported in the assessment of clinical effectiveness.

Types of studies

- Fully published RCTs or systematic reviews of RCTs were considered. Double blinding was not a prerequisite for inclusion, although blinding was assessed as part of critical appraisal (see the section 'Critical appraisal strategy', p. 25). 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. Bibliographic details are listed in Appendix 6. (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.

Population

- Adults and children aged 12 years and over diagnosed with chronic asthma were included. Studies in which the patient group were asthmatics with a specific related co-morbidity (e.g. bronchitis or 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 included only 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 Guideline (see the section 'Asthma management in the UK', p. 6).

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, PEF)
- symptoms (e.g. SFDs and SFNs)
- incidence of mild and severe acute exacerbations (e.g. mild – requiring unscheduled contact with healthcare professional; severe – requiring hospitalisation, systemic corticosteroids or visit to A&E department)
- use of systemic corticosteroids (e.g. prednisolone)
- AEs of treatment
- HRQoL
- mortality.

A list of specific measures for each of these outcomes was devised for the data analysis (see the section 'Narrative synthesis', p. 26).

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 the section 'Methods of data synthesis', next column) to allow efficient retrieval of subsets 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 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.[56,170–173] 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.

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.[56,170–173]

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)[179] (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.[56,170–173]

Methods of data synthesis

Results of the included trials were synthesised narratively (see the next section) with use of meta-analyses where possible and where appropriate (see the section 'Meta-analysis', p. 26). A framework was devised for the analysis and presentation of results, based on the stepwise approach recommended in the BTS/SIGN Guideline for the management of asthma.[1]

The review questions were as follows:

1. Which ICS is the most effective at low doses [200–800 µg/day BDP/BUD equivalent (for FP, CIC and MF, the equivalent doses are 100–400 µg per day)]? (Step 2 of the Guideline)
2. Which ICS is the most effective at high doses (800–2000 µg/day BDP/BUD equivalent (for FP, CIC and MF, high dose is greater than 400 µg per day)]? (Step 4 of the Guideline)
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 Guideline)
   (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 Guideline)
4. Which is the more clinically effective treatment:
   (a) FP and SAL in a combination inhaler or given in separate inhalers?
   (b) 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 Guideline)

Each included trial was coded according to which of the review questions it was relevant. For example, a trial comparing 200 µg/day of BDP with 200 µg/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 400 µg/day of BUD compared with 500 µg/day of FP, the FP arm falls into the high-dose category by an additional 100 µg. 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-analysis.[180] 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 with BUD or BDP.[170] 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 review question, pair-wise comparison, study design and dose ratio. For example:

1. review question1 – low-dose ICS
   (a) pair-wise comparison: FP versus BDP
      (i) parallel-group trial 1:1 ratio
      (ii) parallel-group trial 1:2 ratio
      (iii) cross-over trial 1:1 ratio
      (iv) cross-over trial 1:2 ratio.

It was expected 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 Guideline[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.

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. 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). Further details of the remaining studies are available in the relevant Cochrane reviews.[56,170–173] 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 report only the following measures:

- lung function – FEV_1 (litres); FEV % predicted; morning/evening PEF (litres per minute)
- symptoms – days/nights without symptoms; symptom scores (total daytime; night-time; daily)
- HRQoL – total HRQoL scores
- use of rescue medication – mean number of puffs per day of SABA
- exacerbations – rate of mild or severe exacerbations (where the authors' definition of exacerbations is not covered by one of our existing outcomes)
- AEs – rate of AEs; rate of serious AEs; rate of withdrawals due to AEs; urinary/serum cortisol; BMD; growth.

Meta-analysis

The feasibility and appropriateness of meta-analysis were considered once narrative syntheses had been completed. The decision to pool was mediated by the likelihood that the trials were clinically homogeneous 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. 800–2000 μg/day). It could also be argued that dose is a proxy for severity, with less severe asthma patients 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. Although trials lasting around 3 months are common, some are designed to evaluate longer term effects on asthma control and AEs. 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 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 the section 'Data extraction strategy', p. 25).

For continuous outcome measures (e.g. lung function, symptoms), mean values and SDs were required in order to calculate mean differences. These were entered where available from the trial reports. Where SDs were not reported we converted them from standard errors, *p*-values or CIs provided in the trial reports (where available), using standard equations 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 AEs), 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 advisable as this results in a unit of analysis error.[180] 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.[180] Data were not available to allow within-patient differences to be estimated (e.g. from an appropriate correlation coefficient).

As mentioned, many 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 AEs) were pooled using odds ratios. The 95% CIs were used for all measures of effect. A fixed-effects model was used, with a random-effects model used if statistical heterogeneity was apparent. Statistical heterogeneity was measured using a χ^2 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.[180]

Results

Quantity and quality of research available

A total of 5175 publications were identified through literature searching (*Figure* 7). Of these, 4365 were excluded based 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

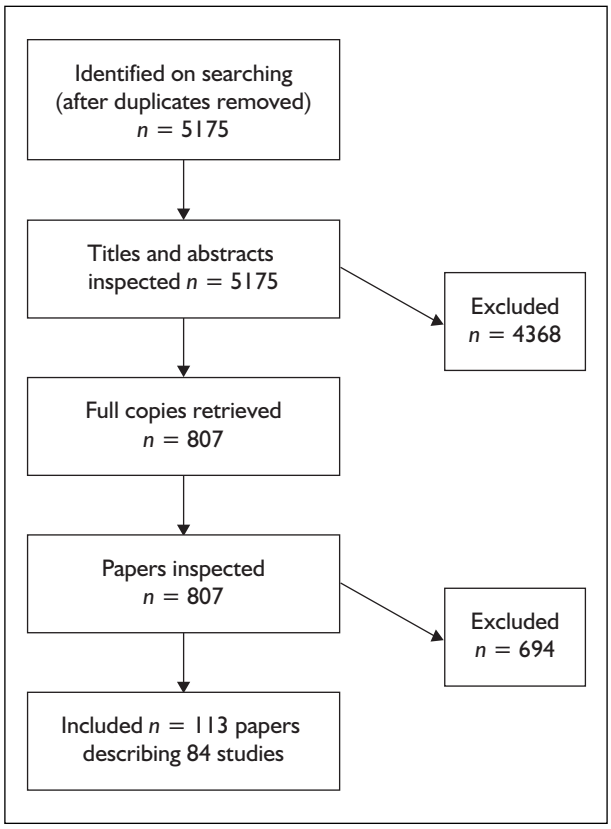

FIGURE 7 *Flowchart of identification of published studies for inclusion in the systematic review of clinical effectiveness*

papers screened were included in that report.[181] Of these, 113 records describing 84 studies were included.

Of the 84 studies:

- 10 were conference abstracts published from 2004 onwards (Appendix 6).
- Seven were systematic reviews (of which five were Cochrane reviews) (see the section 'Related systematic reviews', p. 153).
- 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).

Tables 5–10 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 5 *Breakdown of studies for review question 1 – low-dose ICS*

Pair-wise comparison	No. 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 6 *Breakdown of studies for review question 2 – high-dose ICS*

Pair-wise comparison	No. 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 7 *Breakdown of studies for review question 3a – ICS versus ICS + LABA (ICS dose higher when used alone)*

Pair-wise comparison	No. 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

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

Review question 1 – effectiveness of low-dose ICS

Low-dose corticosteroids are defined as 200–800 µg per day of BDP/BUD or their equivalent (for FP, CIC and MF, the equivalent doses are 100–400 µg/day). This is comparable to Step 2 of the Guideline.

TABLE 8 *Breakdown of studies for review question 3b – ICS versus ICS + LABA (ICS dose similar in both treatments)*

Pair-wise comparison	No. of RCTs included
FP vs FP/SAL	6
BUD vs BUD/FF	3
Total	9

TABLE 9 *Breakdown of studies for review question 4 – combination inhaler versus separate inhalers*

Pair-wise comparison	No. 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 10 *Breakdown of studies for review question 5 – combination inhaler versus combination inhaler*

Pair-wise comparison	No. of RCTs included
FP/SAL (combination) vs BUD/FF (combination)	3
Total	3

To recap, 22 RCTs evaluated low-dose ICS (*Table 11*). The following subsections describe the characteristics and results of these trials.

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

Study characteristics

Five RCTs evaluated the effectiveness of BUD compared with BDP, published between 1985 and 2004 (*Table 12*). Two were parallel designs[182,183] and the other three were cross-over studies.[184–186] 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[184] compared a daily dose of 800 µg/day of BDP with two different regimens of BUD. The total daily dose in both BUD regimens was 800 µg per day, but one group took two puffs daily whereas 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

TABLE 11 *Breakdown of studies for review question 1 – low-dose ICS*

Pair-wise comparison	No. 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

400 µg/day[185] and four were comparisons of a total daily dose of 800 µg/day.[182–184,186]

The five studies used the same delivery device for both inhaled steroids. Rafferty and colleagues[184] (BDP – brand not specified, GSK; BUD – Pulmicort, AZ), Dal Negro and colleagues[182] (BDP – Pulvinal, Chiesi Famaceutici; BUD – Pulmicort Turbuhaler, AZ), Tjwa[185] (BDP – Becotide Rotacap Rotahaler, GSK; BUD – Pulmicort Trubuhaler, AZ) and Jäger and colleagues[186] (BDP – Beclomet Easyhaler, Ranbaxy; BUD – Pulmicort Turbuhaler, AZ) all used DPIs for delivery. Parakh and colleagues[183] used MDIs but did not provide any further details of the devices.

In terms of treatment duration, the trials were relatively similar in length, ranging from 8 to 12 weeks. Three trials lasted for 8 weeks[182,185,186] and one for 12 weeks.[183] In the final study, the length of treatment was described as 'variable'.[184] 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 1 mg until treatment with this drug was withdrawn or asthmatic symptoms 'broke through', or when prednisolone was withdrawn. This 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 40–50 years[182,186] and one trial simply recorded that patients were aged 18 years or over.[185] One of the trials included patients described as having 'mild to moderate' asthma,[186] one study included patients with severe asthma taking oral

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

Study	Design	Intervention	Patients	Outcomes
Dal Negro *et al.*, 1999[182]	RCT Parallel-group	1. BDP 200 μg q.d.s. (daily total 800 μg) 2. BUD 200 μg q.d.s. (daily total 800 μg) *Delivery device:* 1. DPI (Pulvinal, Chiesi Farmaceutici) 2. DPI (Turbuhaler, AZ) *Duration:* 8 wks *Run-in period:* 2 wks	*Number randomised* 32 *Mean age (years)* 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 1000 μg for previous 8 wks	FEV_1 PEF $FEF_{25–75\%}$ MEF_{50} Symptom scores Daily rescue medication use AEs
Parakh *et al.*, 2004[183]	RCT Parallel-group Single-blind	1. FP 50 μg 4 puffs b.d. (daily total 400 μg) 2. BUD 200 μg 2 puffs b.d. (daily total 800 μg) 3. BDP 200 μg 2 puffs b.d. (daily total 800 μg) *Delivery device:* MDI (no further details on 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	Symptom scores FVC FEV_1 FEV_1/FVC PEF Withdrawals
Jäger *et al.*, 2000[186]	RCT Multi-centre Cross-over Open-label	1. BDP 400 μg b.d. (daily total 800 μg) 2. BUD 400 μg b.d. (daily total 800 μg) *Delivery device:* 1. DPI (Beclomet Easyhaler, Ranbaxy) 2. DPI (Pulmicort Turbuhaler, AZ) *Duration:* 8 wks *Run-in period:* 2 wks before randomisation	*Number randomised* 79 *Mean age (years)* 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* Morning PEF *Secondary outcome* FEV_1 (litres) Evening PEF FVC Diurnal variation in PEF Asthma symptom scores day and night Patient-rated treatment efficacy scores Patient-rated acceptability of device Salbutamol inhalations per day Serum cortisol levels AEs

continued

TABLE 12 *Characteristics of studies (BDP and BUD) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Rafferty *et al.*, 1985[184]	RCT Cross-over Double-blind	1. BDP 200 μg 1 puff q.d.s. (daily total 800 μg) + placebo 2. BUD 200 μg 2 puffs b.d. (daily total 800 μg) + placebo 3. BUD 200 μg 4 puffs q.d. (daily total 800 μg) + placebo *Delivery device:* 1. CFC–pMDI (GSK[a]) 2. + 3. CFC–pMDI + Inhalet spacer (Pulmicort, AZ[a]) *Duration:* Variable *Run-in period:* Not reported	*Number randomised* 40 *Age range (years)* 23–72 *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* 5 mg oral prednisolone/day and inhaled BDP 400 μg daily for at least 9 months	Reduction in daily prednisolone (mg/day)
Tjwa, 1995[185]	RCT Cross-over	1. BDP 200 μg 1 actuation b.d. (daily total 400 μg) 2. BUD 200 μg 1 actuation b.d. (daily total 400 μg) *Delivery device:* 1. DPI (Becotide Rotacap, Rotahaler, GSK) 2. DPI (Pulmicort Turbuhaler, AZ) *Duration:* 8 wks *Run-in period:* Not reported	*Number randomised* 16 *Age (years)* >18 *Baseline FEV_1 % predicted* 40–85 *Previous ICS treatment (drug and dose)* Inhaled steroid 150–800 μg/day	FEV_1 FVC Morning PEF Evening PEF 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)

b.d., twice daily; FVC, forced vital capacity; MEF, maximal expiratory flow; PC20, the provocative concentration of methacholine to induce a 20% decline in FEV_1; q.d., once daily; q.d.s., four times daily; wk, week.

[a] Not stated explicitly, but deduced from the text.

corticosteroids[184] and another study included patients with 'moderately severe' asthma.[185] The other two studies did not comment on severity,[182,183] although one reported a baseline FEV_1 % predicted of around 70%.[182] 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.[185,186] One of these aimed to test the hypothesis that there would be no statistically significant differences between the two inhalers,[186] 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[184] 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[182] was to compare the two steroids in order to correlate measures of lung function with serum eosinophil cationic protein. Parakh and colleagues[183] 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 the section 'FP and BDP (review Q1 – low-dose ICS)', p. 34, and the comparison between FP and BUD is reported in the section 'FP and BUD (review Q1 – low-dose ICS)', p. 41].

Reported methodological quality was poor. Details of randomisation methods, whether or not this was concealed and whether or not intention-to-treat (ITT) analysis had been performed were lacking. Only one of the two cross-over studies reported a wash-out period.[185] In the other, no details were given on any attempts to eliminate carry-over effects.[184]

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 800 µg/day, reported FEV_1 (litres). In the trial by Parakh and colleagues,[183] there was an increase of 0.51 litres for the BDP group and 0.66 litres for the BUD group between baseline and end-point ($p > 0.05$ at end-point). In the trial by Dal Negro and colleagues,[182] there was an increase of 0.48 litres for BDP and 0.22 litres 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 8* do not confirm this (mean difference 0.55 litres, 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 to 0.82) (*Figure 8*).

Dal Negro and colleagues[182] reported FEV_1 % 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).

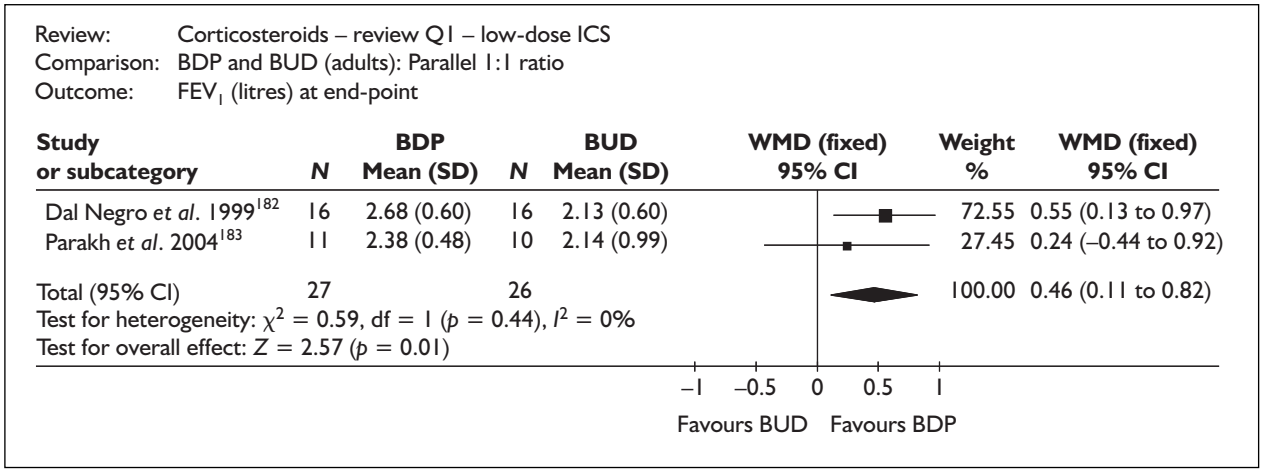

FIGURE 8 *FEV_1 (litres) at end-point (parallel 1:1 dose ratio studies)*

Morning and evening PEF were reported by Dal Negro and colleagues.[182] Data have been estimated from a graph. There was an increase of 70 l/minute for the BDP group and 40 l/minute for the BUD group in morning PEF. The difference at end-point between the groups was not statistically significant (p-value not reported). There was an increase of 65 l/minute for the BDP group and 35 l/minute for the BUD group in evening PEF. 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[186] reported no significant differences between treatments in FEV_1 (litres), and morning/evening PEF.

Tjwa[185] reported 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 PEF during the second month of treatment. The mean between group difference in morning PEF was 17 l/minute (95% CI 2 to 32 l/minute, $p < 0.05$), in favour of BUD. For evening PEF the mean difference was 13 l/minute (95% CI –0.3 to 27 l/minute, $p = 0.054$), in favour of BUD.

Rafferty and colleagues[184] reported that there were no significant differences between treatments for mean morning or evening PEF during the last month of adequate control (no p-values given). For morning PEF, end-point values were 215.7 (SD 110.0) l/minute and 203.7 (SD 107) l/minute for BDP and BUD, respectively. For evening PEF, corresponding values were 238.2 (SD 109.26) and 232.7 (SD 108.3) l/minute.

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[182] 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 with 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[183] 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[186] 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[185] measured symptoms using a scoring system that appears similar to that used by Jäger and colleagues.[186] Scores are presented for individual symptoms, but an overall summary score is not presented.

Rafferty and colleagues[184] reported 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 that 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[182] reported changes in use of salbutamol, which reviewers have estimated from a graph. There was a reduction of 1.6 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.[186] No statistically significant differences in day- or night-time use of SABAs were reported in the study by Tjwa.[185]

Exacerbations

Dal Negro and colleagues[182] 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.[182] Negligible increases in morning serum cortisol were reported in both groups: 0.5 and 1 µg/100 ml in the BDP and BUD groups, respectively. Parakh and colleagues[183] did not report safety as an outcome.

Cross-over 1:1 dose ratio studies. Jäger and colleagues[186] reported three AEs (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[185] and Rafferty and colleagues.[184]

Summary

Five RCTs of varying size and design 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 400 to 800 µg/day. There were few statistically significant differences between the drugs across the outcome measures.

FP and BDP (review Q1 – low-dose ICS)

Study characteristics

Six RCTs, published between 1999 and 2004, evaluated the effectiveness of BDP compared with FP (*Table 13*). 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,[187–189] 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[183] [this study is also referred to in the sections 'BDP and BUD (review Q1 – low-dose ICS)', p. 29 and, 'FP and BUD (review Q1 – low-dose ICS)', p. 41]. The remaining two studies each contained four arms.[190,191] However, in one of these,[191] 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 the section 'FP and BUD (review Q2 – high-dose ICS)', p. 67]. The remaining study[190] can be divided into two separate two-arm comparisons of BDP against FP, each with a dose ratio approximating 1:2 (*Table 13*).

In all six 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 200:400 µg (two studies[187,190]), 250:400 µg (one study[188]), 400:800 µg (three studies[183,190,191]), 500:800 µg (one study[190]) and 750–1500 µg (one study[191]). A study by Szefler and colleagues[189] 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 (100:200 µg in weeks 1–6, 400:800 µg in weeks 6–12 and 800:1600 µg 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 and Beclovent Inhalation Aerosol, all GSK;[190] Szefler and colleagues, FP – Flovent CFC, GSK, and BDP – Vanceril CFD, Schering-Plough;[189] Ige and colleagues, FP – Fluvent, BDP – Becotide, both GSK,[188] no further details of devices were given by Parakh and colleagues[183] or Prasad and colleagues[187]) or an MDI with spacer (no details about devices are reported by Medici and colleagues[191]) (*Table 13*).

The duration of the treatments in most of the studies was relatively short, being 6 weeks (the low-dose comparison of Szefler and colleagues[189]), 8 weeks (by Ige and Sogaolu[188]) or 12 weeks (by Parakh and colleagues,[183] Prasad and colleagues,[187] Raphael and colleagues[190]). An exception is the 12-month study by Medici and colleagues.[191]

The age of patients included in the RCTs ranged from 12 to 83 years. The mean age was reported in five of the studies, and ranged between 28 and 40 years. Two studies mentioned that baseline asthma severity was mild to moderate.[188,191] The severity of asthma was not mentioned in the remaining studies, but in two of the studies it can be inferred from the reported baseline percentage of predicted FEV_1 as being moderate[189] or moderate to severe.[190]

In four of the studies the primary aim was to compare the efficacy of FP against that of BDP[183,187,188,190] 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,[189] p. 411), with the objective of comparing the relative beneficial and systematic effects for two ICS in a dose–response relationship. The remaining study[191] aimed primarily to investigate effects of FP and BDP on bone mass and metabolism. None of the efficacy studies specified

TABLE 13 *Characteristics of studies (FP and BDP)*

Study	Design	Intervention	Patients	Outcomes
Parakh *et al.*, 2004[183]	RCT Parallel-group Single-blind	*Drug(s):* 1. FP 50 μg 4 puffs b.d. (daily total 400 μg) 2. BUD 200 μg 2 puffs b.d. (daily total 800 μg) 3. BDP 200 μg 2 puffs b.d. (daily total 800 μg) *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	Symptoms FEV_1 PEF FVC Withdrawals
Prasad *et al.*, 2004[187]	RCT Parallel-group Double-blind	*Drug(s):* 1. FP 50 μg 2 puffs b.d. (daily total 200 μg) 2. BDP 100 μg 2 puffs b.d. (daily total 400 μg) *Delivery device:* 1, 2. MDI (no further details about devices reported) *Duration:* 12 wks *Run-in period:* Not reported	*Number randomised* 74 *Mean age (years) (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	FEV_1 PEF FEV_1/FVC Symptoms
Raphael *et al.*, 1999[190]	RCT Multi-centre Parallel-group Double-blind	*Drug(s):* 1. FP 44 μg 2 puffs b.d. (daily total 200 μg *ex* valve) 2. FP 110 μg 2 puffs b.d. (daily total 500 μg *ex* valve) 3. BDP 42 μg 4 puffs b.d. (daily total 400 μg *ex* valve) 4. BDP 42 μg 8 puffs b.d. (daily total 800 μg *ex* valve) *Delivery device:* 1, 2. MDI (Flovent Inhalation Aerosol, GSK) 3. MDI (Inhalation Aerosol, GSK) 4. MDI (Beclovent Inhalation Aerosol, GSK) *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 399 *Mean age (years) (± 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 1 month prior to enrolment	FEV_1 $FEF_{25–75\%}$ FVC Morning and evening PEF SABA use Daily asthma symptom score % days with no rescue SABA use % days with no symptoms Asthma exacerbations AEs

continued

TABLE 13 *Characteristics of studies (FP and BDP) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Szefler *et al.*, 2002[189]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP serially increased doses: 88 → 704 μg q.d. (daily total 100 → 800 μg *ex* valve) 2. BDP serially increased doses: 168 → 1344 μg q.d. (daily total 200 → 1600 μg *ex* valve) *Delivery device:* 1. MDI + spacer (Flovent CFC, GSK) 2. MDI + spacer (Vanceril CFC, Schering-Plough) *Duration:* 21 wks (dose escalation every 6 wks) *Run-in period:* 3 wks	*Number randomised* 30 *Mean age (years) (± 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	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
Ige and Sogaolu, 2002[188]	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, GSK[a]) 2. pMDI (Becotide, GSK) *Duration:* 8 wks *Run-in period:* 1 wk	*Number randomised* 20 *Mean age (years) (± 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	FEV_1 PEF Symptoms Rescue medication usage

continued

TABLE 13 *Characteristics of studies (FP and BDP) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Medici *et al.*, 2000[191]	RCT Parallel-group Double-blind	*Drug(s):* 1. FP 200 μg b.d. (daily total 400 μg) 2. BDP 400 μg b.d. (daily total 800 μg) 3. FP 375 μg b.d. (daily total 750 μg) 4. BDP 750 μg b.d. (daily total 1500 μg) 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 months *Run-in period:* 4 wks	*Number randomised* 69 *Mean age (years) (± 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 PEF: 78.4–97.8 across groups *Previous ICS treatment (drug and dose)* BDP 800 μg q.d. or 1500 μg q.d. depending on the dose of ICS use prior to entry	*Primary outcome* BMD of the distal radius *Secondary outcomes* Cortisol Biochemical markers of bone metabolism Lung function: PEF and FEV_1 AEs

FEF, forced expiratory flow.
[a] Not stated explicitly, but deduced from the text.

a null hypothesis in terms of equivalence or superiority. Reasons for carrying out the efficacy studies included an identified need to compare simultaneously FP, BUD and BDP in the same trial,[183] extending knowledge of effects of FP in Nigeria[188] and India,[187] and a need for simultaneous testing of FP and BDP at a range of doses commonly used to treat asthma.[190]

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

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[189] involved three periods with incrementally increasing doses (6 weeks each of 100:200, 400:800 and 800:1600 µg FP:BDP). However, only the 100:200 µg comparison 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[187]), 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 (100:200 µg,[189] 250:400 µg[188] or 400:800 µg[183]).

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 14*). However, these differences were either not tested statistically[189] or were reported in the primary studies as not statistically significant.[183,188]

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 15*). However, statistical significance cannot be ascertained for the individual comparisons because SDs are reported only for the start (baseline) and end-point in three of comparisons.[183,188,189] In the remaining two comparisons, an overall test of the difference between the drugs was carried out for two dose regimes combined (200:400 µg/day and 500:800 µg/day, FP:BDP)[190] (*Table 15*). For the combined comparison, the difference between drugs was statistically significant ($p = 0.006$).[190]

Change in FEV_1 % predicted. Only one study, by Prasad and colleagues,[187] 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, $p > 0.05$).

TABLE 14 *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 (litres)	Mean ± SD FEV_1 for BDP (litres)	Ref.
100:200	3.40 ± 0.61	3.28 ± 0.68	189
250:400	3.06 ± 0.35	2.10 ± 0.41	188
400:800	2.395 ± 0.771	2.389 ± 0.488	183

TABLE 15 *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 (litres)	Mean ± SD change in FEV_1 for BDP (litres)	Ref.
100:200	0.36 ($n = 15$)	0.27 ($n = 15$)	189
200:400	0.31 ± 0.50 ($n = 99$)	0.18 ± 0.41 ($n = 104$)	190
250:400	0.85 ($n = 10$)	–0.13 ($n = 10$)	188
400:800	0.53 ($n = 11$)	0.52 ($n = 11$)	183
500:800	0.36 ± 0.50 ($n = 101$)	0.21 ± 0.49 ($n = 95$)	190

Change in morning PEF. Only one study, by Raphael and colleagues,[190] quantitatively reported the change in morning PEF from baseline to end-point. As mentioned above, Raphael and colleagues[190] compared the effects of two doses each of FP and BDP in a two-arm study (200:400 and 500:800 µg/day FP:BDP). The mean ± SD of the change in morning PEF for these dose regimens were, respectively, 15.8 ± 50.0:0.7 ± 42.0 and 22.8 ± 42.2:7.2 ± 41.0 l/minute. For both dose regimens the change in morning PEF 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 $p \leqslant 0.001$); a separate analysis of treatment effects for each dose regimen is not reported.

Change in evening PEF. As with the change in morning PEF, the study by Raphael and colleagues[190] was the only one that quantitatively evaluated effects of FP and BDP on the change in evening PEF. The mean ± SD of the change in evening PEF is FP 7.8 ± 44.0:BDP 2.10 ± 47.0 l/minute for the lower dose regimen and FP 14.2 ± 38.0:BDP 9.7 ± 36.0 l/minute for the higher dose regimen. For both dose regimens the change in evening PEF is higher in patients treated with FP. Overall, this difference between treatments (excluding the effects of dose) is significant [analysis of variance (ANOVA) excluding dose as a factor, $p = 0.06$].

Symptoms

Change in percentage of symptom-free days. The change from baseline to end-point in the percentage of symptom-free days was reported quantitatively only by Raphael and colleagues.[190] As with the morning and evening PEF, comparisons are available for two dose regimens of each treatment (the details of these are given above). The mean ± SD change in percentage of 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.[190] In another study with a single-dose regimen, Parakh and colleagues[183] provided baseline and final symptom scores but did not include a relevant estimate of the variance (*Table 16*). In the study by Raphael and colleagues,[190] the decrease in symptom scores was largest for FP-treated patients whereas in the study by Parakh and colleagues,[183] the largest decrease in symptom scores was for BDP-treated patients (*Table 16*). Overall, for both dose regimens combined, the change in symptom scores reported by Raphael and colleagues was statistically significant ($p = 0.024$).[190] However, in the study by Parakh and colleagues, the difference between drugs cannot be tested statistically.[183]

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 (by Raphael and colleagues[190]) or differed between studies (Ige and Sogaolu[188] reported sleep disturbances per month, whereas Prasad and colleagues[187] reported night-time awakening per week).

Raphael and colleagues[190] 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 (200–400 and 500–800 µg/day; details are given above).

Ige and Sogaolu[188] reported that the percentage reduction in the frequency of weekly night-time awakening was significantly higher for FP than

TABLE 16 *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	Ref.
200:400	–0.24 ± 0.70 ($n = 99$)	–0.05 ± 0.61 ($n = 104$)	190
400:800	–30.2 ($n = 11$)	–38.4 ($n = 11$)	183
500:800	–0.26 ± 0.60 ($n = 101$)	–0.15 ± 0.58 ($n = 95$)	190

BDP, although it is not clear to which time periods the statistics presented 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[187] 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,[190] quantitatively reported the change from baseline to the end of the study in the use of rescue medication. As described above, Raphael and colleagues[190] 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,[187] 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[191] 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 800 µg/day treatment required a short course of corticosteroids due to an asthma exacerbation. However, Medici and colleagues[191] 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[189] 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 provided 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 coefficient of variation) are not clearly identifiable.

Raphael and colleagues[190] 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, oedema, muscle pain, fatigue, light-headedness, rash or hoarseness). They also reported that, overall (combining both the relatively low- and high-dose comparisons; details are given above), there were no significant differences between FP and BDP in the incidence of AEs potentially related to the study treatment (range 9–15%, $p = 0.664$).

In the remaining study, Medici and colleagues[191] noted that AEs were reported by a similar number of patients in the FP and BDP groups, with no withdrawals having been due to AEs. The geometric mean of the morning serum cortisol concentration (in nmol/l) estimated by Medici and colleagues[191] 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 BMD (in g/cm^3) and other bone metabolism markers. They reported median changes from baseline in trabecular, integral and compact BMD measurements for both the radius and tibia (i.e. six outcomes). Changes in these six outcomes at either 6 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 BMD of the lumbar spine also did not differ between FP and BDP at 6 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[191] 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 800 µg/day BDP than in patients taking 400 µg/day FP ($p = 0.047$). However, absolute concentrations and percentage changes from baseline suggest that the difference would not be clinically significant.[191]

Summary
Six RCTs of varying size and design 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 changes in morning PEF and evening PEF 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[183] 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 AEs 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.

FP and BUD (review Q1 – low-dose ICS)
Study characteristics
Five parallel group RCTs[183,192–195] evaluated the effectiveness of BUD compared with FP, published between 1994 and 2004 (*Table 17*). Four studies were multi-centre studies where the study sample sizes ranged between 157 and 281 participants, whereas the fifth study was a single-centre study where the sample size was 42.[183] 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[183] also had a third intervention arm of BDP and this arm is therefore not reported here.

One trial[192] stratified patients into two groups to compare BUD and FP (low-dose 400 µg/day, high dose 800 µg/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, AZ). However, 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 200 µg/day of FP with 400 µg/day of BUD (no further details on devices were reported by Langdon and Thompson[194] and only the details for FP – Becodisks Diskhaler, Allen and Hanburys, could be deduced from the paper by Connolly[195]) and two trials compared 400 µg/day of FP with 800 µg/day of BUD[183,193] (no further details were reported about devices in either study).

The devices used in three studies were DPIs (Diskhaler for the FP groups and Turbohaler for BUD),[192,193,195] whereas the devices were MDIs for both intervention groups in the other two trials.[183,194]

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 authors 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. Parakh and colleagues' trial also aimed to compare simultaneously three corticosteroids in an adult Indian population.[183]

The ages of participants in four trials are likely to be similar. Three trials report age ranges of 18–70 years[192,193,195] and one trial reports a mean age of approximately 47 years.[194] The other

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

Study	Design	Intervention	Patients	Outcomes
Basran *et al.*, 1997[192]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP 100 or 200 μg b.d. (daily total 200 or 400 μg) 2. BUD 100 or 200 μg b.d. (daily total 200 or 400 μg) *Delivery device:* 1. DPI Diskhaler (Flixotide, no manufacturer reported[a]) 2. DPI (Pulmicort Turbuhaler, AZ) *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 800 μg	FEV_1 FVC Morning and evening PEF Diurnal variation in PEF Day- and night-time asthma symptom score Day- and night-time SABA use
Langdon and Capsey, 1994[193]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP 200 μg b.d. (daily total 400 μg) 2. BUD 400 μg b.d. (daily total 800 μg) *Delivery device:* 1. DPI Diskhaler (Flixotide, GSK[a]) 2. Reservoir DPI (no further details about device reported) *Duration:* 8 wks *Run-in period:* 2 wks	*Number randomised* 281 *Mean age (range) (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 600 μg	Morning and evening PEF Diurnal variation in PEF 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
Langdon and Thompson, 1994[194]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP 50 μg 2 puffs b.d. (daily total 200 μg) 2. BUD 200 b.d. (daily total 400 μg) *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 PEF Morning PEF Evening PEF Daily asthma symptom score Daytime rescue SABA use Night-time rescue SABA use Morning plasma cortisol Patient-assessed degree of asthma control Physician-assessed success of treatment

continued

TABLE 17 *Characteristics of studies (FP and BUD) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Connolly, 1995[195]	RCT Multi-centre Parallel-group Open-label	*Drug(s):* 1. FP 100 μg b.d. (daily total 200 μg) 2. BUD 200 μg b.d. (daily total 400 μg) *Delivery device:* 1. DPI Diskhaler (Becodisk Diskhaler, Allen and Hanburys[a]) 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	Change in morning PEF Change in diurnal variation in PEF % 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
Parakh *et al.*, 2004[183]	RCT Single-centre Parallel-group Single-blind	*Drug(s):* 1. FP 50 μg 4 puffs b.d. (daily total 400 μg) 2. BUD 200 μg 2 puffs b.d. (daily total 800 μg) 3. BDP 200 μg 2 puffs b.d. (daily total 800 μg) *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 PEF FVC Withdrawals

[a] Not stated explicitly, but deduced from the text.

trial[183] 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 trial by Basran and colleagues[192] all patients were already on higher doses of ICS, whereas in the remaining trials some of the patients were steroid-naïve and others were taking ICS. Baseline FEV_1 % predicted was reported in four of the included trials to be either >40 or >50. The fifth trial[183] did not report baseline FEV_1 % predicted.

The quality of the included trials was generally adequate. The method of randomisation was described and appropriate in all trials except that by Parakh and colleagues,[183] which did not report the method used. In two trials the allocation concealment used a central coding of randomisation schedules,[192,194] but in the remainder the method of allocation was unclear. ITT analysis was reported to be undertaken in all but two trials.[183,193] These factors reduce the possibility of selection biases and measurement biases, respectively.

Results

Lung function

Parallel design, 1:1 dose ratio. Basran and colleagues[192] reported values for baseline and end-point FEV_1 (litres) for BUD and FP groups, respectively, but did not present a change value. These values are not presented with an estimate of variance and therefore do not allow change from baseline results to be estimated. They did, 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 PEF (litres per month), Basran and colleagues[192] again only reported 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 PEF ($p = 0.35$ and 0.69, respectively).

Parallel design, 1:2 dose ratio. In the two trials reporting a dose ratio of 1:2 with FP at 200 µg/day and BUD at 400 µg/day, only Langdon and Thompson[194] reported data on FEV_1 (litres). Change from baseline in the FP group was 0.07 (SD 0.34) and in the BUD group 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 PEF to the last 4 weeks of treatment between the FP and BUD groups of the Connolly trial[195] was 39.70 (SD 50.0) for FP versus 26.10 (SD 48.0) for BUD. No statistical significance test was reported. The change from baseline in morning PEF in the FP group versus the BUD group of the Langdon and Thompson[194] 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 PEF 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 400 µg/day and BUD 800 µg/day), Langdon and Capsey,[193] looking at the use of DPI inhalers, reported mean morning PEF values between the two groups but only presented data on the change from baseline morning and evening PEF in a figure. At week eight, the adjusted mean morning PEF in the BUD group was 404.0 and in the FP group was 423.6 (difference 19.6, 95% CI 5.1 to 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 PEF from figures presented in the publication would suggest a change of 23 l/minute for BUD and 35 l/minute for FP at the eighth week ($p < 0.05$). Estimating the change from baseline results for evening PEF from figures presented in the publication would suggest a change of 16 l/minute for BUD and 22 l/minute for FP at the eighth week ($p = 0.057$). No data were reported for mean evening PEF at week eight. Similarly, in the trial by Parakh and colleagues[183] no changes 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 group. These figures were not statistically significantly different but as the analysis also included a third comparison group (BUD) there was unlikely to have been a pairwise comparison between the BUD and FP groups. No data on morning or evening PEF were presented.

Two of the four studies provided data (mean and SD) on end-point FEV_1 that allowed them to be combined in a meta-analysis (*Figure 9*). Pooling the data using a fixed-effects model showed no difference between the two groups [WMD 0.00

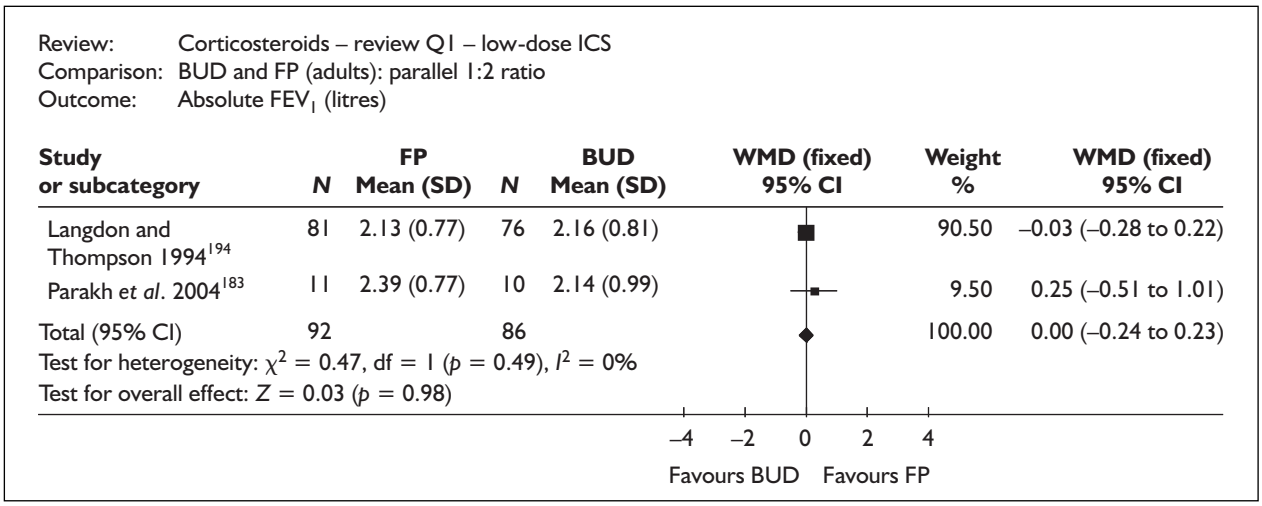

FIGURE 9 *End-point FEV_1 (litres) FP versus BUD, parallel 1:2 nominal dose ratio*

(95% CI –0.21 to 0.23)]. The test for heterogeneity was not significant ($p = 0.49$, $I^2 = 0\%$).

Two of the four studies provided data (mean change and SD) on morning PEF that allowed them to be combined in a meta-analysis (*Figure 10*). 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 to 22.44), $p = 0.06$]. Heterogeneity was not statistically significant at $p = 0.63$, $I^2 = 0\%$.

Symptoms/health-related quality of life

Parallel design, 1:1 dose ratio. Asthma symptom scores were recorded on a four-point scale (0 = none and 3 = severe) in the Basran and colleagues trial.[192] In both arms there was an observed improvement in symptom scores (no data were provided of the change score), but the difference in the change in scores for symptoms during the day or during the night was not statistically significantly different between the two arms ($p = 0.50$ daytime score and 0.42 night-time score).

Parallel design, 1:2 dose ratio. Of the two studies of lower dose FP (200 µg) and BUD (400 µg), Langdon and Thompson[194] 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 trial,[195] 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

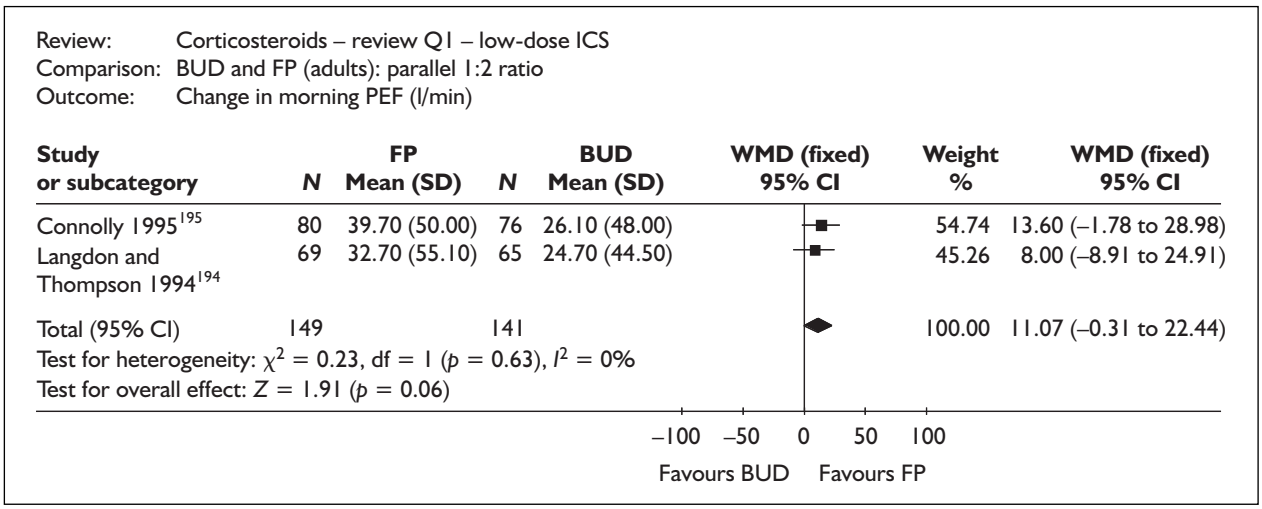

FIGURE 10 *Change in morning PEF, FP versus BUD, parallel 1:2 nominal dose ratio*

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 reported in the paper by Parakh and colleagues.[183] No details of the type of measurement scale were reported. They stated 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[192] reported no statistically significant differences in the change from baseline in SABA use between the BUD and FP arms ($p = 0.31$ daytime use and 0.25 night-time use). Values for these outcomes are presented for baseline and end-point, but no data are given for the change from baseline SABA use.

Parallel design, 1:2 dose ratio. No data on the 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 trial.[192]

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 AEs was similar in both treatment groups in the Basran and colleagues trial[192] (43/83 BUD versus 56/93 FP), although no statistical significance testing was undertaken. Two AEs in the BUD group and three in the FP group were classified as serious.

Parallel design, 1:2 dose ratio. Proportions of patients with AEs were generally higher in the FP arms of the included studies than in the BUD arms, as can be seen in *Figure 11*. 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 11*). Pooling the data using a fixed-effect model showed a statistically significantly more favourable AE profile with BUD [odds ratio (OR) 2.28 (95% CI 1.59 to 3.26, $p < 0.00001$]. Heterogeneity was not significant at $p = 0.13$, $I^2 = 50.4\%$. It is important to note that although these three trials had a dose ratio of 1:2, they did not all have the same dose of FP and BUD.

Four patients in the FP arm of the Langdon and Thompson trial[194] discontinued due to AEs. Two were due to serious AEs, 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 to less severe AEs. Six patients discontinued due to AEs from the BUD arm; four were reported to be asthma related, one due

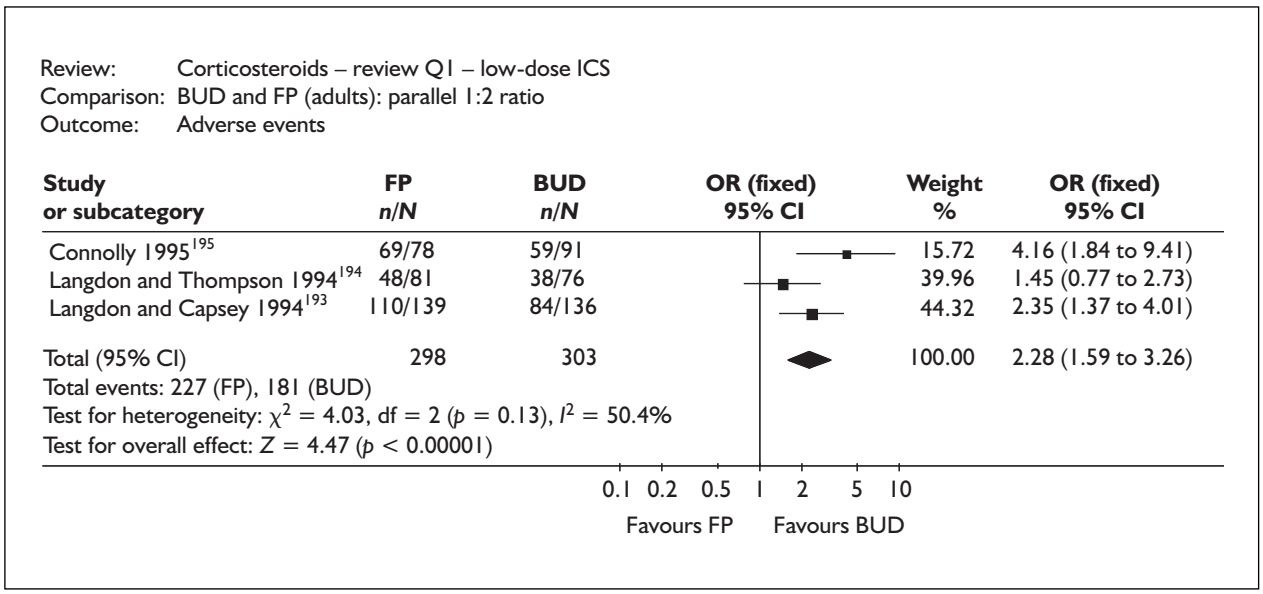

FIGURE 11 *Adverse events, FP versus BUD, parallel nominal 1:2 ratio*

to low cortisol and one to pregnancy. One patient in each arm of the Connolly[195] trial discontinued due to AEs.

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 AEs.

Parallel design, 1:2 dose ratio. No differences on measures of lung function were reported between BUD and FP for either the lower or higher dose studies. Reports of symptoms were favourable for FP compared with BUD. AE profiles, however, were statistically significantly more favourable for BUD.

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

Study characteristics

One RCT,[196] published in 2005, evaluated the effectiveness of CIC compared with BUD (*Table 18*). An unpublished report containing more extensive results for this trial was made available to us by the manufacturer but is considered commercial in confidence.[197] 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: 400 µg BUD, 200 µg CIC given in the morning and 200 µg CIC given in the evening. CIC was delivered by HFA–MDI (not specifically stated – Alvesco, made by Altana) and BUD by MDI (BUD-100, Cipla), and treatment was continued for 12 weeks.

Patients' ages ranged from 18 to 69 years, 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 ≤500 µg/day of BDP or equivalent 4 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. ITT 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 with BUD in terms of efficacy as measured by change in the primary outcome measure, FEV_1 (litres). A two-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 160 µg/day CIC (evening dose) to 400 µg/day BUD. The non-inferiority acceptance limit for FEV_1 was –0.20 litres.

Results

For some outcomes means were calculated using the least-squares method, as indicated by LS in the text. Results presented are for ITT analysis, unless stated otherwise.

Lung function

FEV_1 (litres). Niphadkar and colleagues[196] 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 200 µg CIC in the morning and patients in the 400 µg/day BUD group was –0.036 litres (95% CI –0.120 to 0.045). The difference between the change in those who received an evening dose of 200 µg CIC and those who received 400 µg/day BUD was 0.022 litres (95% CI –0.061 to 0.105). These differences were not statistically significant, and superiority of morning or evening CIC versus BUD was not demonstrated ($p = 0.383$ and $p = 0.598$, respectively). The non-inferiority of CIC to BUD was demonstrated as the lower CIs exceeded the acceptance level of –0.2 litres. **[Commercial-in-confidence data removed.]**

Morning PEF. As with FEV_1, Niphadkar and colleagues[196] reported the results of a comparison between the two CIC groups and the BUD group's change from baseline, but did not report the actual mean changes from baseline **[Commercial-in-confidence data removed]**.

Evening PEF. For evening PEF, Niphadkar and colleagues[196] reported between-group comparisons for change from baseline evening PEF of –1.1 l/minute (95% CI –12.4 to 10.3, $p = 0.855$) for morning CIC versus BUD and 4.0 l/minute (95% CI –7.5 to 15.5, $p = 0.490$) for evening CIC versus BUD. **[Commercial-in-confidence data**

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

Study	Design	Intervention	Patients	Outcomes
Niphadkar *et al.*, 2005[196]	RCT Multi-centre Parallel group Double-blind, double-dummy (CIC) or open-label (BUD)	1. CIC 160 μg *ex*-actuator a.m. q.d. + placebo p.m. (daily total 200 μg *ex* valve) 2. CIC 160 μg *ex*-actuator p.m. q.d. + placebo a.m. (daily total 200 μg *ex* valve) 3. BUD 200 μg b.d. (daily total 400 μg) *Delivery device:* 1, 2. HFA MDI (CIC, Alvesco, made by Altana[a]) 3. MDI (BUD-100, Cipla) *Duration:* 12 wks *Run-in period:* 2–2.5 wks	*Number randomised* 405 *Mean age (range) (years)* 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 (⩽500 μg/day BDP, 200–250 μg/day FP, 400 μg/day BUD, or equivalent)	*Primary outcome* Change in FEV_1 (litres) *Secondary outcomes* Difference in FEV_1 (litres) between randomisation and study visits FVC Morning and evening PEF Diurnal PEF fluctuation Asthma symptom scores Rescue medication use AEs

[a] Not specifically stated in the text.

removed]. Non-inferiority of CIC to BUD was demonstrated as the lower CIs exceeded the acceptance level of –25 l/minute.

Symptoms
Niphadkar and colleagues[196] 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 = not significant for both comparisons with BUD). The percentage of days that were free of nocturnal awakenings was 100% in each group. **[Commercial-in-confidence data removed]**.

Health-related quality of life
Niphadkar and colleagues[196] did not report this outcome.

Use of rescue medication
Niphadkar and colleagues[196] did not report this outcome.

Exacerbations
Niphadkar and colleagues[196] did not report this outcome. **[Commercial-in-confidence data removed]**.

Adverse events
AEs were reported by 24 patients (17.1%) in the morning CIC group, 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 and 0.558, respectively, calculated by reviewer). Severe AEs 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 versus BUD, p = 1.0 for evening CIC versus BUD). One patient in each of the morning CIC and BUD groups withdrew due to AEs (0.7 and 0.8%, respectively), but no patients in the evening CIC group withdrew for this reason.

Summary
One published parallel-group RCT[196] evaluated the effectiveness of CIC compared with 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 PEF. There was no significant difference between the CIC groups and the BUD group in terms of symptom-free days, **[Commercial-in-confidence data removed]**. There was no statistically significant difference between the two drugs in terms of AEs, severe AEs or discontinuations due to AEs.

MF and BUD (review Q1 – low-dose ICS)
Study characteristics
Two multi-centre, parallel-group RCTs compared BUD with MF (*Table 19*). The RCT by Corren and colleagues[198] included 262 patients and ran for 8 weeks and that by Bousquet and colleagues[199] lasted for 12 weeks and randomised 730 patients.

Patients in the study by Corren and colleagues[198] were randomised in an approximately 2:2:1 ratio to one of three treatment groups: placebo, once-daily 440 µg MF (daily metered dose) and once-daily 400 µg 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 the devices were 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[199] had four treatment arms; 100 µg MF twice daily plus placebo, 200 µg MF twice daily plus placebo, 400 µg MF twice daily plus placebo, and 400 µg 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 were 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, AZ (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[198] aimed to compare the efficacy and safety of MF and BUD delivered via DPI. Bousquet and colleagues[199] aimed to compare the efficacy and safety of the two drugs delivered via DPI (MF) or Turbohaler DPI (BUD).

Patients in the two studies were of similar ages. Patients in the study by Corren and colleagues[198] ranged in age from 12 to 82 years, with a mean

TABLE 19 *Characteristics of studies (MF and BUD)*

Study	Design	Intervention	Patients	Outcomes
Corren *et al.*, 2003[198]	RCT Multi-centre Parallel-group Double-blind, double-dummy Placebo- and active-controlled	1. MF 200 μg b.d. (≈ 440 μg *ex*-valve) 2. BUD 160 b.d. (≈ 400 μg *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 (years)* 37.67 *Baseline FEV_1 % predicted* 73.37 *Previous ICS treatment (drug and dose)* 200–2000 μg q.d. of FP, BUD, BDP, flunisolide or triamcinolone	*Primary outcome* FEV_1 (litres) PEF (morning and evening) *Secondary outcomes* $FEF_{25-75\%}$ FVC Asthma symptoms Albuterol use Nocturnal awakenings Physician-evaluated response-to-therapy scores and compliance Percentage of asthma symptom-free days[a] AEs
Bousquet *et al.*, 2000[199]	RCT Multi-centre Parallel-group Evaluator-blind active-controlled	1. MF 100 μg b.d. (daily total 200 μg) + placebo 2. MF 200 μg b.d. (daily total 400 μg) + placebo 3. MF 400 μg b.d. (daily total 800 μg) + placebo 4. BUD 400 μg b.d. (daily total 800 μg) + placebo *Delivery device:* 1, 2, 3. MF DPI (made by Schering-Plough) 4. DPI Turbuhaler (Pulmicort, AZ[a]) *Duration:* 12 wks *Run-in period:* Not reported	*Number randomised* 730 *Mean age (range) (years)* 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 (litres) *Secondary outcomes* FVC PEF Symptom scores Nocturnal awakenings requiring salbutamol use as rescue medication Daily salbutamol use Physician evaluation of response to therapy AEs

[a] Not stated explicitly, but deduced from the text.

age of 37.67 years, and those in the study by Bousquet and colleagues ranged from 12 to 76 years, with a mean age of 41 years. Corren and colleagues did not describe the severity of patients' asthma, but reported that the baseline mean percentage of predicted FEV_1 ranged from 71.6 to 75.1% for the three treatment groups. Bousquet and colleagues[199] did not describe the severity of patients' asthma in their RCT. The baseline mean percentage of predicted FEV_1 ranged from 76.0% in the BUD group to 77.9% in the 400 µg twice-daily 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,[198] being taken by 37% of patients at a mean dose of 388 µg/day. Just over one-quarter (26%) of patients had taken BDP at a mean dose of 328 µg/day, with a further 20% having used 696 µg/day triamcinolone. The remaining patients had used BUD (8%) or flunisolide (8%) at daily doses of 664 and 1136 µg, respectively. In the trial by Bousquet and colleagues,[199] patients had used the following mean doses of ICS: 699 µ/day BDP, 662 µg/day BUD, 659 µg/day flunisolide, 438 µg/day FP or 416 µg/day triamcinolone.

FEV_1 (litres) was used as the primary outcome by both studies (Bousquet and colleagues[199] also reported FEV_1 percentage of predicted value), although Corren and colleagues[198] used both FEV_1 (litres) and PEF as primary outcomes. Neither study used a strictly ITT method of efficacy analysis. One patient in the study by Corren and colleagues and 10 patients in the study by Bousquet and colleagues[199] 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.

Results

Results for the comparison between 400 µg MF twice daily plus placebo and 400 µg BUD twice daily (i.e. the 1:1 dose ratio) in the trial by Bousquet and colleagues[199] are reported in the section 'MF and BUD (review Q2 – high-dose ICS)' (p. 85), as this MF dose falls into the 'high-dose' category (review question 2).

Lung function

Parallel 1:1 dose ratio studies. Corren and colleagues[198] 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 0.19 ± 0.04 litres in the MF group and 0.03 ± 0.04 litres in the BUD group ($p < 0.01$). These represent changes of 8.9 and 2.1% for the two groups, respectively ($p < 0.01$).

Corren and colleagues[198] reported that the change from baseline morning PEF was statistically significantly greater in the MF group (19.96 ± 4.15 l/minute) than in the BUD group (0.54 ± 4.08 l/minute; $p < 0.01$). In terms of change from baseline in evening PEF scores, MF patients had a mean change of 19.04 ± 4.19 l/minute, compared with 4.93 ± 4.13 l/minute in the BUD group. MF was statistically significantly better than BUD ($p < 0.05$). However, baseline mean PEF 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 PEF 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 percentage of predicted FEV_1 value were presented by Bousquet and colleagues.[199] The 200 µg twice-daily MF group reported a mean change from baseline FEV_1 that was statistically significantly greater than change in the BUD group (0.16 ± 0.03 l/minute versus 0.06 ± 0.03 litres in the BUD group, $p < 0.05$). Similarly, the end-point percentage of predicted FEV_1 was statistically significantly different between the 200 µg twice-daily MF group ($81.6 \pm 1.2\%$) and BUD ($77.9 \pm 1.1\%$; $p < 0.05$). In the 100 µg twice-daily MF group, change from baseline (0.10 ± 0.03 litres) and end-point percentage of predicted FEV_1 ($79.6 \pm 1.1\%$) were not statistically significantly different from the BUD group.

Bousquet and colleagues[199] did not find a statistically significant difference between MF and BUD in terms of change in morning PEF. Change from baseline to end-point was 24.75 ± 5.3 l/minute in the BUD group compared with 18.20 ± 5.3 l/minute in the 100 µg twice-daily MF group and 37.84 ± 5.4 l/minute in the 200 µg twice-daily MF group. Changes in evening PEF were not presented, but were reported to be similar to changes in morning PEF.

Symptoms

Parallel 1:1 dose ratio studies. Total morning and evening asthma symptom scores were reported by Corren and colleagues[198] 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 ± 0.12 points. 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, being 39.7 ± 3.4% in the MF group, compared with 26.8 ± 3.3% in the BUD group ($p < 0.01$).

In the trial by Corren and colleagues,[198] 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 = not significant).

Parallel 1:2 or 1:4 dose ratio studies. Bousquet and colleagues[199] did not report symptom-free days, but did report the change from baseline to end-point in the mean number of nocturnal awakenings requiring salbutamol rescue medication. The mean number of awakenings was 0.36 in the 100 µg twice-daily MF group, 0.33 in the 200 µg twice-daily 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 HRQoL.

Use of rescue medication
Parallel 1:1 dose ratio studies. Corren and colleagues[198] 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[199] did not report symptom relief in terms of puffs per day.

Exacerbations
Neither study reported rate of asthma exacerbations.

Adverse events
Corren and colleagues[198] reported that there were no significant differences between the trial arms in overall incidence of AEs. Treatment-related AEs were experienced by 8% of the MF group and 9% of the BUD group. One patient in the MF group and two patients in the BUD group discontinued due to AEs, which were unrelated to treatment.

Bousquet and colleagues[199] reported that the incidence of treatment-related adverse effects was similar for all treatment groups (17–20%). Reports of serious AEs were also similar across treatment arms, and none of these were thought to be related to treatment. Withdrawals due to AEs were reported for six patients in the 100 µg twice-daily MF group, one person in the 200 µg twice-daily MF group, three patients in the 400 µg twice-daily MF group and seven patients in the BUD group.

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 FEV_1 favouring MF was apparent when MF and BUD were compared at a nominal dose ratio of 1:1. Corren and colleagues[198] also reported that the change from baseline morning and evening PEF 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 200 µg twice-daily MF dose was also statistically significantly more effective than 400 µg twice-daily BUD in terms of FEV_1 changes from baseline and percentage 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 400 µg 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, MF appears to improve lung function compared with 400 µg BUD, 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.

CIC and FP (review Q1 – low-dose ICS)
Study characteristics
Two RCTs were identified which compared CIC with FP[200,201] (*Table 20*). An unpublished report of

one of the trials[201] 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[200] was a multi-national, multi-centre trial with 529 participants.

The 12-week study by Buhl and colleagues[200] had two arms and compared CIC 200 µg/day (as a single daily dose in the evening) with FP 200 µg/day (as two daily doses of 100 µg); the dosing ratio was 1:1. Both drugs were delivered by HFA–MDIs (CIC Alvesco, made by Altana; 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.

[Confidential information removed].

In the study by Buhl and colleagues,[200] patients were described as having mild to moderate asthma. Their ages ranged from 12 to 74 years and FEV_1 % predicted from 48 to 108%. Patients were eligible for the study if they had been taking up to 500 µg/day of BDP or equivalent. Both groups were generally similar at baseline in terms of demographics and other characteristics.

[Confidential information removed].

Buhl and colleagues[200] 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). **[Confidential information removed].**

Results

The study by Buhl and colleagues[200] was designed to show non-inferiority of CIC with FP. Both ITT and per protocol (PP) results are presented in the paper. ITT results are reported here.

[Confidential information removed].

Lung function

Parallel 1:1 dose ratio studies. FEV_1 (litres). In the study by Buhl and colleagues,[200] least-squares means were used for the analysis of FEV_1 (litres). The within-treatment mean difference standard error (SE) in the CIC group was 0.489 (0.029), $p < 0.0001$ and in the FP group 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 predefined non-inferiority acceptance limit of –0.2 litres in both the ITT and PP analyses.

[Confidential information removed].

FEV_1 % predicted. Buhl and colleagues[200] did not report on FEV_1 % predicted.

Morning and evening PEF. Buhl and colleagues[200] used least-squares means for the analysis of morning and evening PEF (litres per minute). The morning PEF within-treatment mean difference (SE) in the CIC group was 33 (4) l/minute, $p < 0.0001$, and in the FP group was 36 (4) l/minute, $p < 0.0001$. 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 predefined non-inferiority acceptance limit of –0.25 l/minute in both ITT and PP analyses. Evening PEF values were reported to have significantly improved over the 12 weeks following treatment with CIC and FP but no further details were provided.

[Confidential information removed].

Morning and evening PEF. **[Confidential information removed].**

Symptoms

Parallel 1:1 dose ratio studies. Buhl and colleagues[200] 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 were 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.

[Confidential information removed].

Buhl and colleagues[200] 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,

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

Study	Design	Intervention	Patients	Outcomes
Buhl *et al.*, 2005[200]	RCT Multi-centre Parallel Double-blind Double-dummy	1. CIC 200 μg *ex*-valve p.m. q.d. (daily total 160 μg *ex*-actuator) 2. FP 100 μg *ex*-valve b.d. (daily total 176 μg *ex*-actuator) *Delivery device:* 1, HFA MDI (CIC Alvesco, made by Altana[a]) 2. HFA MDI (no further details about device reported) *Duration:* 12 wks *Run-in period:* 1–4 wks: ICS was discontinued and salbutamol rescue medication only given	*Number randomised* 529 *Median age (range) (years)* 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 500 μg 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 PEF Secondary outcome FVC $FEF_{25–75\%}$ Evening PEF Asthma symptom scores Rescue medication use Rescue-medication-free days Number of days and nights without symptoms Asthma exacerbations AEs

[a] Not specifically stated in the text.

$p < 0.0001$. 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, $p < 0.0001$, in 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, $p < 0.0001$, in the FP group. The between-treatment group difference was not significant (0.00, 95% CI 0.00 to 0.10, $p = 0.530$). CIs for the within-treatment differences were not reported.

[Confidential information removed].

Health-related quality of life
Buhl and colleagues[200] did not report on this outcome.

Use of rescue medication

Parallel 1:1 dose ratio studies. Buhl and colleagues[200] 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, $p = 0.130$).

[Confidential information removed].

Exacerbations

Parallel 1:1 dose ratio studies. Buhl and colleagues[200] did not report on this outcome.

[Confidential information removed].

Adverse events

Parallel 1:1 dose ratio studies. In the study by Buhl and colleagues,[200] 97 participants (36%) in the CIC group and 89 (34%) in the FP group experienced an AE. A total of 270 AEs occurred during the study. One serious AE 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 AEs.

[Confidential information removed].

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,[200] which used a 1:1 dosing ratio (CIC 200 µg/day versus FP 200 µg/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 PEF.

[Confidential information removed].

MF and FP (review Q1 – low-dose ICS)

Study characteristics
One parallel-group RCT, published in 2001, investigated the effectiveness of MF compared with FP (*Table 21*). The study was a multi-centre parallel trial with 733 patients. The study, by O'Connor and colleagues,[202] comprised four arms in which three doses of MF (200, 400 and 800 µg/day) were compared with one dose of FP (500 µg/day). The comparisons are approximately equivalent to rounded nominal dose ratios (MF:FP) of 1:1 (400:500 µg/day), 1:2 (200:500 µg/day) and 2:1 (800:500 µg/day). The 500 µg/day dose of FP is slightly above the upper threshold for a low-dose classification, but 500 µg/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 section 'MF and FP (review Q2 – high-dose ICS)', p. 87].

O'Connor and colleagues[202] 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, GSK).

The study was of relatively short duration, lasting 12 weeks.[202] The mean age of patients included in the study was 41 years, ranging from 12 to 79 years. The enrolled patients had moderate persistent asthma.

O'Connor and colleagues[202] 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 200 and 800 µg/day MF. If there was no significant difference between 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.

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 400 µg/day MF and 500 µg/day FP. The change in FEV_1 (mean ± SD) was the same (0.16 ± 0.54 litres) for MF (n = 182) as for FP (n = 184). The change in morning PEF (mean ± SD) was 29 ± 80.9 l/minute for MF and 32 ± 67.8 l/minute for FP (no p-values reported). The change from baseline to end-point in the evening PEF was not reported quantitatively. However, the authors commented that the changes in evening PEF were similar to changes in morning PEF. Changes in both morning and evening PEF 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 litres for MF (20 µg/day) and 0.16 ± 0.54 litres for FP (500 µg/day) (p = not significant). The change in morning PEF (mean ± SD) was 15 ± 67.5 l/minute for MF (200 µg/day) and 32 ± 67.8 l/minute for FP (500 µg/day). This difference was statistically significant ($p \leqslant 0.05$).

Symptoms

Parallel 1:1 dose ratio. O'Connor and colleagues[202] 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 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 ($p \leqslant 0.05$).

Use of rescue medicine

Parallel 1:1 dose ratio. O'Connor and colleagues[202] expressed the use of rescue medication in micrograms of albuterol used per day. The change from baseline to end-point was –94.84 µg/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 –13.23 µg/day for MF-treated patients and –52.06 µg/day for FP-treated patients; this difference between the treatments is not statistically significant.

Exacerbations

O'Connor and colleagues[202] noted that aggravated asthma was one of the most frequent AEs leading to the discontinuation of treatment. However, the occurrence of asthma aggravation was not reported separately from other AEs (summarised below).

Adverse events

Parallel 1:1 dose ratio. In the study by O'Connor and colleagues,[202] 47 out of 182 patients treated with MF (26%) and 53 out of 184 patients treated with FP (29%) experienced treatment-related AEs. Six patients who received MF and eight patients who received FP did not complete their treatment because of AEs. The most frequent AEs leading to discontinuation were aggravated asthma, bronchitis, pharyngitis and upper respiratory tract infection.

Parallel 1:2 dose ratio. Of 182 patients who were treated with 200 µg/day MF, 36 (20%) experienced treatment-related AEs. Of the patients treated with 500 µg/day FP, 53 out of 184 (29%) experienced treatment-related AEs. Nine patients who received MF and eight patients who received FP did not complete their treatment because of AEs. The most frequent AEs leading to discontinuation were aggravated asthma, bronchitis, pharyngitis and upper respiratory tract infection.

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 PEF 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

TABLE 21 *Characteristics of studies (MF and FP)*

Study	Design	Intervention	Patients	Outcomes
O'Connor *et al.*, 2001[202]	RCT Parallel-group Double-blind (dosage), evaluator-blind (medication)	*Drug(s):* 1. MF 100 μg b.d. (daily total 200 μg) 2. MF 200 μg b.d. (daily total 400 μg) 3. MF 400 μg b.d. (daily total 800 μg) 4. FP 250 μg b.d. (daily total 500 μg) *Delivery device:* 1, 2, 3. MF DPI (Schering-Plough) 4. DPI (Flixotide Diskhaler, GSK) *Duration:* 12 wks *Run-in period:* 1–2 wks	*Number randomised* 733 *Mean age range (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* PEF $FEF_{25-75\%}$ FVC Asthma symptom scores Rescue medication use Nocturnal awakenings Physician evaluation AEs

of 500 µg/day FP over 200 µg/day MF, in terms of both clinical effectiveness and safety. An exception is that a higher frequency of AEs occurred with FP (29%) compared with MF (20%), but these differences were not evaluated statistically.

Summary of Q1 – relative effectiveness of low-dose ICS

According to Step 2 of the BTS/SIGN Guideline, the following drugs at the following doses (excluding considerations of device) are equivalent: BUD 200 µg/BDP 200 µg/FP 100 µg. MF 100 µg is considered the appropriate equivalent dose at this level, likewise CIC 100 µg (by assumption). Similarly, BUD 400 µg/BDP 400 µg/FP 200 µg are considered equivalent, alongside MF 200 µg and CIC 200 µg, and BUD 800 µg/BDP 800 µg/FP 400 µg, alongside MF 400 µg and CIC 400 µg.

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 with BDP. The results are not so consistently in favour of FP when compared with equivalent doses of BUD or MF. In some cases non-inferiority was assessed and demonstrated, such as the comparison of CIC with equivalent doses of FP or BUD.

As a brief summary:

- BDP versus BUD (five RCTs, all 1:1 dose ratio): statistically significant differences only for lung function, in favour of BUD.
- FP versus BDP (six RCTs, all 1:2 dose ratio): few statistically significant differences, except for one RCT which found significant differences in favour of FP across a range of outcomes.
- FP versus BUD (five RCTs, four at 1:2 dose ratio, one at 1:1 dose ratio): mixed findings. Significant difference for symptoms in favour of FP from one trial, significant difference for AEs in favour of BUD from meta-analysis of two trials.
- CIC versus BUD (one RCT, 1:2 dose ratio): no significant differences. Non-inferiority demonstrated for lung function.
- MF versus BUD (two RCTs, one at 1:1 dose ratio, one 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 versus FP (two RCTs, one at 1:1 dose ratio, one at 1:2 dose ratio): no significant differences at 1:1 dose ratio. Non-inferiority demonstrated for lung function.
- MF versus FP (one RCT, with a 1:1 dose ratio and a 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.

Tables 22–28 provide a visual illustration of the results of pair-wise comparisons.

Review question 2 – effectiveness of high-dose ICS

High dose is defined as 800–2000 µg/day BDP/BUD equivalent (for FP, CIC and MF high dose is >400 µg/day) (Step 4 of the Guideline)

To recap, 24 RCTs evaluated high-dose ICS (*Table 29*). The following sub-sections describe the characteristics and results of these trials.

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

Study characteristics

Two double-blind, cross-over RCTs evaluated the effectiveness of BDP compared with BUD (*Table 30*).[81,203] The two studies were small, with 28 patients in the single-centre study by Ebden and colleagues[81] and 15 patients in the multi-centre study by Kaur and colleagues.[203]

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[81] had two treatment periods, each of 6 weeks. Treatment A consisted of three puffs of 250 µg BDP and four puffs of placebo BUD twice daily (total daily dose 1500 µg BDP). Treatment B consisted of four puffs of 200 µg BUD and three puffs of placebo BDP twice daily (total daily dose 1600 µg BUD). The cross-over trial by Kaur and colleagues[203] compared 1000 µg twice daily of each drug (total daily doses 2000 µg), with a 6-week treatment period for each. Treatment drugs in the two RCTs were delivered via MDIs (no details reported for Ebden and colleagues;[81] BDP Beclate and BUD Budecort, both from

Cipla, for Kaur and colleagues[203]), with or without spacers.

Kaur and colleagues[203] aimed to assess whether the same doses of the two drugs produced clinically important differences in side-effects, and Ebden and colleagues[81] 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[81] had a mean age of 54 years (range from 19–72 years). However, those in the study by Kaur and colleagues[203] 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 887.5 µg. Kaur and colleagues did not report prior treatment for their RCT population.

The cross-over study by Kaur and colleagues[203] used computer-generated random numbers to assign patients to treatment groups, but the other RCT[81] 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[81] 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[203] included a 1-week wash-out 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.

Results

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

Lung function

The mean change from baseline FEV_1 value in the cross-over study by Ebden and colleagues[81] was 0.02 litres in the BUD group and –0.09 litres in the BDP group (p = not significant). The mean morning PEF for the last 3 weeks of treatment was similar in the two groups. The mean was 314.1 [standard error of the mean (SEM) 4.0] l/minute during BUD treatment and 311.2 (SEM 4.1) l/minute during BDP treatment. The mean evening PEF during the last 3 weeks of treatment was also very similar for the two treatments. The mean scores were 335.9 (SEM 3.9) l/minute during BUD treatment and 334.0 (SEM 3.7) l/minute during BDP treatment. Significance values were not reported for PEF scores. Ebden and colleagues[81] 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 PEF, evening PEF 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[203] 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 6 weeks was 0.58 litres with BDP treatment and 0.55 litres with BUD treatment. This study did not report individual morning or evening PEF values.

Symptoms

Neither of the cross-over studies[81,203] reported days or nights without symptoms or overall daily symptom scores.

Health-related quality of life

HRQoL 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 in either of the RCTs.

Adverse events

Ebden and colleagues[81] did not report the overall rate of side-effects, but commented that any side-

TABLE 22 *BUD versus BDP (n = 5 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
400 µg BDP vs 400 µg BUD	Jäger *et al.*,[186] weeks, cross-over, open-label DPI; *n* = 79	BDP BUD	NSD	NSD	NSD				NSD		C		2.5% 1.1%
	Tjwa,[185] 8 weeks, cross-over DPI; *n* = 16	BDP BUD	NSD	+ 	+ 						NSD		
800 µg BDP vs 800 µg BUD	**Meta-analysis** Parakh *et al.*,[183] Dal Negro *et al.*[182]	BDP BUD	+										
	Parakh *et al.*,[183] 12 weeks, parallel-group, DPI, *n* = 32	BDP BUD							NSD				
	Dal Negro *et al.*,[182] 8 weeks, parallel-group, MDI; *n* = 42	BDP BUD		NSD	NSD				NSD				
	Rafferty *et al.*,[184] variable, duration cross over, MDI; *n* = 40	BDP BUD		NSD	NSD				NSD				

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

TABLE 23 *FP versus BDP (n = 6 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
800 μg BDP vs 400 μg FP	Parakh *et al.*,[183] parallel-group, single blind RCT, 12 weeks, MDI, *n* = 42	BDP FP	NSD						F				
400 μg BDP vs 200 μg FP	Prasad *et al.*,[187] parallel-group, double-blind RCT, 12 weeks, MDI, *n* = 74	BDP FP	NSD			NSD						NSD	
400 μg BDP vs 200 μg FP; 800 μg BDP vs 500 μg FP	Raphael *et al.*,[90] parallel-group, double-blind RCT, 12 weeks, MDI, *n* = 42 (combined analysis of both doses)	BDP FP	+ (NSD)	+ (NSD)	+ (NSD)	NSD	+ (NSD)		+ (NSD)		+ (NSD)		Range 9–15%
200 μg BDP vs 100 μg FP	Szefler *et al.*,[189] parallel-group, open-label RCT, 21 weeks, MDI + spacer, *n* = 30	BDP FP	F										
400 μg BDP vs 250 μg FP	Ige and Sogaolu[188], parallel-group, open-label RCT, 8 weeks, pMDI, *n* = 20	BDP FP	NSD			+ (NSD)							
800 μg BDP vs 400 μg FP 1500 μg BDP vs 750 μg FP	Medici *et al.*,[191] parallel-group, double-blind RCT, 12 months, MDI + spacer, *n* = 69	BDP FP										NSD	

F, results appear to favour this treatment group, but no tests of statistical significance reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 24 *FP versus BUD (n = 5 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
200 or 400 µg FP vs 200 or 400 µg BUD	Basran *et al.*,[192] parallel-group, open-label RCT, 8 weeks, DPI, *n* = 176 (results only reported for FP vs BUD, not by dose groups)	FP BUD	NSD	NSD	NSD				NSD		NSD		60.2% 51.8%
200 µg FP vs 400 µg BUD	**Meta-analysis** Langdon and Thompson,[194] Connolly,[195]	FP BUD		NSD									
	Langdon and Thompson,[194] parallel-group, open-label RCT, MDI, 8 weeks, *n* = 157	FP BUD			NSD		+	+	+				59.3% 50%
	Connolly,[195] parallel-group, open-label RCT, DPI Diskhaler or reservoir DPI, 8 weeks, *n* = 190	FP BUD											88.5% 64.8%
400 µg FP vs 800 µg BUD and 200 µg FP vs 400 µg BUD	**Meta-analysis** Langdon and Thompson,[194] Parakh *et al.*[183]	FP BUD	NSD										

continued

TABLE 24 *FP versus BUD (n = 5 RCTs) (cont'd)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
400 µg FP vs 800 µg BUD	Langdon and Capsey[193] parallel-group, open-label RCT, DPI Diskhaler or reservoir DPI, 8 weeks, *n* = 281	FP		+	NSD								79.1%
		BUD											61.8%
	Parakh *et al.*,[183] parallel-group, single-blind RCT, MDI, 12 weeks, *n* = 42	FP							NSD				
		BUD											
200 µg FP vs 400 µg BUD and 400 µg FP vs 800 µg BUD	**Meta-analysis** Langdon and Thompson[194] Langdon and Capsey[193] Connolly[195]	FP											+
		BUD											

NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 25 *BUD versus CIC (n = 1 RCT)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
CIC 200 µg *ex*-actuator a.m., CIC 200 µg *ex*-actuator, p.m. vs BUD 400 µg	Niphadkar *et al.*,[196] parallel-group, double-blind RCT, 12 weeks, HFA MDI or MDI, *n* = 405	1. CIC a.m. 2. CIC p.m. 3. BUD	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		[Commercial-in-confidence data removed]			**[Commercial-in-confidence data removed]** **[Commercial-in-confidence data removed]**	

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; F, results appear to favour this treatment group, but no tests of statistical significance reported; NID, non-inferiority demonstrated; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); blank cells signify no data reported on that outcome.

TABLE 26 *BUD versus MF (n = 2 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
400 μg MF vs 320 μg BUD	Corren *et al.*,[198] parallel-group, double-blind, double-dummy RCT, DPI, 8 weeks, *n* = 262	MF	+	+	+	NSD	+				+		8%
		BUD											9%
200 μg/ 400 μg MF vs 800 μg BUD	Bousquet *et al.*,[199] parallel-group, evaluator-blind, active-controlled RCT, DPI, 12 weeks, *n* = 730	1. MF 200 mg	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 400 mg	+ 2 vs 3										2.9%
		3. BUD											2.2%

NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 27 *FP versus CIC (n = 1 RCT)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
200 µg CIC vs 200 µg FP	Buhl *et al.*,[200] parallel-group, double-blind, double-dummy RCT, HFA MDI, 12 weeks, *n* = 529 Non-inferiority (1:1 dose ratio)	CIC 200 µg FP 200 µg					F	C	NSD		NSD		

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; F, results appear to favour this treatment group, but no tests of statistical significance reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); blank cells signify no data reported on that outcome.

TABLE 28 *FP versus MF (n = 1 RCT)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
200 µg/ 400 µg/MF vs 500 µg FP	O'Connor *et al.*,[202] parallel-group, double-blind RCT	1. 200 µg MF 2. 400 µg MF 3. FP	NSD 1 vs 3 2 vs 3	C 2 vs 3 + 1 vs 3	C 2 vs 3	NSD 2 vs 3 + 1 vs 3					NSD 1 vs 3 2 vs 3		20% 26% 29%

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); blank cells signify no data reported on that outcome; +, indicates results favour this trial arm.

TABLE 29 *Breakdown of studies for review question 2 – high-dose ICS*

Pair-wise comparison	No. 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

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[203] did not report rates of AEs in the two trial arms, but did report changes in serum cortisol. The mean 9 a.m. serum cortisol level increased by 0.4 µg per 100 ml in the BDP group and decreased by 0.85 µg per 100 ml in the BUD group. The mean 4 p.m. serum cortisol level decreased by 0.04 µg per 100ml in the BDP group and decreased by 0.96 µg per 100 ml in the BUD group. The changes in serum cortisol level were not found to be statistically significant for either the 9 a.m. or the 4 p.m. level. Analysis of individual patient data by Kaur and colleagues[203] 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 ($p > 0.1$).

Summary

Two small, double-blind cross-over trials compared 1500–2000 µg BDP with 1600–2000 µg 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.

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

Study characteristics

Ten RCTs tested high doses of FP compared with BDP (*Table 31*).[191,204–212] The studies were predominantly parallel in design but three trials used cross-over designs.[210–212] The studies varied considerably in size (from 21 to 340 participants) and length (from 6 weeks to 2 years). Only two were undertaken in single centres.[209,212] 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[205] randomised participants (stratified by their pretrial dose of ICS) to either 2000 µg of FP daily or 1600 µg of BDP daily for 3 months. The study drugs were delivered by Diskhaler DPI (Rotadisk, GSK – not explicitly stated but deduced from the text). Fabbri and colleagues[204] randomised participants to either 1500 µg of FP daily or 1500 µg of BDP daily, delivered by MDIs (no further details about devices were reported), for 12 months. After 3 months, investigators were allowed to increase the dose of the study drug to 2000 µg 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[206] randomised participants to either 1000 µg of FP or 2000 µg of BDP daily, delivered by pressurised inhalers (no further details of devices were reported), for 6 weeks. Egan and colleagues[209] compared 1000 µg of FP or 2000 µg of BDP, daily by MDI (no further details of devices were reported) for 2 years. The trial also contained three open control groups of the same age, although these are not discussed here. Lorentzen and colleagues[208] randomised participants to either 1000 µg of FP or 2000 µg of BDP daily, using MDIs (no further details of devices were reported), for 1 year. Lundbäck and colleagues' study[207] had three arms. Participants took 500 µg of FP daily by either DPI Diskhaler (Rotadisk, GSK – not explicitly stated but deduced from the text) or a pressurised inhaler, or 1000 µg of BDP daily by pressurised inhaler (the DPI Diskhaler group is not reported here). The randomised section of the trial lasted for 6 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[191] had four treatment arms comparing 400 µg of FP, 800 µg of BDP, 750 µg of FP and 1500 µg of BDP, all daily by MDI (no further details were reported), for 1 year. The lower doses of BDP and FP have been reported earlier [see the section 'FP and BDP (review Q1 – low-dose ICS)', p. 34].

TABLE 30 *Characteristics of studies comparing BDP and BUD*

Study	Design	Intervention	Patients	Outcomes
Ebden *et al.*, 1986[81]	RCT Cross-over (no washout Double-blind	1. BDP 250 μg 3 puffs b.d. (daily total 1500 μg) + placebo 4 puffs b.d. 2. BUD 200 μg 4 puffs b.d. (daily total 1600 μg) + placebo 3 puffs b.d. *Delivery device:* 1. pMDI + spacer plus placebo[a] 2. pMDI + spacer plus placebo[a] *Duration:* 6 wks *Run-in period:* Not reported	*Number randomised* 28 *Mean age (years)* 54 *Baseline FEV_1 (litres)* 1.85 *Previous ICS treatment (drug and dose)* Not reported	FEV_1 FVC PEF (morning and evening) Daily SABA (puffs/day) Daytime wheeze score Morning serum cortisol Serum cortisol 30 minutes post 250 μg tetracosactrin
Kaur *et al.*, 2005[203]	RCT Multi-centre Cross-over Double-blind	1. BDP 1000 μg b.d. (daily total 2000 μg) 2. BUD 1000 μg b.d. (daily total 2000 μg) *Delivery device:* 1. MDI + spacer (Beclate, Cipla) 2. MDI + spacer (Budecort, Cipla) *Duration:* 6 wks *Run-in period:* 1 wk	*Number randomised* 15 *Mean age (± SD) (years)* 28.6 (± 8.0) *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* Not reported	Serum cortisol (9 a.m.) μg/100 ml Serum cortisol (4 p.m.) μg/100 ml 24h urinary steroids mg/24 h FVC (litres) FEV_1 (litres)

[a] No further details about devices provided.

All three of the cross-over trials compared FP with BDP in a 1:2 dose ratio (FP:BDP). Bootsma and colleagues[212] compared 750 µg of FP daily with 1500 µg of BDP daily, using MDIs (no further details of devices were reported), for 12 weeks. Participants took placebo for 3 weeks during the wash-out period. In the study by Pauwels and colleagues,[211] which had two arms, participants were randomised to three different strata, depending on their original dose of ICS: 500 µg of FP or 1000 µg of BDP, 750 µg of FP or 1500 µg of BDP and 1000 µg of FP or 2000 µg of BDP. All were delivered by MDI (no further details reported) and the trial lasted for 12 months, with no wash-out period. Malo and colleagues' study[210] had two arms. Participants were randomised to 1000, 1500 or 2000 µg 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 were reported) and there was no wash-out period.

The average/median age of participants in the trials ranged from mid-thirties to early fifties. Almost all participants (except one patient[212]) were previously taking either BDP or BUD with doses ranging from 400 to 2000 µg/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. Although most focused 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.[191,209–211] Pauwels and colleagues' study[211] was the only one analysed on an ITT basis. In the study by Bootsma and colleagues,[212] no carry-over effects were detected for any variables.

Results

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

Lung function

FEV_1 (litres). Parallel design, 1:1 dose ratio. Boe and colleagues[205] reported an increase in FEV_1 of 0.19 and 0.06 litres in the FP and BDP groups, respectively. The end-point mean values (SE) were 2.23 (0.11) and 2.16 (0.13) litres 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,[204] the mean FEV_1 increased from 2.14 and 1.81 litres for FP and BDP to 2.39 and 1.97 litres, respectively, over the 1-year treatment period. The adjusted mean difference was 0.15 litres (95% CI 0.01 to 0.29, $p < 0.05$).

Parallel design, 1:2 dose ratio. In the study by Barnes and colleagues,[206] there was an increase in FEV_1 of 0.07 and 0.16 litres in the FP and BDP groups, respectively. At end-point the adjusted means were 1.95 and 1.89 litres, respectively. The adjusted mean difference in end-point FEV_1 was non-significant, 0.66 litres (95% CI –0.07 to 0.19), $p = 0.343$. There was significant difference between groups at 12 months in the study by Lorentzen and colleagues,[208] in favour of FP (mean difference 0.12 litres, 95% CI 0.01 to 0.24, $p = 0.044$).

In the trial by Lundbäck and colleagues,[207] the adjusted mean change from baseline in FEV_1 was 0.13 and 0.09 litres in the FP and BDP groups, respectively. End-point values were 2.44 and 2.51 litres, respectively. There was no significant difference between groups (no *p*-value reported). Medici and colleagues[191] did not formally analyse lung function measures, but reported that mean FEV_1 values taken at bimonthly intervals over the 12-month study either remained similar or tended to increase above baseline values. Egan and colleagues[209] did not measure this outcome.

Cross-over design, 1:2 dose ratio. Bootsma and colleagues[212] 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 to 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[206] 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 to 6), $p = 0.358$].

Cross-over design, 1:2 dose ratio. In the study by Malo and colleagues,[210] there was no significant

TABLE 31 *Study characteristics (FP and BDP)*

Study	Design	Intervention	Patients	Outcomes
Fabbri *et al.*, 1993[204]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 750 μg b.d. (daily total 1500 μg) 2. BDP 750 μg b.d. (daily total 1500 μg) After first 3 months dose could be increased to 2000 μg q.d. if needed *Delivery device:* 1, 2. MDI ± spacer *Duration:* 52 wks *Run-in period:* 2 wks	*Number randomised* 274 *Age range (years)* 1. 17–77 2. 19–80 *Baseline FEV_1 % predicted* Not stated *Previous ICS treatment (drug and dose)* BUD or BDP ⩾1000 μg but <2000 μg q.d.	PEF (morning and evening) FEV_1 (litres) Clinic PEF FVC Day and night symptom scores Use of study medication Use of rescue medication AEs Morning plasma cortisol 24-hour urinary free cortisol Asthma exacerbations
Barnes *et al.*, 1993[206]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 250 μg 2 puffs b.d. (daily total 1000 μg) 2. BDP 250 μg 2 puffs b.d. from 2 inhalers (daily total 2000 μg) *Delivery device:* 1, 2. MDI + placebo *Duration:* 6 wks *Run-in period:* 2 wks	*Number randomised* 154 *Median age (range) (years)* 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 1500–2000 μg q.d.	PEF (morning and evening) FEV_1 (litres), (% predicted) FVC Clinic PEF Day and night symptom scores Use of rescue medication Patient assessed asthma AEs Plasma cortisol
Boe *et al.*, 1994[205]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 1000 μg b.d. (daily total 2000 μg) 2. BDP 800 μg b.d. (daily total 1600 μg) *Delivery device:* 1. Diskhaler (Rotadisk, GSK[a]) 2. Diskhaler (Rotadisk, GSK[a]) *Duration:* 3 months *Run-in period:* 2 wks	*Number randomised* 134 *Mean age (range) (years)* 1. 51 (20–74) 2. 51 (27–75) *Mean baseline FEV_1 litres (± SD)* 1. 2.04 (± 0.66) 2. 2.10 (± 0.93) *Previous ICS treatment (drug and dose)* BDP or BUD 400–2000 μg q.d.	*Primary outcome* PEF (morning and evening) *Secondary outcomes* Clinic PEF FEV_1 (litres) FVC Day and night symptom score Use of bronchodilator Serum cortisol Plasma ACTH AEs Asthma exacerbations

continued

TABLE 31 *Study characteristics (FP and BDP) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Lundbäck *et al.*, 1993[207]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 125 μg 2 puffs b.d. (daily total 500 μg) 2. FP 125 μg 2 puffs b.d. (daily total 500 μg) 3. BDP 250 μg 2 puffs b.d. (daily total 1000 μg) *Delivery device:* 1, 3. MDI + placebo 2. DPI Diskhaler (Rotadisk, GSK[a]) + placebo Only groups 1 and 3 considered here *Duration:* 6 wks *Run-in period:* 2 wks	*Number randomised* 585 *Mean age (± SD, range) (years)* 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 400–1000 μg q.d.	PEF (morning and evening) FEV_1 (litres) FVC Clinic PEF Day and night symptoms Use of rescue medication Plasma cortisol Asthma exacerbations
Lorentzen *et al.*, 1996[208]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 250 μg 2 puffs b.d. (daily total 1000 μg) 2. BDP 250 μg 4 puffs b.d. (daily total 2000 μg) *Delivery device:* 1, 2. MDI ± spacer + placebo *Duration:* 52 wks *Run-in period:* 2 wks	*Number randomised* 213 *Median age (range) (years)* 1. 51 (18–77) 2. 54 (21–76) *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* BDP or BUD 1000–2000 μg q.d.	Clinic PEF FEV_1 (litres) FVC AEs Asthma exacerbations Morning plasma cortisol
Egan *et al.*, 1999[209]	RCT Single-centre Parallel-group Double-blind	*Drugs:* 1. FP 500 μg b.d. (daily total 1000 μg) 2. BDP 1000 μg b.d. (daily total 2000 μg) *Delivery device:* 1, 2. MDI + spacer *Duration:* 108 wks *Run-in period:* 2 wks	*Number randomised* 33 *Mean age (± SD, range) (years)* 1. 36 (± 8, 20–48) 2. 33 (± 10, 20–50) *Mean baseline FEV_1 (SD) (litres)* 1. 2.91 (0.7) 2. 3.13 (1.1) *Previous ICS treatment (drug and dose)* BDP or BUD 1000–2000 μg q.d.	*Primary outcome* Absolute BMD values *Secondary outcome* Biochemical markers of bone turnover Clinic PEF AEs

continued

TABLE 31 *Study characteristics (FP and BDP) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Medici *et al.*, 2000[191]	RCT Multi-centre Parallel-group Double-blind	*Drug(s):* 1. FP 200 μg b.d. (daily total 400 μg) 2. BDP 400 μg b.d. (daily total 800 μg) 3. FP 375 μg b.d. (daily total 750 μg) 4. BDP 750 μg b.d. (daily total 1500 μg) 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 age (± SD) (years)* 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 400–1600 μg q.d.	*Primary outcome* BMD of the distal radius *Secondary outcome* PEF (morning and evening) FEV_1 (litres) Serum cortisol Markers of bone metabolism (serum and urine) Use of rescue medication
Malo *et al.*, 1999[210]	RCT Multi-centre Cross-over (no wash-out) Double-blind	*Drugs:* 1. FP daily dose half dose of BDP[b] 2. BDP 1000, 1500 or 2000 μg q.d.[b] *Delivery device:* 1, 2. MDI *Duration:* 4 months for each treatment *Run-in period:* 2 wks	*Number randomised* 67 *Mean age (± SD) (years)* 48.4 (14.5) *Baseline FEV_1 % predicted (± SD)* 76 (± 18) *Previous ICS treatment (drug and dose)* BDP or BUD 800–2000 μg q.d.	Daily asthma symptoms FEV_1 (litres) (% predicted) FVC Use of rescue medication Skin bruising Short synacthen test Urinary cortisol, phosphorus, calcium, *N*-telopeptides Serum intact osteocalcin Serum procollagen and specific alkaline phosphatase

continued

TABLE 31 *Study characteristics (FP and BDP) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Pauwels *et al.*, 1998[211]	RCT Multi-centre Cross-over (no wash-out) Double-blind	*Drugs:* 1. FP 500 or BDP 1000 μg q.d.[c] 2. FP 750 or BDP 1500 μg q.d.[c] 3. FP 1000 or BDP 2000 μg q.d.[c] *Delivery device:* 1, 2, 3. MDI ± spacer *Duration:* 52 wks *Run-in period:* 4 wks	*Number randomised* 340 *Mean age (± SD) (years)* FP/BDP 46.6 (± 14.6) BDP/FP 46.2 (± 15.0) *Baseline FEV_1 % predicted (± SD)* FP/BDP 78.4 (± 21.1) BDP/FP 80.0 (± 20.7) *Previous ICS treatment (drug and dose)* BDP 1000–2000 μg q.d. or BUD 800–1600 μg q.d.	*Primary outcome* Serum cortisol level *Secondary outcomes* FEV_1 (% predicted) FVC PEF (morning and evening) Use of 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) AEs Asthma exacerbations
Bootsma *et al.*, 1995[212]	RCT Single-centre Cross-over (3 wks wash-out period) Double-blind	*Drugs:* 1. FP 125 μg 3 puffs b.d. (daily total 750 μg) 2. BDP 250 μg 3 puffs b.d. (daily total 1500 μg) *Delivery device:* 1, 2. MDI + placebo *Duration:* 12 wks *Run-in period:* 3 wks	*Number randomised* 21 *Mean age (± SD) (years)* 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 790 μg q.d. (SE 54)	PEF (morning and evening) FEV_1 Histamine and ultrasonically nebulised distilled water provocation test Use of rescue inhaler Asthma symptoms AEs Severity of symptoms (day and night) Eosinophils Serum cortisol Serum and urinary markers of bone turnover

[a] Not stated explicitly, but deduced from the text.
[b] 3 different doses of FP and BDP in each group depending on normal dose of ICS.
[c] Dose received depended on dose of current ICS.

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[211] also found no significant difference (results were presented as a graph – it was not possible to determine the values accurately). Bootsma and colleagues[212] did not report this outcome measure.

Morning and evening PEF (l/min)

Parallel design, 1:1 dose ratio. Boe and colleagues[205] only reported morning and evening PEF as estimated increases per day over the treatment period. Baseline and end-point values were also reported, but for morning and evening PEF combined.

The study by Fabbri and colleagues,[204] which only measured this outcome for the first 12 weeks, reported that changes in both morning and evening PEF 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 PEF was 15 l/minute (95% CI 6 to 25), $p < 0.005$, and 10 l/minute (95% CI 0 to 19, $p < 0.05$) for evening PEF.

Parallel design, 1:2 dose ratio. Barnes and colleagues[206] reported an increase in morning PEF of 14 and 30 l/minute in the FP and BDP groups, respectively. At end-point the adjusted mean values were 317 and 324 l/minute, respectively. The adjusted mean difference for morning PEF at end-point was –7 l/minute (95% CI –21 to 7), $p = 0.346$. For evening PEF there was a decrease of 1 l/minute in the FP group, compared with an increase of 15 l/minute in the BDP group, respectively. At end-point the adjusted mean values were 336 and 348 l/minute, respectively. The adjusted mean difference for evening PEF at end-point was –13 l/minute (95% CI –26 to 1). The *p*-value reported for the evening PEF (0.07) was incompatible with the other values.

Lundbäck and colleagues[207] found no significant difference between the different treatment arms in either morning or evening PEF. The adjusted mean change from baseline in morning PEF was 19 and 14 l/minute in the FP and BDP groups, respectively. End-point values were 383 and 394 l/minute, respectively. For evening PEF the adjusted mean change from baseline was 11 and 14 l/minute in the FP and BDP groups, respectively. End-point values were 400 and 411 l/minute, respectively. No *p*-values were reported for between-group comparisons. Medici and colleagues[191] did not perform a formal statistical analysis on lung function data. However, mean daily morning and evening PEF values either remained similar or tended to increase slightly above baseline values (no data shown). Egan and colleagues[209] only reported clinic PEF, rather than morning and evening PEF.

Cross-over design, 1:2 dose ratio. The mean (SE) difference in treatment effect for morning PEF between FP and BDP in the study by Bootsma and colleagues[212] was 5.57 l/minute (5.5), 95% CI 6.31 to 17.5 (note that it appears that the lower limit of the CI is incorrect). The corresponding figures for evening PEF were 2.69 l/minute (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[204] reported an increase in the mean percentage of symptom-free days of 19% in both the FP and BDP groups between run-in and 12 weeks of 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 were presented). Increases in mean percentage of symptom-free nights of 14 and 13% in the treatment groups, respectively, were also reported. 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[205] did not report this outcome measure.

Parallel design, 1:2 dose ratio. In the study by Barnes and colleagues,[206] 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 for BDP 37%, $p = 0.212$. There was an increase in the 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 for BDP 50%, $p = 0.854$. Lundbäck and colleagues[207] 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[211] did not differ significantly (no *p*-values reported). The percentage (SD) of symptom-free days at 6 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[205] 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 the 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 and 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[204] 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[206] 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- or night-time symptom score of 0 was reported. Lundbäck and colleagues[207] 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 1–6, median daytime scores were significantly lower for BDP than for FP ($p = 0.03$).

Cross-over design, 1:2 dose ratio. Bootsma and colleagues[212] measured symptom scores (dyspnoea) using a visual analogue scale ranging from 0 to 100 mm (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 on this outcome.

Cross-over design, 1:2 dose ratio. In the study by Pauwels and colleagues,[211] 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 6 months was 0.02 (95% CI 0.00 to 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[205] 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[204] 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,[206] both treatment groups reduced their use of rescue medication (salbutamol) by three times per day. End-point values were 10 for the FP group and 11 for the BDP group, $p = 0.866$. There was a reduction of one and two times per night for these groups, respectively. Corresponding end-point values were 5 and 6, $p = 0.875$. Lundbäck and colleagues[207] did not report the 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,[212] 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,[204] 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 these groups, respectively ($p < 0.02$). Boe and colleagues[205] 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[206] reported that six patients taking FP and two taking BDP were withdrawn due to exacerbations. During the study by Egan and colleagues,[209] 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).

Lundbäck and colleagues[207] only reported exacerbation data for the non-randomised 12-month study period, as opposed to the 6-week randomised period of interest to the current report. In the study by Lorentzen and colleagues,[208] 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[191] 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,[210] 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 3 hours, waking due to asthma symptoms or loss of a day at work because of asthma symptoms. Pauwels and colleagues[211] reported that exacerbation of asthma was the reason for withdrawal in 10 of 28 patients. Withdrawals due to exacerbation were numerically more frequent under BDP than FP (seven and three, respectively. There was no statistically significant difference, *p*-value not reported). Bootsma and colleagues[212] 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,[204] there were 276 AEs in 70% of FP participants and 267 AEs in 73% of BDP participants. About 16% of patients in the FP group experienced a serious AE compared with 23% of patients in the BDP group; 8% of patients withdrew from both groups due to AEs.

Parallel design, 1:2 dose ratio. In the study by Barnes and colleagues,[206] there were 71 AEs in 43 (52%) patients in the FP group and 60 AEs 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 AEs. The numbers of withdrawals due to AEs were eight (10%) and five (7%), respectively.

Egan and colleagues[209] reported that the AE profile and overall incidence of AEs were similar for both groups, but no data were provided. In the trial by Lorentzen and colleagues,[208] equal proportions of patients reported AEs, FP 114 (72%) and BDP 39 (72%). The number of patients experiencing serious AEs in the FP group was 11 (7%) and in the BDP group three (6%). The corresponding numbers of patients withdrawing from the trial because of AEs were 20 (13%) and five (9%) respectively.

In the study by Lundbäck and colleagues,[207] the numbers of people experiencing AEs 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 AEs (including exacerbations) were 13 and 16. Medici and colleagues[191] reported a similar number of patients from both groups experiencing AEs but no further details were provided. There were no serious AEs.

Cross-over design, 1:2 dose ratio. In the study by Bootsma and colleagues,[212] there were no serious AEs, however, it was not possible to extract any further data. Pauwels and colleagues[211] found a similar number of AEs in both groups (FP, 217 in 66.8% of patients; BDP, 215 in 66.2% of patients), which was not statistically significant (*p*-value not reported). There were 13 serious AEs in 4% of

patients in the FP group and 10 serious AEs in 3% of patients in the BDP group. Twenty-eight patients discontinued the study due to AEs, thirteen in the FP group and 15 in the BDP group. Malo and colleagues[210] did not report on this outcome measure.

Cortisol levels

Parallel design, 1:1 dose ratio. In the trial by Boe and colleagues,[205] the mean (SE) change from baseline to end of treatment in serum cortisol was –133.5 nmol/1 (26.5) and 40.4 nmol l/1 (26.9) in the FP and BDP groups, respectively [$p < 0.001$, from analysis of covariance (ANCOVA)]. At 14-week follow-up the difference was not statistically significant (p-value not reported). Fabbri and colleagues[204] 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 to 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,[206] the ratio of the FP adjusted geometric mean to the BDP mean for plasma cortisol concentration was 1.27 (95% CI 1.03 to 1.56), $p = 0.026$. Egan and colleagues[209] did not find a statistically significant treatment difference between FP and BDP at 12 months (data were provided in a figure, but the reviewers were unable to estimate the values). In the study by Lorentzen and colleagues,[208] the ratio of the FP adjusted geometric mean to BDP was significantly increased, 1.22 (95% CI 1.05 to 1.43), $p = 0.01$. Lundbäck and colleagues[207] 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[191] 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[212] found no significant difference between groups (no p-value reported). The mean cortisol end-point value was 0.61 µmol/l for FP and 0.51 µmol/l for BDP. In the study by Malo and colleagues,[210] 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) and 418 (245) µmol/dl, respectively, $p = 0.7$. The corresponding values for mean 24-hour urinary cortisol levels were 105 (64) 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) and 13.29 (6.26) µg%, respectively (the authors state no differences between groups, no p-values reported).

Bone mineral density

Parallel design, 1:2 dose ratio. Egan and colleagues[209] found a significant difference in single-energy quantitative computed tomography (QCT) of vertebral trabecular (T12 to L3) at 12 ($p = 0.006$) and 24 months ($p = 0.004$) in favour of FP. The mean (SD) end-point value for BMD in the FP group at 12 and 24 months was 154 (29.2) and 153 (26.8) mg/cm^3 respectively. The corresponding values for BDP were 144 (19.5) 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) and 161 (24.2) mg/cm^3, respectively. The corresponding values for BDP were 148 (21.3) and 148 (24.6) mg/cm^3. 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[191] provided a detailed evaluation of the impact of FP and BDP on BMD (in g/cm^3) and other bone metabolism markers. Peripheral quantitative computed tomography (pQCT) of the distal radius showed no significant difference in the BMD between the two groups at 6 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 vertebrae showed no differences between the high-dose treatments at 6 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 (measured in µg/l) which suggested greater bone resorption 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[211] measured 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 6 months the mean end-point BMD (SE) in the lumbar spine was 1.118 (0.016) and 1.116 (0.018) g/cm^2 in the FP and BDP groups, respectively. In the neck of the femur the results for FP were 0.932 (0.015) g/cm^2 and for BDP 0.912 (0.014) g/cm^2. The corresponding values for the trochanter were 0.736 (0.013) and 0.741 (0.013) g/cm^2. The values for Ward's triangle were 0.728 (0.017) and 0.693 (0.018) g/cm^2, respectively. The treatments were not directly compared and no other values were presented.

Pauwels and colleagues[211] also reported biochemical markers of bone metabolism. Mean end-point (SD) values for osteocalcin were 1.72 (1.40) and 1.53 (1.02) ng/ml in the FP and BDP groups, respectively (mean difference 0.28 ng/ml; 95% CI 0.12 to 0.44, $p < 0.001$).

Of the biochemical markers of bone metabolism measured by Malo and colleagues,[210] there was only one statistically significant difference. Osteocalcin was significantly lower when patients were on BDP than FP. Mean end-point (SD) values were 3.5 (1.9) and 2.8 (1.7) ngm/l, respectively, $p = 0.003$.

Bootsma and colleagues[212] did not report this outcome measure.

Summary

Ten studies comparing FP with BDP at high doses (according to the BTS/SIGN Guideline) 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 1500–2000 µg FP with 1500–1600 µg BDP in a nominal 1:1 dose ratio. Five parallel group trials compared 500 –1000 µg FP with 1000–2000 µg BDP in a nominal 1:2 (FP:BDP) dose ratio. The cross-over trials compared 500–1500 µg FP with 1000–2000 µg 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 PEF, and exacerbations in favour of FP. There were no statistically significant differences between groups for use of rescue medication and symptoms. The AEs profiles seemed similar, except for 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. The AE profiles seemed similar. However, cortisol levels were increased in the FP group and the results for impact on BMD were mixed.

One of the three cross-over trials comparing FP and BDP at a 1:2 ratio found a small, significant increase in HRQoL. However, neither drug demonstrated clear superiority on efficacy outcomes. The AE profiles appeared similar.

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

Study characteristics

One study, by Aubier and colleagues,[213] published in 2001, compared high doses of HFA–BDP with HFA–FP (*Table 32*). 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 198 patients. The drugs were compared in a nominal 1:1 daily dose ratio (800 µg/day HFA–BDP versus 1000 µg/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 ($p < 0.05$).[213]

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 PEF from baseline.

The objective of Aubier and colleagues[213] 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

TABLE 32 *Study characteristics (HFA BDP and HFA FP)*

Study	Design	Intervention	Patients	Outcomes
Aubier *et al.*, 2001[213]	RCT Parallel-group Open-label	1. BDP 800 μg q.d. 2. FP 1000 μg 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 ± 2 days	*Number randomised* ITT total 198 *Mean age (range) (years)* 1. 50.1[a] (19–76) 2. 51.9[a] (20–78) *Baseline FEV_1 % predicted* 1. 71.7[a] 2. 71.8[a] *Previous ICS treatment (drug and dose)* 500–1000 μg q.d. CFC BDP (or equivalent)	Change from baseline in morning and evening PEF FEV_1 (litres) Asthma symptom scores Sleep disturbance scores Rescue medication usage

[a] Assumed by the reviewers to be mean values (not stated in trial report).

PEF would differ between the drugs by more than ±25 l/minute. The remainder of the outcomes were analysed using statistical tests to detect significant differences between treatments.

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) versus 0.07 (0.49), respectively; $p = 0.21$].

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

Symptoms

Aubier and colleagues[213] 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 3 weeks was 18.32 ± 34.2 for BDP and 6.84 ± 25.6 for FP ($p = 0.03$). Aubier and colleagues[213] 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[213] 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 versus 38.3%). Three patients in the HFA–BDP group (7.8%) withdrew from the study due to AEs (dysphonia and headache, cough and asthma symptoms), and one patient in the HFA–FP treatment withdrew due to AEs (dysphonia and increasing asthma symptoms).

Summary

The systematic review included one parallel-group RCT[213] which compared 800 µg/day HFA–BDP with 1000 µg/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.

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

Study characteristics

Six parallel-group RCTs[214–219] evaluated the effectiveness of BUD compared with FP, published between 1995 and 2005 (*Table 33*). One study[219] reported additional data in a secondary publication.[220] Four studies were multi-centre studies where study sample sizes ranged between 395 and 671 participants, and 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.[214,215,217,219]

Four included trials had two-arm comparisons of BUD versus FP.[214,215,217,218] The remaining trials were three-arm comparisons; one had two FP groups (at different doses)[216] and the other had a BDP treatment group (not described here).[219]

Two trials had a nominal dose ratio of 1:1,[214,215] three a nominal dose ratio of 1:2[217–219] 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.[216] Of the three 1:1 nominal dose ratio comparisons, two were of higher doses (one comparing 2000 µg FP with 2000 µg BUD[214] and one 2000 µg FP with 1600 µg BUD[216]) and one

was of a lower dose comparison (800 µg FP versus 800 µg BUD[215]). In the four 1:2 nominal dose ratio comparisons, the dose of FP was 1000 µg compared with BUD 1600 µg in three[216,218,219] and FP 800 µg versus BUD 1600 µg in one.[217]

The devices used in four studies were DPIs (FP, Flixotide Diskhaler, GSK; BUD, Pulmicort Turbuhaler, AZ)[214,215,217,219] and MDIs in two studies (no further details of devices were reported in either study).[216,218] The treatment duration in the studies ranged from 5 weeks[215] to 12 months.[218] Two of the three studies with 1:1 dose comparisons were of short duration (5 weeks[215] and 6 weeks,[216] respectively) and one of long duration (24 weeks).[214] Two of the four studies with 1:2 dose comparisons were of medium duration (12 weeks)[217,219] and one was a long-term study.[218] The fourth comparison was from a study with a shorter 6-week duration.[216]

All included trials aimed to compare the clinical efficacy and safety of the two drugs. The trial by Ringdal and colleagues[217] was reported to be an equivalence trial, assessing morning PEF as their primary outcome. The longer term study (by Hughes and colleagues[218]) 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[215] was designed to estimate the minimal effective doses of the two drugs.

The ages of participants in the trials were similar, with mean ages ranging from 41 to 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[215] and severe in two trials.[214,216] In the 1:2 dose ratio comparisons participants were described as moderate to severe in three trials[217–219] and severe in one.[216] This last 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.[214] 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.[214,218] These factors limit the possibility of selection bias. Five studies reported that their analyses were based on an ITT population, which minimises the possibility of measurement bias.

Results

Lung function

Parallel design, 1:1 dose ratio. One trial[216] reported data on change from baseline on FEV_1, although it did not report any measure of variance around the point estimates. Adjusted for baseline differences, the mean change from baseline after 6 weeks of treatment was 0.28 litres in the FP 2 mg/day arm compared with 0.12 litres in the BUD 1.6 mg/day arm. The difference between the study groups was shown to be statistically significant, $p < 0.05$. This analysis was not on an ITT population.

After 24 weeks, participants in the Heinig and colleagues[214] trial had similar end-point FEV_1 values regardless of treatment [2.30 (SD 0.90) litres for FP 2 mg versus 2.30 (SD 0.90) litres for BUD 2 mg]. Similar end-point values of FEV_1 were also seen in both arms of the 5-week study by Kuna.[215] No point estimates were provided but the mean FEV_1 was 2.63 litres in the FP (800 µg) arm compared with 2.61 litres in the BUD (800 µg) arm. The study reported no statistically significant difference between treatments, $p = 0.69$. In this study, no statistically significant differences between treatments were demonstrated on FEV_1 % predicted: FP 80.7% versus BUD 79.7%, $p = 0.48$.

The change in morning PEF was 3.36 (SD 43.62) l/minute in the FP arm of the Kuna trial[215] and –0.81 (SD 41.05) l/minute in the BUD arm. The treatment difference (4.17 l/minute) was not statistically significantly different (95% CI –7.65 to 15.99). The evening PEF 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 and BUD 392 l/minute, $p = 0.08$).

Parallel design, 1:2 dose ratio. Two trials[216,219] reported data on change from baseline on FEV_1. Molimard and colleagues[219] reported that the mean change in FEV_1 after 12 weeks was 0.28 (SD 0.49) litres in the FP arm compared with 0.21 (SD 0.4) litres in the BUD arm. Molimard and colleagues[219] 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

TABLE 33 *Characteristics of studies: FP versus BUD*

Study	Design	Intervention	Patients	Outcomes
Heinig *et al.*, 1999[214]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 1000 μg b.d. (daily total 2000 μg) 2. BUD 1200 μg a.m. and 800 μg p.m. (daily total 2000 μg) *Delivery device:* 1. DPI (Flixotide Diskhaler, GSK) + placebo Turbuhaler 2. DPI (Pulmicort Turbuhaler, AZ) + 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 reported	FEV_1 PEF Symptoms Exacerbations Rescue medication AEs
Kuna, 2003[215]	RCT: Single-centre Parallel-group Double-blind	*Drugs:* 1. FP 400 μg b.d.[a] (daily total 800 μg) 2. BUD 400 μg b.d.[a] (daily total 800 μg) *Delivery device:* 1. DPI (Flixotide Diskhaler, GSK) 2. DPI (Pulmicort Turbuhaler, AZ) *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)* 800–1600 μg b.d. ICS other than FP or BUD	Time to withdrawal Morning PEF FEV_1 Tolerability
Ayres *et al.*, 1995[216]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 125 μg 4 puffs b.d. *ex* actuator (daily total 1000 μg) 2. FP 250 μg 4 puffs b.d. *ex* actuator (daily total 2000 μg) 3. BUD 200 μg 4 puffs b.d. *ex* actuator (daily total 1600 μg) *Delivery device:* 1, 2, 3. MDI (no further details reported) *Duration:* 6 wks *Run-in period:* 2 wks	*Number randomised* 671 *Mean age (years)* 49 *Baseline FEV_1 % predicted* <80 *Previous ICS treatment (drug and dose)* BDP 1000–2000 μg q.d. or BUD 800–1600 μg q.d.	FEV_1 PEF (morning and evening) 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

continued

TABLE 33 *Characteristics of studies: FP versus BUD (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Ringdal *et al.*, 1996[217]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 800 μg q.d. 2. BUD 1600 μg q.d. *Delivery device:* 1. DPI (Flixotide Diskhaler, GSK[b]) 2. DPI (Pulmicort Turbuhaler, AZ[b]) *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 518 *Mean age (SD) (years)* 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 400–2000 μg q.d., BUD 400–2400 μg q.d. or FP 400–1000 μg q.d.	FEV_1 PEF (morning and evening) 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[218]	RCT Single-centre Parallel-group Open-label	*Drugs:* 1. FP 500 μg b.d. (daily total 1000 μg) 2. BUD 800 μg b.d. (daily total 1600 μg) *Delivery device:* 1, 2. MDI + large spacer (no further details reported) *Duration:* 52 wks *Run-in period:* 2 wks	*Number randomised* 59 *Mean age (range) (years)* 1. 50 (29–70) 2. 56 (25–68) *Baseline FEV_1 % predicted* >30 *Previous ICS treatment (drug and dose)* BDP 1500–2000 μg q.d. or BUD 1600 μg q.d. or equivalent doses of other ICS	BMD assessment Biochemical markers of bone turnover Change in urinary free cortisol level Change in plasma cortisol level
Molimard *et al.*, 2005[219]	RCT Multi-centre Parallel-group Open-label	*Drugs:* 1. BDP 800 μg q.d. 2. FP 1000 μg q.d. 3. BUD 1600 μg q.d. *Delivery device:* 1. HFA MDI (QVAR Autohaler, 3M) 2. DPI (Flixotide Diskhaler, GSK) 3. DPI (Pulmicort Turbuhaler, AZ) 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 age (SD) (years)* 1. 42.4 (14.1) 2. 42.1 (13.5) 3. 42.9 (13.8) *Baseline FEV_1 % predicted (± SD)* 1. 76.6 (± 18.5) 2. 76.7 (± 16.8) 3. 79.3 (± 18.0) *Previous ICS treatment (drug and dose)* FP ≤500 μg q.d., BUD ≤1000 μg q.d. or BDP ≤1000 μg q.d.	*Primary outcome* Change from baseline in asthma control score, assessed with Juniper questionnaire (ACQ), incorporating FEV_1% predicted value and rescue medication usage *Secondary outcomes* FEV_1 (litres) AEs

[a] At 5-week intervals dose was reduced to 200 and then 100 μg b.d. if asthma control maintained.
[b] Not stated explicitly, but deduced from the text.

colleagues,[216] the adjusted mean change from baseline after 6 weeks of treatment was 0.22 litres in the FP 1000 µg/day arm compared with 0.12 litres in the BUD 1600 µg/day arm. The difference between the study groups was shown to be statistically significant, $p < 0.05$. This analysis was not on an ITT population.

The FEV_1 at end-point in the Ringdal and colleagues[217] trial was 2.38 (SD 0.77) litres in the FP arm and 2.27 (SD 0.77) litres in the BUD arm after 12 weeks of treatment. The treatment difference was shown not to be statistically significantly different [0.11 litres (95% CI –0.02 to 0.24)].

The change in morning PEF was shown to be statistically significantly better after 12 weeks of treatment with FP compared with BUD after 12 weeks of treatment with BUD in the Ringdal and colleagues trial ($p = 0.003$).[217] The change in morning PEF was 20.90 l/minute (SD 37.92) and 12.40 (SD 35.45) l/minute, respectively [treatment difference 8.50 l/minute (95% CI 2.18 to 14.83)]. This CI was not provided by Ringdal and colleagues,[217] and was calculated by a reviewer. Ringdal and colleagues[217] stated in their paper that treatment groups were considered equivalent if the 95% CI for the difference between treatments was ⩽15 l/minute. The CI 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. The percentage of symptom-free days in the Heinig and colleagues[214] trial at end-point (after 24 weeks) showed a trend for improved symptoms in the FP arm [29.90 (SD 38.70)%] compared with BUD [23.30 (SD 36.40)%]; the treatment difference was not statistically significantly different between groups [difference 6.60 (95% CI –1.48 to 14.68)].

Symptom ratings on a four-point scale in the Kuna study[215] showed no statistically significant differences between treatment groups after 5 weeks of treatment. In the FP arm the rating at end-point was 0.46 and in the BUD arm it was 0.56, $p = 0.44$.

Although Ayres and colleagues[216] 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[219] 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 percentage 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[216] reported some data on symptoms in their trial for the comparison between 1000 µg FP and 1600 µg 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[216] and Kuna[215] 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[216] 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.

Exacerbations

Parallel design, 1:1 dose ratio. The proportion of patients experiencing exacerbations in the Ayres and colleagues trial[216] was slightly higher in the BUD 1.6 mg/day group than the FP 2 mg/day 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 trial[216] was slightly higher in the BUD 1600 µg/day group than the FP 1000 µg/day group (17% FP versus 22% BUD, *p*-value not reported).

Adverse events

Parallel design, 1:1 dose ratio. AEs were experienced by 49% of the participants in the FP arm and 51% of the participants in the BUD arm of the Ayres and colleagues trial.[216]

Parallel design, 1:2 dose ratio. Three trials reported the number of participants experiencing an AE, and these data were combined in a meta-analysis (*Figure 12*). Using a fixed-effects model, the meta-analysis showed a trend to better odds of not having an AE in the BUD treatment groups, but this was not statistically significant [OR 1.20 (95% CI 0.95, 1.50)]. The duration of

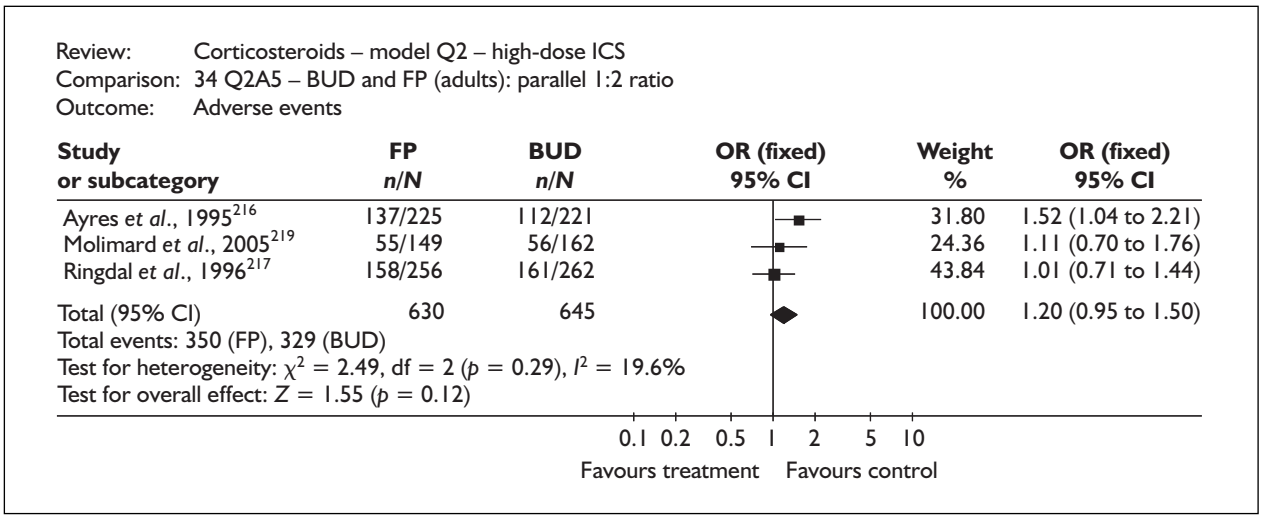

FIGURE 12 *Adverse events FP versus BUD, parallel 1:2 dose ratio*

two of these studies was 12 weeks and the other was of 6 weeks.

In the Ringdal and colleagues study,[217] 10/256 participants in the FP group and 13/262 participants in the BUD group discontinued due to AEs. This was not statistically significantly different [OR 0.78 (95% CI 0.34 to 1.81)].

Cortisol levels and bone mineral density
In the Hughes and colleagues study,[218] 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 = not significant). The study also reported 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 BMD at the spine, neck or trochanter were observed in participants treated with either FP or BUD.

Summary
Six parallel-group RCTs[214–219] evaluated the effectiveness of BUD compared with FP. Two trials had a nominal dose ratio of 1:1,[214,215] three a nominal dose ratio of 1:2[217–219] 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.[216] The nominal 1:1 dose ratio comparisons compared 800–2000 µg FP with 800–2000 µg BUD. The nominal 1:2 dose ratio comparisons compared 800–1000 µg FP with 1600 µg 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 FEV_1. This was not on an ITT population and therefore may be subject to measurement bias. No statistically significant differences between treated groups were observed on measures of symptoms, exacerbations or AEs.

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 FEV_1; however, care is required in interpreting these data as they were not on an ITT population and therefore may be subject to measurement bias. One other trial reported a difference in favour of FP on morning PEF. 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 AE profiles of the groups.

MF and BUD (review Q2 – high-dose ICS)
Study characteristics
One trial reported a comparison of MF and BUD, by Bousquet and colleagues[199] (*Table 34*). This study had four treatment arms: 100 µg MF twice daily plus placebo; 200 µg MF twice daily plus placebo; 400 µg MF twice daily plus placebo; and 400 µg BUD twice daily. Daily dose ratios were therefore 1:4, 1:2 and 1:1, respectively. Only the

TABLE 34 *Characteristics of studies (MF and BUD)*

Study	Design	Intervention	Patients	Outcomes
Bousquet *et al.*, 2000[199]	RCT Multi-centre Parallel-group Evaluator-blind Active-controlled	1. MF 100 μg b.d. (daily total 200 μg) + placebo 2. MF 200 μg b.d. (daily total 400 μg) + placebo 3. MF 400 μg b.d. (daily total 800 μg) + placebo 4. BUD 400 μg b.d. (daily total 800 μg) *Delivery device:* 1, 2, 3. MF DPI (made by Schering-Plough) 4. DPI (Pulmicort Turbuhaler, AZ) *Duration:* 12 wks *Run-in period:* Not reported	*Number randomised* 730 *Mean age (range) (years)* 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 (litres) *Secondary outcomes* FVC PEF Symptom scores Nocturnal awakenings requiring salbutamol use as rescue medication Daily salbutamol use Physician evaluation of response to therapy AEs

comparison between 400 µg MF twice daily plus placebo and 400 µg 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 in the section 'MF and BUD (review Q1 – low-dose ICS)' (p. 49).

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, AZ), 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 the section 'MF and BUD (review Q1 – low-dose ICS)' (p. 49).

Results

Lung function

The 400 µg twice daily MF group in the study by Bousquet and colleagues[199] showed a mean change from baseline FEV_1 that was statistically significantly greater than change in the BUD group (0.16 ± 0.03 litres for 400 µg twice daily MF versus 0.06 ± 0.03 litres in the BUD group, $p < 0.05$). Similarly, the end-point percentage of predicted FEV_1 was statistically significantly different between the 400 µg twice daily MF group (83.0 ± 1.2%) and BUD (77.9 ± 1.1%), $p < 0.05$.

Bousquet and colleagues[199] did not find a statistically significant difference between MF and BUD in terms of change in morning PEF. The change from baseline to end-point was 24.75 ± 5.3 l/minute in the BUD group compared with 37.3 ± 5.2 l/minute in the 400 µg twice daily MF group. Changes in evening PEF were not presented, but were reported to be similar to changes in morning PEF.

Symptoms

Bousquet and colleagues[199] reported the change from baseline in mean number of nocturnal awakenings to be 0.41 in the 400 µg twice daily MF group and 0.30 in the BUD group (p = not significant).

Use of rescue medication

Bousquet and colleagues[199] reported relief use of salbuterol as change from baseline dose. The change from baseline in the BUD group was –33.90 µg/day, compared with –72.13 µg/day in the –400 µg twice daily MF group. Although the decrease in use in the MF group was greater than that in the BUD group, the difference was not statistically significant.

Summary

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

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

[Confidential information removed].

Study characteristics

[Confidential information removed].

TABLE 35 *Characteristics of studies (CIC versus FP)*

[Confidential information removed].

Results

[Confidential information removed].

Summary

[Confidential information removed].

MF and FP (review Q2 – high-dose ICS)

Study characteristics

One trial comparing MF and FP at high doses was identified, by O'Connor and colleagues[202] (*Table 36*). The study comprised four arms in which three doses of MF (200, 400 and 800 µg/day) were compared with one dose of FP (500 µg/day). The comparisons of 200 and 400 µg/day MF with FP are reported in the section 'MF and FP (review Q1 – low-dose ICS)' (p. 55). The comparison of 800 µg/day MF with 500 µg/day FP approximates a rounded nominal dose ratio of 2:1.

O'Connor and colleagues[202] 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, GSK).

The study was a large-scale international dose-ranging trial (with 60 centres in 20 countries). The duration was relatively short, 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 years for MF and 40 years for FP. The enrolled patients had moderate persistent asthma.

TABLE 36 *Characteristics of the study comparing MF and FP*

Study	Design	Intervention	Patients	Outcomes
O'Connor *et al.*, 2001[202]	RCT Parallel-group Double-blind (dosage) Evaluator-blind (medication)	*Drug(s):* 1. MF 100 μg b.d. (daily total 200 μg) 2. MF 200 μg b.d. (daily total 400 μg) 3. MF 400 μg b.d. (daily total 800 μg) 4. FP 250 μg b.d. (daily total 500 μg) *Delivery device:* 1, 2, 3. MF DPI (made by Schering-Plough) 4. DPI (Flixotide Diskhaler, GSK) *Duration:* 12 wks *Run-in period:* 1–2 wks	*Number randomised* 733 *Mean age (range) (years)* 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 400–1000 μg q.d., BUD 400–800 μg q.d., flunisolide 500–1000 μg q.d., FP 200–500 or triamcinolone acetonide 600–800 μg q.d.	*Primary outcome* Mean change in FEV_1 from baseline to end-point *Secondary outcomes* PEF $FEF_{25–75\%}$ FVC Asthma symptom scores Rescue medication use Nocturnal awakenings Physician evaluation AEs

The objective of the work was to compare the 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.

Results

Parallel 2:1 dose ratio studies

The study by O'Connor and colleagues[202] had a parallel design and provided a single comparison of high-dose (800 µg/day) MF with high-dose (500 µg/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 litres for MF (800 µg/day) and 0.16 ± 0.54 litres for FP (500 µg/day). The change in morning PEF (mean ± SD) was 30 ± 67.8 l/minute for MF (800 µg/day) and 32 ± 67.8 l/minute for FP (500 µg/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 –38.10 µg/day for MF-treated patients and –52.06 µg/day for FP-treated patients. This difference between the treatments was not statistically significant.

Exacerbations

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

Adverse events

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

Summary

One parallel-group RCT compared 800 µg/day MF and 500 µg/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.

Summary of Q2 – relative effectiveness of high-dose ICS

According to the BTS/SIGN Guideline, BDP and BUD are comparable at the same daily dose. FP and MF are 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 Guideline the following drugs at the following doses (excluding considerations of device) are equivalent: BUD 800 µg/BDP 800 µg/FP 400 µg/MF 400 µg/CIC 400 µg. The exception to this is for HFA-propelled pMDI BDP compared with FP, which, it is suggested,[173] 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 versus BUD (two RCTs, 1:1 dose ratio) – The only significant difference was for exacerbations in favour of BUD.
- FP versus BDP (10 RCTs, two at 1:1 and eight at 1:2 dose ratio) – Significant differences in favour of FP for lung function and exacerbations, otherwise few significant differences.

- HFA BDP versus HFA FP (one RCT, 1:1 dose ratio) – No significant differences. Non-inferiority demonstrated for lung function (in ITT analysis, but not PP analysis).
- FP versus BUD (six RCTs, three at 1:1 and three at 1:2 dose ratio) – FP significantly favourable for lung function, from one RCT (at 1:1 and 1:2 rounded nominal dose ratios, FP:BUD). No significant differences for AEs based on meta-analysis of three RCTs.
- MF versus BUD (one RCT, 1:1 dose ratio) – Significant difference in favour of MF for lung function.
- CIC versus FP **[Confidential information removed]**.
- MF versus FP (one RCT, 1:2 dose ratio) – No significant differences on any outcomes.

Tables 37–43 provide a visual illustration of the results of pair-wise comparisons.

Review question 3a – ICS versus ICS + LABA (ICS dose higher when used alone)

To recap, 10 RCTs evaluated ICS versus ICS + LABA, where the ICS alone arm used a higher dose than that used in the combination inhaler arm (*Table 44*). The following sub-sections describe the characteristics and results of these trials.

ICS versus ICS + LABA (FP versus FP/SAL)

Study characteristics

Two RCTs evaluated the effectiveness of FP/SAL in a combination inhaler compared with FP alone, and were published in 2003[221] and 2004.[222] 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 45*).

The trials differed in the doses of FP/SAL administered to patients. Bergmann and colleagues[222] compared FP/SAL in a combination inhaler with a total daily dose of 500 µg/100 µg with FP given at a dose of 1000 µg/day. The total daily doses of FP in the study by Busse and colleagues[221] were lower, with patients receiving 200 µg/100 µg FP/SAL in a combination inhaler compared with 500 µg/day FP alone. Both trials used Diskus inhaler devices (all by GSK) to deliver both the combination drugs and the ICS alone (Busse and colleagues[221] used Advair and Flovent Diskus; no further details are reported by Bergmann and colleagues[222]).

The treatment duration was 12 weeks in the Bergmann and colleagues study.[222] Busse and colleagues[221] 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[222] 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[221] was an equivalence trial and was designed to evaluate whether FP/SAL delivered via a combination inhaler was ICS-sparing in patients requiring 500 µg/day FP for asthma stability.

The mean age of participants was similar, ranging from around 40 to 50 years. Patients in both trials had previously been managed on medium-dose ICS therapy of 500–1000 µg BDP or equivalent (*Table 45*). Patients were described as having moderate asthma in one trial,[222] but severity was not reported in the other trial. Baseline FEV_1 % predicted was similar, around 75–80%.

Bergmann and colleagues[222] reported change in morning PEF as their primary outcome measure. The trial was designed to identify a difference of 15 l/minute between treatment groups with a power of 80% at $\alpha = 0.05$, requiring 174 patients in each group. Busse and colleagues[221] 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 ($\Delta = 0.15$, 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[222] 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[221] 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 ITT principle in both studies.

Results

For a number of outcomes, Busse and colleagues[221] reported that differences between treatment groups were within the 90% CI for

TABLE 37 *BUD versus BDP (n = 2 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
1500 µg BDP) vs 1600 µg BUD)	Ebden *et al.*,[81] cross-over (no wash-out), 6 weeks, pMDI + spacer, *n* = 28	BDP BUD	NSD	C	C						+		
2000 µg BDP vs 2000 µg BUD)	Kaur *et al.*,[203] cross-over, 6 weeks, MDI + spacer, *n* = 15	BDP BUD	NSD										

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; *n*, number of events; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 38 *FP versus BDP (n = 10 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
1500 µg vs 1500 µg	Fabbri *et al.*,[304] parallel, 12 months, MDI, *n* = 274	FP	+	+	+		NSD	NSD				+	70%
		BDP											73%
2000 µg vs 1600 µg	Boe *et al.*,[205] parallel, 3 months, DPI, *n* = 134	FP	NSD						NSD		NSD	F	C
		BDP											
500 µg vs 1000 µg	Lundbäck *et al.*,[207] parallel, 6 weeks, MDI, *n* = 585	FP	NSD	NSD	NSD		NSD	NSD					97 (50%)
		BDP							+				89 (46%)
750 µg vs 1500 µg	Medici *et al.*,[191] parallel, 12 months, MDI, *n* = 69	FP										NSD	C
		BDP											
1000 µg vs 2000 µg	Barnes *et al.*,[206] parallel, 6 weeks, MDI, *n* = 154	FP	NSD	NSD	NSD		NSD	NSD			NSD		43 (52%)
		BDP											37 (51%)
	Lorentzen *et al.*,[208] parallel, 12 months, MDI, *n* = 213	FP										NSD	114 (72%)
		BDP											39 (72%)
	Egan *et al.*,[209] parallel, 2 years, MDI, *n* = 33	FP											C
		BDP										F	
BDP 1000 µg, 1500 µg or 2000 µg vs FP half the BDP dose	Malo *et al.*,[210] cross-over, 4 months, MDI, *n* = 67	FP	NSD									NSD	
		BDP											
	Pauwels *et al.*,[211] cross-over, 12 months, MDI, *n* = 340	FP	NSD				NSD	NSD		+		NSD	66.8%
		BDP											66.2%

continued

TABLE 38 *FP versus BDP (n = 10 RCTs) (cont'd)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
750 μg FP vs 1500 μg BDP	Bootsma *et al.*,[212] cross-over, 12 weeks, MDI, *n* = 21	FP BDP	NSD		NSD				NSD		NSD		

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; F, results appear to favour this treatment group, but no tests of statistical significance reported; *n*, number of events; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 39 *HFA BDP versus FP (n = 1 RCT)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
800 μg BDP vs 1000 μg FP	Aubier *et al.*,[213] parallel, 28 weeks, DPI, *n* = 503	BDP FP	NSD	NSD NID (in ITT but not PP)	NSD	NSD	NSD						38.3% 24.8%

ITT, intent-to-treat population; NID, non-inferiority demonstrated; NW, nocturnal waking; NSD, no significant difference between trial arms; PP, per protocol population; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); blank cells signify no data reported on that outcome.

TABLE 40 *FP versus BUD (n = 6 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
2000 µg FP vs 2000 µg BUD	Heinig *et al.*,[214] parallel, 24 weeks, DPI (Diskhaler or Turbuhaler), *n* = 395	FP BUD	C				F						
800 µg FP vs 800 µg BUD	Kuna *et al.*,[215] parallel, 5 weeks, DPI Diskhaler or Turbuhaler, *n* = 197	FP BUD	NSD	NSD	NSD				NSD				
800–1000 µg FP vs 1600 µg BUD	**Meta-analysis** Ayres *et al.*,[216] (1000 µg FP arm), Molimard,[219] Ringdal[217]	FP BUD											NSD
1000 µg FP 2000 µg FP 1600 µg BUD	Ayres *et al.*,[216] parallel, 6 weeks, MDI, *n* = 671	1. 1000 µg FP 2. 2000 µg FP 3. BUD	+ 1 vs 3 + 2 vs 3								F 1 vs 3 F 2 vs 3		49% 51%
800 µg FP vs 1600 µg BUD	Ringdal *et al.*,[217] parallel, 12 weeks, DPI (Diskhaler or Turbuhaler), *n* = 518	FP BUD	NSD	+									
1000 µg FP vs 1600 µg BUD	Molimard *et al.*,[219] parallel, 12 weeks, DPI (Diskhaler or Turbuhaler), *n* = 460	FP BUD	NSD						NSD				

continued

TABLE 40 *FP versus BUD (n = 6 RCTs) (cont'd)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
	Hughes *et al.*,[218] parallel, 52 weeks, MDI + spacer, *n* = 59	FP BUD											

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; F, results appear to favour this treatment group, but no tests of statistical significance reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 41 *MF versus BUD (n = 1 RCT)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
800 µg MF vs 800 µg BUD	Bousquet *et al.*,[199] parallel, 12 weeks, DPI, *n* = 730	MF BUD	+	NSD		NSD					F		

F, results appear to favour this treatment group, but no tests of statistical significance reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 42 *FP vs CIC (n = 3 RCTs)*
[Confidential information removed].

TABLE 43 *FP versus MF (n = 1 RCT)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
MF 800 μg vs FP 500 μg	O'Connor *et al.*,[202] parallel, 12 weeks, DPI, *n* = 733	MF FP	NSD	NSD		NSD					NSD		30% 29%

n, number of events; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; ; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 44 *Breakdown of studies for review question 3a – ICS versus ICS + LABA (ICS dose higher when used alone)*

Pair-wise comparison	No. 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

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[222] trial was twice that administered in the Busse and colleagues trial.[221] This should be taken into consideration when interpreting the results of the meta-analyses.

Lung function
Data on FEV_1 were reported in different ways in the two studies. Busse and colleagues[221] reported a mean change from baseline to end-point at 12 weeks in FEV_1 of 0.07 (±0.17) litres in the FP/SAL group compared with –0.03 (±0.17) litres ($p \leq 0.001$) in the FP group. In the subgroup of patients who received treatment for 24 weeks, improvements from baseline in FEV_1 were 0.10 (± SEM 0.02) litres and 0.00 (± SEM 0.02) litres ($p \leq 0.007$) 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[222] reported a mean change from baseline in FEV_1 % predicted of 12.30% (± 1.70) in the FP/SAL group compared with 8.40% (± 1.40) in the FP group, with no statistically significant differences between groups (p-value not reported).

Change in morning PEF (litres/minute) was reported by both trials, and data at 12 weeks were combined in a meta-analysis (*Figure 13*). 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 to 25.72); $p < 0.0001$]. Heterogeneity was not statistically significant ($p = 0.81$, $I^2 = 0\%$).

Change in evening PEF (litres/minute) from baseline to end-point at 12 weeks was also reported by both trials. Combining the data in a meta-analysis (*Figure 14*) using a fixed-effects model showed a statistically significant improvement with FP/SAL treatment compared with FP [WMD 16.26 (95% CI 7.90 to 24.62); $p < 0.0001$]. Heterogeneity was not statistically significant ($p = 0.90$, $I^2 = 0\%$).

In the Busse and colleagues trial,[221] the change from baseline to end-point at 24 weeks in morning PEF was 45.2 (± SEM 5.9) l/minute in the combination treatment group compared with 32.5 (± SEM 6.8) l/minute in the FP group ($p = 0.180$). Differences between groups in evening PEF (24-week data) were 49.4 (± SEM 5.9) l/minute and 31.3 (± SEM 6.2) l/minute, respectively ($p = 0.039$). For both morning and evening PEF, 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 15*). 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 to 11.90); $p = 0.001$]. Heterogeneity was not statistically significant ($p = 0.32$, $I^2 = 0.9\%$).

For patients receiving treatment for 24 weeks,[221] the mean change from baseline was 11.6 (± SEM 3.0) days for FP/SAL compared with 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[221] 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) versus –0.12 (± SEM 0.04), $p = 0.232$ for FP/SAL versus FP, respectively], and at 24 weeks [–0.22 (± SEM 0.06) versus –0.14 (± SEM 0.06), $p = 0.137$ for FP/SAL versus FP, respectively]. Differences between treatments were within the 90% CIs for equivalence (the CIs were not reported). In the trial by Bergmann and colleagues,[222] 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 HRQoL were reported in one trial[222] using a validated asthma quality of life questionnaire

TABLE 45 *Study characteristics (FP versus FP/SAL)*

Study	Design	Intervention	Patients	Outcomes
Bergmann *et al.*, 2004[222]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 250 μg/50 μg b.d. (daily total 500 μg/100 μg) 2. FP 500 μg b.d. (daily total 1000 μg) *Delivery device:* 1, 2. DPI Diskus (GSK[a]) *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 365 *Mean age (± SD) (years)* 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 800–1000 μg q.d. or FP 500 μg q.d.	*Primary outcome* Change in morning PEF *Secondary outcomes* Evening PEF FEV_1 (% predicted) FVC Asthma symptom score % symptom-free days/nights Use of rescue medication AEs Quality of life
Busse *et al.*, 2003[221]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 100 μg/50 μg b.d. (daily total 200 μg + 100 μg) 2. FP 250 μg b.d. (daily total 500 μg) *Delivery device:* 1. DPI Advair Diskus (GSK) 2. DPI Flovent Diskus (GSK) *Duration:* 12–24 wks *Run-in period:* 3 run-in periods: 10–14 days 5–28 days 26–30 days	*Number randomised* 558 (12 wks treatment $n = 250$; 24 wks treatment $n = 308$) *Mean age (range) (years)* 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 504–840 μg q.d., BUD 400–800 μg q.d., FP 440–660 μg q.d., flunisolide 1000–1500 μg q.d. or triamcinolone acetonide 1200–1600 μg q.d.	*Primary outcome* Proportion of patients with no worsening asthma *Secondary outcomes* FEV_1 (litres) PEF (morning and evening) Asthma symptom score % symptom-free days Rescue medication use Rescue medication-free days AEs

[a] Not stated explicitly, but deduced from the text.

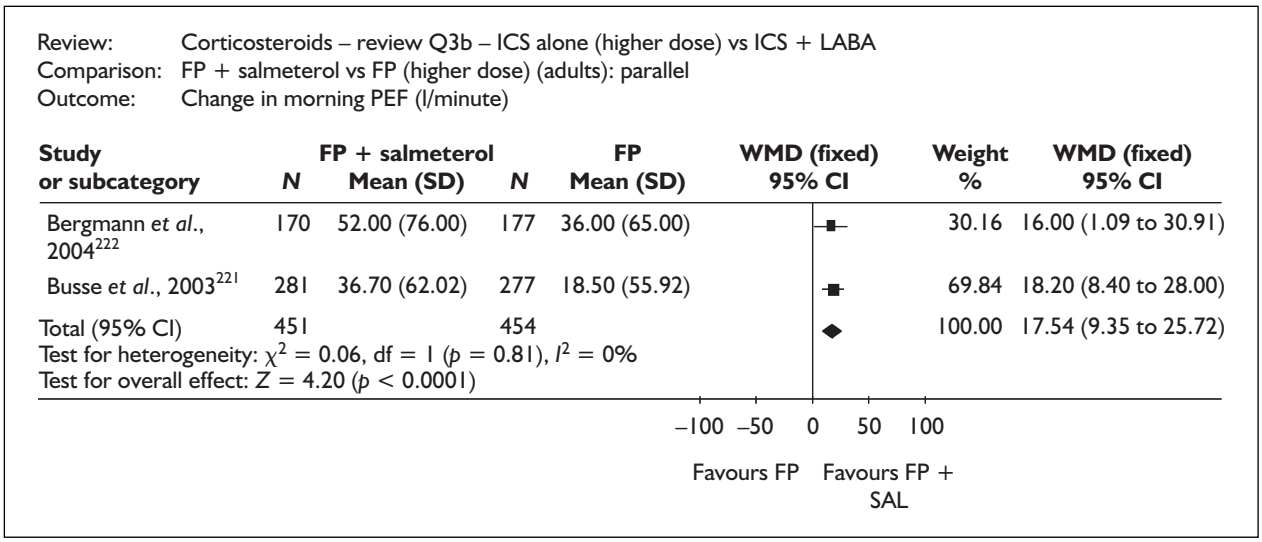

FIGURE 13 *Change in morning PEF (l/minute), FP/SAL versus FP*

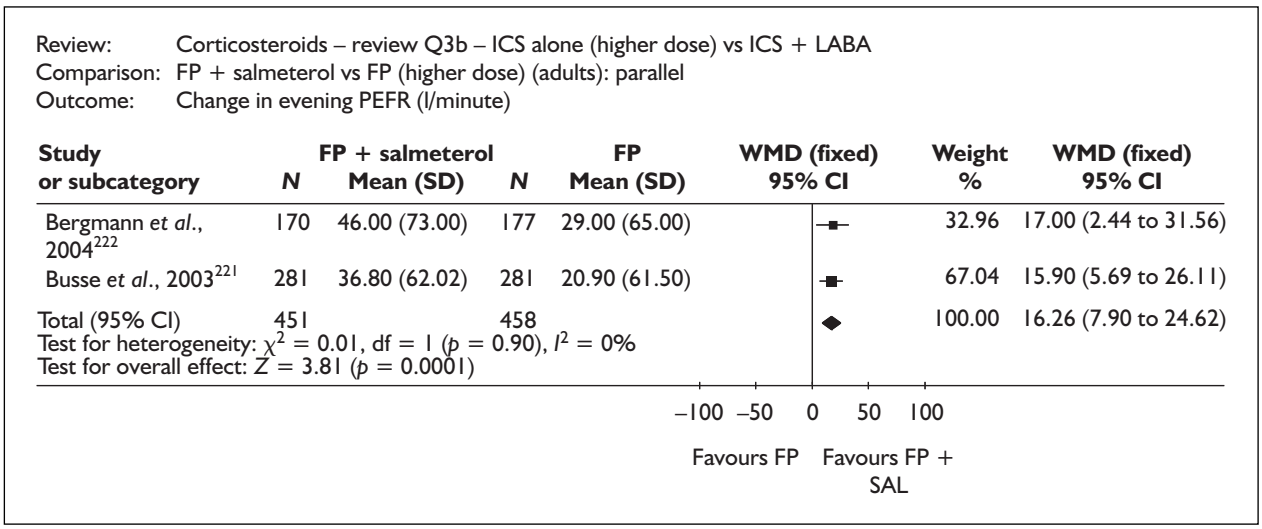

FIGURE 14 *Change in evening PEF (l/minute), FP/SAL versus FP*

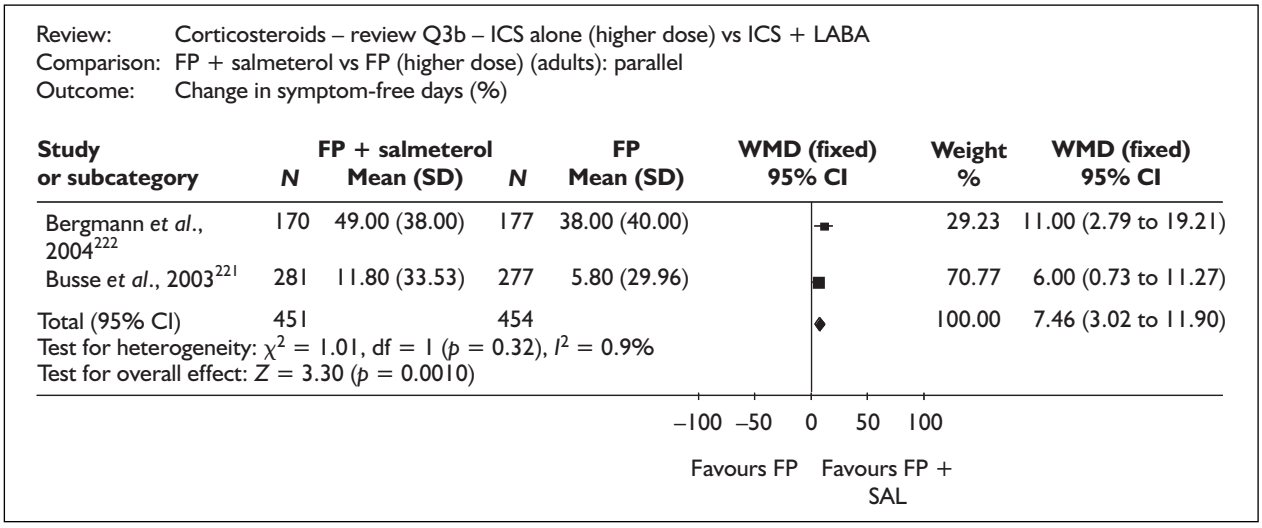

FIGURE 15 *Change in symptom-free days (%), FP/SAL versus FP*

(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 with 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 16*). Using a fixed-effects model, the WMD was –0.19 puffs (95% CI –0.36 to –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 to 0.14)], and heterogeneity remained. Therefore, care needs to be taken in interpreting this outcome. *Figure 16* provides an illustration of the direction of the results.

For patients receiving treatment for 24 weeks,[221] 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 with –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,[222] one (0.6%) patient in the combination therapy group compared with 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,[221] 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 AEs were reported in the two trials to be combined in a meta-analysis (*Figure 17*). The fixed-effects model's pooled OR was 0.89 (95% CI 0.67 to 1.17) suggesting no statistically significant difference between the two treatments ($p = 0.39$). Heterogeneity was not statistically significant ($p = 0.25$, $I^2 = 25.5\%$).

In the subgroup of patients who received treatment for 24 weeks, the incidence of AEs was also similar for the two treatment groups (44% of FP/SAL patients and 47% of FP patients reported one or more AEs).[221]

Discontinuations due to AEs were similar for the two treatment groups in one trial.[221] One patient (<1%) receiving combination therapy and two patients (<1%) receiving FP withdrew from the study as a result of AEs (no *p*-value reported).

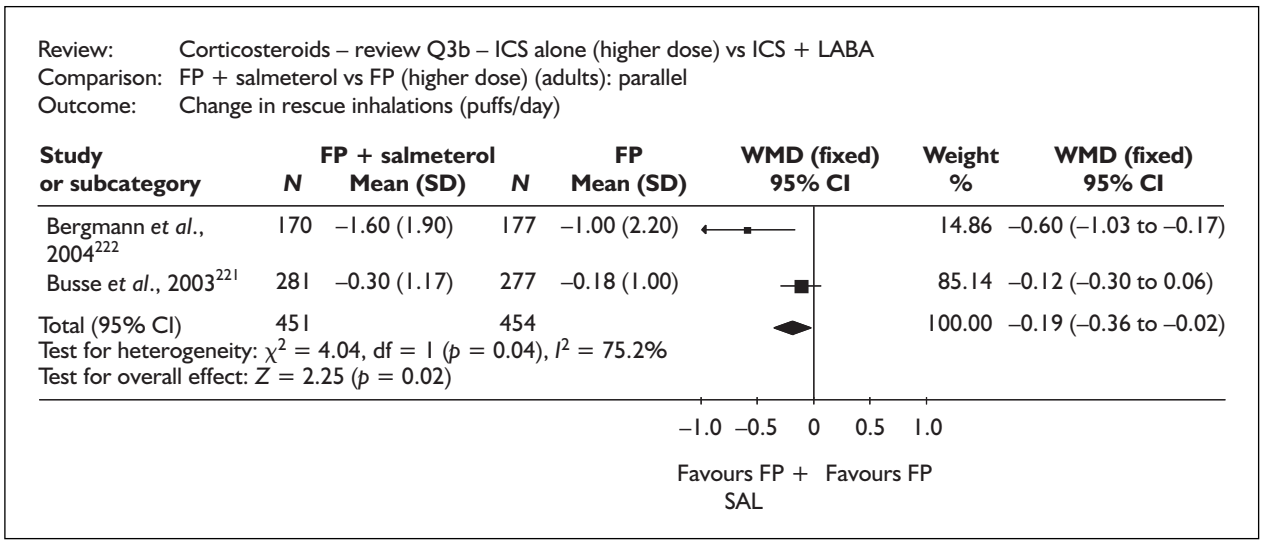

FIGURE 16 *Change in use of rescue medication (puffs/day), FP/SAL versus FP*

Summary
Two large, parallel-group RCTs compared 200–500 µg/day FP and 100 µg/day SAL in a combination inhaler with 500–1000 µg/day FP in adult participants. The Busse and colleagues study[221] 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 CIs for clinical equivalence (but the data to support this were not provided).

Treatment with FP/SAL was significantly more favourable than FP treatment alone on measures of PEF but not FEV_1. Data on symptoms were 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 AEs, and no observed differences for exacerbations or discontinuations due to AEs where reported. Although patients receiving FP/SAL had a significantly reduced need for rescue medication, the trials were statistically heterogeneous and this difference did not remain when the data were analysed in a random-effects model.

ICS versus ICS + LABA (BUD versus FP/SAL)

Study characteristics
Three RCTs, published between 2000 and 2004,[223–225] evaluated BUD compared with FP/SAL combination therapy (*Table 46*). 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[224] and Zhong and colleagues,[225] compared the combination of 200 µg/100 µg/day FP/SAL with 800 µg/day BUD (representing a low dose of BUD). The third study, by Jenkins and colleagues,[223] compared the combination of 500 µg/100 µg/day FP/SAL with 1600 µg/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 Turbuhaler (Pulmicort Turbuhaler, AZ). All three studies delivered the FP/SAL via a Diskus combination inhaler (Seretide Accuhaler, GSK). Two studies also used a placebo Turbuhaler with the FP/SAL treatment and a placebo Diskus inhaler with the BUD treatment.[223,224] The studies were relatively short, at 6, 12 and 24 weeks. Two of the studies evaluated the superiority of FP/SAL combination therapy compared with BUD.[223,225] Zhong and colleagues[225] assessed the efficacy and safety of the treatments in patients with asthma that was uncontrolled with low-dose ICS treatment. Jenkins and colleagues[223] compared treatment with a combination of a LABA and ICS with another ICS alone via a different inhaler. The third study (Johansson and colleagues[224]) 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

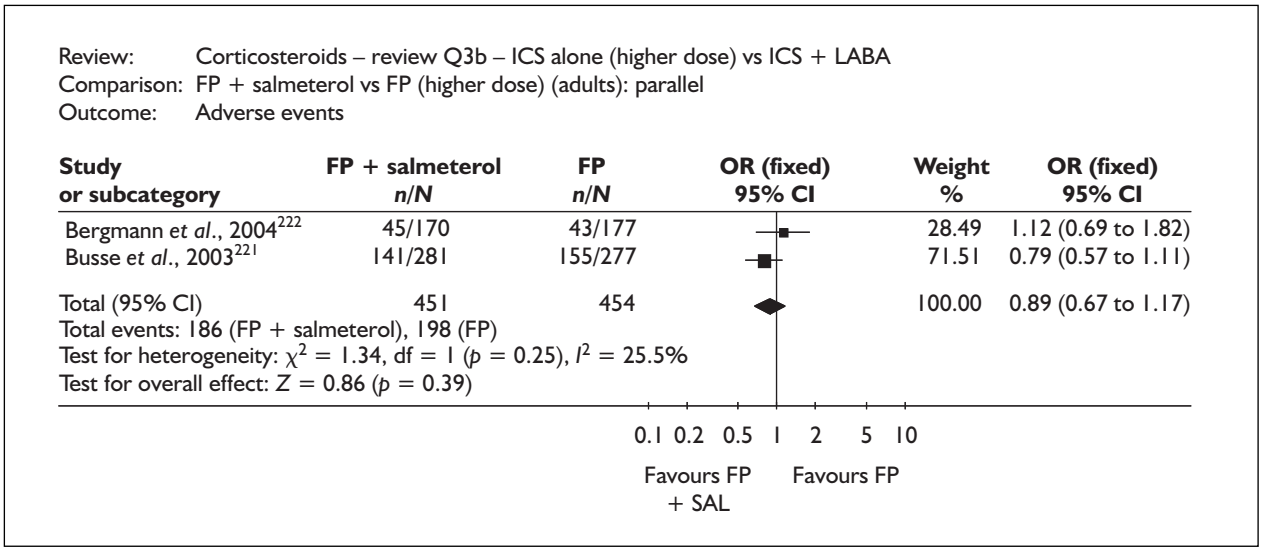

FIGURE 17 *Adverse events, FP/SAL versus FP*

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 400–600 µg daily of FP or 800–1200 µg daily of BUD or BDP.[223] Two trials reported patients as having been previously treated with a daily dose of 500 µg BUD or BDP.[224,225] In two of the studies the mean baseline FEV_1 % predicted is reported as between 68 and 77.[223,224] The third study did not report FEV_1 % predicted.[225] Johansson and colleagues[224] described patients as suffering from mild to moderate asthma, whereas the other two studies described patients as suffering from moderate to severe asthma.[223,225]

Two studies reported their primary outcome as the mean morning PEF,[224,225] whereas Jenkins and colleagues[223] 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/minute in the PEF with 95% confidence, based on the assumption that the maximum SD of the PEF is 40 l/minute and that the minimum number of subjects per treatment group would be 150. One study provided no details of their randomisation procedure,[223] whereas the other two studies used computer-generated randomisation codes.[224,225] Johansson and colleagues[224] provided full details of blinding and concealment of treatment allocation, whereas no details of treatment allocation concealment were provided in the other two studies.[223,225] All three studies reported an ITT analysis, using the ITT population for analysis.

Results

Some of the symptom scores reported by Jenkins and colleagues[223] were also summarised briefly in a secondary publication by Lundbäck and colleagues.[226] Quality of life scores originating from the study carried out by Jenkins and colleagues are reported in a secondary publication by Juniper and colleagues.[227]

Lung function

FEV_1. Two studies reported the FEV_1 at end-point,[223,224] one study reported the change in FEV_1 from baseline to end-point[225] and one study briefly mentioned the percentage predicted FEV_1 at end-point.[223]

Johansson and colleagues[224] reported that the mean ± SD of the FEV_1 at end-point (12 weeks) was 2.79 ± 0.81 litres for FP/SAL and 2.83 ± 0.86 litres for low-dose (800 µg/day) BUD; however, this difference was not tested statistically. Jenkins and colleagues[223] reported that the FEV_1 at end-point (24 weeks) differed significantly between FP/SAL (mean 2.53 litres) and high-dose (1600 µg/day) BUD (mean 2.44 litres); the treatment difference was 0.091 litres, (95% CI 0.0 to 0.17, $p < 0.05$). Zhong and colleagues[225] 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 (800 µg/day) BUD. This difference was not statistically significant ($p = 0.2614$). Jenkins and colleagues[223] commented (without presenting data) that the percentage 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 PEF. The change from baseline in the morning and evening PEF was reported in all three studies but the data and statistics were presented in different ways that preclude combining the studies in a meta-analysis. Johansson and colleagues[224] reported a change in the morning PEF from baseline to end-point (12 weeks) of 383–426 l/minute in subjects receiving FP/SAL and of 382–415 l/minute in subjects receiving low-dose (800 µg/day) BUD. Statistics presented by Johansson and colleagues[224] appear to refer to the difference in morning PEF between the drugs at end-point [11 l/minute (95% CI 2 to 20 l/minute, $p = 0.022$)] rather than the difference of the change in morning PEF from baseline (10 l/minute). Accordingly, it is unclear in that study whether the changes from baseline in the morning PEF differed significantly between the treatments. Johansson and colleagues[224] also reported that the predicted percentage morning PEF differed significantly between the treatments, with a change from baseline to end-point of 83–94% in the FP/SAL subject group and of 80–89% in the BUD subject group (95% CI 1 to 5%, $p = 0.009$).

Zhong and colleagues[225] reported that the mean change from baseline to end-point (6 weeks) in the morning PEF was 52.4 l/minute for subjects on FP/SAL (95% CI from 44.2 to 60.6 l/minute) and 29.9 l/minute for subjects on low-dose (800 µg/day) BUD (95% CI from 22.2 to 37.6 l/minute). This difference between the drugs was statistically significant ($p < 0.0001$). At end-point, the least-squares-adjusted mean morning PEF was 326 l/minute (95% CI 318 to 334 l/minute) for the FP/SAL group and 303 l/minute (95% CI from 295 to 311 l/minute) for the BUD group (no p-value reported).

TABLE 46 *Characteristics of studies (BUD versus FP/SAL)*

Study	Design	Intervention	Patients	Outcomes
Jenkins *et al.*, 2000[223] Lundbäck *et al.*, 2000[226] Juniper *et al.*, 2002[227]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. FP/SAL 250/50 μg b.d. (daily total 500/100 μg) 2. BUD 800 μg b.d. (daily total 1600 μg) *Delivery device:* 1. DPI Diskus (Seretide Accuhaler, GSK) + placebo Turbuhaler 2. DPI Turbuhaler (Pulmicort Turbuhaler, AZ) + placebo Diskus *Duration:* 24 wks *Run-in period:* 2 wks	*Number randomised* 353 *Mean age (range) (years)* 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 800–1200 μg q.d.	Change in PEF (morning and evening) Change in FEV_1 Symptom-free days and nights % salbutamol-free days in each group % exacerbations
Johansson *et al.*, 2001[224]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. FP/SAL 100/50 μg b.d. (daily total 200/100 μg) 2. BUD 400 μg b.d. (daily total 800 μg) *Delivery device:* 1. DPI Diskus (Seretide Accuhaler, GSK) + placebo Turbuhaler 2. DPI Turbuhaler (Pulmicort Turbuhaler, AZ) + placebo Diskus *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 349 *Mean age (± SD) (years)* 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 500 μg q.d.	*Primary outcome* Morning PEF *Secondary outcomes* Evening PEF Rescue salbutamol usage Day- and night-time symptom scores Asthma exacerbations
Zhong *et al.*, 2004[225]	RCT Multi-centre Parallel-group Open-label	1. FP/SAL 100/50 μg b.d. (daily total 200/100 μg) 2. BUD 400 μg b.d. (daily total 800 μg) *Delivery device:* 1. DPI Diskus (Seretide Accuhaler, GSK) 2. DPI Turbuhaler (Pulmicort Turbuhaler, AZ) *Duration:* 6 wks *Run-in period:* 2 wks	*Number randomised* 398 *Mean age (range) (years)* 1. 46 (44–47) 2. 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 PEF *Secondary outcomes* Evening PEF Use of rescue medication Day- and night-time asthma symptoms scores % symptom-free days and nights FEV_1

Jenkins and colleagues[223] presented data on the morning PEF for several 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 PEF from baseline (adjusted by ANCOVA for sex, age and country) was 410 ± 4.49 l/minute for subjects on FP/SAL and 384 ± 4.69 l/minute for subjects on high-dose (1600 µg/day) BUD. The difference between treatments of 26 l/minute (95% CI 14 to 38 l/minute) was statistically significant ($p < 0.001$). The corresponding figures for the morning PEF averaged over the whole study (weeks 1–24) showed a similar pattern, with a mean ± SD change from baseline of 406 ± 3.67 l/minute for FP/SAL subjects and 380 ± 3.81 l/minute for BUD subjects. This difference of 25 l/minute (95% CI 15 to 35 l/minute; $p < 0.001$) was statistically significant.

Evening PEF. Johansson and colleagues[224] reported (without giving details) that the change from baseline in the evening PEF was significantly larger (by 11 l/minute) for subjects on FP/SAL than for subjects on low-dose (800 µg/day) BUD (95% CI 3 to 20 l/minute, $p = 0.008$). The predicted percentage evening PEF was also significantly larger in the FP/SAL subject group (95 CI 1 to 5%; $p = 0.003$).

Zhong and colleagues[225] reported that the mean change from baseline to end-point (6 weeks) in the evening PEF was 45.6 l/minute for subjects on FP/SAL and 32.1 l/minute for subjects on low-dose (800 µg/day) BUD. This difference between the drugs was statistically significant ($p = 0.0066$).

For weeks 13–24 of their study, Jenkins and colleagues[223] reported a mean ± SD change from baseline in the evening PEF (adjusted in ANCOVA for sex, age and country) of 420 ± 3.85 l/minute for subjects on FP/SAL and 401 ± 4.03 l/minute for subjects on high-dose (1600 µg/day) BUD. This difference of 19 (95% CI 9 to 29) l/minute was statistically significant ($p < 0.001$). The corresponding figures for the evening PEF averaged over the whole study (weeks 1–24) show a similar pattern, with a mean ± SD change from baseline of 416 ± 3.14 l/minute for the FP/SAL subject group and 398 ± 3.25 l/minute for the BUD subject group. This difference of 18 (95% CI 9 to 26) l/minute was statistically significant ($p < 0.001$).

Symptoms

All three studies[223–225] reported the percentage of symptom-free days and nights. Johansson and colleagues[224] 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 (800 µg/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 day- or night-time symptoms did not differ between the drugs (no p-value provided).

In their study, Zhong and colleagues[225] reported that the mean percentage of symptom-free days at end-point (6 weeks) was 57% for subjects treated with FP/SAL and 41.0% for subjects on low-dose (800 µg/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-hour periods) the difference between the drugs was statistically significant ($p < 0.001$).

Jenkins and colleagues[223] did not report symptoms at the end-point but did report the mean percentage of symptom-free days for several periods during their study. In the 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 (1600 µg/day) BUD (these data were estimated by the reviewers from Figure 3a of Jenkins and colleagues[223]). The respective median percentages of symptom-free days over the whole study (weeks 1–24) for these drugs were 60 and 34% (95% CI 2 to 11). For each of these periods the difference in the percentage of symptom-free days between the drugs was statistically significant ($p < 0.001$). The differences between drugs were also statistically significant for other 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[223] 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
HRQoL was analysed in one study. Juniper and colleagues227 calculated asthma quality of life scores based on a 32-item AQLQ for a subset of the subjects in the study reported by Jenkins and colleagues[223] (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, and also an overall AQLQ 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 $\geqslant 0.5$ from baseline), deterioration (a score increase of $\geqslant 0.5$) 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 (1600 µg/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 to 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 HRQoL scores, 30% remained unchanged and none deteriorated. For BUD, scores for 43% of subjects improved, 45% remained unchanged and 12% deteriorated.

Use of rescue medication
All three studies[223,226,227] 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[224] reported that seven participants in the FP/SAL group and 10 participants in the low-dose (800 µg/day) BUD group experienced exacerbations. Of these, three in the FP/SAL group were withdrawn due to exacerbations after randomisation.

Jenkins and colleagues[223] reported that 65 patients in the FP/SAL group and 58 patients in the high-dose (1600 µg/day) BUD group experienced at least one exacerbation. Of these subjects, 36 (20%) and 27 (16%), respectively, had mild exacerbations (95% CI 0.74 to 2.25, $p = 0.382$ for the difference between treatments); 28 (16%) and 29 (17%), respectively, had moderate exacerbations (95% CI 0.54 to 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 AEs in the FP/SAL and in the BUD groups were not tested statistically in the three studies but appear similar between the drugs (*Table 47*). The largest difference was in the comparison with high-dose (800 µg/day) BUD (Johansson and colleagues[224]), where six more subjects in the BUD group than in the FP/SAL group experienced at least one AE (a difference of 4%). Three serious AEs in the FP/SAL group reported by Johansson and colleagues[224] were acute asthma, asthma exacerbation and cough and sputum production. The serious AEs reported by Zhong and colleagues[225] (one in each treatment group) and by Jenkins and colleagues[223] (six in each treatment group) were not considered to be related to the study treatment. Withdrawals due to AEs that were possibly or probably related to the study treatment (*Table 47*) 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[225]). Jenkins and colleagues[223] did not specify whether seven withdrawals due to adverse events in their study were related to the study treatments.

Summary
Three parallel-group RCTs demonstrated larger improvements in lung function outcomes for subjects treated with 200–500 µg/day SAL + 100 µg/day FP than for subjects treated with 800–1600 µg/day BUD. Estimates of the FEV_1 at end-point, the change in FEV_1 from baseline, the

TABLE 47 *Adverse events reported in comparisons of FP/SAL against BUD (number of subjects experiencing at least one adverse event)*

Study	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.*[225]	47 (24%)	45 (24%)	1	1	3	2
Jenkins *et al.*[223]	25 (14%)	31 (18%)	6	6	3	4

percentage predicted FEV_1, morning and evening PEF at end-point and the change from baseline in the PEF were larger in the FP/SAL group in all cases, although statistically significant differences were not reported in all studies. A notable finding from the study of Jenkins and colleagues[223] was that the percentage predicted FEV_1 differed statistically significantly between the two drugs prior to the end-point (at 4 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 AQLQ 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 (6–24 weeks). Accordingly, the longer term relevance of the findings is unclear.

ICS versus ICS + LABA (FP versus BUD/FF)

Study characteristics

One RCT, by Bateman and colleagues published in 2003, evaluated the combination of BUD/FF compared with FP alone.[228] It was a multi-centre study conducted in 37 centres across six countries, 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 twice daily (total daily dose 320/9 µg) or to FP 250 µg (twice daily) (total daily dose 500 µg). It was reported that a BUD metered dose of 200 µg was equivalent to 160 µg delivered dose. The BUD/FF combination was delivered via a combination inhaler (Symbicort Turbuhaler, AZ) plus a placebo device, whereas the FP was delivered via a Diskhaler (Flixotide Diskhaler, GSK), 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 PEF. 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 17–75 years, with a mean age of 42.6 years for the BUD/FF group and 41.8 years for the FP group (*Table 48*). All patients had previously received a range of ICS therapy at a consistent daily dose of 200–1000 µg for at least 30 days. The 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 ITT 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.

Results

Lung function

A significantly greater mean change from baseline in morning PEF was reported for the BUD/FF treatment group compared with the FP group (27.4 versus 7.7 l/minute; $p < 0.001$). Similar increases were also found for evening PEF (24.0 versus 6.8 l/minute; $p < 0.001$). Geometric means of average FEV_1 increased significantly across clinic visits in the BUD/FF group compared with the FP group (2.57 versus 2.46 litres, $p < 0.001$).

TABLE 48 *Characteristics of study (BUD/FF versus FP)*

Study	Design	Intervention	Patients	Outcomes
Bateman *et al.*, 2003[228]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. BUD/FF 200/6 μg b.d. *ex*-valve (daily total 320/9 μg *ex*-actuator) + placebo 2. FP 250 μg b.d. (daily total 500 μg) + placebo *Delivery device:* 1. DPI (Symbicort Turbuhaler, AZ) + placebo Diskhaler 2. DPI (Flixotide Diskhaler, GSK) + placebo Turbuhaler *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 344 *Mean age (range) (years)* 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: 200–1000 μg ICS therapy daily	*Primary outcome* PEF (morning) *Secondary outcomes* PEF (evening) FEV_1 Reduction in reliever medication (inhalations/day) % reliever-free days % symptom-free days % night-time awakenings % asthma control days

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 slightly higher percentage of symptom-free days than the FP group (60.4 versus 55.5%), these differences were not statistically significant (no *p*-value reported). The percentage of night-time awakenings due to asthma was lower in the BUD/FF group than the FP group (7.9 versus 9.6%), but the differences were also not statistically significant (no *p*-value reported).

Use of rescue medication
Patients were provided with either terbutaline sulfate 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 versus 0.13, $p = 0.04$).

Exacerbations
Bateman and colleagues[228] 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 PEF 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 PEF 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 with patients treated with FP alone, occurring in 13 patients (8%) and 19 patients (11%) respectively. No statistical tests were reported.

Adverse events
Bateman and colleagues[228] reported that AE profiles were similar between the two treatments (no data given on rate of AEs). Out of five serious AEs 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 AEs were asthma exacerbations and not considered to be treatment related.

Summary
One large parallel-group RCT compared 500 µg/day FP with 400 µg/day BUD and 12 µg/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 PEF, and FEV_1 (litres), 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. The incidence of severe exacerbations was low, and appeared to be similar between treatments, as were AEs.

ICS versus ICS + LABA (BUD versus BUD/FF)

Study characteristics
Four trials[229–232] compared BUD/FF in a combined inhaler with higher doses of BUD (*Table 49*). There was considerable variation in overall design and quality. The trials were all parallel group, multi-national studies except that of Pohl and colleagues,[230] 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 and 1 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[229] had two arms comparing BUD 80 µg/FF 4.5 µg twice daily with BUD 200 µg twice daily. Patients in the combined treatment arm used a Symbicort inhaler (Symbicort Turbuhaler, AZ), but the delivery device for the other arm was not documented. They used terbutaline as a reliever.

Pohl and colleagues[230] compared two different treatments, BUD 1280 µg/day (two inhalations twice per day) and BUD 640 µg/FF 18 µg/day (two inhalations twice per day) using either Symbicort or Pulmicort Turbohalers (AZ). 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 5–8, and one to four inhalations per day in weeks 9–20). Participants were free to choose between terbutaline and salbutamol as reliever medication.

The O'Byrne and colleagues trial[231] had three arms. The first arm was BUD 80 µg/FF 4.5 µg twice daily with the combination inhaler as reliever. The second arm was BUD 80 µg/FF

4.5 µg twice daily with terbutaline as reliever, and the final arm was BUD 320 µg twice daily with terbutaline as reliever. All study medication was delivered by Turbohaler (BUD – Pulmicort Turbuhaler, AZ).

There were two treatment arms in the study by Scicchitano and colleagues.[232] Patients in the first group received *ex*-actuator doses of 320 µg BUD plus 9 µg FF per day (metered doses of 400 and 12 µg, respectively). The drugs were delivered via a combined DPI Turbohaler (Symbicort Turbuhaler, AZ) as two inhalations each evening. Patients could take up to 10 additional inhalations per day as needed. Patients in the second treatment arm took two inhalations of BUD twice per day (total dose *ex*-actuator 640 µg/day, metered dose 800 µg/day) delivered via a DPI Turbohaler (Pulmicort Turbuhaler, AZ). Patients were permitted to take up to 10 inhalations of 0.4 µg/day (metered dose 0.5 µg).

The ages of patients in the study by Lalloo and colleagues[229] ranged from 18 to 78 years (average age around 40 years), had a baseline mean FEV_1 % predicted of over 80%, and required ICS at a dose between 200 and 500 µg/day (any brand) prior to study entry. The patients' ages in the study by Pohl and colleagues[230] ranged from 20 to 82 years (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[231] included children (aged 4–11 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 200–500 µg/day of ICS and adults with 400–1000 µg/day. In the study by Scicchitano and colleagues,[232] 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 746 µg (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[229] nor Scicchitano and colleagues[232] provided any further details on randomisation, concealment and blinding. In the study by Pohl and colleagues,[230] a computer-generated random number list was used, but no other details are available. O'Byrne and colleagues[231] 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 ITT 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.[229] In the study by Pohl and colleagues,[230] the primary outcome was the number of people who had one or more treatment failures. Both O'Byrne and colleagues[231] and Scicchitano and colleagues[232] used time to first severe asthma exacerbation as the primary outcome.

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[230] was an adjustable maintenance dosing study. Furthermore, one of the three arms in the study by O'Byrne and colleagues[231] used the combination inhaler as both maintenance and reliever. In addition, 12% of the patients in this trial were aged between 4 and 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.[181]

Lung function

FEV_1 (litres). Lalloo and colleagues[229] 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[230] 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% CIs and other measures were not presented). In the trial by O'Byrne colleagues,[231] the baseline mean of FEV_1 (range) was 2.14 (0.64 to 4.02), 2.10 (0.62 to 4.50), and 2.13 (0.65 to 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 ANCOVA with

TABLE 49 *Study characteristics (BUD versus BUD/FF)*

Study	Design	Intervention	Patients	Outcomes
Lalloo *et al.*, 2003[229]	RCT Multi-centre Parallel-group Double-blind	1. BUD/FF 80 μg/4.5 μg b.d. (daily total 160 μg/9 μg) 2. BUD 200 μg b.d. (daily total 400 μg) *Delivery device:* 1. DPI (Symbicort Turbuhaler, AZ) 2. BUD inhaler not specified *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 467 *Mean age (range) (years)* 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 200–500 μg/day for at least 1 month	FEV_1 FEV_1 % predicted FVC PEF (morning and evening) Day- and night-time symptom scores Use of reliever medication Night-time awakenings AEs
Pohl *et al.*, 2006[230]	RCT Multi-centre Parallel-group Double-blind Adjustable maintenance dose (AMD)	1. BUD 320 μg 2 puffs b.d. fixed dosing for wks 1–4 (daily total 1280 μg). ADM from wk 4. 2–4 puffs/day, wks 5–8, then 1–4 puffs/day wks 9–20) 2. BUD/FF 160 μg/4.5 μg 2 puffs b.d. (daily total 640 μg/9 μg). ADM from wk 4. 2–4 puffs/day, wks 5–8, then 1–4 puffs/day wks 9–20) *Delivery device:* 1. DPI (Symbicort, Turbuhaler, AZ) 2. DPI (Pulmicort Turbuhaler, AZ) *Duration:* 20 wks *Run-in period:* none	*Number randomised* 133 *Mean age (range) (years)* 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 PEF HRQoL (SF-36) Treatment satisfaction Dose of study medication % days patients required reliever medication AEs

continued

TABLE 49 *Study characteristics (BUD versus BUD/FF) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
O'Byrne *et al.*, 2005[231]	RCT Multi-centre Parallel-group Double-blind NB. This trial also examines the effects of the combination inhaler as a reliever. 12% are children (4–11 years)	1. BUD/FF 80 μg/4.5 μg b.d. (daily total 160 μg/9 μg) + combination inhaler as reliever[a] 2. BUD/FF 80 μg/4.5 μg b.d. (daily total 160 μg/9 μg) + terbutaline as reliever as needed[a] 3. BUD 320 μg b.d. (daily total 640 μg) + terbutaline as reliever as needed[a] *Delivery device:* 1, 2. DPI (Symbicort Turbuhaler, AZ) 3. DPI (Pulmicort Turbuhaler, AZ) *Duration:* 12 months *Run-in period:* 14–18 days	*Number randomised* 2760 *Mean age (range) (years)* 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 400–1000 μg q.d, children 200–500 μg q.d.	*Primary outcome* The time to first severe asthma exacerbation *Secondary outcomes* FEV_1 PEF (morning and evening) Asthma symptom scores (day/night) Awakenings Reliever medication use Symptom-free days Rescue medication-free days Asthma control days Study drug use AEs Height (children) Morning plasma cortisol Mild exacerbations Severe exacerbations requiring medical attention

continued

TABLE 49 *Study characteristics (BUD versus BUD/FF) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Scicchitano *et al.*, 2004[232]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. BUD/FF, 400 μg/6 μg[b] 2 puffs q.d. (total 320 μg/9 μg/day[c]) + additional puffs as needed 2. BUD 200 μg[b] 2 puffs b.d. (total 640 μg/day[c]) + terbutaline as needed *Delivery device:* 1. DPI (Symbicort, Turbuhaler, AZ) 2. DPI (Pulmicort Turbuhaler, AZ) *Duration:* 52 wks *Run-in period:* 2 wks	*Number randomised* 1890 *Mean age (range) (years)* 43 (11–80) *Baseline FEV_1 % predicted* 70 (37–102%) *Previous ICS treatment (drug and dose)* ICS 400–1600 μg/day	*Primary outcome* Time to first severe asthma exacerbation *Secondary outcomes* FEV_1 PEF (morning and evening) Asthma symptom scores (day/night/total) Awakenings Symptom-free days Reliever medication use Reliever medication-free days Asthma control days AEs Mild exacerbations Severe exacerbations requiring medical attention

[a] Children (aged 4–11 years) received half the stated maintenance dose, once daily.
[b] *Ex*-valve.
[c] *Ex*-actuator.

the baseline value as covariate. The respective values were 2.41, 2.43 and 2.51. The *p*-values for the comparison were 0.09 and <0.001 for BUD/FF with terbutaline compared with BUD and BUD/FF as maintenance and reliever compared with BUD respectively, Scicchitano and colleagues[232] reported mean FEV_1 throughout the study, but did not report change from baseline. A statistically significant mean difference between the groups of 0.1 litres was reported ($p < 0.001$). Patients using the combined inhaler treatment of BUD/FF had a mean FEV_1 level of 2.54 litres, compared with 2.45 litres in those receiving BUD plus terbutaline.

Morning and evening PEF. Lalloo and colleagues[229] presented data on morning and evening PEF. The baseline value was the average value over the last 10 days of run-in and treatment was the average value for the entire treatment period. These were analysed using ANCOVA. For morning PEF, the change from baseline was 16.5 and 7.3 l/minute for BUD/FF and BUD only, respectively (other statistics for these values were not provided). The between-group difference was 9.2 l/minute (95% CI 3.4 to 14.9 l/minute, $p = 0.02$). For evening PEF, the change from baseline was 13.7 and 4.2 l/minute, respectively; the between-group difference was 9.5 l/minute (95% CI 4.0 to 15.0, $p < 0.001$).

In the study by Pohl and colleagues,[230] the mean morning PEF for patients in the BUD/FF and BUD treatment groups was 407 and 398 l/minute, respectively; corresponding values for mean evening PEF were 411 and 404 l/minute. Other statistics for these values were not provided. No baseline values were presented in the trial by O'Byrne and colleagues.[231] End-point values were analysed using ANCOVA and were based on the mean of data over the 12-month period. The morning PEF was 339, 346 and 355 l/minute for BUD, BUD/FF with terbutaline reliever and BUD/FF as maintenance and reliever, respectively. The *p*-values for the comparisons of BUD/FF with terbutaline reliever versus BUD and BUD/FF as maintenance and reliever versus BUD were all <0.001, showing statistical significance. The equivalent values for evening PEF were 345, 349 and 360 l/minute. As with morning PEF, between-group comparisons showed statistical significance ($p < 0.001$ for all comparisons). Other statistics for these values were not provided.

Scicchitano and colleagues[232] reported the mean and range of treatment PEF values. People who received BUD/FF had a mean treatment morning PEF value of 372.1 l/minute (range 100–751 l/minute) compared with 348.5 l/minute (range 93–805 l/minute) in the BUD with terbutaline group. The mean difference of 20.3 l/minute (95% CI 17 to 24) was statistically significantly different ($p < 0.001$). A slightly smaller but still statistically significant difference of 14 l/minute (95% CI 10 to 18) was seen between the two groups' evening PEF values ($p < 0.001$). In the BUD/FF group, the treatment mean was 369.6 l/minute (range 99–720 l/minute) compared with 354.7 l/minute (range 91–808 l/minute) in the BUD with terbutaline group.

Symptoms

Symptom-free days. Lalloo and colleagues[229] reported improvements in the proportion of symptom-free days of 16% versus 10% for the 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[231] 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[230] did not present data on this variable. The percentages of symptom-free days and nocturnal awakenings reported by Scicchitano and colleagues[232] ranged from 0 to 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 to 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 group versus 13.0 in the BUD/terbutaline group, $p < 0.001$).

Symptom scores. Pohl and colleagues[230] did not present data on this variable. Lalloo and colleagues[229] presented very limited data. Day- 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[231] presented data on day- and night-time symptom scores. The symptoms were scored from 0 (no symptoms) to 3 (unable to undertake normal activities/sleep)(no reference supplied). Day- 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 *p*-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. The *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, respectively, showing statistical significance. Corresponding values for night-time symptom scores were 0.42, 0.36 and 0.31. The *p*-values were 0.01 and <0.001, respectively. Other statistics for these values were not presented.

Scicchitano and colleagues[232] 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 was given for the 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[230] measured HRQoL using the Short Form with 36 Items (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,[229] 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 to 0), which was statistically significant ($p = 0.025$). In the study by O'Byrne and colleagues,[231] the baseline mean of number of inhalations per day was 1.69 (range 0.0 to 7.0), 1.69 (range 0.0 to 9.4), and 1.74 (range 0.0 to 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 (range 0.0 to 3.7), 0.73 (range 0.0 to 6.6) and 0.72 (range 0.0 to 5.7), respectively. 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. The *p*-values for the comparisons of BUD/FF with terbutaline reliever versus BUD and BUD/FF as maintenance and reliever versus BUD were all <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 it was <0.001.

Other statistics for these values were not provided. Neither Pohl and colleagues[230] nor Scicchitano and colleagues[232] reported data for this outcome.

Exacerbations
In the study by Lalloo and colleagues,[229] 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 PEF 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 PEF on two consecutive days or discontinuation due to asthma worsening) or time to first severe exacerbation.

In the study by Pohl and colleagues,[230] the number of exacerbations was not documented very clearly. However, in the BUD/FF group, five out of 63 (8%) of patients had treatment failures (all used nebulised $beta_2$ agonists); in the BUD group there were two 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,[231] the percentages of patients experiencing a severe exacerbation (including a fall in PEF 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 the 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 with BUD and of BUD/FF as maintenance and reliever with BUD, respectively.

A statistically significantly lower percentage of people in the Scicchitano and colleagues[232] BUD/FF group reported an acute exacerbation than those in the BUD/terbutaline group [18% versus 27%; hazard ratio 0.61 (95% CI 0.50 to 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 to 0.75, $p < 0.001$).

Adverse events

In the study by Lalloo and colleagues,[229] there were no between-group differences in the profile and frequency of all AEs. There were 134 AEs in 230 patients in the BUD/FF group and 128 AEs in 237 patients in the BUD group. There were five serious AEs in the BUD/FF group and two in the BUD group. Three patients withdrew from each group because of AEs.

In the study by Pohl and colleagues,[230] there were 74 AEs 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 AEs, two in the BUD/FF group and one in the BUD group; none was treatment related. A total of four patients withdrew because of AEs (not split by group).

In the trial by O'Byrne and colleagues,[231] the proportion of patients experiencing one or more AEs 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 AEs 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 AEs. The study reported no significant findings in plasma cortisol in the subgroup of patients aged 12–80 years, but data were not presented in sufficient detail to include here.

No statistically significant differences between groups were reported by Scicchitano and colleagues[232] for the rate of AEs, serious AEs or withdrawals due to AEs. AEs were experienced by 56% of the BUD/FF group compared with 57% of the BUD/terbutaline group ($p = 0.677$). The rate of serious AEs was 6% in both groups ($p = 0.846$). Discontinuations due to AEs were low: 3% of the BUD/FF group and 4% of the BUD/terbutaline group ($p = 0.072$).

Summary

Four parallel-group RCTs were identified which compared 400–1280 µg BUD with 160–640 µg BUD with 9–18 µg 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[230] 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 with BUD with terbutaline as a reliever. There did not appear to be any difference in AEs between the different combinations.

Summary of Q3a – ICS versus ICS + LABA (ICS dose higher when used alone)

Five RCTs evaluated FP/SAL combination inhaler versus higher dose of ICS, and five evaluated BUD/FF combination inhaler versus 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. *Tables 50–53* provide a visual illustration of the results of pair-wise comparisons.

TABLE 50 *FP versus FP/SAL (n = 2 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
	Meta-analysis, Bergmann *et al.*,[222] Busse *et al.*,[221]	FP											NSD
		FP/SAL		+	+		+				+		
1000 µg FP vs 500 µg/100 µg FP/SAL	Bergmann *et al.*,[222] parallel-group, 12 weeks, DPI, *n* = 365	FP	NSD							F		F	
		FP/SAL							+				
500 µg FP vs 200 µg/100 µg FP/SAL	Busse *et al.*,[221] parallel-group, 12–24 weeks, DPI, *n* = 558	FP							NSD			NSD	
		FP/SAL	+										

F, results appear to favour this treatment group, but no tests of statistical significance reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 51 *BUD versus FP/SAL (n = 3 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
1600 µg BUD vs 500 µg/100 µg FP/SAL	Jenkins *et al.*,[223] parallel-group, 24 weeks, DPI, *n* = 353	BUD						NSD				NSD	18%
		FP/SAL	+	+	+		+			+			14%
800 µg BUD vs 200 µg/100 µg FP/SAL	Johansson *et al.*,[224] parallel group, 12 weeks, DPI, *n* = 349	BUD	C				C	C					38%
		FP/SAL		+[a]	+							F	38%
	Zhong *et al.*,[225] parallel group, 6 weeks, DPI, *n* = 398	BUD	NSD										24%
		FP/SAL		+	+		+	+					24%

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; F, results appear to favour this treatment group, but no tests of statistical significance reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

[a] See text. Chapter 3, Results, ICS versus ICS + LABA (BUD versus FP/SAL), page 102, morning PEF.

TABLE 52 *FP versus BUD/FF (n = 1 RCT)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
500 µg FP vs 400 µg/9 µg BUD/FF	Bateman *et al.*,[228] parallel-group, 12 weeks, DPI, *n* = 344	FP				NSD	NSD						
		BUD/FF	+	+	+						+	F	

F, results appear to favour this treatment group, but no tests of statistical significance reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm, blank cells signify no data reported on that outcome.

TABLE 53 *BUD versus BUD/FF (n = 4 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
400 µg BUD vs 200 µg/9 µg BUD/FF	Lalloo *et al.*,[229] parallel-group, 12 weeks, DPI, *n* = 467	BUD	NSD										54%
		BUD/FF		+	+		+				+	+	58%
1600 µg BUD vs 800 µg/ 18 µg AMD BUD/FF	Pohl *et al.*,[230] parallel-group, 20 weeks, DPI, *n* = 133	BUD	C	F	F							C	81 events
		BUD/FF								+			74 events
800 µg BUD vs 200 µg/ 9 µg BUD/FF	O'Byrne *et al.*,[231] parallel-group, 52 weeks, DPI, *n* = 2760	1. BUD	NSD 1 vs 2									NSD 1 vs 2	57%
		2. BUD/FF[a]		+ 2 vs 1	+ 2 vs 1		+ 2 vs 1		+ 2 vs 1		+ 2 vs 1		52%
		3. BUD/FF[b]	+ 3 vs 1	+ 3 vs 1	+ 3 vs 1		+ 3 vs 1		+ 3 vs 1		+ 3 vs 1	+ 3 vs 1	54%
800 µg BUD vs 400 µg/ 9 µg BUD/FF	Scicchitano *et al.*,[232] parallel-group, 52 weeks, DPI, *n* = 1890	BUD											NSD
		BUD/FF	+	+	+	+	+		+			+	

AMD, adjustable maintenance dose; C, results stated to be comparable between treatment arms, but no other data presented; F, results or to favour this trial arm but no significance testing reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

[a] Terbutaline only used as reliever in this arm.

[b] Combination inhaler used as both maintenance and reliever in this arm.

Review question 3b – ICS versus ICS + LABA (ICS dose similar in both groups)

To recap, nine RCTs evaluated ICS versus ICS + LABA, where a similar ICS dose has been used in both trial arms (*Table 54*). The following sub-sections describe the characteristics and results of these trials.

ICS versus ICS + LABA (FP versus FP/SAL)

Study characteristics

Six parallel-group RCTs evaluated the effectiveness of FP/SAL in a combination inhaler compared with FP alone.[233–238] The trials were published between 1999 and 2006 (*Table 55*). Four were multi-centre studies and two single-centre studies. Sample sizes were 54 and 282 in the two single-centre studies[236,237] and ranged between 349 and 3421 participants in the multi-centre studies. All but one trial[233] reported that a power calculation was undertaken and sample sizes suggest that adequate power was met. However, in the Koopmans and colleagues study[236] 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[233,235,237,238] 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,[234] 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 (i.e. only patients who had received ICS prior to commencing LABA therapy were included, in accordance with the BTS/SIGN Guideline).

There was variability in the doses used in the trials, with the FP dose varying from 200 to 1000 µg/day (both as monotherapy and combined with SAL).

One trial compared 200 µg/day of FP with FP/SAL combination 100/200 µg/day.[235] Three trials compared 500 µg/day FP with FP/SAL 500/100 µg/day.[236–238] One trial compared FP 1000 µg/day with FP/SAL 1000/100 µg/day.[233]

In the GOAL trial by Bateman and colleagues,[234] a variable dose was applied through two phases of treatment therapy. In the stratum with participants previously on lower dose ICS therapy (≤500 µg/day) the FP/SAL arm in phase I was stepped up between 200/100, 500/100 or 1000/100 µg/day, until total control was met or the highest dose reached. Then, in phase II, participants continued on the final dose reached in phase I. The FP arm was similarly stepped up between 200, 500 or 1000 µg/day (until control or highest dose) in phase I and continued in phase II. In the stratum with participants previously on higher dose ICS therapy (500–1000 µg/day) the dose ranges were 500/100 and 1000/100 µg/day for both treatments and both phases of treatment, respectively.

The treatment duration across the included trials varied. Two trials lasted 12 weeks,[235,238] one trial lasted 28 weeks[233] and three trials lasted 1 year.[234,236,237] The inhaler devices used were DPIs in all six trials. 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[234] study, where stepped-up doses 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 GINA/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.[234] The severity of asthma was mild to moderate in three of the trials[236–238] and moderate in three.[233–235] Baseline FEV_1 % predicted was between 40 and 92% but in most trials was between 67 and 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[234] and the method to conceal allocation to groups was similarly assessed to be adequate only 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. ITT analysis was assessed to be adequate in only three included studies.[233,234,237] This factor limits the possibility of measurement bias.

Results

Lung function

FEV_1 (litres). Four of the six studies reported mean change from baseline in FEV_1 (litres).[233,235,237,238] In the Kavaru and colleagues[235]

TABLE 54 *Breakdown of studies for review question 3b – ICS versus ICS + LABA (ICS dose similar in both treatments)*

Pair-wise comparison	No. of RCTs included
FP vs FP/SAL	6
BUD vs BUD/FF	3
Total	9

trial (FP doses of 200 µg/day) the mean change in FEV_1 was 0.51 (SD 0.46) litres in the combination FP/SAL group compared with 0.28 (SD 0.46) litres in the FP group [mean difference 0.23 (95% CI 0.09 to 0.37, $p < 0.001$)]. Two studies that treated participants with FP doses of 500 µg/day (in the combination and FP-alone arms, respectively) showed greater improvement in patients treated with combination treatment compared with FP alone.[237,238] In the Lundbäck and colleagues[237] 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; the study by Lundbäck and colleagues[237] was a 12-month study whereas that of Shapiro and colleagues[238] was shorter at 12 weeks. Lundbäck and colleagues[237] reported that the FEV_1 change from baseline was 0.09 litres in the FP/SAL group compared with 0.02 litres in the FP arm. Shapiro and colleagues[238] demonstrated a mean change in FEV_1 litres of 0.48 (SD 0.45) litres in the FP/SAL arm compared with 0.25 (SD 0.45) litres in the FP arm ($p = 0.003$).

The study by Aubier and colleagues,[233] which used daily doses of 1000 µg FP in both combination and monotherapy arms, found no statistically significant difference between groups (figures derived from graphs; FP/SAL 0.25 litres vs FP 0.18 litres, $p = 0.061$). This was a 28-week study.

FEV_1 % predicted. FEV_1 % predicted was reported in the trial by Koopmans and colleagues[236] but the data presented were 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[234] 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 I and 0.22% in the FP treatment group. During phase II 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 I was 0.29% in the FP/SAL group and 0.17% in the FP group. For phase II the 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 the first stratum, the latter not being relevant to the present review.

Morning PEF. Data on change in morning PEF (l/minute) were reported in three of the included RCTs[233,235,238] but due to wide variations in the doses meta-analysis was not appropriate. Using daily fluticasone doses of 200 µg, the Kavaru and colleagues trial[235] demonstrated a statistically significant difference in change in morning PEF. The mean change was 52.50 (SD 49.44) l/minute in the FP/SAL arm compared with 17.30 (SD 40.57) l/minute in the FP arm [mean treatment difference 35.20 (95% CI 21.70 to 48.70, $p \leqslant 0.025$)]. The Shapiro and colleagues[238] trial similarly showed a statistically significant difference in change in morning PEF between combination treatment group and the FP alone group [FP/SAL 53.50 (SD 50.40) l/minute versus FP 15.20 (SD 41.40) l/minute, mean difference 38.30 (95% CI 24.10 to 52.50) l/minute, $p = 0.015$]. The dose of FP in this study was 500 µg/day. Lundbäck and colleagues' trial[237] (also using FP 500 µg/day) reported data on mean change from baseline in morning PEF (l/minute) but no measures of variance around the point estimates were presented. The mean change was 38 l/minute in the FP/SAL group and 21 l/minute in the FP group ($p < 0.01$).

Using higher doses of FP (1000 µg/day), Aubier and colleagues[233] also showed a statistically significant difference in change in morning PEF, although the magnitude of this difference was less than in the other studies [FP/SAL 38.00 (SD 50.40) l/minute versus FP 22.00 (SD 51.40) l/minute, mean difference 16.00 (95% CI 5.04 to 26.95) l/minute]. This study was of 28 weeks' duration whereas the Kavaru and colleagues[235] and Shapiro and colleagues[238] studies were of 12 weeks' duration.

At end-point in the Koopmans and colleagues[236] trial, morning PEF was 459 (SD 67.50) l/minute in the FP/SAL arm compared with 419 (SD 67.50) l/minute in the FP arm. No statistical analysis of the difference between groups was undertaken.

TABLE 55 *Characteristics of studies (FP versus FP/SAL)*

Study	Design	Intervention	Patients	Outcomes
Aubier *et al.*, 1999[233]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP/SAL 500/50 μg b.d. (daily total 1000/100 μg) 2. FP 500 μg + SAL 50 μg b.d. (daily total 1000/100 μg) 3. FP 500 μg b.d. (daily total 1000 μg) Only groups 1 and 3 relevant to this section *Delivery device:* 1. Diskus (Seretide Accuhaler, GSK[a]) + placebo 2. Diskus inhaler (Flixotide Diskhaler, GSK[a]) 3. Diskus inhaler (Flixotide Diskhaler, GSK[a]) + placebo *Duration:* 28 wks *Run-in period:* 2 wks	*Number randomised* 503 *Mean age (years)* 1. 46 3. 50 *Baseline FEV_1 % predicted (± SD)* 1. 73 (± 1.2) 3. 73 (± 1.4) *Previous ICS treatment (drug and dose)* BDP or BUD 1500–2000 μg q.d. or FP 750–1000 μg q.d.	PEF (morning and evening) Daytime asthma score Night-time asthma score AEs Serum cortisol Urinary cortisol
Bateman *et al.*, 2004[234]	RCT Multi-centre Parallel-group Double-blind Stratified	*Drugs:* Stratum 1: no ICS therefore not included here Stratum 2: previous low ICS, use ⩽500 μg BDP or equivalent daily 1. FP/SAL – phase I: 100/50, 250/50 or 500/50 μg b.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 500 μg b.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 ⩽1000 μg BDP or equivalent daily 1. FP/SAL – Phase I: 250/50 or 500/50 μg b.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: 250 μg or 500 μg b.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, GSK) 2. DPI (Flixotide Diskhaler, GSK) *Duration:* 52 wks *Run-in period:* 4 wks	*Number randomised* 3421 *Mean age (range) (years)* 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 FEV_1 % 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 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 and time to achievement of the first well-controlled asthma week Proportion of patients and dose to achieve totally controlled asthma Time to achieve the first totally controlled week Asthma quality of life (using AQLQ) Exacerbation rates Morning predose FEV_1 AEs

continued

TABLE 55 *Characteristics of studies (FP versus FP/SAL) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Kavuru *et al.*, 2000[235]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP/SAL 100/50 μg b.d. (daily total 200/100 μg) 2. SAL 50 μg b.d. (daily total 100 μg) 3. FP 100 μg b.d. (daily total 200 μg) 4. Placebo b.d. Only groups 1 and 3 reported here. *Delivery device:* 1. DPI Diskus (Seretide Accuhaler, GSK[a]) 2. DPI Diskus (GSK) 3. DPI Diskus (Flixotide Diskhaler, GSK[a]) 4. DPI Diskus (GSK) *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 356 *Mean age (range) (years)* 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 252–420 μg 6–10 puffs q.d. or flunisolide 1000 μg 4 puffs q.d. or FP 176 μg 4 puffs q.d.	FEV_1 (Under the 12-hour serial curve relative to baseline) Morning predose FEV_1 Probability that patients remain in the study without withdrawal for worsening asthma PEF Daily patient-rated diary card symptom scores Albuterol use Night-time awakenings requiring albuterol
Koopmans *et al.*, 2006[236]	RCT Single-centre Parallel-group Double-blind	*Drugs:* 1. FP 250 μg b.d. (daily total 500 μg) 2. FP/SAL 250/50 μg b.d. (daily total 500/100 μg) *Delivery device:* 1. DPI Diskus (Flixotide Diskhaler, GSK) 2. DPI Diskus (Seretide Accuhaler, GSK) *Duration:* 52 wks *Run-in period:* 4 wks	*Number randomised* 54 *Median age (range) (years)* 1. 32 (19–57) 2. 32 (21–59) *Baseline FEV_1 % predicted (± SD)* 1. 89.9 (± 14) 2. 88.8 (± 18) *Previous ICS treatment (median daily dose) (range)* 1. ICS 593 μg q.d. (200–1200) 2. ICS 619 μg q.d. (200–1000)	FEV_1 PEF Symptom scores Rescue medicine use

continued

TABLE 55 *Characteristics of studies (FP versus FP/SAL) (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Lundbäck *et al.*, 2006[237]	RCT Single-centre Parallel-group Double-blind	*Drugs:* 1. FP/SAL 250/50 μg b.d. (daily total 500/100 μg) 2. FP 250 μg b.d. (daily total 500 μg) 3. SAL 50 μg b.d. Only groups 1 and 2 reported here *Delivery device:* 1. DPI Diskus (Seretide Accuhaler, GSK[a]) 2. DPI Diskus (Flixotide Diskhaler, GSK[a]) 3. DPI Diskus (GSK[a]) *Duration:* 12 months *Run-in period:* 2 months	*Number randomised* 282 *Mean age (± SD) (years)* 1. 39.9 (± 11.9) 2. 39.1 (± 12.0) 3. 40.7 (± 12.3) *Baseline FEV_1 % predicted* 1. 92.1 2. 93.0 3. 94.9 *Previous ICS treatment (drug and dose)* 68% of patients had previously received ICS – BUD median dose 500 μg or equivalent	No. of patients requiring an increase in study medication No. of patients experiencing ⩾2 exacerbations Morning PEF PEF diurnal variation FEV_1 Day- and night-time symptom scores Rescue medication use AEs
Shapiro *et al.*, 2000[238]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP/SAL 250/50 μg b.d. (daily total 500/100 μg) 2. FP 250 μg b.d. (daily total 500 μg) 3. SAL 4. Placebo Only groups 1 and 2 reported here *Delivery device:* 1. Diskus (Seretide Accuhaler, GSK[a]) 2. Diskus (Flixotide Diskhaler, GSK[a]) 3, 4. Diskus *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 349 *Mean age (range) (years)* 1. 38 (12–69) 2. 40 (12–67) 3. 39 (12–68) 4. 38 (12–69) *Baseline FEV_1 % predicted* 1. 69 2. 66 3. 67 4. 68 *Previous ICS treatment (drug and dose)* BDP 462–672 μg q.d. or triamcinolone acetonide 1100–1600 μg q.d. or FP 440 μg q.d. or flunisolide 1250–2000 μg q.d.	FEV_1 (under the 12-hour serial curve relative to baseline) Morning predose FEV_1 Probability of remaining in study PEF Symptom scores Albuterol use Night-time awakenings Safety

[a] Not stated explicitly, but deduced from the text.

Evening PEF. Change in evening PEF was reported in three included trials,[233,235,238] but differences in doses prevented a meta-analysis. Using daily doses of 200 µg FP, the Kavaru and colleagues trial[235] demonstrated a statistically significant difference in change on evening PEF (as observed by the 95% CI). The mean change was 35.00 (SD 43.84) l/minute in the FP/SAL arm compared with 18.00 (SD 12.40) l/minute in the FP arm [mean treatment difference 17.00 (95% CI 7.42 to 26.58) l/minute, $p \leqslant 0.025$]. The Shapiro and colleagues[238] trial similarly showed a statistically significant difference in change in evening PEF between combination treatment group and the FP alone group [FP/SAL 45.40 (SD 46.80) l/minute versus FP 7.90 (SD 40.50) l/minute, mean difference 37.50 (95% CI 24.02, 50.98) l/minute $p = 0.015$]. The dose of FP in this study was 500 µg/day. In the study which used higher doses of FP (1000 µg/day)[233] there was a statistically significant difference in change in evening PEF, although the magnitude of this difference was less than in the previous studies [FP/SAL 31.00 (SD 49.10) l/minute versus FP 13.00 (SD 50.10) l/minute, mean difference 18.00 (95% CI 7.33 to 28.67) l/minute, $p < 0.01$]. This study was of 28 weeks' duration whereas the Kavaru and colleagues[235] and Shapiro and colleagues[238] studies were of 12 weeks' duration.

In the trial by Koopmans and colleagues,[236] the mean change in evening PEF (l/minute) was only reported in terms of the treatment difference. The difference between FP/SAL and FP alone was 36 (SE 9) l/minute ($p < 0.001$).

Symptoms/health-related quality of life

Two of the included trials reported data on the change from baseline in symptom-free days.[235,238] One study used treatment doses of FP of 200 µg/day[235] and the other 500 µg/day.[238] In both studies there was a statistically significant difference between groups in favour of FP/SAL combination therapy. In the Kavaru and colleagues study,[235] 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 to 27.45, $p \leqslant 0.025$)]. 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 to 7.90, no statistically significant difference, no *p*-value reported)].

In the Shapiro and colleagues[238] 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 to 30.61, $p = 0.015$)]. Corresponding values for the 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 to 10.40); $p = 0.015$)].

Symptom-free days were reported in the Aubier and colleagues study[233] but no measure of variance was reported for the data. In the FP/SAL treatment group the proportion of symptom-free days was 38% compared with 28% in the FP group. This was not statistically significantly different between the two groups (no *p*-value given).

Three studies reported symptom scores.[235,236,238] In the study by Koopmans and colleagues[236] morning symptoms were measured on a five-point scale (0–4; no further details reported). Only mean differences were reported for the change over the 1-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 details reported). The mean difference between groups was –0.2 (SE 0.1; $p = 0.01$).

In the study by Kavaru and colleagues[235] 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 with a change of –0.2 (SE 0.09) in the FP group ($p \leqslant 0.025$). Shapiro and colleagues[238] also reported changes in symptom scores using a scoring system which appears to be identical with that of Kavaru and colleagues.[235] In the FP/SAL group there was a change in score of –0.8 (SE 0.12) compared with a change of –0.4 (SE 0.09) in the FP group ($p = 0.015$).

Bateman and colleagues[234] reported data on the 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 I and 1.0 in the FP treatment group. During phase II 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 I was 1.1 in the FP/SAL treatment group and 0.8 in the FP treatment group. For phase II

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 being combined with the data from the first stratum 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[235] there was a –1.90 (SD 2.43) change in inhalations per day in the combination treatment arm compared with a –0.40 (SD 1.94) change in the FP treatment arm [difference –1.50 (95% CI –2.16 to –0.84, $p \leqslant 0.025$)]. This trial used low doses of FP in both treatment groups (200 µg/day). In the Shapiro and colleagues trial[238] (using doses of 500 µg/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 with a –0.90 (SD 1.80) change in inhalations per day in the FP group [difference –1.40 (95% CI –2.28 to –0.52), $p = 0.015$)].

The treatment difference between the FP/SAL group and the FP group of the Koopmans and colleagues trial[236] 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 have been 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[238] reported that 2 and 7% of patients withdrew due to clinical exacerbations in the FP/SAL and 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,[235] 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.[238]

In the trial by Lundbäck and colleagues,[237] 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/day for ⩾2 consecutive days, or an increase of ⩾2 doses/day in regular inhaled medication (study medication or additional ICS) for ⩾2 days by the patient's own decision, or ⩾2 days when asthma symptoms prevented the patient's work or normal activities. If rescue medication was insufficient, exacerbations were treated with oral prednisolone (25 mg) for 5 days. The percentage of patients experiencing two or more acute exacerbations was 4.2% for the FP/SAL combination compared with 17.4% for FP, $p < 0.01$.

Bateman and colleagues[234] defined exacerbations as deterioration in asthma requiring treatment with an oral corticosteroid or an emergency department visit or hospitalisation, based on the 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 ($p \leqslant 0.009$). Rates for each stratum were not reported.

Adverse events
Numbers of participants experiencing AEs were reported in three trials.[233,237,238] In the Shapiro and colleagues[238] trial, no AEs were experienced in either treatment group. In the Lundbäck and colleagues[237] trial, 92/95 (96%) participants in the combination treatment group and 88/92 (95%) participants in the FP treatment group experienced an AE. In the Aubier and colleagues[233] trial, 28/167 (16%) participants in the FP/SAL arm experienced an AE compared to 32/165 (19%) participants in the FP arm. The variation in the proportions of patients experiencing AEs between the studies may be related to differences in the way in which events are classified by different studies.

Three trials[233,235,238] provided data on numbers discontinuing due to AEs. In the Shapiro and colleagues[238] trial, no participants were classed as withdrawing due to AEs in either treatment arms. In the Kavaru and colleagues[235] trial, one participant in the FP arm discontinued due to an AE compared with no participants in the combination arm. In the Aubier and colleagues[233] trial, 16/167 (9%) participants in the FP/SAL arm discontinued due to AEs (9%) compared with 22/165 (13%) in the FP arm.

Summary
Six parallel-group RCTs were identified that compared FP/SAL in a combination inhaler with

FP. These trials varied in terms of FP dose ranging from 200 to 1000 µg/day (both as monotherapy and combined with SAL), and duration (between 12 weeks and 1 year).

FP/SAL treatment was generally more favourable than FP treatment alone on measures of lung function, and statistically significant differences were reported in 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 AEs and discontinuations due to AEs were reported between the two treatment options, where data were reported.

ICS versus ICS + LABA (BUD versus BUD/FF)

Study characteristics

Three trials were included in this comparison[239–241] (*Table 56*). 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[240] compared two regimens of BUD combined with FF against BUD. In one of the regimens patients took two inhalations (160/4.5 µg) once per day, whereas in the other they inhaled twice per day (160/4.5 µg) (a total daily dose of 320/9 µg). Patients receiving BUD only took 400 µg/day. The trial by Kuna and colleagues[241] tested similar regimens, but with higher doses. They compared BUD/FF (80/4.5 µg) at two inhalations once per day (evening), BUD/FF (80/4.5 µg) at one inhalation twice per day (total BUD/FF dose of 160/9 µg/day in both groups) and BUD at 200 µg/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,[239] compared BUD/FF in a combination inhaler (160/4.5 µg, two inhalations twice daily; total daily dose total 640/18 µg), with the two agents in separate inhalers (200/4.5 µg, two inhalations twice daily; total daily dose total 800/18 µg), and with BUD monotherapy [200 µg, two inhalations twice daily (total 800 µg/day)]. For the purposes of this section, only the combination inhaler and the BUD monotherapy arms are compared. A comparison of the combination inhaler and the separate inhalers is given in the section 'BUD/FF in a combination inhaler versus BUD + FF in separate inhalers' (p. 139). In summary, the three trials compared BUD/FF combination inhaler with BUD. The dose of BUD was similar in both comparisons, ranging from 200 to 800 µg/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) for others. This reflects changes in labelling, whereby the combination inhalers (Symbicort Turbuhaler, AZ – not explicitly stated in only one study,[240] but deduced from the text) express doses as delivered, compared with the separate inhalers (BUD: Pulmicort Turbuhaler, AZ – 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 160/4.5 µg from the combination inhaler delivers the same quantity as a 200-µg metered inhalation of BUD and as a 6-µg metered inhalation of FF.

Two of the trials had similar rationales. The aim of the study by Buhl and colleagues[240] was to evaluate the efficacy of once-daily combination therapy compared with twice-daily combination therapy and with once-daily BUD. It was suggested that a "simple treatment regimen" (i.e. one inhaler taken once per day) would be effective in patients with moderate persistent asthma. Similarly, Kuna and colleagues[241] 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 underestimate their condition, may be more likely to use their medication if taken once per day. The third trial, by Zetterström and colleagues,[239] 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 and 40 years, ranging from 18 to 80 years. 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 Guideline).[1] Patients in the trial by Kuna and colleagues[241] were defined by the authors as having mild to moderate asthma which

TABLE 56 *Study characteristics: BUD versus BUD/FF*

Study	Design	Intervention	Patients	Outcomes
Kuna *et al.*, 2006[241]	RCT Multi-centre Double-blind Double-dummy	*Drugs:* 1. BUD/FF 80/4.5 μg[a] 2 puffs q.d. p.m. (daily total 160/9 μg) 2. BUD/FF 80/4.5 μg[a] b.d. (daily total 160/9 μg) 3. BUD 200 μg[b] q.d. p.m. *Delivery device:* 1. DPI Turbuhaler (Symbicort Turbuhaler, AZ) 2. DPI Turbuhaler (Symbicort Turbuhaler, AZ) 3. DPI Turbuhaler (Pulmicort Turbuhaler, AZ[c]) *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 617 *Mean age (range) (years)* 1. 45.8 (18–80) 2. 43.9 (19–80) 3. 45.1 (18–78) *Mean baseline FEV_1 % predicted* 1. 79.3 2. 77.9 3. 78.3 *Previous ICS treatment (drug and dose)* ICS 200–500 μg q.d.	*Primary outcome* Mean change in morning PEF from baseline *Secondary outcomes* Evening PEF Symptom-free days Use of reliever medication Nocturnal awakenings Asthma control days FEV_1 AEs
Buhl *et al.*, 2003[240]	RCT Multi-centre Parallel-group Double-blind Double-dummy	*Drugs:* 1. BUD/FF 160/4.5 μg[a] 2 puffs q.d. (daily total 320/9 μg) 2. BUD/FF 160/4.5 μg[a] b.d. (daily total 320/9 μg) 3. BUD 400 μg[b] q.d. *Delivery device:* 1. DPI Turbuhaler (Symbicort Turbuhaler, AZ[c]) 2. DPI Turbuhaler (Symbicort Turbuhaler, AZ[c]) 3. DPI Turbuhaler (Pulmicort Turbuhaler, AZ[c]) *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 523 *Mean age (range) (years)* 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 400–1000 μg q.d.	PEF (morning and evening) FEV_1 Day and night-time asthma symptoms Totally daily asthma symptom score Night-time awakenings Use of relief medication Mild and severe exacerbations AEs

continued

TABLE 56 *Study characteristics: BUD versus BUD/FF (cont'd)*

Study	Design	Intervention	Patients	Outcomes
Zetterström *et al.*, 2001[239]	RCT Multi-centre Parallel-group Double-blind Double-dummy	*Drugs:* 1. BUD/FF 160/4.5 μg[a] 2 puffs b.d. (daily total 640/18 μg) (combination inhaler) 2. BUD + FF 200 μg[b] + 4.5 μg 2 puffs b.d. (daily total 800 μg + 18 μg) (separate inhalers) 3. BUD 200 μg[b] 2 puffs b.d. (daily total 800 μg) Only groups 1 and 3 relevant here *Delivery device:* 1. DPI Turbuhaler (Symbicort Turbuhaler, AZ) + placebo 2. DPI Turbuhaler (Pulmicort Turbuhaler, AZ[c]) + placebo 3. DPI Turbuhaler (Pulmicort Turbuhaler, AZ[c]) + placebo *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 362 *Mean age (range) (years)* 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 ⩾ 500 μg	PEF FEV_1 Day- and night-time symptoms scores Symptom-free days Night-time awakenings Asthma control days Use of relief medication Mild and severe exacerbations AEs

[a] *Ex*-actuator.
[b] *Ex*-valve.
[c] Not stated explicitly, but deduced from the text.

was not optimally controlled, despite taking 200–500 µg/day of inhaled steroids (unspecified as to which steroid). The other two trials included patients who had been managed on higher doses: 400–1000 µg/day of any corticosteroid in the trial by Buhl and colleagues[240] (patients described by the authors as having moderate persistent suboptimally controlled asthma) and ⩾500 µg/day in the trial by Zetterström and colleagues[239] (patients described as having symptomatic asthma despite treatment with ICS). Mean baseline FEV_1 as a percentage of predicted was between 70 and 80% across the trials, suggestive of moderate asthma.[2]

Only one of the trials specified a primary outcome measure. Kuna and colleagues[241] measured mean change in morning PEF 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 PEF), measures of symptoms (symptom scores, symptom-free days, nocturnal awakenings), use of reliever medication, mild and severe exacerbations and AEs.

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.[239] 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 ITT analysis.

Results

Results are reported narratively by outcome in the following sections. Meta-analysis was not possible due to limitations in the trial data and to differences in dose between the trials.

Lung function

All trials reported FEV_1 in terms of litres, with results generally favouring BUD/FF compared with BUD. In the trial by Kuna and colleagues,[241] increases in FEV_1 (geometric mean) from baseline to end-point were 0.08 and 0.12 litres for the once- and twice-daily BUD/FF groups, respectively. In the BUD group there was a decrease of 0.01 litres. 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,[240] there was no change in FEV_1 between baseline and end-point for the once-daily BUD/FF group, an increase of 0.12 litres in the twice-daily group and a decrease of 0.06 litres in the BUD group. There was a statistically significant difference between the once-daily group and the twice-daily group compared with the BUD group in end-point values (2.32, 2.37 and 2.21 litres, respectively, $p < 0.001$). Increases in FEV_1 in the study by Zetterström and colleagues[239] were 0.19 litres for the combination inhaler group and 0.11 litres for the BUD group. The difference between the groups was statistically significant for end-point values, 2.47 litres (95% CI 2.40 to 2.55) and 2.35 litres (95% CI 2.28 to 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 PEF, and in all cases increases were statistically significant for BUD/FF compared with BUD. Increases of 23.4 l/minute (95% CI 18.1 to 28.6), 24.1 l/minute (95% CI 19.0 to 29.2) and 5.5 l/minute (95% CI 0.3 to 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[241] ($p < 0.001$ for both combination inhaler groups compared with the BUD group). In the trial by Buhl and colleagues,[240] statistically significant increases of 27.4 and 22.8 l/minute were reported for the once- and twice-daily BUD/FF groups compared with the BUD group (values not provided for this group) ($p < 0.001$). Increases of 35.7 l/minute (95% CI 28.4 to 43.0) and 0.2 l/minute (95% CI –7.1 to 7.6) were reported for the BUD/FF group and the BUD group, respectively, in the trial by Zetterström and colleagues[239] ($p < 0.01$).

Evening PEF was also reported in all three trials. As with morning PEF, increases were statistically significant for BUD/FF compared with BUD. Increases of 9.6 l/minute (95% CI 4.4 to 14.8) and 18.3 l/minute (95% CI 13.2 to 23.4) and a decrease of 1.7 l/minute (95% CI –6.8 to 3.5) were reported for the BUD/FF once-daily group, twice-daily group and BUD group, respectively, in the trial by Kuna and colleagues.[241] The difference was statistically significant for both combination inhaler groups compared with the BUD group ($p < 0.01$ and $p < 0.001$, respectively). In the trial by Buhl and colleagues,[240] increases of 11.8 and 18.8 l/minute and a decrease of 4.8 l/minute 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/minute (95% CI 18.2 to 31.4) and a decrease of 3.7 l/minute (95% CI –10.3 to 3.0) were reported for the BUD/FF group and the BUD group, respectively, in the trial by Zetterström and colleagues[239] ($p < 0.01$).

Symptoms

Two of the trials reported asthma symptom scores. Buhl and colleagues[240] and Zetterström and colleagues[239] measured day- and night-time 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 the Buhl and colleagues study,[240] scores decreased (indicating fewer symptoms) by 0.24, 0.32 and 0.2 in the once- and 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 with the BUD group ($p < 0.05$), but not for the twice-daily group compared with BUD. In the trial by Zetterström and colleagues,[239] scores decreased by 0.52 (95% CI, –0.65 to –0.39) and by 0.20 (95% CI, –0.33 to –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[241] 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 with BUD). Buhl and colleagues[240] 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 with BUD). Zetterström and colleagues[239] used the definition of days with a total asthma score of zero and no night-time awakening. The increase in percentage of symptom-free days between baseline and end-point was 25.0% (95% CI 19.5 to 30.6) and 8.0% (95% CI 2.4 to 13.6) for the BUD/FF group and the BUD group, respectively ($p < 0.01$). Night-time awakenings were reported in all three trials. In the trial by Kuna and colleagues,[241] 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[240] reported percentage of 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 with the BUD group ($p < 0.05$). Zetterström and colleagues[239] reported changes in the percentage of night-time awakenings due to asthma. Reductions were 8.4% (95% CI –11.4 to –5.4) and 5.8% (95% CI –8.8 to –2.7) for the BUD/FF group and the BUD group, respectively. Differences between groups were 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,[240] 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 with the BUD group; $p < 0.001$ for the twice daily group compared with the BUD group). In the trial by Zetterström and colleagues,[239] reductions in puffs/day from baseline to end-point were 0.99 (95% CI –1.29 to –0.69) and 0.44 (95% CI –0.74 to –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[240] 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 night-time awakening due to asthma, ⩾20% decrease in PEF from baseline or ⩾4 inhalations of reliever medication over a 24-hour period. Severe exacerbation was defined as asthma deterioration requiring oral corticosteroid treatment, ⩾30% decrease in PEF 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[239] defined severe exacerbations as the need for oral steroids, discontinuations due to worsening asthma or PEF <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 AEs, where reported, appeared similar between treatments. No statistical significance values were reported in any of the trials.

In the trial by Kuna and colleagues,[241] 76 (38%), 78 (38%) and 74 (36%) of patients experienced at least one AE in the BUD/FF once-daily group, twice-daily group and BUD group, respectively. Seven serious AEs were reported: two, one and four in these study groups, respectively. The proportion of patients experiencing at least one AE in the trial by Buhl and colleagues[240] was 71 (40%), 60 (34%) and 78 (46%) in the once-daily and twice-daily BUD/FF groups and the BUD group, respectively. None of the five serious AEs were considered to be related to treatment. The number of patients experiencing at least one AE was not reported by Zetterström and colleagues.[239] However, it was reported that the number, nature and intensity of AEs were similar across the treatment groups. None of the five serious AEs were considered to be related to treatment.

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 200–1000 µg/day). The dose of BUD was similar in both comparisons, ranging from 200 to 800 µg/day.

There were statistically significant differences between treatment groups favouring BUD/FF in nearly all outcomes (morning and evening PEF; symptom scores; symptom-free days; use of rescue medication; FEV_1). Statistically significant differences between treatments in night-time awakenings were reported in only one of the three trials. The incidence of mild exacerbations (reported in one trial) and severe exacerbations (reported in two of the trials) appeared similar between treatments, although no statistical significance values were reported. The incidence of AEs 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 symptoms despite treatment with ICS.

Summary of Q3b – ICS versus ICS + LABA (ICS dose similar in both groups)
Six RCTs evaluated FP/SAL combination inhaler versus a similar dose of ICS, and four evaluated BUD/FF combination inhaler versus a similar dose of ICS. In all trials the same ICS was used in both comparators. ICS and LABA were statistically superior to ICS alone across most outcomes. *Tables 57* and *58* provide a visual illustration of the results of pair-wise comparisons.

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 AEs is noted for FP versus FP/SAL, but this effect is less certain for BUD versus BUD/FF.

Review question 4 – ICS + LABA in combination versus separate inhalers
To recap, six RCTs compared ICS and LABA in a combination inhaler with the two drugs delivered in separate inhalers (*Table 59*). The following subsections describe the characteristics and results of these trials.

FP/SAL in a combination inhaler versus BUD + FF in separate inhalers
Study characteristics
One parallel-group RCT[242] evaluated the effectiveness of FP/SAL in combination compared with BUD + FF given concurrently and was published in 2002 (*Table 60*). 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.

TABLE 57 *FP versus FP/SAL (n = 6)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
1000 µg FP vs 1000 µg/100 µg FP/SAL	Aubier *et al.*,[233] parallel-group, 28 weeks, DPI, *n* = 503	FP	NSD				NSD						19%
		FP/SAL		+	+								16%
500 µg FP vs 500 µg/100 µg FP/SAL	Koopmans *et al.*,[236] parallel-group, 52 weeks, DPI, *n* = 54	FP	NSD										96%
		FP/SAL		F	+				+		+		95%
	Lundbäck *et al.*,[237] parallel-group, 52 weeks, DPI, *n* = 282	FP	NSD										
		FP/SAL		+								+	
	Shapiro *et al.*,[238] parallel-group, 12 weeks, DPI, *n* = 349	FP											0
		FP/SAL	+	+	+	+	+		+		+	F	0
200 µg FP vs 200 µg/100 µg FP/SAL	Kavaru *et al.*,[235] parallel-group, 12 weeks, DPI, *n* = 356	FP				NSD							
		FP/SAL	+	+	+		+		+		+	F	
Variable	Bateman *et al.*,[234] parallel-group, 52 weeks, DPI, *n* = 3421	FP											
		FP/SAL	F							F		+	

F, results appear to favour this treatment group, but no tests of statistical significance reported; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 58 *BUD versus BUD/FF (n = 3 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
800 μg BUD vs 800 μg/9 μg BUD/FF	Zetterström *et al.*,[239] parallel-group, DPI, *n* = 362	BUD											C
		BUD/FF	+	+	+	F	+		+		+	F	
400 μg BUD vs 400 μg/9 μg BUD/FF	Buhl *et al.*,[240] parallel-group, 12 weeks, DPI, *n* = 523	1. BUD				NSD 1 vs 2							46%
		2. BUD/FF q.d	+ 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 b.d.	+ 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%
200 μg BUD vs 200 μg/ 9 μg BUD/FF	Kuna *et al.*,[241] 12 weeks, DPI, *n* = 617	1. BUD				F 1 vs 2 1 vs 3							36%
		2. BUD/FF q.d	+ 2 vs 1	+ 2 vs 1	+ 2 vs 1		+ 2 vs 1						38%
		3. BUD/FF b.d.	+ 3 vs 1	+ 3 vs 1	+ 3 vs 1		+ 3 vs 1						38%

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

The trial compared FP/SAL 100/500 µg/day via DPI (Seretide Diskus, GSK) in one trial arm with BUD 800 µg/day (Pulmicort Turbuhaler, AZ – not explicitly stated but deduced from the text) and FF 12 µg/day also via DPI Turbuhaler in the second trial arm. The treatment duration was 12 weeks.

The aim of the study was to compare the 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. The severity of asthma was moderate to severe, with participants on daily ICS doses between 1000 and 1600 µg/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 ITT population, but the method undertaken was assessed to be inadequate. This factor, when adequate, helps to minimise the risk of measurement bias.

Results

Lung function

The Ringdal and colleagues trial[242] presented 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 to 0.07; $p = 0.796$), suggesting that lower doses of the combination therapy were not inferior to higher doses of BUD + FF therapy.

Morning PEF changes from baseline were also reported to be similar between the two groups, but no *p*-value was reported for the ITT population (FP/SAL 43 l/minute, BUD + FF 47 l/minute), only for a PP 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 trial[242] but no data were reported to support this. The proportion of nights without awakenings was only reported as a median and hence is not reported here.

TABLE 59 *Breakdown of studies for review question 4 – combination inhaler versus separate inhalers*

Pair-wise comparison	No. 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

Use of rescue medication

Ringdal and colleagues[242] reported that there were no differences between the FP/SAL and BUD + FF groups in 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.[242] 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 with 0.73 in the BUD + FF group and was shown to be statistically significantly different (ratio 0.64, 95% CI 0.51 to 0.80, $p < 0.001$).

Adverse events

There were 91 AEs in total in the FP/SAL group and 78 in the BUD + FF group of the Ringdal and colleagues' trial.[242] No analysis of statistical significance was undertaken on these data. Serious AEs were reported by two participants in the FP/SAL group and three in the BUD + FF group.

Summary

One RCT compared 500 µg/day FP and 100 µg/day SAL with 1600 µg/day BUD and 24 µg/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 than the separate inhaler arm of the included trial. AEs appeared to be greater in the FP/SAL arm but this was not tested for statistical significance compared with the BUD + FF arm.

FP/SAL in a combination inhaler versus FP + SAL in separate inhalers

Study characteristics

Three parallel-group RCTs[233,243,244] evaluated the effectiveness of FP/SAL in combination compared

TABLE 60 *Characteristics of study (FP/SAL versus BUD + FF)*

Study	Design	Intervention	Patients	Outcomes
Ringdal *et al.*, 2002[242]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 250/50 μg b.d. (daily total 500/100 μg) 2. BUD + FF 800 μg + 12 μg b.d. (daily total 1600 μg + 24 μg) *Delivery device:* 1. DPI (Seretide Diskus, GSK) + 2 placebo Turbuhalers 2. DPI Turbuhaler (BUD – Pulmicort Turbuhaler, AZ[a]) + placebo Diskus *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 428 *Mean age (SD) (years)* 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 1000–1600 μg q.d. or FP 500–800 μg q.d.	Mean morning PEF PEF (morning and evening) PEF % diurnal variation Clinical FEV_1 Severity of exacerbations Day- and night-time symptom scores Night-time awakenings Use of rescue salbutamol Withdrawals from study Asthma-related healthcare resource utilisation (Norwegian healthcare system and costs – not data extracted) AEs

[a] Not stated explicitly, but deduced from the text.

with FP + SAL taken concurrently and were published between 1998 and 1999 (*Table 61*). All three studies were multi-centre trials with study sample sizes ranging between 224 and 503 participants. None of the included trials reported undertaking a power calculation.

All three included trials had comparisons of FP/SAL in combination with FP + SAL separately. One of the included trials, Aubier and colleagues,[233] also had a third arm comparison with FP alone (reported in the 'Review question 3b – ICS versus ICS + LABA (ICS dose similar in both groups)'; 'ICS versus ICS + LABA (FP versus FP/SAL)', 'Study characteristics', p. 119. The three trials used the same dose of SAL but varying doses of FP. One trial compared FP/SAL 200/100 µg/day with FP 200 µg/day + SAL 100 µg/day.[243] Another compared FP/SAL 500/100 µg/day with FP 500 µg/day + SAL 100 µg/day[244] and the third study FP/SAL 1000/100 µg/day with FP 1000 µg/day + SAL 100 µg/day.[233]

The devices used in all three studies were DPIs for both the combination treatment groups (Seretide Diskus, GSK) and the separate treatment groups (Flixotide, Accuhaler, GSK, deduced from the text of the paper by Aubier and colleagues[233]).

The treatment duration was 12 weeks in one study[243] and 28 weeks in the other two studies.[233,244]

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 PEF in all three included trials,[233,243,244] where *a priori* equivalence was regarded as a 90% CI within ±15 l/minute (reported to be defined and validated in previous clinical studies, references given).

The ages of participants in the trials were reasonably similar, ranging in the three studies between 33 and 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 400–500 µg/day of BDP or equivalent drug in the Bateman and colleagues trial,[243] 800–1200 µg/day BDP or equivalent in the Chapman and colleagues trial[244] and 1500–2000 µg/day BDP or equivalent in the Aubier and colleagues trial.[233] 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.[233] The other two trials reported absolute FEV_1 as 2.4[243] and 2.5[244] litres, respectively, although this is reported as % predicted (we assume this to be 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[243] and not reported in the other two trials.[233,244] 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 ITT principle in all three trials, but the method used was only assessed as being adequate in two of these[233,243] as participants appeared to be excluded from some of the analyses in the other trial.[244] An ITT analysis minimises the potential for measurement bias.

Results

Lung function

The adjusted mean change from baseline in FEV_1 in the Aubier and colleagues study[233] (estimated from figures) was 0.25 litres in the combination FP/SAL arm and 0.15 litres 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 trial[244] was 0.26 litres in the combination treatment group and 0.24 litres in the separate inhaler group. The 90% CI of the treatment difference (-0.02) was –4 to –1. The FEV_1 adjusted change from baseline was also reported after 12 weeks of therapy in the Bateman and colleagues trial.[243] Although the 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 litres, FP + SAL 0.17 litres).

The change from baseline in morning PEF was measured for the first 12 weeks to be 38 (SD 50.4) l/minute in the FP/SAL arm compared with 36 (SD 49.7) l/minute in the FP + SAL arm of the Aubier and colleagues trial.[233] The 90% CI around the mean difference (–2 l/minute) was –10 to 7 l/minute, $p = 0.77$. This was within predefined equivalence limits (±15 l/minute). In the Chapman and colleagues trial,[244] the change from baseline in morning PEF was also measured for just the

TABLE 61 *Characteristics of studies (FP/SAL versus FP + SAL)*

Study	Design	Intervention	Patients	Outcomes
Aubier *et al.*, 1999[233]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 500/50 μg b.d. (daily total 1000/100 μg) 2. FP + SAL 500 μg + 50 μg b.d. (daily total 1000 + 100 μg) 3. FP 500 μg b.d. (daily total 1000 μg) Only groups 1 and 2 reported here *Delivery device:* 1. DPI (Seretide Diskus, GSK) + placebo 2, 3. DPI Diskus (Flixotide, GSK[a]) + placebo *Duration:* 28 wks *Run-in period:* 2 wks	*Number randomised* 503 *Mean age (range) (years)* 1. 46 (12–78) 2. 48 (19–79) 3. 50 (12–76) *Baseline FEV_1 % predicted (± SD)* 1. 73 (± 1.2) 2. 73 (± 1.2) 3. 73 (± 1.4) *Previous ICS treatment (drug and dose)* BDP 1500–200 μg/day or FP 750–1000 μg/day	PEF (morning and evening) Daytime asthma score Night-time asthma score AEs Serum cortisol Urinary cortisol
Bateman *et al.*, 1998[243]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 100/50 μg b.d.+ placebo (daily total 200/100 μg) 2. FP + SAL 100 μg + 50 μg b.d. (daily total 200 μg + 100 μg) *Delivery device:* 1. DPI (Seretide Diskus, GSK) 2. DPI (Flixotide, Accuhaler, GSK[a]) *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 244 *Mean age (range) (years)* 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)	PEF (morning and evening) FEV_1 Use of rescue salbutamol Day- and night-time symptom score
Chapman *et al.*, 1999[244]	RCT Multi-centre Parallel-group Double-blind	1. FP/SAL 250/50 μg b.d. (daily total 500/100 μg) + placebo 2. FP+SAL 250 μg + 50 μg b.d. (daily total 500 μg + 100 μg) *Delivery device:* 1. DPI (Seretide Diskus, GSK) 2. DPI (Flixotide Accuhaler, GSK) *Duration:* 28 wks *Run-in period:* 2 wks	*Number randomised* 371 *Mean age (range) (years)* 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 400–600 μg q.d.	PEF (morning and evening) FEV_1 Use of salbutamol Daily and nightly symptom score Compliance AEs

[a] Not stated explicitly, but deduced from the text.

first 12 weeks of therapy. This was reported to be 43 l/minute in the combination inhaler group and 36 l/minute in the separate inhaler group. The treatment difference 90% CI was within the equivalence definition of the study (–6), 90% CI –13 to 0. The results of these studies suggest no difference between treatment with a combination inhaler and separate inhalers on morning PEF. In the Bateman and colleagues trial,[243] the adjusted mean change in morning PEF was 47 l/minute in the FP/SAL arm compared with 39 l/minute 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 (–17 to 0) was outside the defined equivalence interval, showing superiority of the combination treatment therapy.

The change from baseline in evening PEF was measured for the first 12 weeks to be 31 (SD 49.1) l/minute in the FP/SAL arm compared with 26 (SD 48.4) l/minute in the FP + SAL arm of the Aubier and colleagues trial.[233] These figures were not statistically significantly different ($p = 0.27$). In the Chapman and colleagues trial,[244] the change from baseline in evening PEF was also measured for just the first 12 weeks of therapy. This was reported to be 36 l/minute in the combination therapy group and 26 l/minute in the separate therapy group. The treatment difference was reported to be statistically significantly different ($p = 0.008$) favouring the combination product. In the Bateman and colleagues trial,[243] the adjusted mean change in evening PEF was 39 l/minute in the FP/SAL arm compared with 34 l/minute 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 PEF, although the study stated that the results were equivalent (we therefore assume that 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 was 38% in both comparison groups in the Aubier and colleagues trial[233] (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 trial.[233]

Use of rescue medication

No appropriate data were reported.

Exacerbations

No appropriate data were reported.

Adverse events

Sufficient data on numbers of AEs were reported in the two 28-week trials to be combined in a meta-analysis (*Figure 18*). The severity of the participants' asthma was likely to be slightly different as the patients in the trial by Aubier and colleagues[233] received higher doses than the patients in the Chapman and colleagues trial,[244] and this needs to be considered when interpreting the results of the meta-analysis. The fixed-effects pooled OR was 1.27 (95% CI 0.83 to 1.95; $p = 0.27$), suggesting no statistically significant difference between the combination FP/SAL treatment and the separate

Review: Corticosteroids – review Q4 – combination inhalers vs separate inhalers
Comparison: FP + salmeterol combination inhaler vs FP + salmeterol separate inhalers (adults): parallel
Outcome: Adverse events

Study or subcategory	Combined inhaler n/N	Separate inhalers n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Aubier *et al.*, 1999[233]	28/167	24/171		52.75	1.23 (0.68 to 2.23)
Chapman *et al.*, 1999[244]	160/180	164/191		47.25	1.32 (0.71 to 2.44)
Total (95% CI)	347	362		100.00	1.27 (0.83 to 1.95)

Total events: 188 (Combined inhaler), 188 (Separate inhalers)
Test for heterogeneity: $\chi^2 = 0.02$, df = 1 ($p = 0.88$), $I^2 = 0\%$
Test for overall effect: $Z = 1.11$ ($p = 0.27$)

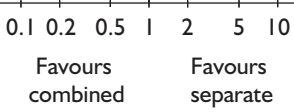

FIGURE 18 *Adverse events, FP/SAL versus FP + SAL*

FP + SAL treatment. Heterogeneity was not statistically significant ($p = 0.88$, $I^2 = 0\%$).

Data on discontinuations due to AEs were also reported in the two 28-week trials and combined in a meta-analysis (*Figure 19*). The fixed-effects pooled OR was 1.18 (95% CI 0.67 to 2.07, $p = 0.57$), similarly suggesting no statistically significant difference between the combination therapy and the separate therapies. Heterogeneity was not statistically significant ($p = 0.56$, $I^2 = 0\%$).

Summary

Three parallel-group RCTs compared combination use of 200–1000 µg/day FP/100 µg/day SAL with separate use of 200–1000 µg/day FP and 100 µg/day SAL.

On measures of lung function, no statistically significant differences were observed between treatment with FP/SAL in a combination inhaler compared with 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 AE profiles of the two treatments were not statistically significantly different.

BUD/FF in a combination inhaler versus BUD + FF in separate inhalers

Study characteristics

Two RCTs[239,245] evaluated the effectiveness of BUD/FF in a combination inhaler compared with BUD + FF administered via separate inhalers, and were published in 2001[239] and 2002.[245] 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 62*).

The doses of BUD and FF were the same in the two studies. One study[245] compared BUD/FF in a combination inhaler with a total daily dose of 640 µg/18 µg (160 µg/4.5 µg, two inhalations twice daily) with BUD + FF delivered via separate inhalers but with the same total daily dose of 640 µg + 18 µg (160 µg + 4.5 µg, two inhalations twice daily). Zetterström and colleagues[239] also compared BUD/FF in a combination inhaler with a total daily dose of 640 µg/18 µg (160 µg/4.5 µg, two inhalations twice daily), with the two agents in separate inhalers and a total daily dose of 800 µg BUD + 18 µg FF (200 µg + 4.5 µg, two inhalations twice daily). This trial also had a third arm comparison with BUD alone (200 µg, two inhalations twice daily; total 800 µg/day). For the purposes of this section, only the combination inhaler and the separate inhaler arms are compared. A comparison of the combination inhaler and the BUD monotherapy arms is given in the section 'ICS versus ICS + LABA (BUD versus BDD/FF)' (p. 126).

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 AZ). In the Zetterström and colleagues trial,[239] metered (*ex*-actuator) doses are reported for the separate inhalers and BUD monotherapy arms, and delivered (*ex*-valve) doses are reported for the combination inhaler. This reflects changes in labelling for newer inhaled

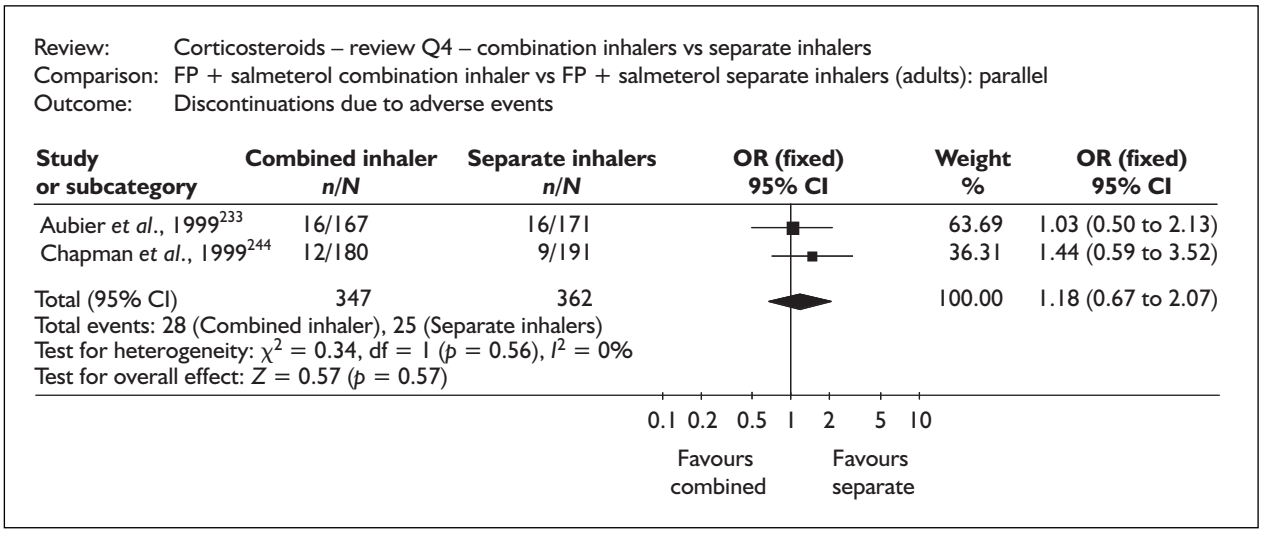

FIGURE 19 *Discontinuations due to adverse events, FP/SAL versus FP+SAL*

drugs which require the delivered dose rather than the metered dose to be reported. An inhalation of BUD/FF 160 µg/4.5 µg from the combination inhaler (Symbicort Turbuhaler, AZ) delivers the same quantity as a 200-µg metered inhalation of BUD (Pulmicort Turbuhaler, AZ) and a 6-µg metered inhalation of FF from separate inhalers.

The treatment duration was 6 months in one study[245] and 12 weeks in the second study.[239] Zetterström and colleagues[239] 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[245] also aimed to compare the combination inhaler with treatment administered via separate inhalers, but the focus in this study was more on the longer term safety (and also efficacy) of the combination inhaler, particularly in terms of HRQoL.

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 700 µg/day[245] and 950 µg/day[239] 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[245] and 74% in the other trial.[239]

Rosenhall and colleagues[245] reported safety (AEs) as their primary outcome measure, whereas Zetterström and colleagues[239] reported change in morning PEF as the primary outcome.

The quality of reporting and methodology of the included RCTs was mixed. In the Zetterström and colleagues trial[239] 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,[245] details of the randomisation procedure and concealment of allocation were unknown. The analysis was reported to be by ITT principle in both trials.

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[239] reported a mean FEV_1 of 2.28 litres at baseline and 2.47 litres at end-point in the BUD/FF group (a change of 0.19 litres), compared with 2.33 litres at baseline and 2.50 litres at end-point (a change of 0.17 litres) in the separate BUD + FF arm, with no statistically significant difference between groups ($p > 0.05$). Rosenhall and colleagues[245] did not report the data at end-point but stated that the mean FEV_1 increased by approximately 5–6% compared with baseline in both the combination inhaler and separate inhaler treatment groups.

Data on change in morning and evening PEF were reported in one study.[239] The change from baseline in morning PEF was 35.7 (95% CI 28.4 to 43.0) l/minute in the BUD/FF combination inhaler group and 32.0 (95% CI 24.5 to 39.4) l/minute in the BUD + FF separate inhaler group. These differences were not statistically significant ($p > 0.05$). Similarly, the change from baseline in evening PEF was 24.8 (95% CI 18.2 to 31.4) l/minute and 22.3 (95% CI 15.5 to 29.0) l/minute in the combination 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[239] reported data on symptoms.

The mean change from baseline in percentage of symptom-free days was 25.0% in the BUD/FF combination inhaler group compared with 22.3% in the BUD + FF separate inhaler group. The difference was not statistically significant ($p > 0.05$). Day- and night-time asthma symptoms were recorded using a four-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[245] did not report specifically on symptoms, but did report data on HRQoL using the 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).

TABLE 62 *Characteristics of studies (BUD/FF versus BUD + FF)*

Study	Design	Intervention	Patients	Outcomes
Rosenhall *et al.*, 2002[245]	RCT Multi-centre Parallel-group Open-label	1. BUD/FF 160/4.5 μg 2 puffs b.d.[a] (daily total 640/18 μg) 2. BUD + FF 160 μg + 4.5 μg 2 puffs b.d.[a] (daily total 640 μg +18 μg) *Delivery device:* 1. DPI (Symbicort Turbuhaler, AZ) 2. DPI (Pulmicort Turbuhaler + Oxis Turbuhaler, AZ) *Duration:* 6 months *Run-in period:* Not reported	*Number randomised* 586 *Mean age (range) (years)* 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 400–1200 μg/day	*Primary outcome* AEs *Secondary outcomes* FEV_1 FVC AEs Exacerbations HRQoL
Zetterström *et al.*, 2001[239]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. BUD/FF 160/4.5 μg[a] 2 puffs b.d. (daily total 640/18 μg) 2. BUD+FF 200 μg[b] + 4.5 μg 2 puffs b.d. (daily total 800 μg + 18 μg) 3. BUD 200 μg[b] 2 puffs b.d. (daily total 800 μg) Only groups 1 and 2 reported here *Delivery device:* 1. DPI (Symbicort Turbuhaler, AZ) 2,3. DPI (Pulmicort Turbuhaler, AZ[c]) *Duration:* 12 wks *Run-in period:* 2 wks	*Number randomised* 362 *Mean age (range) (years)* 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 ⩾500 μg/day	PEF (morning and evening) FEV_1 FVC Day- and night-time symptom score Symptom-free days Night-time awakenings Asthma control days Use of rescue medication AEs Exacerbations

[a] *Ex*-actuator.
[b] *Ex*-valve.
[c] Not stated explicitly, but deduced from the text.

Improvements were seen in both groups. For the BUD/FF combination inhaler group, the mean change from baseline total MiniAQLQ score was 0.48 compared with 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 sulfate or salbutamol rescue medication (number of puffs per day) was similar in both treatment groups in the Zetterström and colleagues trial (–0.99 versus –1.13 for BUD/FF and BUD + FF, respectively, $p > 0.05$).[239]

Exacerbations

Sufficient data on numbers of serious AEs were reported in the two trials to be combined in a meta-analysis (*Figure 20*). However, it should be noted that in the Rosenhall and colleagues trial,[245] 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,[239] a severe asthma exacerbation was defined as the need for oral steroids, discontinuation due to worsening of asthma or PEF <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 OR was 1.00 (95% CI 0.65 to 1.54), suggesting no statistically significant difference between the combination treatment and the separate treatment ($p = 0.33$). Heterogeneity was not statistically significant ($p = 0.33$, $I^2 = 0\%$).

Adverse events. Neither trial reported the total number of AEs experienced by each treatment group. In the Rosenhall and colleagues trial,[245] at least one AE was reported by 77% of patients treated with the combination inhaler compared with 69% treated with the separate inhalers. Zetterström and colleagues[239] reported that the number, nature and intensity of AEs were similar across groups.

Sufficient data on numbers of serious AEs were reported in the two trials to be combined in a meta-analysis (*Figure 21*). 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 OR was 1.85 (95% CI 0.71 to 4.82), suggesting no statistically significant difference between the two treatments ($p = 0.21$). Heterogeneity was not statistically significant ($p = 0.23$, $I^2 = 31.9\%$).

Data on discontinuations due to AEs were also reported in the two trials and combined in a meta-analysis (*Figure 22*). The fixed-effects pooled OR was 0.88 (95% CI 0.43 to 1.77), similarly suggesting no statistically significant difference between treatments ($p = 0.71$). Heterogeneity was not statistically significant ($p = 0.21$, $I^2 = 36.0\%$).

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

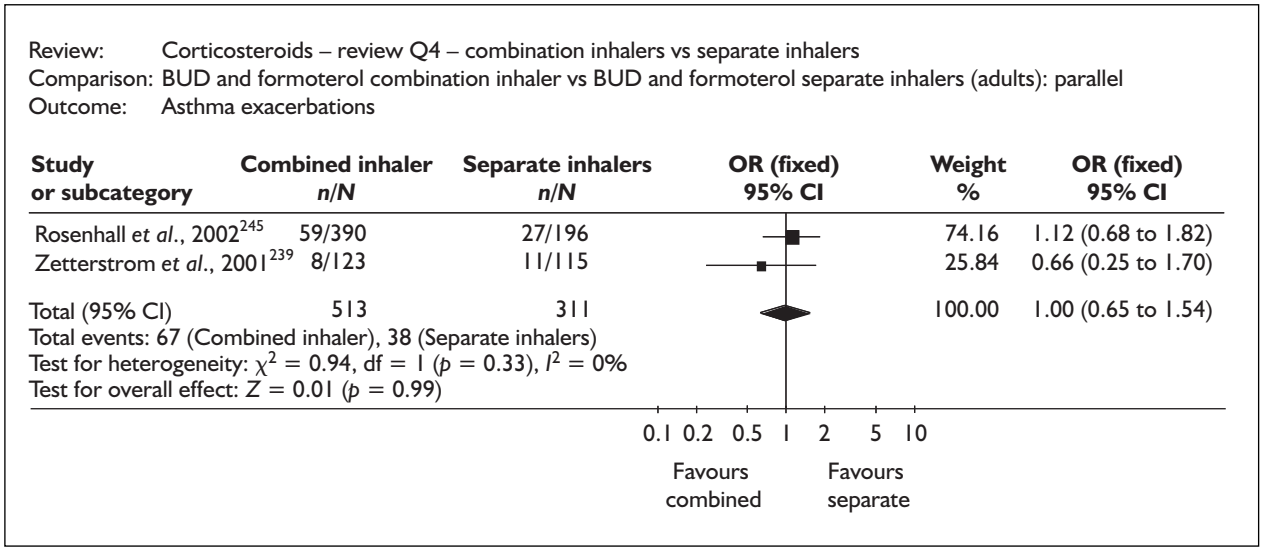

FIGURE 20 *Asthma exacerbations, BUD/FF versus BUD + FF*

two treatment groups on measures of symptoms or HRQoL. Furthermore, the AE profiles of the two treatments were also found to be comparable, with no statistically significant differences between them for serious AEs and discontinuations due to AEs.

Summary of Q4 – ICS + LABA in combination versus 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 AEs found no statistically significant differences in AEs, serious AEs and discontinuations in AEs. *Tables 63–65* provide a visual illustration of the results of pair-wise comparisons.

Review question 5 – combination inhaler compared with combination inhaler

To recap, three RCTs compared the two combination inhalers head-to-head (*Table 66*). The following subsection describes the characteristics and results of these trials.

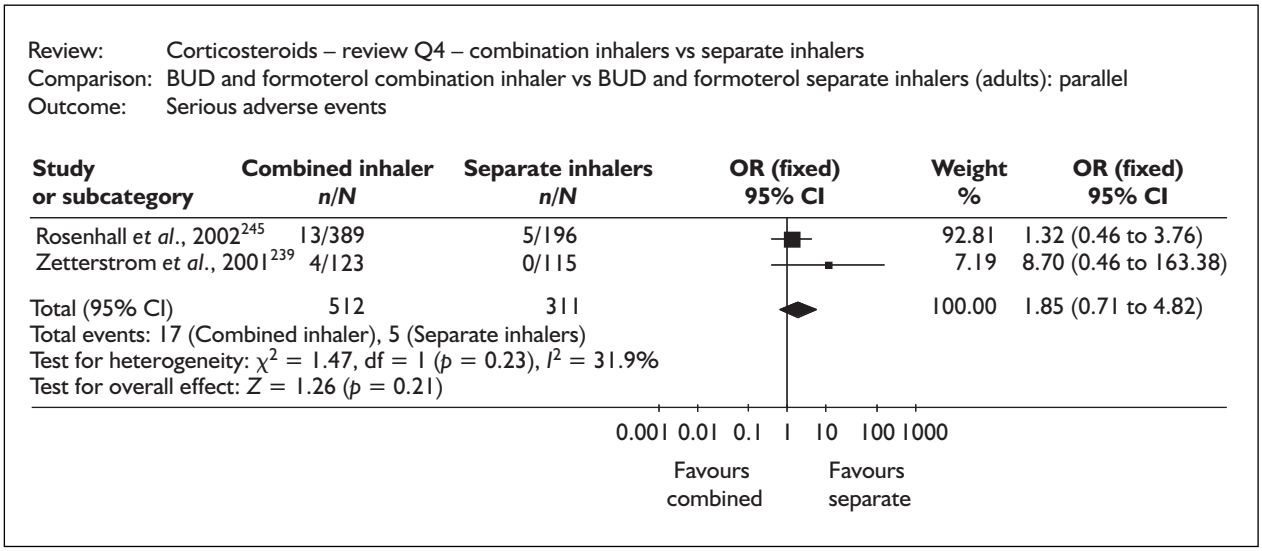

FIGURE 21 *Serious adverse events, BUD/FF versus BUD + FF*

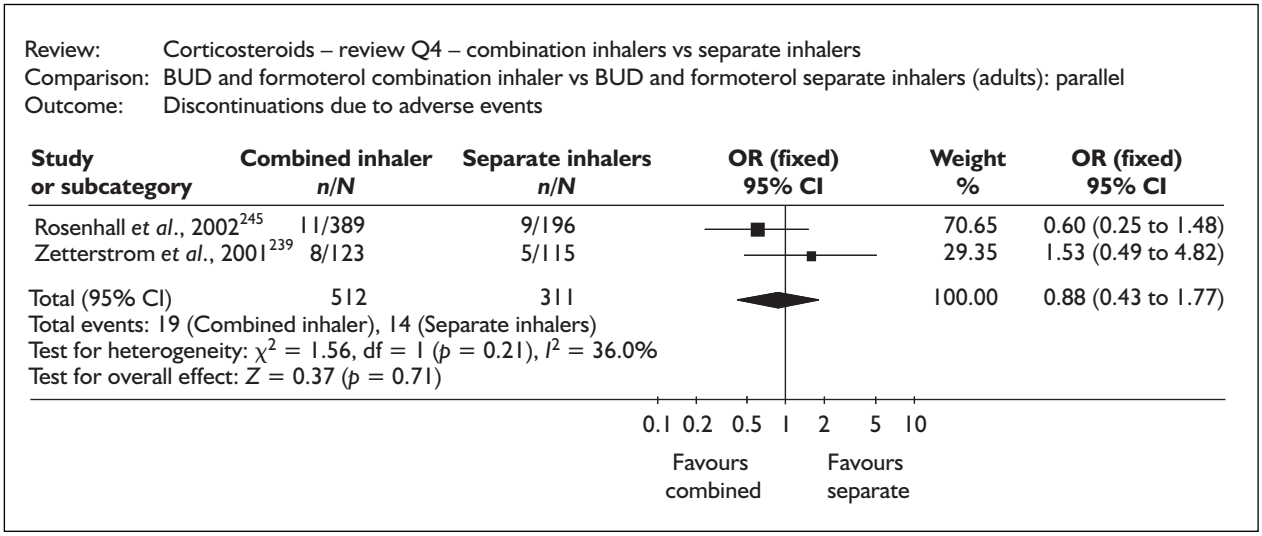

FIGURE 22 *Discontinuations due to adverse events, BUD/FF versus BUD + FF*

TABLE 63 *FP/SAL in a combination inhaler versus BUD + FF in separate inhalers (n = 1 RCT)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
500/100 µg FP/SAL vs 1600 + 24 µg BUD + FF	Ringdal *et al.*,[242] parallel-group 2 weeks, DPI, *n* = 428	FP/SAL combination	NSD	C			C				C	+	91 events
		BUD + FF separate											78 events

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; *n*, number of events; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

TABLE 64 *FP/SAL in a combination inhaler versus FP + SAL in separate inhalers (n = 3 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
	Meta-analysis Aubier *et al.*,[233] Chapman *et al.*,[244]	FP/SAL combination FP + SAL separate											NSD
1000/100 μg FP + SAL vs 1000 + 100 μg FP + SAL	Aubier *et al.*,[233] parallel-group, 28 weeks DPI, *n* = 503	FP/SAL combination FP + SAL separate	NSD	NSD NID	NSD		NSD	NSD					
200/100 μg FP/SAL vs 200 + 100 μg FP + SAL	Bateman *et al.*,[243] parallel-group, 12 weeks, DPI, *n* = 244	FP/SAL combination FP + SAL separate	C	NSD	NSD								
500/100 μg FP/SAL vs 500 + 100 μg FP + SAL	Chapman *et al.*,[244] parallel-group, 28 weeks, DPI, *n* = 371	FP/SAL combination FP + SAL separate	NSD	NSD NID	+								

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; *n*, number of events; NID, non-inferiority demonstrated; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); blank cells signify no data reported on that outcome.

TABLE 65 *BUD/FF in a combination inhaler versus BUD + FF in separate inhalers (n = 2 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
800/18 μg BUD/FF vs 800 + 18 μg BUD + FF	Rosenhall *et al.*,[245] parallel-group, open-label, 26 weeks, DPI, *n* = 586	BUD/FF combination	C							NSD			77%
		BUD + FF separate											69%
	Zetterström *et al.*,[239] parallel-group, 12 weeks, DPI, *n* = 362	BUD/FF combination	NSD	NSD	NSD		NSD		NSD		NSD		C
		BUD + FF separate											

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; *n*, number of events; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); blank cells signify no data reported on that outcome.

BUD/FF versus FP/SAL

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 67*). There were 706 patients in the 52-week trial by FitzGerald and colleagues[246] and 2143 in the 52-week trial by Vogelmeier and colleagues.[247] The RCT by Aalbers and colleagues[248] included 658 patients. For the first 4 weeks of treatment, patients in the BUD/FF AMD group did not adjust their dose. Aalbers and colleagues[248] combined the results for this period for the AMD and fixed dose (FD) BUD/FF groups. Following this double-blind month, there was a 6-month open-label extension during which patients were treated in the original three randomised groups, FD BUD/FF, AMD BUD/FF or FD FP/SAL. Only data from the 6-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[246] and Vogelmeier and colleagues[247] were two-arm trials. However, Aalbers and colleagues[248] reported a three-arm trial comparing the FP/SAL arm with either FD or AMD BUD/FF. The studies all used the same standard doses of 250 µg FP and 50 µg SAL, delivered twice per day. Patients in this arm of the study by Vogelmeier and colleagues[247] 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[246] were also required to take two doses of placebo via a Turbohaler twice per day. The standard doses of BUD/FF in the trials by Vogelmeier and colleagues[247] and Aalbers and colleagues[248] were 320 µg BUD and 9 µg FF *ex*-actuator, delivered twice a day. Patients in the Vogelmeier study[247] 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[248] study were adjustable to 160–640 µg BUD and 4.5–18 µg FF *ex*-actuator twice daily. The study by FitzGerald and colleagues[246] started with a higher dose of 400 µg BUD plus 12 µg FF *ex*-valve twice per day, but these doses were halved after 4 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 per day (BUD/FF – Seretide Diskus, GSK; FP/SAL – Symbicort Turbuhaler, AZ, for all studies).

The aim of the trial by Vogelmeier and colleagues[247] 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[248] investigated whether asthma control improved if patients adjusted the maintenance dose of BUD/FF according to asthma severity, compared with traditional FD 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 and colleagues study[246] was to compare the efficacy of FD of FP/SAL with AMD of BUD/FF.

Patients were of similar mean ages across the trials (44–46 years), with age ranges of 12–84/85 years reported by two trials[247,248] and an SD of 14 years reported by FitzGerald and colleagues.[246] None of the included studies commented on the severity of asthma in the RCT 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,[248] the mean baseline FEV_1 was 84% of the predicted normal value. This was slightly lower in the study by FitzGerald and colleagues,[246] 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[247] (73%). This suggests mild to moderate asthma, according to guidelines.

At entry to the study by Aalbers and colleagues,[248] 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[246] had used either an ICS at a dose equivalent to 200–500 µg BDP per day, combined with a LABA, or an ICS alone at a dose equivalent to >500–1000 µg BDP per day for at least 12 weeks before enrolment. Patients were eligible for inclusion in the study by Vogelmeier and colleagues[247] if they had used at least 500 µg BUD or FP per day, or at least 1000 µg/day of another ICS for at least 1 month before study entry.

TABLE 66 *Breakdown of studies for review question 5 – combination inhaler versus combination inhaler*

Pair-wise comparison	No. of RCTs included
FP/SAL (combination) vs BUD/FF (combination)	3
Total	3

TABLE 67 *Characteristics of studies comparing BUD/FF with FP/SAL*

Study	Design	Intervention	Patients	Outcomes
Aalbers *et al.*, 2004[248]	RCT Multi-centre Parallel-group Double-blind Double-dummy Open-extension	1. BUD/FF FD 160/4.5 μg[a] 2 puffs b.d. (daily total 800/24 μg) 2. BUD/FF AMD 160/4.5 μg[a] 2 puffs b.d. (daily total 800/24 μg – adjustable to 1 puff b.d. at end of double-blind – up to 4 puffs b.d. in open extension period for 7–14 days if needed) 3. FP/SAL 250/50 μg b.d. (daily total 500/100 μg) *Delivery device:* 1, 2. DPI (Symbicort Turbuhaler, AZ) 3. DPI (Seretide Diskus, GSK) *Duration:* 1 month (double-blind) + 6 months (open-label) *Run-in period:* 10–14 days	*Number randomised* 658 *Mean age (range) (years)* 46 (12–85) *Baseline FEV_1 % predicted* 84–85 *Previous ICS treatment (drug and dose)* BUD 500–1200 μg (with or without $beta_2$ agonist)	*Primary outcome* Odds of having a well-controlled asthma week, defined as: no night awakenings, no exacerbations, no change in treatment due to AEs At least two of the following: asthma symptom score >1 on ⩽2 days, ⩽2days, with reliever use, ⩽4 reliever uses, morning PEF ⩾80% of predicted every day *Secondary outcomes* PEF (morning and evening) 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, morning PEF ⩾80% of predicted every day Exacerbations (oral steroids for ⩾3 days, ER visits and/or hospitalisation)

continued

TABLE 67 *Characteristics of studies comparing BUD/FF with FP/SAL (cont'd)*

Study	Design	Intervention	Patients	Outcomes
FitzGerald *et al.*, 2005[246]	RCT Multi-centre Parallel-group Double-blind Double-dummy	1. BUD/FF AMD 200/6 μg[b] 2 puffs b.d. (daily total 800/24 μg – adjustable to 1 puff b.d. after 4 weeks – up to 4 puffs b.d. for 7–14 days if needed) + 1 puff b.d. placebo 2. FP/SAL 250/50 μg 1 puff b.d. (daily total 500/100 μg) + 2 puffs placebo b.d. *Delivery device:* 1. DPI (Symbicort, Turbuhaler, AZ) + placebo Diskus 2. DPI (Seretide Diskus, GSK[c]) + placebo Turbuhaler *Duration:* 52 wks *Run-in period:* 2 wks	*Number randomised* 706 *Mean age (± SD) (years)* 1. 44 (± 14) 2. 46 (± 14) *Baseline FEV_1 % predicted (± SD)* 1. 81 (± 13) 2. 82 (± 21) *Previous ICS treatment (drug and dose)* ~200–500 μg/day BDP + LABA, or ICS dose equivalent to >500–1000 μg/day BDP	*Primary outcome* Mean % symptom-free days (over 24-hour period) on daily record card *Secondary outcomes* % rescue-free days Daily rescue medication use Daily asthma symptom score % nights awoken due to asthma Mean morning PEF % well-controlled asthma weeks Incidence of asthma exacerbations (hospital treatment or oral corticosteroids, either in the opinion of the investigator or based on a morning PEF <70% of the mean of the last 7 days in weeks 1–4 for >2 consecutive days) AEs Compliance
Vogelmeier *et al.*, 2005[247]	RCT Multi-centre Parallel-group Open-label NB. This trial also examines the effects of the combination inhaler as a reliever	1. BUD/FF 160/4.5 μg[a] 2 puffs b.d. (daily total 800/24 μg – titrated up to 4 puffs or down to 2 puffs to improve control + additional inhalations for relief as needed) 2. FP/SAL 250/50 μg b.d. (daily total 500/100 μg – titrated up to 500/50 μg b.d. or down to 100/50 μg b.d. to improve control) + salbutamol relief *Delivery device:* 1. DPI (Symbicort, Turbuhaler, AZ) 2. DPI (Seretide Diskus, GSK) *Duration:* 52 wks *Run-in period:* 2 wks	*Number randomised* 2143 *Mean age (range) (years)* 45 (12–84) *Baseline FEV_1 % predicted (range)* 73 (28–115 across groups) *Previous ICS treatment (drug and dose)* >500 μg/day BUD or FP, or >1000 μg/day of another ICS (with LABA, if appropriate)	*Primary outcome* Time to first severe exacerbation (defined as hospitalisation/ER treatment, oral steroids for ⩾3 days, or an unscheduled visit leading to treatment change) *Secondary outcomes* Pre- and post-terbutaline FEV_1 As-needed medication use Symptoms (Asthma Control Questionnaire, ACQ-5) HRQoL [AQLQ(S)] AEs Severe exacerbations (no. of days with exacerbations and days with oral steroids)

AMD, adjustable maintenance dose; ER, emergency room; FD, fixed dose.
[a] *Ex*-actuator.
[b] *Ex*-valve.
[c] Not stated explicitly, but deduced from the text.

The primary outcomes were different for the three included RCTs. Aalbers and colleagues[248] used the odds of having a well-controlled asthma week, defined as no night awakenings; no exacerbations; no change in treatment due to AE; and at least two other criteria relating to asthma score of >1 on fewer than 2 days, fewer than 2 days or four instances of use of relief medication, and morning PEF rate higher than 80% of predicted value every day. FitzGerald and colleagues[246] reported the mean percentage of symptom-free days as the primary outcome measure, and Vogelmeier and colleagues[247] 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[246,247] were double-blind, but the study by Aalbers and colleagues[248] was open-label after an initial month of double-blind treatment. Analysis of outcome data by Aalbers and colleagues[248] was on an ITT basis, but the studies by FitzGerald and colleagues[246] and by Vogelmeier and colleagues[247] excluded small numbers of randomised patients from efficacy analyses.

Results

Lung function

Aalbers and colleagues[248] reported mean change from baseline in morning PEF as a secondary outcome measure. FEV_1 was only reported for the first month of the study, which was not fully randomised and so will not be discussed here. Changes in morning PEF were estimated from a graph. Mean values changed by 27.5 l/minute in the BUD/FF AMD group, by 34 l/minute in the BUD/FF FD group and by 35 l/minute in the FP/SAL group. The study reported no statistically significant differences between the three treatment groups. Aalbers and colleagues also reported that evening PEF 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 8.4 l/minute (95% CI 0.7 to 16.1, $p < 0.05$).

FitzGerald and colleagues[246] reported morning PEF, but not FEV_1, as measures of lung function. The average morning PEF at end-point was 395 l/minute (SD 104) in the FP/SAL group and 390 l/minute (SD 100) in the BUD/FF group. FitzGerald and colleagues[246] then adjusted these values using ANCOVA to allow for treatment, baseline, group country, sex and age. The resulting values (400.1 l/minute for the FP/SAL group and 390.6 l/minute for the BUD/FF group) were statistically significantly different ($p = 0.006$).

Vogelmeier and colleagues[247] measured lung function using pre- and post-terbutaline FEV_1 changes from baseline, but did not report morning or evening PEF. There was a statistically significant difference between the two treatment groups for both pre- and post-terbutaline FEV_1 mean change from baseline. The adjusted mean change from baseline pre-terbutaline FEV_1 was 0.17 litres in the BUD/FF group and 0.14 litres in the FP/SAL group ($p = 0.066$). For the post-terbutaline FEV_1 mean change from baseline, values of 0.07 and 0.04 litres were reported for the BUD/FF group and the FP/SAL group, respectively ($p = 0.045$).

Symptoms

Aalbers and colleagues[248] 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[246] 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% [interquartile range (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 night-time awakenings (p = not significant). 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 ACQ-5 by patients in the study by Vogelmeier and colleagues.[247] The questionnaire has five questions on the burden of symptoms, and each question is scored on a scale of 0–6 (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[247] considered these changes to be clinically relevant (references cited).

Health-related quality of life

HRQoL was only reported by Vogelmeier and colleagues,[247] who used the 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[247] 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[248] reported the mean number of occasions per day on which reliever medication was used; an occasion was defined as ⩾1 inhalations taken together, without waiting for peak bronchodilator response to each inhalation. The mean number of occasions per day during run-in was 1.83 in the BUD/FF group and 1.76 in the FP/SAL group and after 1 month the changes from baseline were –0.86 and –0.81, respectively. The difference between groups in the change from baseline (0.04) was not statistically significant (based on the 95% CI –0.12 to 0.21). FitzGerald and colleagues[246] 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[247] reported, over the entire treatment period, that patients receiving BUD/FF for maintenance plus as-needed medication used significantly (38%) less as-needed medication than those receiving FP/SAL plus salmeterol (mean numbers of inhalations per day were 0.58 and 0.93 respectively; $p < 0.001$).

Exacerbations

All three studies reported the rates of asthma exacerbations experienced by the patients in their trials. Aalbers and colleagues[248] 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 to 60.3%, $p = 0.018$).

FitzGerald and colleagues[246] 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 PEF that was <70% of the mean of the last 7 days (during the first 4 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 versus 0.33, $p = 0.008$).

Vogelmeier and colleagues[247] defined a severe exacerbation as a deterioration requiring hospitalisation or ER treatment, oral steroids for at least 3 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[247] 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[248] and Fitzgerald and colleagues[246] reported data on rates of AEs, which were pooled for meta-analysis using a fixed-effects model (*Figure 23*). (Both the AMD and FD groups in the trial by Aalbers and colleagues are entered into the meta-analysis.) The two trials showed small differences in direction of effect, and statistical tests indicate that heterogeneity is significant for this outcome measure ($\chi^2 = 5.33$, $p = 0.07$; $I^2 = 62.5\%$). 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 (7 months versus 1 year), which could have had an effect on the results. The OR from the pooled results was 1.09 (95% CI 0.87 to 1.36, $p = 0.45$) using the fixed-effects model and 1.18 (95% CI 0.80 to 1.73, $p = 0.41$) using the random-effects model. This suggests that there is no statistically significant difference between the two drug regimens, in

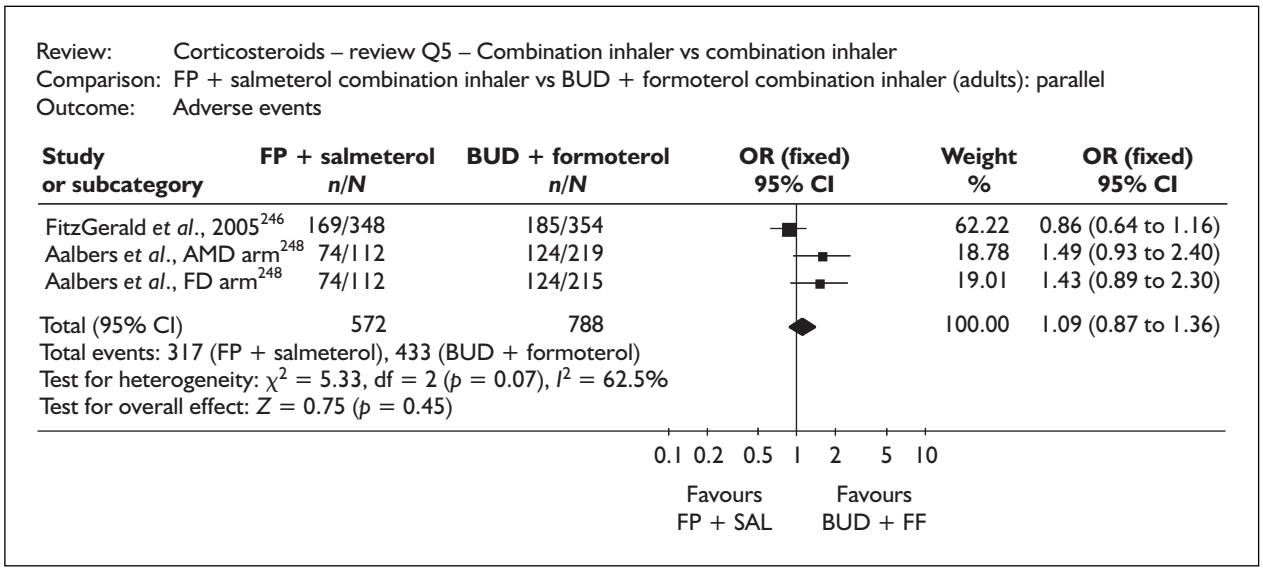

FIGURE 23 *Rate of adverse events*

terms of rate of adverse effects, but the studies' heterogeneity suggests that this result should be interpreted with caution.

The studies by FitzGerald and colleagues[246] and Vogelmeier and colleagues[247] reported rates of serious AEs. These were pooled for meta-analysis using a fixed-effects model (*Figure 24*). Statistical tests indicated that there was no significant heterogeneity ($\chi^2 = 0.02$, $p = 0.88$; $I^2 = 0\%$). Although the pooled results slightly favour BUD/FF, the OR was 1.09 (95% CI 0.81 to 1.47) and there was no statistically significant difference between the two treatments ($p = 0.57$).

The studies by FitzGerald and colleagues[246] and Aalbers and colleagues[248] reported rates of withdrawals due to AEs, and these were pooled using a fixed-effects model (*Figure 25*). Statistical tests did not indicate any significant heterogeneity ($\chi^2 = 0.73$, $p = 0.69$; $I^2 = 0\%$). Both of the studies indicated a slightly higher rate of withdrawals due to AEs in the BUD/FF arms, and the overall treatment effect favours FP/SAL for this outcome, with an OR of 0.78 (95% CI 0.50 to 1.21). However, the difference between the two treatment arms was not found to be statistically significant ($p = 0.27$).

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 800 µg BUD, 24 µg FF, 500 µg FP and 100 µg SAL. The studies were generally of good methodological quality, but lack of ITT analysis in the two of the studies[246,247] and lack of blinding in the six-month extension period of the other trial[248] may have allowed some bias to affect the 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[248] reported no statistically significant difference between the three treatment groups in morning PEF change from baseline value. However, evening PEF was significantly lower in the BUD/FF AMD group compared with the FP/SAL group. FitzGerald and colleagues[246] reported similar average morning PEF 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[247] reported a 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

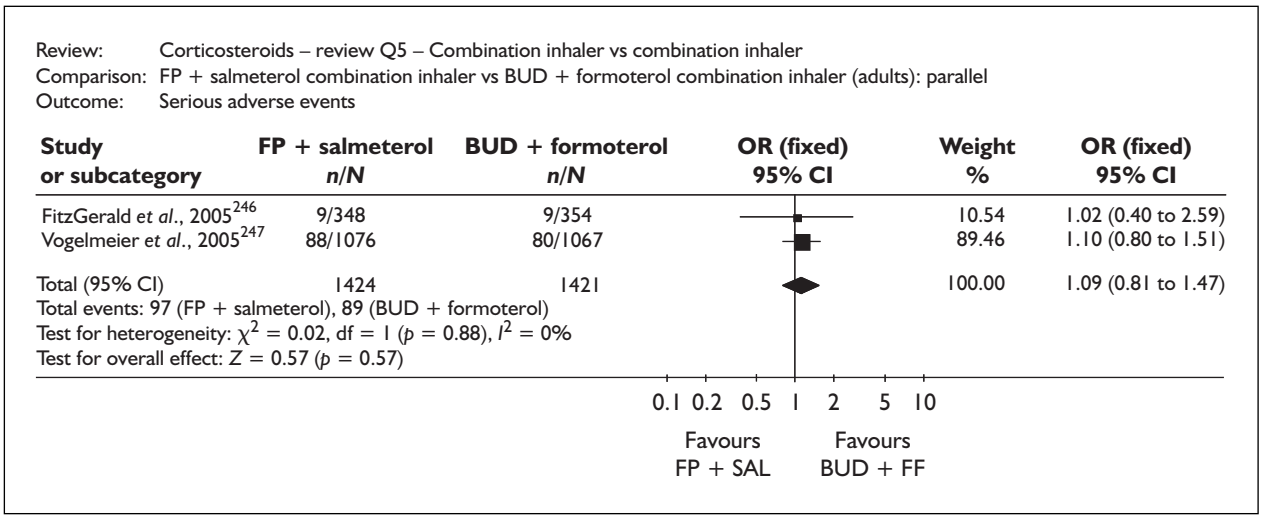

FIGURE 24 *Rate of serious adverse events*

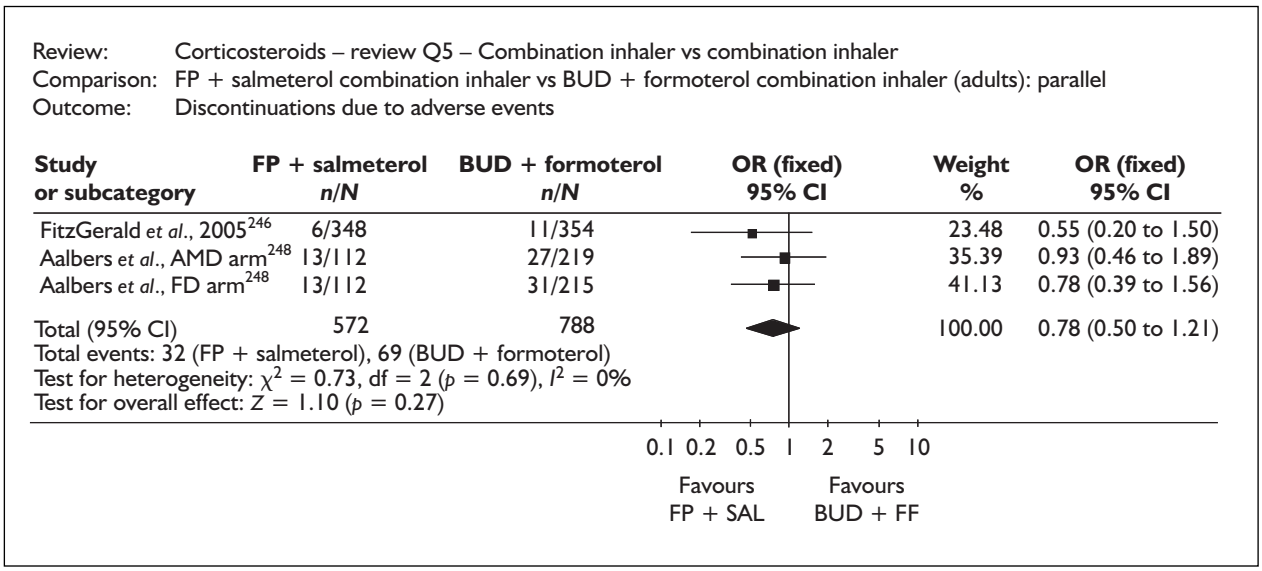

FIGURE 25 *Rate of withdrawals due to adverse events*

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 AEs, serious AEs or withdrawals due to AEs.

Summary of Q5 – combination inhaler compared with 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 the BUD/FF combination superior on others. Meta-analysis found that there were no significant differences between the treatment groups in rates of AEs, serious AEs or withdrawals due to AEs. *Table 68* provides a visual illustration of the results of pair-wise comparisons.

Related systematic reviews

Cochrane systematic reviews

Five Cochrane systematic reviews[56,170–173] evaluating various ICS treatments for chronic asthma in adults and children were identified in searches. As mentioned in the section 'Methods for reviewing effectiveness' (p. 23), this assessment has attempted to build on these reviews. The

TABLE 68 *BUD/FF versus FP/SAL both in combination inhalers, (n = 3 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	AEs (% of patients)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS				
	Meta-analysis Aalbers *et al.*,[248] Fitzgerald *et al.*,[246]	BUD/FF FP/SAL											NSD
800/18 μg BUD/FF vs 500/100 μg FP/SAL	Aalbers *et al.*,[248] parallel-group, double-blind/open-extension 4/26 weeks, DPI, *n* = 658	1. BUD/FF 2. BUD/FF AMD 3. FP/SAL		NSD	+ 2 vs 1 2 vs 3	F 2 vs 1 2 vs 3 F 3 vs 1			C			+ 2 vs 3	
	Fitzgerald *et al.*,[246] parallel-group, 52 weeks, DPI, *n* = 706	BUD/FF FP/SAL		+		NSD	+				+	+	
	Vogelmeier *et al.*,[247] parallel-group, 52 weeks. DPI, *n* = 2143	BUD/FF FP/SAL	+						NSD	NSD		+	

C, results appear to be comparable between treatment groups, but no tests of statistical significance reported; F, results appear to favour this treatment group, but no tests of statistical significance reported; *n*, number of events; NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score (varies between studies); + indicates results favour this trial arm; blank cells signify no data reported on that outcome.

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 in addition to combination inhalers). Further, the reviews included studies of adults and children under the age of 12 years, 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[170] – FP versus BDP or BUD

This review[170] 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 (aged >2 years) with chronic asthma. The interventions included any dose of FP compared with any dose of BDP or BUD, with a treatment period of 1 week or longer.

The review found 57 studies which met the inclusion criteria, involving 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 (eight studies), mild to moderate (12 studies), moderate (12 studies), moderate to severe (16 studies), severe (six studies) and mild to severe (two 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 with 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 PEF compared with BDP/BUD (mean difference 9.32 l/minute, 95% CI 5.96 to 12.69 l/minute), but not evening PEF (mean difference 4.67 l/minute, 95% CI –1.36 to 10.7 l/minute). When reported as change from baseline, there was no significant difference between groups (mean difference 1.68 l/minute, 95% CI –1.93 to 5.29 l/minute).

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 AEs, and data on morning plasma cortisol and 24-hour urinary cortisol were 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, three 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 PEF was significantly better with FP compared with BDP (mean difference 8.78 l/minute, 95% CI 5.14 to 12.41 l/minute). Evening PEF was also significantly better with FP (mean difference 6.37 l/minute, 95% CI 2.75 to 9.99 l/minute).

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, four 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, five studies). Differences in the reporting of measures of symptoms and rescue medication use meant that relatively few of the studies could be included in a meta-analysis. There was no significant difference between groups in the proportion of symptom-free days (three studies), day- or night-time score (two studies), the number of participants experiencing symptom-free days or nights (two studies) or the use of rescue medication use (two studies).

Lasserson and colleagues[173] – FP versus HFA–BDP for chronic asthma in adults and children

This review[173] aimed to determine the efficacy of FP compared with 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 with HFA–BDP.

The review found eight studies which met the inclusion criteria, involving 1260 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 PEF (WMD –2.31 l/minute, 95% CI –12.53 to 7.91).

Differences in the way in which 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, HRQoL or asthma exacerbations. Whereas 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 versus 0 puffs/day, $p = 0.04$). No significant difference was found in the rate of any AE [relative risk (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 are limited data to report in this category.

One trial reported no significant difference between FP and HFA–BDP in FEV_1 % predicted or morning PEF. One trial also reported in the text that there were no differences between treatment groups in FEV_1 or morning PEF 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[172] – LABAs versus placebo in addition to ICS in children and adults with chronic asthma

This review[172] assessed the effectiveness and safety of adding a LABA to ICS compared with 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 (aged >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 8147 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 and 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 the 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, whereas in children the mean age ranged from 8.5 to 14 years.

Results

Compared with 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 PEF (WMD 23.28 l/minute, 95% CI 18.38 to 28.18 l/minute) and evening PEF (WMD 21.33 l/minute, 95% CI 14.53 to 28.12 l/minute).

Use of ICS + LABA significantly reduced daytime 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, two studies) and overall 24-hour symptoms (SMD –0.28, 95% CI –0.45 to –0.11, two 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%, six studies) and symptom-free nights (SMD 0.51, 95% CI 0.28 to 0.74, four 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, eight 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 AEs (RR 0.98, 95% CI 0.92 to 1.05, 11 studies), serious AEs (RR 1.16, 95% CI 0.30 to 4.42, four studies) or withdrawals due to AEs (RR 1.29, 95% CI 0.96 to 1.75, 23 studies).

Adams and colleagues[56] – 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 aged over 2 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 (five parallel-group and 19 cross-over trials) published between 1982 and 1988 which met the inclusion criteria. Four of these were available only 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 2 to 4 weeks, 10 treated patients from 6 to 12 weeks and one study treated patients for 2 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 wash-out period. The majority of trials assessed doses of 400 µg/day (n = 10) or 800 µg/day (n = 7), although one study assessed doses of 200 µg/day and two studies used higher doses of 1500–1600 µg/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[56] 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 versus BUD.

FEV_1 was reported by six cross-over studies of patients with no prior OCS and two parallel-group studies. The weighted mean difference was –0.08 litres (95% CI –0.27 to 0.12) in the cross-over studies of patients with no prior OCS and –0.02 (95% CI –0.23 to 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 –5.04 litres (95% CI –11.98 to 1.89)]. Morning and evening PEF 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 –2.99 l/minute (95% CI –28.43 to 22.45) for morning PEF (six trials) and –5.47 l/minute (95% CI –31.50 to 20.56) for the five trials reporting evening PEF. 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/minute (95% CI –54.76 to 18.76) for morning PEF and –8.00 l/minute (95% CI –49.29 to 33.29) for evening PEF.

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 to 0.39)]. Similarly, use of rescue medication was not reported to differ statistically significantly between the two drugs. AEs were not pooled due to lack of clear reporting in the original trials. One parallel-group study reported an RR of 1.76 (BDP versus BUD) for withdrawal due to an asthma exacerbation (95% CI 0.44 to 7.10).

Greenstone and colleagues[171] – combination of LABA and ICS versus 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 aged over 2 years 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 with a control group, and these were analysed as separate trials, so the review was therefore based on data from 30 trials with 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 focused 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 1–3 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 10 used FP. Three trials compared FP and LABA with 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 with FP. The median ICS dose in the combined LABA group was 400 µg/day (range 200–1000 µg/day) and 1000 µg/day (range 400–2000 µg/day) in the higher ICS dose group. ICS and LABA drugs were delivered via separate devices in 22 trials, but eight trials used a combination device to deliver the drugs. Most of the trials lasted for 12 weeks (n = 14) or 24 weeks (n = 9), with others lasting 4 weeks (n = 1), 6 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 an RR of 0.88 (95% CI 0.77 to 1.02), with no significant group difference [relative difference = 2% (95% CI 0 to 4%)]. Although the similarity between treatments did not meet Greenstone and colleagues' *a priori* definition of equivalence,[171] the upper CI 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 versus 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 WMD in FEV_1 at end-point was 0.13 litres (95% CI 0.08 to 0.19). Similarly, change from baseline FEV_1 showed a WMD of 0.10 litres (95% CI 0.07 to 0.12; n = 7 trials) and FEV_1 % predicted at end-point had a WMD of 3.93% (95% CI 1.33 to 6.53; n = 4 trials). The WMDs for morning and evening PEF at end-point were 27.33 l/minute (95% CI 21.39 to 33.26; n = 14 trials) and 20.18 l/minute (95% CI 12.75 to 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 an SMD of –0.23 (95% CI –0.41 to –0.05). The percentage of symptom-free days at end-point also favoured combination therapy in pooled analysis of eight trials [WMD = 11.9% (95% CI 7.37 to 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 an SMD of –0.22 (95% CI –0.29 to –0.14). There were no statistically significant differences between the groups in daytime symptoms at end-point, night-time symptoms, percentage of symptom-free days

at end-point, change from baseline in night-time awakenings and quality of life as measured by the Juniper Questionnaire. There were no group differences in overall side-effects [RR = 0.93 (95% CI 0.84 to 1.03); n = 15 trials], serious AEs [RR = 1.54 (95% CI 0.72 to 3.21); n = 5 trials] or withdrawals due to AEs [RR = 0.94 (95% CI 0.71 to 1.24); n = 18 trials].

Other systematic reviews

Two systematic reviews evaluating ICS treatments for chronic asthma in adults and adolescents (aged >12 years) were identified, published in 1999[249] and 2004.[250]

Kankaanranta and colleagues[250] aimed to review systematically 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[249] 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 descriptions of the methodology and results which follow are only of those which are applicable here.

Kankaanranta and colleagues[250] included 14 blinded RCTs with either parallel-group or cross-over designs, whereas Jarvis and Faulds[249] 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[250] defined adolescents as aged >12 years) with mild to moderate asthma[249] or asthma that was inadequately controlled with ICS[250] (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 in either review, and assessment of publication bias was not carried out in one review[250] and not reported in the other.[249] Heterogeneity between studies was partially described by Kankaanranta and colleagues,[250] but not by Jarvis and Faulds.[249] Both reviews were narrative and neither included a meta-analysis. The quality of the reviews was mixed. Kankaanranta and colleagues[250] 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[249] were not clear in stating their research question, used only limited keywords 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 is outlined below.

Results

Kankaanranta and colleagues' review main findings[250]

- In patients with moderate to severe asthma, addition of FF was superior to the increase in steroid dose in increasing FEV_1 and morning PEF, 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 PEF, 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[249]

- In one study, morning PEF and FEV_1 increased significantly in patients receiving FP (88 or 220 µg twice daily) compared with those receiving BDP (168 µg 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 difference in the frequency of as-needed salbutamol usage between the two groups.
- Mean improvement in morning and/or evening PEF in patients with FP was similar to or

greater than those in patients receiving BUD; morning PEF 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 PEF 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[250] 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[249] 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.

Chapter 4
Economic analyses

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.
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.
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.

Additionally, 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. 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 Appendix 10 for one of the research questions). Finally, we attempt to provide an overview of the economic evidence from the different analyses, and comment on any consistent or conflicting findings.

Systematic review of published economic evaluations

A systematic review of existing published economic evaluations was undertaken.

The aims of this systematic review were to (1) 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 (2) 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.

Search strategy and critical appraisal methods

Ten electronic databases 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 Guideline.[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. These 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.[181] 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[251] and for judging the policy/decision relevance of each study to this assessment.

Inclusion and exclusion criteria

Full, published cost-effectiveness analyses (CEAs), cost–utility analyses (CUAs), cost–benefit analyses and cost–consequence analyses were eligible for inclusion in the cost-effectiveness review.

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.

Summary of the included cost-effectiveness studies

A total of 15[226,252–265] 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.

Study types and settings

As *Tables 69* and *70* show, of the 15 included studies, four[253,260,264,265] 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[266] and Barnes and colleagues,[267] 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, among 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[262] and Palmqvist and colleagues[261] and Johansson and colleagues[257] also appearing in the paper by Lundbäck and colleagues[259]). The wide variation in the comparators in different studies, in terms of both the drug types and daily dosages, is such that few meaningful comparisons can be made between studies.

Of the 11 studies which compared ICS against ICS plus LABA, all except two (by Johansson and colleagues[256] and Jönsson and colleagues[258]) involved adding a LABA to the same daily dose of ICS as in the ICS monotherapy with which it is compared. 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 Guideline.

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.[252,258,262]

Of the 15 economic evaluations, 12 were CEAs, one[260] was a CUA, one[265] was a cost-minimisation analysis (CMA) and one[254] contained both CEA

TABLE 69 *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[253]	800		400		
Marchetti *et al.*, 2004[260]	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[264]	500		1200		
Venables *et al.*, 1996[265]	400		400		

TABLE 70 *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/SAL Seretide**	**BUD/FF**	**FP/SAL**
ICS + LABA in combination inhaler vs ICS									
Briggs *et al.*, 2006[254]			100 250 500				100/50 250/50 500/50		
Ericsson *et al.*, 2006[255]			400			400/12			
Johansson *et al.*, 2006[256]						800/24 + additional inhalations as needed	500/100 + additional inhalations as needed		
Johansson *et al.*, 1999[257]			200				200/100		
Lundbäck *et al.*, 1999[259]			200 500 1000				200/100 500/100		1000/100
Lundbäck *et al.*, 2000[226]	1600						500/50		
Palmqvist *et al.*, 1999[261]			500				500/50		
Price and Briggs, 2002[263]			200				200/100		
ICS + LABA in separate inhalers vs ICS									
Andersson *et al.*, 2001[252]	200 800							200/24 800/24	
Jönsson *et al.*, 2004[258]	200 400							200/9 400/9	
Pieters et al., 1999[262]			500						500/50

and CUA results. Some of the CEAs reported cost-effectiveness ratios for more than one outcome measure.

Four studies[252–254,265] 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[252] 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 the 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[266] and Barnes and colleagues,[267] comparing BUD with FP at half the dose.

The time horizon of the studies ranged from 6 weeks to 1 year. Discounting was applied only in one study (and for utility only[260]). Most of the studies were funded by pharmaceutical companies; some also involved co-authors employed by such companies.

TABLE 71 *Summary of published full-text economic evaluation studies in adults*

Study	Study type	Analysis type	Country, setting	Comparators[a]	Perspective
Andersson *et al.*, 2001[252]	Trial-based	CEA	UK, Spain, etc., 9 countries. Setting NR	BUD + FF (separate inhalers) BUD	Society (Sweden, UK and Spain)
Booth *et al.*, 1995[253]	Trial-based	CEA	UK, in 57 general practices	FP BUD	UK NHS
Steinmetz *et al.*, 1998[264]	Trial-based	CEA	Germany. Ambulatory or outpatient centres	FP BUD	German third-party payer
Venables *et al.*, 1996[265]	Trial-based	CMA	UK, in general practice. Setting NR	FP BUD	UK NHS
Briggs *et al.*, 2006[254]	Trial- and regression model-based	CEA CUA	44 countries. General practice and hospital clinics	FP/SAL FP	UK NHS
Ericsson *et al.*, 2006[255]	Trial-based	CEA	6 countries (4 in Europe). Setting NR	BUD/FF FP	Healthcare payer, society and drug budget holder
Johansson *et al.*, 2006[256]	Trial-based	CEA	16 countries (10 in Europe including the UK). Setting NR	BUD/FF FP/SAL	Societal perspective
Johansson *et al.*, 1999[257]	Trial-based	CEA	North American clinical data. Setting NR	FP/SAL FP	Swedish healthcare system
Jönsson *et al.*, 2004[258]	Trial-based	CEA	17 countries (15 in Europe). Setting NR	BUD + FF (separate inhalers) BUD	Both healthcare payer and society
Lundbäck *et al.*, 1999[259]	Trial-based	CEA	North America and Europe. Setting NR	FP+SAL (both combination and separate inhalers) FP	Swedish healthcare system
Lundbäck *et al.*, 2000[226]	Trial-based	CEA	Sweden. Setting NR	FP/SAL BUD	Swedish healthcare system
Marchetti *et al.*, 2004[260]	Decision model-based	CUA	Italy. Setting NR	BDP BDP extra-fine FP BUD	Both the Italian healthcare system and society
Palmqvist *et al.*, 1999[261]	Trial-based	CEA	North America. Setting NR	FP/SAL FP	Swedish healthcare system
Pieters *et al.*, 1999[262]	Trial-based	CEA	France, Germany and The Netherlands. Setting NR	FP + SAL (separate inhalers) FP	Swedish healthcare system
Price and Briggs, 2002[263]	Decision model-based	CEA	42 centres in the US[b]. Setting NR	FP/SAL FP	UK healthcare system (implied by results in £)

NR, not reported.
[a] LABA with ICS in combination inhalers, unless otherwise specified.
[b] Data from supplement of the trial by Kavuru *et al.*,[268] Palmqvist *et al.*,[261] Pieters *et al.*[262] and Johansson *et al.*[257] involve duplicate publication of the cost-effectiveness comparisons reported in Lundbäck *et al.*[259]

In summary, although there are a number of economic evaluations that could be relevant to the current decision problem, the very wide variations 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.

A summary of the published economics evaluation studies in adults is given in *Table 71*.

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,[253,254,263,265] and another included an analysis from the UK NHS perspective[252] (and also 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 CUAs are more likely to produce favourable cost-effectiveness ratios.[269]

Summary information on the comparators, analysis design and results are shown in *Table 72*. Only the most recent study by Briggs and colleagues[254] calculated an incremental cost per QALY, and two of the studies are over a decade old.

The most recent UK NHS study, by Briggs and colleagues[254] based on the GOAL study (see clinical effectiveness review),[234] examined the cost–utility of the combination of FP/SAL 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 allow "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 GPs versus hospital services are different from those in 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,[234] this probably deserved more description.

Another good-quality study comparing FP/SAL with FF from an implicit (not stated) UK NHS perspective, by Price and Briggs,[263] mainly emphasised the development of the five-state Markov model, but also presented both deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) 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/SAL combination inhaler with FP at the same dose,[235] and also did not use a more generic measure of HRQoL, it is less relevant to the present decision problem.

The economic analysis by Andersson and colleagues,[252] 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[253] (of FP 200 µg twice daily versus BUD 400 µg twice daily) and by Venables and colleagues[265] (of FP 200 µg twice daily versus BUD 400 µg once daily versus BUD 200 µg twice daily) were in a treatment setting which is highly relevant to this technology review, but both are over 10 years old. In addition to 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 8 weeks, omitting the non-medication care costs of treating exacerbations and not being based on RCTs.

TABLE 72 *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[252]	1999	Not reported	1-year results of a 9-country RCT (FACET study)	(Separate inhalers) BUD 200 μg/FF 24 μg vs BUD 200 μg	£2.86 per SFD
				(Separate inhalers) BUD 800 μg/FF 24 μg vs BUD 800 μg	£4.06 per SFD
Booth *et al.*, 1995[253]	1995	57 general practices in the UK	UK-based 8-week RCT, of people with no or low ICS	BUD 800 μg vs FP 400 μg	Not reported
Briggs *et al.*, 2006[254]	2003–04	GP and hospital clinics	1-year results of a 44 country RCT (GOAL study)	Combination inhaler of FP (100 or 250 or 500 μg) + SAL 50 μg vs FP 100 or 250 or 500 μg (previously no ICS)	£7600 per QALY (95% CI £4800 to £10,700)
				Combination inhaler of FP (100 or 250 or 500 μg)/ SAL 50 μg vs FP 100 or 250 or 500 μg (previously on low-dose ICS)	£11,000 per QALY (95% CI £8600 to £14,600)
				Combination inhaler of FP (100 or 250 or 500 μg)/ SAL 50 μg vs FP 100 or 250 or 500 μg (previously on moderate dose ICS)	£13,700 per QALY (95% CI £11,000 to £18,300)
Price and Briggs, 2002[263]	2000	Trial: US treatment 'centres' Model: health system perspective	12-week efficacy and safety RCT in 42 US 'centres'	Combination inhaler of FP/SAL 200/50 μg vs FP 200 μg	£20.83 per successfully controlled week (95% CI £–65[b] to £113 per successfully controlled week)
Venables *et al.*, 1996[265]	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 400 μg vs BUD 200 μg vs FP 200 μg	Not reported

[a] All these ICERs are undiscounted and for ICS plus LABA compared with ICS alone.
[b] Negative because FP/SAL dominates FP.
Using same exchange rate as used in the published paper, of €1 = £0.613.

Summary of evidence from published economic evaluations

In summary, only the economic evaluation by Briggs and colleagues[254] comparing FP/SAL 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 HRQoL (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 £18,300 per QALY gained, they concluded that achieving optimal asthma control via a combination of FP and SAL 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 analysis 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.

Review of cost-effectiveness studies provided by industry

Seven submissions to NICE included CEA. Two of these included CEA and five included CMA. Submissions were made by GSK, AZ, Altana Pharma, Meda Pharmaceuticals, Ivax Pharmaceuticals and Trinity-Chiesi Pharmaceuticals. *Table 73* shows a summary of the submissions received by industry through the appraisal process. No submissions were received for the ICS MF.

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 CEAs by Drummond and colleagues[251] and the requirements of NICE for submissions on CEA (reference case) by NICE[270] and, where appropriate, a suggested guideline for good practice in model-based cost-effectiveness analysis by Philips and colleagues.[271]

Review of the submission by GlaxoSmithKline

Overview

The submission by GSK to NICE includes economics commentary and CEA 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 CEA for BDP and FP versus other ICS products, with a CMA approach assumed due to clinical equivalence across these products.

The submission is focused on four specific research questions:

- 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

TABLE 73 *Summary of the submissions received from the drug manufacturers through the appraisal process*

Manufacturer	Product	Generic name	Type of inhaler device	Type of analysis
GSK	Becotide Flixotide Seretide	BDP FP FP/SAL	pMDI pMDI/DPI	CEA
AZ	Pulmicort Symbicort	BUD BUD/FF	 pMDI DPI	CEA
Altana Pharma	Alvesco	CIC	MDI	CMA
Ivax Pharmaceuticals	Qvar	BDP	pMDI/MDI	CMA
Meda Pharmaceuticals	Novolizer	BUD	DPI	CMA
Trinity-Chiesi Pharmaceuticals	Clenil Modulite Pulvinal	BDP	pMDI	CMA

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 with BUD/FF (Symbicort)?

The submission presents outline detail of a systematic search of the literature on CEAs for the 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 CEA, and a 'generic' cost-effectiveness model to address cost-effectiveness in the context of questions 2–4, but question 1 is not covered further (as above, a CMA approach is assumed).

Model on cost-effectiveness of Seretide

In the submission, a new model is developed by GSK to estimate the 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 percentage 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 these 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 % SFDs at the trial end-point. This end-point is chosen as it was (1) commonly reported and considered, (2) based on clinical opinion and (3) judged to be more appropriate than lung function for representing patients' clinical response to treatment. This reported end-point (% SFDs) was taken to represent the proportion of time spent in the symptom-free state (p. 52). 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 are 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 1 year, corresponding to the duration of the GOAL trial used to estimate costs and utilities" (p. 53). However, given the nature of the model, it is a 'snap-shot' or cross-sectional approach to estimating CEA.

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.[254] 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 200 µg/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. The 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 (five for children, 16 for adults). All costs are reported in UK£ 2006.

Model/cost-effectiveness results

The CEA is arranged around the comparison of FP/SAL (at low, medium and high dose) to (1) ICS alone (at low, medium and high dose), (2) ICS plus LABA in separate inhalers (at low, medium and high dose) and (3) BUD/FF (at low, medium and high dose). The submission reports results for different product costs and an average product cost, hence the analysis results in approximately 65 different summary statistics. These are summarised below.

FP/SAL versus ICS alone

- Low dose: FP/SAL 200 µg/100 µg per day versus FP 200 µg/day, results in small differences in incremental cost and QALYs, with an ICER range of £6350–20,151.
- Medium dose: FP/SAL 500 µg/100 µg versus FP 400/500 µg/day, results in small differences in incremental cost and QALYs, with an ICER range of £12,100–24,020.
- High dose: FP/SAL 1000 µg/100 µg versus FP 1000 µg/day, results in small differences in incremental cost and QALYs, with an ICER range of £3660–£50,017.
- Low dose versus medium dose: FP/SAL 200 µg/100 µg/day versus FP 400–500 µg/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 500 µg/100 µg/day versus FP 1000 µg/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 200 µg/100 µg/day versus separate inhalers 200 µg + 100 µg/day (and BUD + SAL – 400 µg/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 £16,519–59,442.
- Medium dose: FP/SAL combination 500 µg/100 µg/day versus separate inhalers 400–500 µg+100 µg/day (and also compared with BUD + SAL 800–1000 µg/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 1000 µg/100 µg/day versus separate inhalers 1000 µg + 100 µg/day (and also compared with BUD + SAL 1600–2000 µg/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 200 µg/100 µg/day versus BUD/FF 400 µg/100 µg/day: no CEA (estimated cost saving –£22 to –£183).
- Low dose: FP/SAL 200 µg/100 µg versus BUD/FF 400 µg/200 µg/day: no CEA (estimated cost –£11 to + £149).
- Medium dose versus high dose: FP/SAL 500 µg/100 µg/day versus BUD/FF 800 µg/100 µg/day: no CEA (estimated cost saving –£357).
- Medium dose versus low dose: FP/SAL 500 µg/100 µg/day versus BUD/FF 800 µg/200 µg/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 500 µg/100 µg/day versus BUD/FF 800 µg/400 µg/day: no CEA (estimated cost saving –£18).
- High dose versus low dose: fluticasone/SAL 1000 µg/100 µg/day versus BUD/FF 1600 µg/200 µg/day: no CEA (estimated cost saving –£164 to –£427).
- High dose versus low dose: FP/SAL 1000 µg/100 µg/day versus BUD/FF 1600 µg/400 µg/day: no CEA (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 compared with BUD/FF, this is based on a very small QALY gain (0.0005).

Appraisal of the cost-effectiveness analysis undertaken

A critical appraisal checklist is given in *Tables 74* and NICE reference case requirements in *Table 75*.

Review of modelling approach

Model structure/structural assumptions

The model structure is based around the clinical end-point of difference in the % SFDs, 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

TABLE 74 *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 end-point (% SFDs) – mainly over 12 weeks. Although the study demonstrates effectiveness over this one end-point, it does not discuss, in the context of CEA, the other effectiveness end-points across treatments. The study assumes that 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?[a]	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

PSS, Personal Social Services.
[a] More on data inputs for costs and consequences is given in the review of modelling methods below.

TABLE 75 *NICE reference case requirements – GSK submission*

NICE reference case requirement	Critical appraisal	Reviewer comment
Decision problem: as per the scope developed by NICE (especially technologies and 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 SFDs were used to consider QALY values
Type of economic evaluation: CEA	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% per year for costs and health effects	NA	

NA, not applicable; PSS, Personal Social Services; SG, standard gamble; TTO, time trade-off.

presented in the submission indicate that differences between percentage of symptom-free nights (% 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;[254] 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 end-point 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 although there are guidelines for the treatment of asthma (e.g. the BTS/SIGN Guideline[1]), it is generally difficult (given the current evidence base) to structure and populate a model which is driven by such guidelines.

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 CEA. Data used on resource for 'other costs' are taken from the GOAL trial by Bateman and colleagues,[234] 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 reduced 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;[254] 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.[254]

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 costs 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 although the values used for symptom-free in the analysis seem relatively high (compared with 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 these 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 periods (e.g. 1 year).

The meta-analysis reported in the analysis, to inform the CEA, presents the trials used according to the research question addressed. Where FP/SAL is compared with 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 with increased dose ICS, three from a possible six trials present data on % SFDs, but only two of these trials could be used in the CEA. Where FP/SAL is compared with 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.

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 PSA (additional material was submitted, providing a cost-effectiveness plane and cost-effectiveness acceptability curve 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 subgroups.

Model validation

The submission states that checks were undertaken to consider the validity of the model, with a rebuild undertaken using a different software package. This presents evidence of the internal consistency (logic) of the model structure and data structure used.

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 costs'.
- Concerns over the lack of transparency in estimating health state utilities and other cost estimates.

Review of the submission by Astra-Zeneca

Overview

The submission by AZ to NICE includes an economic commentary and CEA 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 CEA 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" (p. 32). There is limited discussion of the relative cost-effectiveness of different ICS products, with a CMA approach assumed due to clinical equivalence across these products.

The CEA presented in the submission is to support the use of BUD/FF. The submission refers to BUD/FF FD, BUD/FF AMD, and BUD/FF as both main maintenance and reliever therapy (SMART). The submission used BUD/FF FD as the base case for CEA, 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 and SMART) with the use of ICS alone (high-dose FP), BUD + FF in separate format and with 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 with BUD/FF 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.

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 and Briggs[263] is reported to be the most appropriate approach for CEA considering the use of BUD/FF in UK practice.

Although the submission states that the approach presented by Price and Briggs[263] 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. It is a Markov-type model with four health states: non-exacerbation, mild exacerbation, severe exacerbation and treatment change. The last 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. When treatment is changed, it is in line with recommendations in the BTS/SIGN Guideline. 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 analysis. The model uses transition probabilities derived from individual level patient data from a UK clinical trial of a 12-week duration that compared BUD/FF FD with BUD/FF AMD, (cited: Ind and colleagues, 2004, unpublished AZ data). The data on the relative effects of comparator products (RRs 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 use of different transition probabilities for BUD/FF over months 1–3, 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 years and above. In the model, all persons start in the 'non-exacerbation' (controlled) health state. The perspective of the analysis is stated as UK NHS and PSS. Prices for asthma treatment are at a 2005–6 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).[316]

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 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.

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 –£8185 per 1000 persons). However, ICS alone is a lower cost compared to BUD/FF FD (with ICS alone showing a cost advantage of £245,152 per 1000 persons).

In the 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 with 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 is compared with 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.

Although AZ state that BUD/FF dominates FP/SAL the TAR team would suggest that the difference between the two treatments, which is of interest, is the lower number of exacerbations predicted for BUD/FF versus FP/SAL (per 1000 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.

Appraisal of the cost-effectiveness analysis undertaken

A critical appraisal checklist is given in *Table 76* and NICE reference case requirements in *Table 77*.

Review of modelling approach

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 who are without symptoms and those patients with symptoms but not requiring any intervention from a healthcare 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 the frequency of events in the trials used is based on exacerbations requiring hospitalisation or A&E visit. Many 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

TABLE 76 *Critical appraisal checklist of economic evaluation by AZ*

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 aged 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 and 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 end-point (exacerbation related outcomes) – mainly over 12 weeks. Primary effectiveness data (for BUD/FF transition probabilities) from only one UK RCT. The study assumes that 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-year horizon in sensitivity analysis
Are the costs and consequences consistent with the perspective employed?[a]	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.

[a] More on data inputs for costs and consequences is given in the review of modelling methods, p. 174.

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 the use of an outcome related more directly to control, such as % SFDs, 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.

TABLE 77 *NICE reference case requirements – AZ submission*

NICE reference case requirement	Critical appraisal	Reviewer comment
Decision problem: as per the scope developed by NICE (especially technologies and patient group)	Yes	
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	Partial	Health effects partly limited to effect of treatment on exacerbation rate
Type of economic evaluation: CEA	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% per year for costs and health effects	NA	Base case is 1-year analysis, no discounting necessary. Sensitivity analysis at 5 years, with 3.5% rate used for costs and effects

NA, not applicable; SG, standard gamble; TTO, time trade-off.

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.

Although not stated in the submission, the model assumes the same toxicity profile for treatments and the same profile for any longer term AEs.

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 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 is important to acknowledge that the literature on modelling cost-effectiveness in asthma treatment is indeed sparse, and although there are guidelines for the treatment of asthma (e.g. the BTS/SIGN Guideline[1]), it is generally difficult (given the current evidence base) to set up a model which is consistent with such guidelines.

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.

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. Data on other costs are presented clearly and, although 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 £1752 (dependent on need for hospitalisation).

Although 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 commercial in-confidence 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.

Assessment of uncertainty

Uncertainty is addressed in the submission using deterministic sensitivity analysis and PSA. PSA has addressed parameter uncertainty in a number of cases, (number of inhalations, utility values, transition probabilities, RRs). However, although the choice of distributions would seem to follow accepted methods, in many cases the uncertainty around parameter inputs is very small, with SEs (around the mean) being very small [e.g. for number of inhalations at 3.85, SE = 0.003; health utility for non-exacerbation (without SABA) at 0.927, with SE at 0.016]. The report refers to the use of probabilistic methods for transition probabilities; however, it is unclear how the probabilities were sampled (either rescaled to sum to 1.00, or via some correlation matrix; the submission states "normalised to give a sum of one", p. 99).

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 may be an issue related to very small incremental costs and effects, or a more substantive effect in analyses).

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, that is, the arm of one RCT used to estimate the transition probabilities for BUD/FF.
- There is a 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.

Review of the submission by Altana Pharma

Overview

The submission by Altana Pharma to NICE includes economic analysis comprising a CMA 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, beclomethasone and BUD, and concludes that CIC 160 µg once daily will be of comparable clinical effectiveness to FP100 µg twice daily, BUD 200 µg twice daily and BDP 200 µg twice daily.

The submission also concludes that CIC 160 µg/day will have a potentially lower overall cost to the UK NHS and PSS budget. The annual drug cost for patients prescribed CIC 160 µg/day daily is estimated at £102.20. This cost is compared with estimates of £73–219 for FP 200 µg/day, £73–138.70 for BUD 400 µg/day and £14–146 for BDP 400 µg/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 160 µg/day, they are based on products that use CFC propellants which will soon become obsolete (2007).[272,273] In Table 10 in the submission appendices, a range of CFC-free products are listed for comparison; in five 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 160 µg/day is also compared with the combination therapies of FP/SAL and

BUD/FF. For these cost comparisons, CIC 160 μg/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.

Review of the submission by Ivax Pharmaceuticals

Overview

The submission by Ivax Pharmaceuticals 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) with 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 CEAs in addition to these.

Review of CEAs 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:

1. BDP – published in 2002 (by Price and colleagues[274])
2. HFA-propelled FP – ERS conference poster presentation only.
3. BUD via Turbuhaler – ERS conference poster presentation only.

Table 78 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.

Cost-effectiveness results

The cost-effectiveness results of the studies summarised in the submission are given in *Table 79*.

These cost-effectiveness results should be treated with 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.

Review of the submission by Meda Pharmaceuticals

Overview

The submission by Meda Pharmaceuticals to NICE includes evidence summaries of the Novolizer BUD (DPI) device's technical performance, tolerability and acceptability to patients and also general discussion of the burden of asthma and the role of BUD in asthma. The emphasis throughout their report, including in their CMA, is on the documented or estimated patient benefits and NHS savings of the Novolizer device compared with its main DPI competitor product, the Pulmicort Turbuhaler. The majority of the submitted material, and the whole of the economic analysis, are 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.

TABLE 78 *Cost-effectiveness studies comparing Qvar with other ICS – study designs*

Comparator	Country, setting	Patients	Time	Outcomes	Costs
BDP	International, multi-centre	*n* = 473	1 year	SFDs HRQoL (AQLQ > 0.5)	Study drugs; other respiratory drugs; 2 GP visits; hospitalisation and A&E visits
HFA-propelled FP	International, multi-centre	*n* = 198 Age 18–75 years, on 500–1000 μg/day (BDP equivalent)	8 weeks	Change in % SFDs	Study drugs; other respiratory drugs; 2 GP visits
BUD (Turbohaler)	International, multi-centre	*n* = 209 Age 18–75 years, on 500–1000 μg/day (BDP equivalent)	8 weeks	Change in % SFDs	Study drugs; other respiratory drugs; 2 GP visits

TABLE 79 *Cost-effectiveness studies comparing Qvar with other ICS: base case results*

Comparator	Costs per patient (£)	Effectiveness	ICER
BDP	Qvar = 226	166 SFDs; 44% of patients >+0.5 change in AQLQ	Qvar both slightly cheaper and more effective (more SFDs) than CFC–BDP
	CFC–BDP = 231	128 SFDs; 36% of patients >+0.5 change in AQLQ	
HFA-propelled FP	Qvar = 143	24% increase in SFDs	Qvar both cheaper and more effective (greater increase in SFDs) than comparator
	HFA-propelled FP = 164	18% increase in SFDs	
BUD (Turbohaler)	Qvar = 174	25% increase in SFDs	Qvar both cheaper and more effective (greater increase in SFDs) than comparator
	BUD = 219	12% increase in SFDs	

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 *Tables 80* and *81* we appraise the main features of the basic (two-page) economic evaluation submitted by Meda Pharmaceuticals.

Review of the submission by Trinity-Chiesi Pharmaceuticals

Overview of the submission for Clenil Modulite

The submission by Trinity-Chiesi Pharmaceuticals 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 3 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 1 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 retitrate 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.

Cost minimisation results

Table 82 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.

Overview of the submission for Pulvinal

The submission by Trinity-Chiesi Pharmaceuticals to NICE focuses on the clinical effectiveness and cost of the BDP product Pulvinal for use with its own DPI device.

The submission includes some discussion of evidence of the claimed clinical benefits of this product over other DPI products that are licensed

TABLE 80 *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 400 μg daily (=200 μg b.d.)
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*. *Respiration* 2002;**69**(6):502–8
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?	NA	
Is differential timing considered?	NA	
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	

NA, not applicable.

for adults, and also summarises some evidence from published research literature to support the cost-effectiveness of inhaler devices that are easier to use or reduce dose wastage.

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.

Summary of the cost-effectiveness submissions made by the 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 CMA with a general assumption of an equivalent level of clinical effectiveness across ICS products being compared. The submissions by Ivax Pharmaceuticals and Trinity-Chiesi Pharmaceuticals were both limited to a presentation of the costs of their respective BDP products, Qvar and Clenil Modulite, respectively. Likewise, the submissions by Altana Pharma and Meda Pharmaceuticals 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 CMA. 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. 100, 200 or 400 μg 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.

TABLE 81 *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 (especially technologies and 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	NA	CMA
Type of economic evaluation: CEA	No	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	NA	CMA
Description of health states for QALY calculations: use of a standardised and validated generic instrument	NA	CMA
Method of preference elicitation for health state values: choice-based method (e.g. TTO, SG, not rating scale)	NA	CMA
Source of preference data: representative sample of the UK public	NA	CMA
Evidence on costs: prices relevant to NHS and PSS	Yes	Inhaler with drug and inhaler refill costs only
Discount rate: 3.5% per year for costs and health effects	No	

NA, not applicable.

TABLE 82 *Costs of Clenil Modulite and Qvar*

Product	Annual cost of 50 μg doses (£)	Annual cost of 100 μg doses (£)	Annual cost of 200 μg doses (£)	Annual cost of 250 μg doses (£)
Qvar (at half the dose of Clenil Modulite)	14.13	28.25	61.87	61.87
Clenil Modulite	14.05	28.18	61.43	61.87

For the combination therapies of Seretide (FP/SAL; GSK) and Symbicort (BUD/FF; AZ), more complex cost-effectiveness models were presented. However, once again, both of the models were developed from a product-specific perspective.

Original economic analyses: introduction and rationale

The systematic review of economic evaluations in the section 'Systematic review of published economic evaluations' (p. 161) identified a number of limitations in the existing research literature on the relative cost-effectiveness 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 Guideline.[1]

The CMAs and other cost analyses submitted by industry mostly provide fairly 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 CEAs (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 that 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 Guideline.

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 (200–800 µg BDP/day or equivalent), which is the most cost-effective of the five ICS? (Step 2 of the Guideline).
Q2. At high doses (800–2000 µg BDP/day or equivalent), which is the most cost-effective of the five ICS? (Step 4 of the Guideline).

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 into 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 Guideline).
Question 3a is viewed as the more clinically relevant of the original two sub-questions for question 3, 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 Guideline, 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 Guideline).

Types of analysis used

Given the lack of consistent evidence of differential clinical effectiveness for questions 1, 2, 4, and 5, 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 CUA, 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 Steps 2/3 of the BTS/SIGN Guideline) (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 that 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 Guideline.[1] A brief summary of the model design, input parameters and main probabilistic outputs is given 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 SFDs, as a basis for the CUAs 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 present only an abbreviated version of our cost–utility model and analysis (as Appendix 10), these two reviews are also presented in Appendices 8 and 9, respectively, as background to that analysis and as a resource for future modelling studies in this area.

Original economic analyses

Rationale for cost comparisons

Cost comparisons, like CMAs, should normally be used when there is valid and reliable evidence of equivalent effectiveness of the alternative technologies being compared.[251] However, as previous sections of this report have concluded, among 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. 100, 200 or 400 µg 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 such as 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 allow 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.

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 + µg BDP–CFC equivalent per dose) × 365

where 'BNF £ pack price' is the specific BNF per pack price for a specific preparation (e.g. 50, 100, 200, 250 or 400 µg per dose).[275] 'Doses per day' is the number of doses of a given preparation needed to achieve a particular target daily dose level (e.g. 400 µg/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 = 400 µg CFC–BDP (or equivalent) per day
LD_{max}: low-dose maximum dosage = 800 µg CFC–BDP (or equivalent) per day

These equate to, respectively, 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 either 1500 or 1600 μg 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 Guideline.

Assumptions about number of doses per day

For simplicity, and unless recommended otherwise 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 *Table 83*.

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 purposes of informing dosage decisions when switching patients between ICS products, both the GINA Guidelines and the BTS/SIGN Guideline publish ratios of dose equivalence. These are summarised in *Table 84*.

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.

TABLE 83 *Base-case assumptions about number of doses per day*

Daily dosage (BDP–CFC equivalent) (μg)	Taken either as	Or as
400	100 μg[a] × 4 doses	200 μg[a] × 2 doses
800	200 μg[a] × 4 doses	400 μg[a] × 2 doses
1500 or 1600	250 μg[a] × 6 doses	400 μg[a] × 4 doses

[a] BDP–CFC or equivalent (see *Table 84*); except CIC (Alvesco) and MF (Asmanex), which are more usually prescribed as a single daily dose.

TABLE 84 *Base-case assumptions about dose equivalence with CFC–BDP*

Drug	Equivalent amount of BDP–CFC		Ratio used in CMA
	BTS/SIGN Guideline	GINA Pocket Guide to Asthma	
BDP HFA-propelled[a]	×2	×2	×2
BUD	~ ×1	Not stated	×1
BUD–DPI	~ ×1[b]	~ ×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 the 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 Guideline, by "a relatively limited number of studies".

[d] Based on stated equivalence in the GINA Pocket Guide of 400 μg MF with 500 μg BDP–CFC and 800 μg MF with 1000 μg BDP–CFC.

[e] A suggested dose ratio for CIC has not been published 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.[276] The assumption that 160 μg CIC (*ex*-actuator) = 200 μg CIC (*ex*-valve) = 400 μg BDP–CFC is based on information supplied by Altana Pharmaceuticals and based on the fact that trials have tended to compare once-daily CIC with other ICS at a dose ratio of 1:2.

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 forms (aerosol versus dry powder), for different inhaler devices, and either propelled by CFC-containing or non-CFC containing propellants. To compare between ICS drugs, it is therefore necessary to generate a single, average cost for a given level of daily dosage.

We have used two methods for doing this: (1) using an unweighted mean annual cost and (2) 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. LD_{start} = 400 µg BDP–CFC equivalent), calculate the annual cost of achieving this dose (e.g. all products available as 100 µg BDP–CFC equivalent doses and/or 200 µg 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 Prescribing Cost Analysis (PCA) database for 2005). However, for a product of this drug sold in 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 allowed 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).

Results

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 the section 'Review question 1 – effectiveness of low-dose ICS', p. 28). *Tables 85* and *86* summarise the unweighted and weighted mean annual cost of the five ICS drugs, by inhaler and propellant type. *Figures 26* and *27* 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 results show that overall BDP appears to be the current cheapest ICS drug at starting low doses (400 µg 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 between BDP and FP, is strongly dependent on the crude assumed dose equivalence ratio of 1:2 with BDP–CFC products.

Tables 87 and *88* summarise the unweighted and weighted mean annual cost of the five ICS drugs, by inhaler and propellant type, when taken at 800 µg/day (BDP–CFC equivalent). *Figures 28* and *29* 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.

TABLE 85 *Unweighted mean annual cost of ICS by drug if on 400µg BDP equivalent per day*

Drug	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	NA	113	106	113
FP	NA	66	149	133	133
MF	NA	NA	170	170	170
CIC	NA	87	NA	87	87

NA, not applicable.

TABLE 86 *Weighted mean annual cost of ICS by drug if on 400 µg BDP equivalent per day*

Drug	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	NA	134	120	134
FP	NA	66	142	106	106
MF	NA	NA	162	162	162
CIC	NA	87	NA	87	87

NA, not applicable.

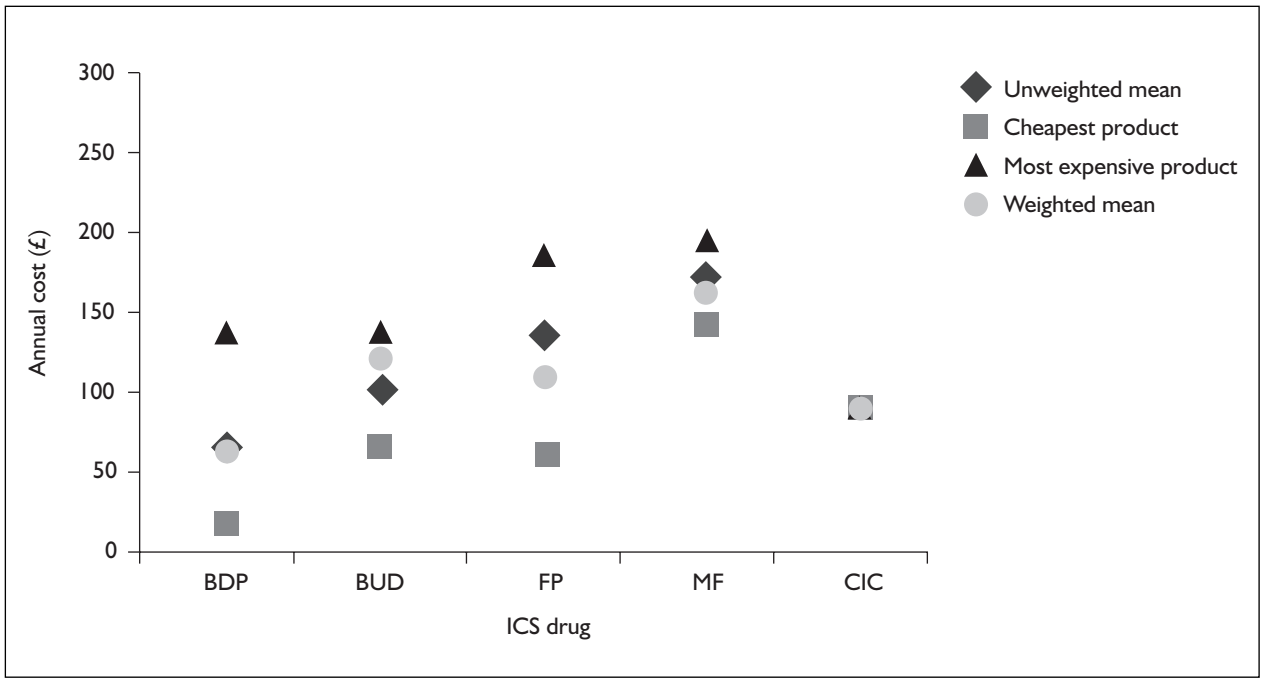

FIGURE 26 *Annual cost of 400 μg ICS per day by ICS drug, including all products. Cheapest products of each drug: BDP = Becotide 100 μg (200 D); BUD = Novolizer 200 μg (100 D Ref.); FP = Flixotide Evohaler 50 μg (120 D); MF = Asmanex Twisthaler 200 μg (60 D); CIC = Alvesco 80 μg (120 D). Most expensive products of each drug: BDP = Becodisks 100 μg (120 D Ref.); BUD = Pulmicort Turbohaler 100 μg (200 D); FP = Flixotide Disk 50 μg (60 D Ref.); MF = Asmanex Twisthaler 200 μg (30 D); CIC = Alvesco 80 μg (120 D). D = number of doses in pack; Ref. = refill pack price where the same preparation is also available with inhaler device included.*

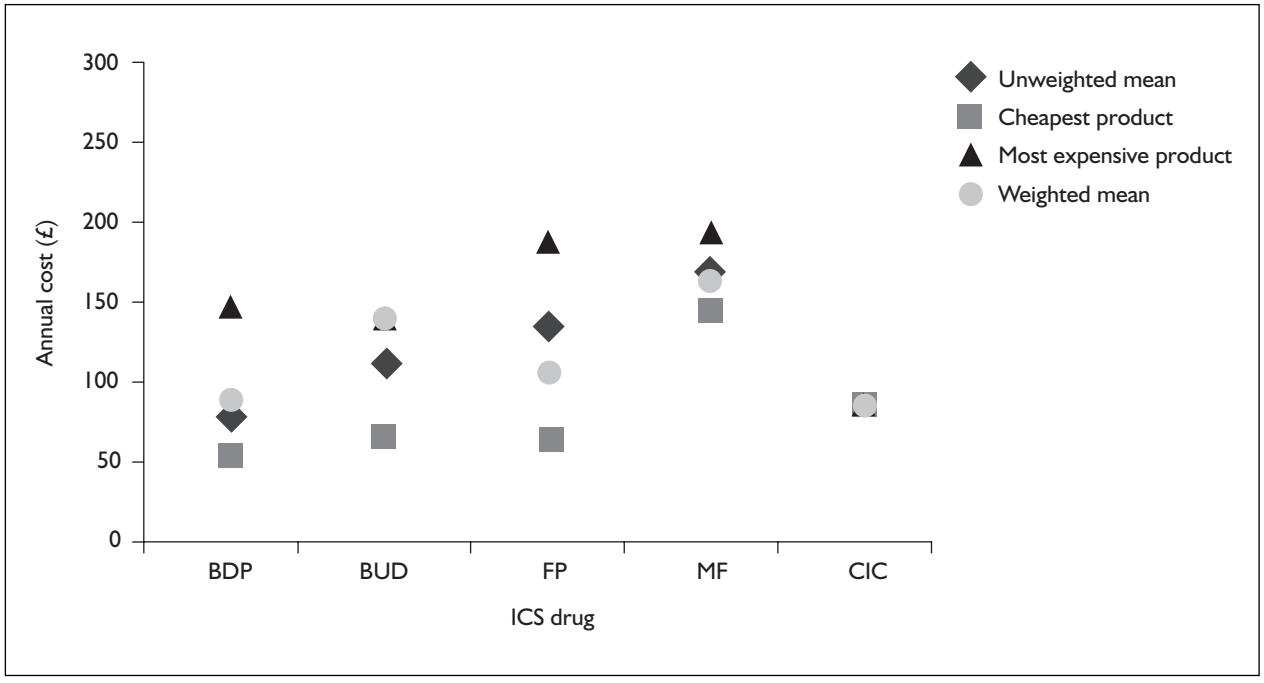

FIGURE 27 *Annual cost of 400 μg ICS per day by drug, excluding CFC-propelled products. Cheapest products of each drug: BDP = Clenil Modulite 100 μg (200 D); BUD = Novolizer 200 μg (100 D Ref.); FP = Flixotide Evohaler 50 μg (120 D); MF = Asmanex Twisthaler 200 μg (60 D); CIC = Alvesco 80 μg (120 D). Most expensive products of each drug: BDP = Becodisks 100 μg (120 D Ref.); BUD = Pulmicort Turbohaler 100 μg (200 D); FP = Flixotide Disk 50 μg (60 D Ref.); MF = Asmanex Twisthaler 200 μg (30 D); CIC = Alvesco 80 μg (120 D). D, Ref.:* see Figure 26.

TABLE 87 *Unweighted mean annual cost of ICS by drug if on 800 μg BDP equivalent per day*

Drug	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	NA	227	212	227
FP	NA	176	218	204	204
MF	NA	NA	249	249	249
CIC	NA	204	NA	204	204

NA, not applicable.

TABLE 88 *Weighted mean annual cost of ICS by drug if on 800 μg BDP equivalent per day*

Drug	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	NA	268	225	268
FP	NA	176	225	195	195
MF	NA	NA	235	235	235
CIC	NA	204	NA	204	204

NA, not applicable.

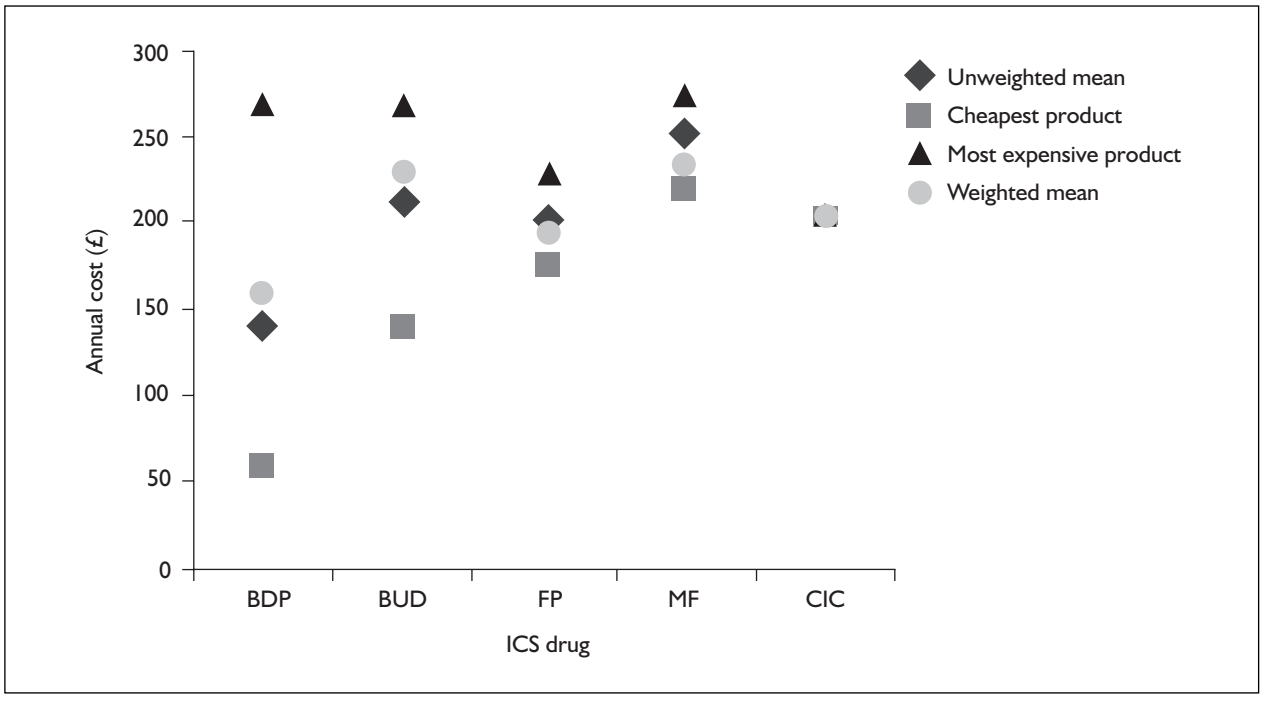

FIGURE 28 *Annual cost of 800 μg ICS per day by drug, including all products. Cheapest products of each drug: BDP = Becotide 200 μg (200 D); BUD = Novolizer 200 μg (100 D Ref.); FP = Flixotide Evohaler 250 μg (120 D); MF = Asmanex Twisthaler 400 μg (60 D); CIC = Alvesco 160 μg (120 D). Most expensive products of each drug: BDP = Becodisks 400 μg (120 D Ref.); BUD = Pulmicort Turbohaler 200 μg (100 D) or 400 μg (50 D); FP = Flixotide Disk 250 μg (60 D Ref.); MF = Asmanex Twisthaler 400 μg (30 D); CIC = Alvesco 160 μg (120 D). D, Ref.:* see Figure 26.

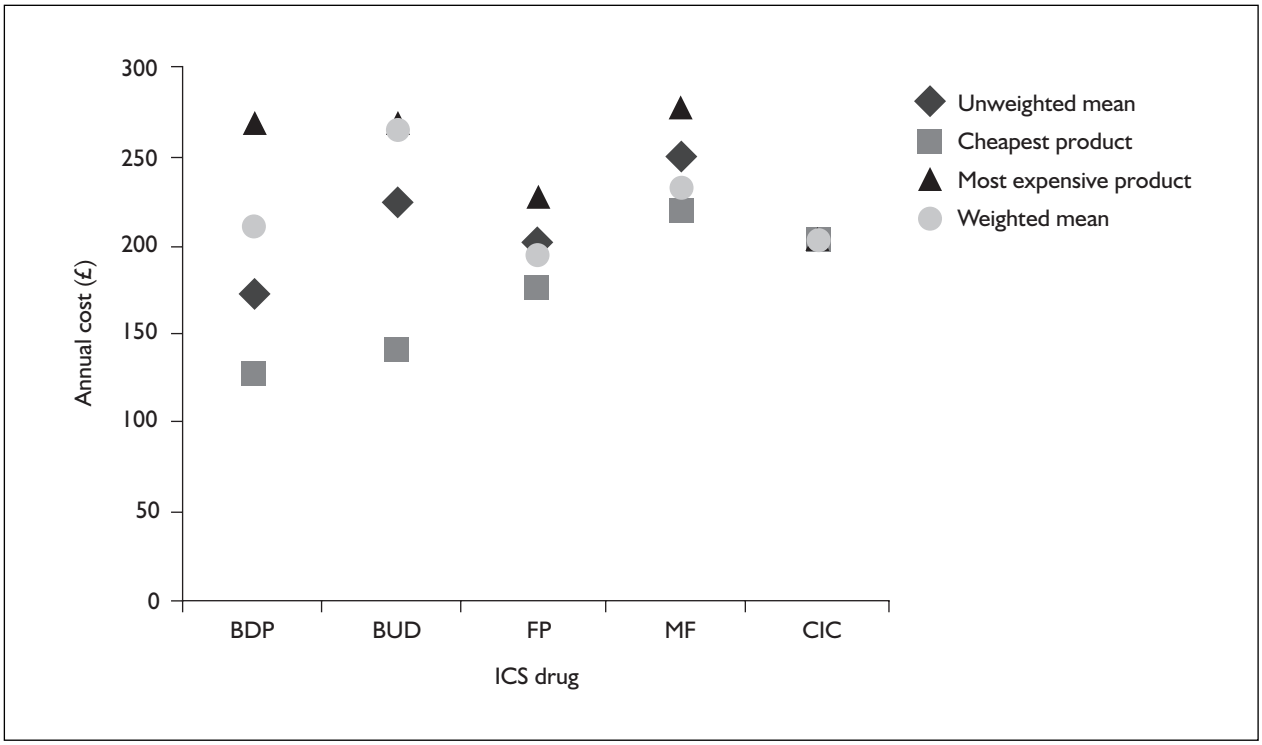

FIGURE 29 *Annual cost of 800 μg ICS per day by drug, excluding CFC-propelled products. Cheapest products of each drug: BDP = Qvar 100 μg (200 D); BUD = Novolizer 200 μg (100 D Ref.); FP = Flixotide Evohaler 250 μg (120 D); MF = Asmanex Twisthaler 400 μg (60 D); CIC = Alvesco 160 μg (120 D). Most expensive products of each drug: BDP = Becodisks 400 μg (120 D Ref.); BUD = Pulmicort Turbohaler 200 μg (100 D) or 400 μg (50 D); FP = Flixotide Disk 250 μg (60 D Ref.); MF = Asmanex Twisthaler 400 μg (30 D); CIC = Alvesco 160 μg (120 D).D, Ref.:* see Figure 26.

The results 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, cause 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 between BUD and FP, is strongly dependent on the crude assumed dose-equivalence ratio of 1:2 with BDP–CFC products.

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 the section 'Review question 2 – effectiveness of high-dose ICS', p. 58).

Tables 89 and *90* 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 1600 μg/day (BDP–CFC equivalent). *Figures 30* and *31* plot the weighted and unweighted mean annual cost and the estimated annual cost of using the cheapest and the most expensive product for each ICS.

The results 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

TABLE 89 *Unweighted mean annual cost of ICS by drug if on 1500 or 1600 μg BDP equivalent per day*

Drug	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	NA	NA	540	540	540
FP	NA	352	391	383	383
MF	NA	NA	499	499	499

NA, not applicable.

TABLE 90 *Weighted mean annual cost of ICS by drug if on 1500 or 1600 μg BDP equivalent per day*

Drug	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	NA	497	260	497
BUD	NA	NA	540	540	540
FP	NA	352	425	385	385
MF	NA	NA	469	469	469

NA, not applicable.

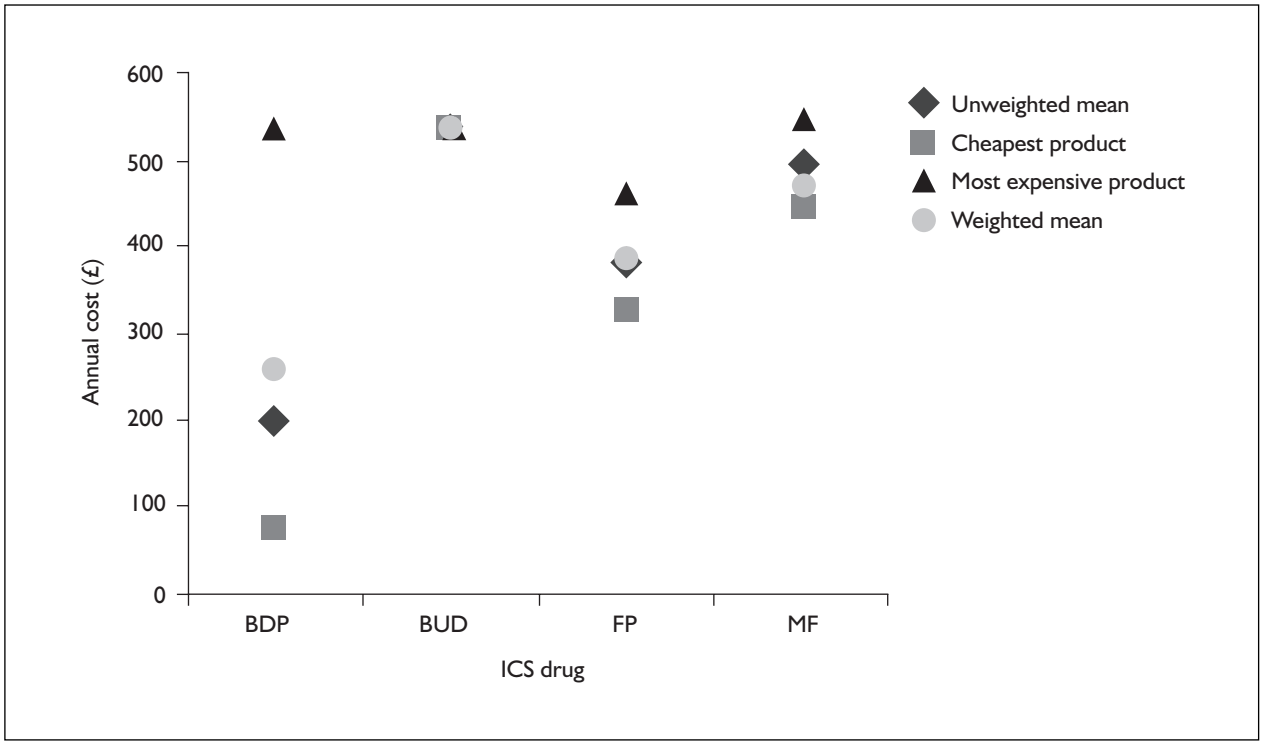

FIGURE 30 *Annual cost of 1500 or 1600 μg ICS per day by drug, including all products. Cheapest products of each drug: BDP = Becloforte 250 μg (200 D); BUD = Pulmicort Turbohaler 400 μg (50 D); FP = Flixotide Disk 250 μg (60 D with device); MF = Asmanex Twisthaler 400 μg (60 D). Most expensive products of each drug: BDP = Becodisks 400 μg (120 D Ref.); BUD = Pulmicort Turbohaler 400 μg (50 D); FP = Flixotide Disk 250 μg (60 D Ref.); MF = Asmanex Twisthaler 400 μg (30 D). D, Ref.:* see Figure 26.

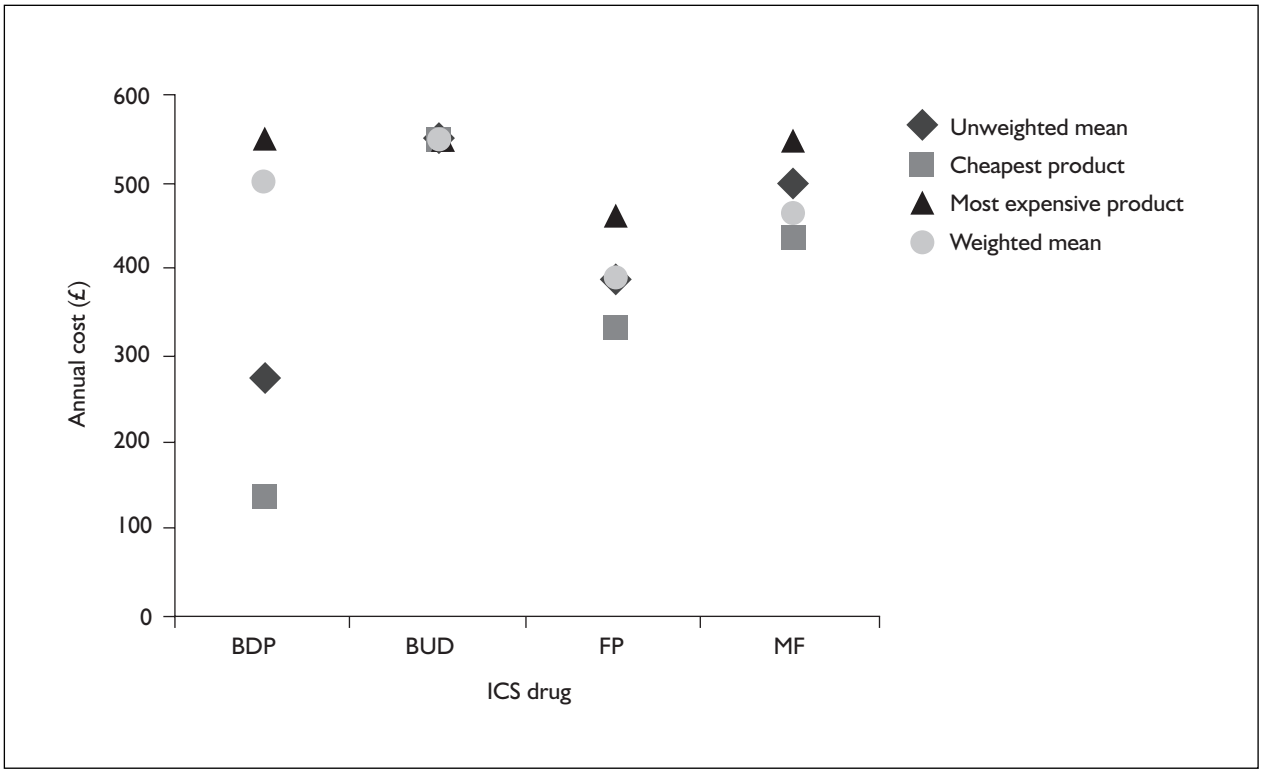

FIGURE 31 *Annual cost of 1500 or 1600 µg ICS per day by drug, excluding CFC-propelled products. Cheapest products of each drug: BDP = Asmabec Clickhaler 250 µg (100 D); BUD = Pulmicort Turbohaler 400 µg (50 D Ref.); FP = Flixotide Accuhaler 500 µg (60 D); MF = Asmanex Twisthaler 400 µg (60 D). Most expensive products of each drug: BDP = Becodisks 400 µg (120 D Ref.); BUD = Pulmicort Turbohaler 400 µg (50 D); FP = Flixotide Disk 250 µg (60 D Ref.); MF = Asmanex Twisthaler 400 µg (30 D). D, Ref.:* see Figure 26.

using the weighted mean annual cost. Excluding CFC-propelled products, and using current prices, cause 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. Although the most expensive MF, BUD and BDP products are very similar in annual cost, using the cheapest CFC-free products for each drug varies from £135 per year (BDP using Asmabec Clickhaler 250 µg) to £447 (MF using Asmanex Twishaler 400 µg) or £540 (BUD using Pulmicort Turbohaler 400 µg).

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).

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 CUAs (Appendix 10), and we incorporate some insights from that analysis below.

Chapter 3 on clinical effectiveness described and summarised the general pattern of outcome differences according to the particular ICS plus LABA drugs being compared with ICS at a higher dose. In this section, we repeat those summary tables, but additionally (1) indicate the magnitude of any measured differences in the common trial outcomes, and (2) 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,[229] 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 (BNF) (No. 51, March 2006).[275]

Cost–consequence comparisons

There are five RCTs which compare FP/SAL with a higher dose of FP or BUD. Of the two trials which compared FP/SAL with higher dose FP only one showed a significant difference in any outcome (a +0.1 litres 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/SAL combination (500 µg/100 µg/day) is £35 less than the higher dose of FP. In contrast, for the comparison at lower doses, the annual cost of the FP/SAL combination (200 µg/100 µg/day) is £92 higher per year. For the three trials which compare FP/SAL with BUD at higher dose, there seems to be a more consistent pattern of significant improvements in PEF (morning and evening) and in SFDs and SFNs, favouring the combination inhaler. However, for these trials, the estimated annual cost of the FP/SAL 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/FF 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 PEF (morning and evening), and in symptom-free days with combination therapy compared with an increased dose of ICS alone. In these trials, the annual cost of BUD/FF varies from being £163 cheaper to £66 more expensive than the ICS alone at higher daily dose.

Overall, the comparisons in *Tables 91–94* show that although 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 CUA 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 strictly limited to the particular ICS versus ICS plus LABA comparators that have been included in existing trials (and they therefore over-represent comparisons with increased FP or BUD, and include no comparisons with increased BDP or other ICS), and also, for decision-making purposes, suffer from the same limitations as any single short-term trial-based economic evaluation.[277] 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.

Research question 4

Combination versus separate inhalers at Step 3

For the comparison of 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 the section 'Review question 4 – ICS + LABA in combination versus separate inhalers', p. 131).

As *Tables 95* and *96* show, for both currently available combination products (Seretide and Symbicort), the combination ICS with LABA product is cheaper than taking the same drugs in separate inhalers at lower doses (800 µg/day or less), but may be more expensive at higher doses. For taking BUD with FF, using Symbicort via

TABLE 91 *Consequences and cost of FP versus FP/SAL (n = 2 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results												
			Lung function			Symptoms								AEs (% of patients)	Annual cost (£)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS	HRQoL	SABA	Exacerbations		
1000 µg vs 500/100 µg	Bergmann *et al.*, 2004[222] parallel-group, 12 weeks, DPI, *n* = 365	FP	NSD							+0.3[a] (in AQLQ score change)		3 fewer[a] (1 vs 4)		481
		FP/SAL												446 = 35 less
500 µg vs 200/100 µg	Busse *et al.*, 2003[221] parallel-group, 12–24 weeks, DPI, *n* = 558	FP	+0.10 litres*** difference in change from baseline							NSD		NSD		287
		FP/SAL												379 = 92 more

NSD, no significant difference between trial arms; NW, nocturnal waking; SABA, short-acting beta-agonist use; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score.
[a] Results favour this trial arm but no significance testing has been reported.
*** $p < 0.001$.

TABLE 92 *Consequences and cost of BUD versus FP/SAL (n = 3 RCTs)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms							AEs (% of patients)	Annual cost (£)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS	HRQoL	SABA	Exacerbations		
1600 µg vs 500/100 µg	Jenkins *et al.*, 2000[223] parallel-group, 24 weeks, DPI, *n* = 353	BUD						NSD				NSD	18%	540
		FP/SAL	+0.09 litres*** difference in mean at end-point	+25*** l/min difference in mean over whole trial	+18*** l/min difference in mean over whole trial		+26*** median days (in 24-week trial)			+0.45** (in AQLQ score change)			14%	446 = 94 less
800 µg vs 200/100 µg	Johansson *et al.*, 2001[224] parallel-group, 12 weeks, DPI, *n* = 349	BUD	C				C	C					38%	270
		FP/SAL		+11*[a] l/min difference in adjusted mean over whole trial	+11** l/min difference in adjusted mean over whole trial							3 fewer[b] (7 vs 10)	38%	379 = 109 more
	Zhong *et al.*, 2004[225] parallel-group, 6 weeks DPI, *n* = 398	BUD	NSD										24%	270
		FP/SAL		+23*** l/min difference in mean change from baseline	+13** l/min difference in mean change from baseline		+18%*** (difference in day SFDs) +19%*** (difference in 24-hour SFDs)	+20%***					24%	379 = 109 more

C, stated as comparable between trial arms, but no other data presented; NSD, no significant difference between trial arms; NW, nocturnal waking; SABA, short-acting beta-agonist use; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score.

[a] See text.

[b] Results favour this trial arm but no significance testing has been reported.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

TABLE 93 *Consequences and cost of FP vs BUD/FF (n = 1 RCT)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results										
			Lung function			Symptoms							
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS	HRQoL	SABA	Exacerbations	AEs (% of patients)	Annual cost (£)
500 μg vs 400/9 μg	Bateman *et al.*, 2003[228] parallel-group, 12 weeks, DPI, *n* = 344	FP				NSD	NSD							287
		BUD/FF	+0.11 litres*** difference in geometric mean at end-point	+20*** difference in mean change from baseline	+17*** difference in mean change from baseline						–0.18* difference in mean change from baseline	12.2% fewer mild exacerbations		231 = 56 less

NSD, no significant difference between trial arms; NW, nocturnal waking; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score; SABA, short-acting beta-agonist use.
* $p < 0.05$; *** $p < 0.001$.

TABLE 94 *Consequences and cost of BUD/FF vs BUD* (n = *4 RCTs*)

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms							AEs (% of patients)	Annual cost (£)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS	HRQoL	SABA	Exacerbations		
400 µg vs 200/9 µg	Lalloo *et al.*, 2003[229] parallel-group, 12 weeks, DPI, *n* = 467	BUD	NSD										54%	135
		BUD/FF		+9* difference in mean change from baseline	+9*** difference in mean change from baseline		+6%** (difference in 24-hour SFDs)				–0.2* difference in change from baseline	26[b] fewer patients (136 vs 110) having mild exacerbations	58%	201 = 66 more
400 µg vs 200/9 µg	O'Byrne[a] *et al.*, 2005[231] parallel-group, 52 weeks, DPI, *n* = 2760	1. BUD										NSD 1 vs 2	57%	270
		2. BUD/FF[to]	NSD 1 vs 2	+7*** difference in mean over whole trial	+4*** difference in mean over whole trial		+7%				–0.25 (fewer) puffs per day		52%	201 = 69 less
		3. BUD/FF[mar]	+0.1 litres difference in mean over whole trial	+16*** difference in mean over whole trial	+15*** difference 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/FF as reliever is added

continued

TABLE 94 *Consequences and cost of BUD vs BUD/FF (n = 4 RCTs) (cont'd)*

Daily dose	Study, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms							AEs (% of patients)	Annual cost (£)
			FEV_1	PEF morning	PEF evening	NW	SFD	SFN	SS	HRQoL	SABA	Exacerbations		
400 µg vs 200/9 µg	Pohl *et al.*,[230] parallel-group, 20 weeks, AMD, DPI, *n* = 133	BUD	C									C	81 events	486
		BUD/FF		+9[b] difference in mean at end-point	+7[b] difference in mean at end-point					+6* difference in SF-36 score (at end-point?)			74 events	324 = 163 less
800 µg vs 400/9 µg	Scicchitano *et al.*, 2004[232] parallel-group, 52 weeks, DPI, *n* = 1890	BUD to											NSD	270
		BUD/FF[mar]	+0.1[b] difference in mean at end-point	+20*** difference in mean at end-point	+14*** difference in mean at end-point	–3.3% difference	+7.5%*** difference in 24 hour SFDs					0.61*** hazard ratio for severe exacerbations		231 = 39 less

AMD, adjustable maintenance dose in which those receiving BUD had a mean of 560 µg/day, metered (448 µg/day delivered), and those receiving BUD/FF had a mean of 1440/43 µg/day, metered (1152/35 µg/day delivered); C, results stated to be comparable between treatment arms, but no other data presented; [mar], combination inhaler used as both maintenance and reliever medication in this arm; NSD, no significant difference between trial arms; NW, nocturnal waking; SABA, short-acting beta-agonist use; SFD, symptom-free days; SFN, symptom-free nights; SS, symptom score; [to], terbutaline only used as reliever in this arm.

[a] All outcome and cost differences for O'Byrne *et 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 £5–25 per year.

[b] Results favour this trial arm but no significance testing has been reported.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

TABLE 95 *Annual cost of combination versus separate inhalers: BUD with FF added*

Combination or BUD	FF	Annual cost (£) by daily dose of BUD				
		200 μg/day	400 μg/day	800 μg/day	1200 μg /day	1600 μg/day
Symbicort Turbohaler (combination product)		201	231	462	694	925
Separate inhalers: Pulmicort Turbohaler, plus:	Atimos Modulite 10.1 μg	296	363	498	634	769
	Oxis 4.5 μg (or 9 μg)[a]	369	437	572	707	842
	Foradil 12 μg	391	458	593	728	863
Difference in annual cost (separate minus combination)						
Separate inhalers: Pulmicort Turbohaler, plus:	Atimos Modulite 10.1 μg	+95	+132	+36	–60	–156
	Oxis 4.5 μg (or 9 μg)[a]	+169	+206	+110	14	–83
	Foradil 12 μg	+190	+227	+131	35	–61

[a] Oxis 4.5 μg and 9 μg are the same price per dose.

TABLE 96 *Annual cost of combination versus separate inhalers: FP/SAL added*

Preparation	Taken as	Annual cost (£) by daily dose of FP		
		200 μg/day	500 μg/day	1000 μg/day
As dry powder				
Flixotide Accuhaler	2 blisters/day	109	259	440
Serevent Accuhaler (or aerosol inhaler)[a]	2 blisters/day[b]	356	356	356
Both (total)		465	615	796
Seretide Accuhaler (FP and SAL combined)	2 blisters/day[b]	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[b]	356	356	356
Both (total)		422	615	796
Seretide Evohaler (FP and SAL combined)	4 puffs/day[b]	219	446	760
Difference in annual cost		+203	+169	+36

[a] Serevent Accuhaler and aerosol inhaler are the same price per μg.
[b] Each blister contains 50 μg of SAL and each puff contains 25 μg of SAL.

Turbuhaler is cheaper than taking Pulmicort via Turbuhaler (at the same BUD dose) and taking FF separately, except when taking 1200 μg BUD/day as Pulmicort Turbohaler with Atimos Modulite, or when taking 1600 μg BUD/day as Pulmicort Turbohaler with any of the three FF products. Depending on the exact preparation of FF used (in combination with Pulmicort Turbohaler) and the daily dose of BUD required, the combination product may cost anything from £156 more to £227 less per year.

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 200 μg FP/day) and £298 (if on 1000 μg FP/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.

Research question 5
FP/SAL versus BUD/FF at Step 3

The clinical effectiveness review did not identify any consistent differences in effectiveness between the two combination inhalers (see the section 'Review question 5 – combination inhaler compared with combination inhaler', p. 143), and so we believe it was reasonable to assume clinical equivalence between these two treatment strategies.

Table 97 compares the cost of taking ICS with LABA in the two currently licensed combination inhalers, Seretide and Symbicort. In making the comparison between these products we have assumed that 400 and 800 µg (metered dose) of BUD are equivalent to 200 and 500 µg of FP, respectively, and also that 12 µg (metered) of FF/day has effectiveness equivalent to 100 µg of SAL/day. Although this assumption partly reflects the levels of drugs used in the existing head-to-head trials of Symbicort versus Seretide (which compare Symbicort 800 µg BUD versus Seretide 500 µg FF/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 FP/SAL as aerosol for pMDI (Seretide Evohaler = £219 per year), but this is only slightly cheaper than BUD/FF as a DPI (Symbicort Turbohaler = £231 per year). At the higher dose level FP/SS both as an aerosol for pMDI and as a DPI (Seretide Evohaler and Seretide Accuhaler, respectively) are the cheapest at £446 per year, but this is only £16 cheaper than having the ICS 'equivalent' dose of BUD/FF Symbicort Turbohaler.

Summary of the economic analyses

The economic analyses and/or cost comparisons are summarised for each of 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 Guideline?

At low ICS doses at Step 2 of the Guideline, the weighted mean annual cost of taking an ICS drug at 400 µg 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 800 µg 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 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 400 µg ICS/day dose level) and from £157 to £208 (at a 800 µg ICS/day dose level). Consequently, among 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

TABLE 97 *Annual cost (£) of combination inhalers compared*

Combination product	Taken as	400 µg[a] BUD/day	800 µg[a] BUD/day
Symbicort Turbohaler (BUD/FF)	2 puffs/day	231 **200 µg FP/day**	462 **500 µg FP/day**
Seretide Accuhaler (FP and SAL combined)	2 blisters/day	379	446
Seretide Evohaler (FP and SAL combined)	4 puffs/day	219	446

[a] Metered dose.

particularly for BDP, BUD and FP products. For example, currently the cheapest way of obtaining 800 µg of BDP/day is with Becotide 200 µg four times daily (£0.0407 per dose = £59.42 per year); the most expensive way is to use Becodisks 400 µg twice daily (£0.3714 per dose = £271.13 per year). Similarly, for obtaining 800 µg of BUD/day, the cheapest product is Novolizer BUD 200 µg taken four times daily (£0.0959 per dose = £140.01 per year); the most expensive products are Pulmicort Turbohaler 200 and 400 µg (£0.185 and £0.37 per dose = £270.10 per year).

Q2. What is the cheapest type of ICS at Step 4 of the BTS/SIGN Guideline?

At a dose level of either 1500 or 1600 µg 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 CUA (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 more frequently cheaper than taking the relevant ingredient drugs in separate inhalers, especially at the lower doses at which most patients are managed. 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 200 µg FP/day) and £298 (if on 1000 µg FP/day). Similarly, using Seretide via Evohaler is always cheaper than taking Flixotide via Evohaler (at the same FP dose) and taking SAL separately.

For the combination of BUD/FF at doses up to 800 µg/day, taking the combination inhaler is between £36 to £227 cheaper per year than taking the equivalent ingredient drugs in separate inhalers. However, at high doses (of 1200 µg/day or greater) the combination product may cost as much as £156 more per year than taking FF and BUD separately, depending on the exact preparation of FF used and the daily dose of BUD required.

Q5. Which combination inhaler is the cheapest?

This comparison crudely assumed that 400 and 800 µg of BUD are equivalent to 200 and 500 µg of FP, respectively, and also that 12 µg of FF/day has effectiveness equivalent to 100 µg of SAL/day. At the lower daily dose of 400 µg BUD or 200 µg FP/day, Seretide Evohaler and Symbicort Turbohaler are very similar in annual cost (£219 and £231), with Seretide Accuhaler being more expensive than both of these (£379 per year). At a dose of 800 µg BUD or 500 µg FP/day, the annual cost of taking FP/SAL by either Seretide Evohaler or Seretide Acuhaler is the same at £446, whereas the combination of BUD/FF by Symbicort Turbohaler is only slightly more expensive at £462.

Chapter 5

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.[11] Therefore, the economic burden of asthma in both direct and indirect 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 to 89.4 per 1000 patients for men aged 15 years and over and from 52.2 to 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, A&E department visits and hospital admissions. Each of these is associated with a varying level of cost.

ICS therapy alone

The cost comparisons presented in this review indicate that there are currently considerable relative differences in the mean annual cost between the different ICS preparations, and also large cost differences between individual products for 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 offset 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, which obviously has an associated cost in terms of patient education, follow-up and any further treatment changes that may need to be made if the treatment regimen is unsuitable.

Additionally, it must be noted that any potential cost savings made by switching patients between either ICS drugs or individual preparations can easily be offset by the costs incurred by potentially higher exacerbation rates. The BTS/SIGN Guideline states 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 bearing in mind the patient's ability to use the different inhaler types. This is particularly pertinent within both an adolescent age group and in the elderly.

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. At doses lower than 1200 µg/day, taking Symbicort (BUD/FF) via Turbohaler is associated with an estimated annual saving between £36 and £227 compared with 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/SAL) via Accuhaler is associated with an estimated annual saving of between £85 (if on 200 µg FP/day) and £298 (if on 1000 µg FP/day) compared with taking Flixotide and Serevent via Accuhaler. Likewise, using Seretide via Evohaler is always cheaper than taking Flixotide via Evohaler (at the same FP dose) and taking SAL separately.

However, it is not clear to what extent the drugs are currently prescribed in separate inhalers.

Given the concerns that the clinicians consulted for this report have expressed about the potential hazards of using LABAs without ICS, it is likely that most ICS plus LABA therapy is not prescribed in combination inhalers and so the potential for cost savings in this area may be limited.

We are also aware from discussions with clinicians for this report that there is an increasing tendency to prescribe ICS and LABA in combination inhalers instead of ICS alone at Step 2 of the BTS/SIGN Guideline. Reasons given for this practice include ease of use for patients, to get both preventer and reliever therapy in one device and concerns about overuse of reliever medication, particularly LABAs, on their own. As this practice is not in line with the Guideline, assessing the effectiveness and cost-effectiveness of this treatment strategy is outside the scope of this report and has not been investigated. It is likely, however, that a significant proportion of current prescribing cost may reflect ICS and LABA use that is not strictly according to the Guideline, making the estimation of potential cost savings more difficult.

Chapter 6

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.

Assessing the effectiveness 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 considered 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, use of rescue medication and AEs, but no standardised measures are used consistently in trials. Measures of lung function such as FEV_1 and morning and evening PEF 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 SFDs or SFNs. For example, SFDs were defined as diversely as "a 24-hour period with a symptom score of zero" and "percentage of days without cough/wheeze/shortness of breath/chest tightness". Very few studies provided any indication of whether symptom measurement instruments had been validated. Similarly, definitions of exacerbations are highly heterogeneous, ranging from those defined as a fall in PEF of at least 30% on two consecutive days to those necessitating emergency treatment at a healthcare institution. This variety of definitions makes it very difficult to compare the therapeutic activities of different anti-asthma drugs on an outcome such as exacerbations. Very few trials report HRQoL, which, in addition to being important in its own right, is needed to inform CUAs. Composite outcomes are also reported, but again there is no consistency across trials in the way in which such outcomes are defined, thus preventing clear comparisons being made across all relevant technologies. Additionally, the way in which AEs are defined is often poorly reported, and it is often unclear as to which events are measured and the severity of these. This limits the degree to which comparisons of differences in the type and rate of AEs can be made between trials.

Although lung function provides the most objective assessment of response to treatment, and probably more closely reflects the underlying disease process, the clinical significance of reported changes in lung function is 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), in addition to 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 either be managed 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 healthcare 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 healthcare 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 Guideline for assessing intervention effects of the different comparators under consideration. Although the Guideline is well established and has been used for a number of years within the UK, it is clear its many clinical trials are not set within its 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 Guideline 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 type of device under evaluation effectively will be eligible for inclusion in the trial. Evidence for the effectiveness of inhaled corticosteroids and beta$_2$ agonists for asthma from clinical trials should therefore be considered carefully for its generalisability to the typical population with asthma, as opposed to a subgroup of patients selected for their ability to use the inhaler effectively. Additionally, 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 in routine practice. Although concordance rates were not formally assessed in the clinical effectiveness review, they were around 70–95% 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 Chapter 1). This figure is likely to vary considerably depending on the level of support patients receive in primary care and from asthma specialist nurses and their ability to use their prescribed inhaler devices.

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 6 weeks to 2 years, with the majority lasting 12–24 weeks. These trials do not adequately capture the longer term effects of ICS and LABA therapy, particularly long-term AEs and impact on BMD and growth, especially for younger patients. Relatively few of the trials followed up patients beyond 6 months to 1 year.

It is also not clear in the trials what constitutes 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, whereas 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.

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 2–4 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 800 µg/day BDP/BUD or equivalent (corresponding to Step 2 of the BTS/SIGN Guideline[1]) were identified. Within this dose range there was a high degree of variability in the doses used in the trials, ranging from 100/800 µg/day. There did not appear to be a particular dose that was more commonly tested than others.

Baseline populations, where sufficiently reported, were generally appropriate for Step 2 of the Guideline.

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 Guideline notes that BDP and BUD are approximately equivalent in clinical practice.[1] Similarly, the Cochrane review of BDP and BUD[56] 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 PEF there was a significant difference in favour of BUD, although this was reported in one small trial. AEs appeared similar.

The BTS/SIGN Guideline also notes 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 with BDP or BUD,[170] the only significant differences between the drugs when administered at a 1:2 dose ratio (FP:BDP/BUD) were for FEV_1 and morning PEF, 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 AE was significantly in favour of BUD.

As yet there are no published Cochrane reviews of the newer ICS, specifically CIC and MF, compared with either each other or with the established corticosteroids. This assessment is therefore one of the first to review systematically 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 therefore advised when interpreting the results of trials. Trials of CIC compared with BUD and FP were included. However, no trials of CIC versus MF were included.

Comparing CIC with 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.

The BTS/SIGN Guideline[1] notes 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 400 µg and BUD 400 µg delivered by a DPI inhaler), results from one trial showed statistically significant differences in favour of MF on measures of lung function, SFDs and use of rescue medication. AEs were comparable. However, in another trial, which used double the dose of both drugs (thus on the borderline of Steps 2 and 4 of the BTS/SIGN Guideline 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 800 µg per day), but this effect is diminished when the dose of BUD is doubled. It should be noted that this study did 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 PEF 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 800 µg/day (BDP/BUD or equivalent, corresponding to Step 4 of the BTS/SIGN Guideline) were included. There was variability in the doses used in the trials, ranging from 800 to 2000 µg/day (*ex*-valve) (lower

for CIC and MF). The baseline populations for the trials, where sufficiently reported, were appropriate for this step of the Guideline, 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 Guideline, 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 with 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 PEF 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 AEs. 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 or study methods or whether there is another explanation.

In common with the lower dose ICS comparisons discussed earlier, there is a paucity of evidence on 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. The evidence for CIC compared with FP was supplied by the manufacturer of CIC, and is commercial-in-confidence.

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 with 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 800 µg/day dose threshold for Step 3 of the Guideline, or adding in a supplemental drug treatment. The BTS/SIGN Guideline[1] recommends a trial of an add-on therapy for such patients before increasing the ICS dose above 800 µg/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 Guideline in that they were not steroid naïve. Half of the studies used the FP/SAL combination inhaler, whereas the other half used the BUD/FF combination inhaler. ICS doses, when used in combination with LABAs, varied from 200 to 800 µg/day for BUD and from 200 to 500 µg/day for FP. When used alone, the ICS doses

varied from 400 to 1600 µg/day for BUD and from 500 to 1000 µg/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 Guideline and with the results of a Cochrane review.[171] Morning and evening PEF were 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 AEs 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 with ICS alone. This was evaluated in one study[231] which compared BUD/FF with 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 with 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 800 µg/day of BUD compared with 200 µg/day 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 with those where the same ICS was used in both trial arms. Although 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 Guideline recommends 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 with 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 200 to 1000 µg/day for FP and from 200 to 800 µg/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-to-persistent asthma and in others as having mild-to-moderate asthma. In general, patients enrolled were those whose asthma was symptomatic, or suboptimally controlled, and treated with ICS, as appropriate for Steps 2–3 of the Guideline. The results of these trials therefore cannot be extrapolated to the situation of using ICS and LABA in combination in steroid naïve patients, which is outside the context of the Guideline 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 AEs 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, and improved lung function, symptoms and use of rescue medication.[172]

As was the case with the ICS and LABA compared with 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 with 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 with ICS alone, as summarised by the Cochrane Collaboration.[171,172] The scope does, however, include the use of ICS and LABA in a combination inhaler compared with the two in separate inhalers.

Six trials were included, three comparing FP and SAL combination inhaler with separate inhalers, two comparing BUD and FF combination inhaler with separate inhalers and one comparing FP/SAL in a combination inhaler with BUD + FF in separate inhalers. The ICS doses were similar in both treatment strategies, and ranged from 200 to 1000 µg/day for FP and 800 µg/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 PEF) non-inferiority was demonstrated. The findings of this assessment are in accord with the BTS/SIGN Guideline, which states 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 AEs. Meta-analysis of AEs found no statistically significant differences in AEs, serious AEs and withdrawals due to AEs. 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 Guideline[1] makes it clear that LABAs should not be used without ICS.

Review question 5: combination inhaler compared with 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 800 µg for BUD and 500 µg for FP. Results were mixed, with the FP/SAL combination significantly superior on some outcomes and the BUD/FF combination superior on others. In the one trial that reported FEV_1, BUD with FF was significantly superior, as it was for SFDs. There were no statistically significant differences between groups in symptom scores, or HRQoL in one trial whereas symptom scores were described as being "comparable" between groups in another study. In two trials BUD/FF was significantly superior in terms of exacerbations, whereas in a third FP/SAL was superior. Meta-analysis found that there were no significant differences between the treatment groups in rates of AEs, serious AEs or withdrawals due to AEs. 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,[278] 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, 6-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.

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 Guideline. The reasons for not reporting the full model methods and results in the main body of the report have been outlined previously in the section 'Original economic analyses: introduction and rationale' (p. 181). 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 3a). Here the overall pattern of effectiveness differences identified in the systematic review were presented alongside the estimated current NHS preventer medication costs for each of the comparators in the trials.

Cost comparisons

These cost comparisons have been shown in the section 'Original economic analyses' (p. 183). They relied on 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 used 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, and also 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 present, at the starting low dose of 400 µg/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 800 and 1500–1600 µg/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 diminish. As there are currently no CFC-propelled products available for FP, CIC and MF, their costs remain constant. However, although 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 population 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 healthcare resource use, through an increase in exacerbations resulting from poorer control of asthma. Although we cannot quantify this theoretical increase, as discussed previously, concordance with treatment in trials is around 80%, but in the general population of adolescents and adults with asthma it may be that fewer than 50% take the full amount of prescribed medication (see Chapter 1). Choosing a more expensive delivery device that the patient prefers and can easily use correctly might well improve concordance, thus minimising other healthcare 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 on 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 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 healthcare consultations due to exacerbations may well be reduced.

At lower doses, the cheapest combination inhaler is FP/SAL delivered as an pMDI, but this is only slightly cheaper than BUD/FF delivered as a DPI. At higher dose levels, both the FP/SAL combination inhalers (pMDI and DPI) are slightly cheaper than BUD/FF as a DPI.

Summary of the cost comparisons

At present there are large variations in the costs between the five ICS and two LABA products available. These variations are dependent on 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 MF consistently appears to be marginally more expensive than the other four ICS products. It should be noted that although the use of weighted averages can provide a useful way of representing the major differences between the drugs, these 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.

Strengths and limitations of the assessment

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, GPs and health economists has provided advice throughout the assessment and 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 PEF, 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 for which trials were not necessarily powered to detect differences. This should be borne 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 potential 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 to summarise 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 that 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. Further details of the remaining studies can be found in the Cochrane reviews.[56,170–173]

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 SFDs, 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 include all relevant technologies in a single evaluation and also capture the consequences of differences in all levels of control, most comparisons have focused on an analysis of the costs associated with the mean annual treatment costs for each ICS and LABA drug.

Strengths

The cost comparison approach that 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 CUA or CEA, 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 CUA 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 is 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 (1) the relative doses of different ICS drugs which are currently assumed to have equivalent effectiveness, (2) the exact mix of products which would probably be used to achieve any particular daily dose level of ICS or ICS with LABA and (3) 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.

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. adherence-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, 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, in terms of both drug types and inhaler devices, given acceptable variations in average effectiveness and costs. In addition to variations 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.

Chapter 7
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 2–4 of the BTS/SIGN Guideline. 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 and 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 Guideline is broadly similar. Although 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 on both the required dose and the specific product used, which includes the delivery device. In general, at a typical starting dose of 400 µg/day BDP devices currently tend to be the cheapest, and remain so even when CFC-propelled devices are excluded. At doses of 800 and 1500–1600 µg/day BDP CFC-propelled products remain the cheapest available. At these doses, when CFC-propelled products are excluded, 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, there are currently no CFC-propelled products available so their costs remain unchanged. However, it should be highlighted that 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 draw 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 CUA (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 + 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 appear 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 that at lower dose levels, the cheapest combination inhaler is FP/SAL as an aerosol for pMDI (Seretide Evohaler), but this is only slightly cheaper than BUD/FF as a DPI (Symbicort Turbohaler). At this dose level, FP/SAL as a DPI (Seretide Accuhaler) is the most expensive of the three combination products assessed. At the higher dose level, FP/SAL both as an aerosol for pMDI and as a DPI (Seretide Evohaler and Seretide Accuhaler, respectively) are the cheapest combination products available, but they are both only slightly cheaper than having the ICS 'equivalent' dose of BUD/FF Symbicort Turbohaler.

Research recommendations

Primary research

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 were 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 Guideline 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 that individual patients may make in their ICS dose over time.

For informing future CUAs and CEAs 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 10 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).

Secondary research

AEs are also not well specified and reported in the clinical trial literature reviewed here. Concerns about the long-term adverse effects of the different ICS do influence the choice of ICS by both patients and clinicians, but most trials are not of sufficient power or duration to provide adequate data on differential adverse outcomes. Further research synthesis, quantifying the adverse effects of the different ICS, is required for treatment choices by patients and clinicians to be fully informed.

Initial searches undertaken for this assessment indicate that there are at present no good-quality systematic reviews available that have assessed all potential long-term AEs associated with the different ICS comparators. Published reviews have tended to focus on the use of short-term RCT

safety data with a length of follow-up between 1 and 2 years. Therefore, to assess adequately the longer term sequel of ICS use, future reviews should aim to examine studies of longer term follow-up, and use appropriate data sources such as cohort, case–control studies and registry data where available.

Standardisation of outcome measures

The evidence base that was assessed in this review was highly heterogeneous in terms of both the way in which outcome measures had been defined and measured and 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 SDs 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[279] standard of reporting being made a priority.

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