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Extended Research Article

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This article

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Abstract

Background: There is no clear preferential option for initial step-up of treatment for children with uncontrolled asthma on inhaled corticosteroid.

Objectives: Evaluate the clinical effectiveness of pharmacological treatments to use in children with uncontrolled asthma on inhaled corticosteroid; identify and evaluate the potential for treatment effect modification to optimise treatment delivery; assess the cost-effectiveness of treatments.

Methods: Systematic review and individual participant data network meta-analysis. Studies were eligible if they were parallel or crossover randomised controlled trials comparing at least one of the pharmacological treatments of interest in participants aged < 18 years with uncontrolled asthma on any dose inhaled corticosteroid alone. We searched MEDLINE®, Cochrane Library, Cochrane Central Register of Controlled Trials, EMBASE, National Institute for Health and Care Excellence Technology Appraisals, and the National Institute for Health and Care Research Health Technology Assessment series. Primary outcomes: exacerbation and asthma control. Secondary outcomes: health-related quality of life, mortality, forced expiratory volume in 1 second, adverse events, hospital admissions, symptoms (not analysed). We assessed the Risk Of Bias using the Cochrane Risk Of Bias tool and carried out Bayesian meta-analyses, network meta-analysis and network meta-regression, including treatment by covariate (age, sex, ethnicity, eczema, eosinophilia, asthma severity) interactions.

A Markov decision-analytic model with a 12-month time horizon, which adopted the perspective of the National Health Service and Personal Social Services in the United Kingdom, was developed to compare alternative treatments. Cost-effectiveness was based on incremental costs per quality-adjusted life-years gained, with uncertainty considered in one-way, structural and probabilistic sensitivity analyses.

Results: We identified and screened 4708 publications from the search and confirmed 144 randomised controlled trials as eligible. We obtained individual participant data from 29 trials (5381 participants) and extracted limited aggregate data from a further 19 trials. The majority of trials had low risk of bias. The network meta-analysis suggests that medium-dose inhaled corticosteroid + long-acting β_2-agonist is the preferred treatment for reducing odds of exacerbation [odds ratio 95% credibility interval: 0.43 (0.20 to 0.92) vs. low-dose inhaled corticosteroid; 40 studies, 8168 patients] and increasing forced expiratory volume in 1 second [mean difference 95% credibility interval: 0.71 (0.35 to 1.06) vs. low-dose inhaled corticosteroid; 23 studies, 2518 patients] while leukotriene receptor antagonist alone is the least preferred. No clear differences were found for asthma control (16 studies, 3027 patients). Limited pairwise analyses suggest some improvement in health-related quality of life for medium-dose inhaled corticosteroid versus inhaled corticosteroid + long-acting β_2-agonist [two studies, paediatric asthma quality of life questionnaire, mean difference 95% credibility interval: 0.91 (0.29 to 1.53)]. The rate of hospitalisation due to an asthma attack ranged from 0.5% to 2.7% of patients across five trials. Slightly fewer patients reported neurological disorders (mild/moderate) on inhaled corticosteroid + long-acting β_2-agonist versus inhaled corticosteroid + leukotriene receptor antagonist [odds ratio 95% confidence interval: 0.09 (0.01 to 0.82), one study]. There were no deaths recorded. We did not find convincing, consistent evidence to suggest that age, sex, ethnicity, eczema, eosinophilia, asthma severity would be regarded as an effect modifier. The economic analysis indicated that low-dose inhaled corticosteroid was the most cost-effective treatment option while medium-dose inhaled corticosteroid (alone and + long-acting β_2-agonist) was associated with the highest number of quality-adjusted life-years, but their incremental cost-effectiveness exceeded the National Institute for Health and Care Excellence threshold.

Discussion: Medium-dose inhaled corticosteroid + long-acting β_2-agonist is recommended for children with asthma that is uncontrolled on inhaled corticosteroid alone; leukotriene receptor antagonist alone should be avoided. We could not include data from 67% of the eligible trials, conclusions should therefore be viewed with some caution.

Study registration: This study is registered as PROSPERO CRD42019127599.

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List of abbreviations

ACQ	asthma control questionnaire
ACT	asthma control test
AE	adverse event
AgD	aggregate data
AP	asthmatic phenotype
AQLQ	asthma quality of life questionnaire
ATS	American Thoracic Society
BDP	beclomethasone dipropionate
BTS	British Thoracic Society
BUD	budesonide
CIC	ciclesonide
CRF	case report form
CrI	credibility interval
DIC	deviance information criterion
DPI	dry powder inhaler
ECG	electrocardiogram
ED	emergency department
eNO	exhaled nitric oxide
EQ-5D	EuroQol-5 Dimensions
ERS	European Respiratory Society
ESS	effective samples size
EVPI	expected value of perfect information
FE	fixed effect
FEV_1	forced expiratory volume in 1 second
FF	fluticasone furoate
FORM	formoterol
FP	fluticasone propionate
GINA	Global Initiative for Asthma
GP	general practitioner
HR	heart rate
HRG	Healthcare Resource Group
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
ID	patient identifier
IPD	individual participant data
ITT	intention to treat
IV	inverse variance
LABA	long-acting β_2-agonist
LTRA	leukotriene receptor antagonist
MA	meta-analysis
MART	maintenance and reliever therapy
MD	mean difference
MF	mometasone furoate
ML-NMR	multilevel network meta-regression
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	network meta-analysis
NMR	network meta-regression
OCSs	oral corticosteroids
OR	odds ratio
PAQLQ	paediatric asthma quality of life questionnaire
PEF	peak expiratory flow
pMDI	pressurised metered-dose inhaler
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RE	random effect
RR	relative risk
SABA	short-acting β2-adrenoceptor agonist
SAL	salmeterol
SAP	statistical analysis plan
SR	sustained release
UME	unrelated mean effect
VI	vilanterol
WHO	World Health Organization

Plain language summary

Asthma causes symptoms of cough and difficulty in breathing. An asthma attack happens when symptoms get really bad. The first choice of medicine is a low-dose steroid inhaler. If asthma symptoms continue, then other medicines can be given.

We used a systematic review to identify all available clinical trials about medicines for children with asthma whose symptoms continue even when taking a low-dose steroid inhaler. We asked all researchers to share the data they had originally collected with us and combined results using a network meta-analysis. We performed an economic assessment to identify which treatment option might represent the best value for money for the National Health Service.

We found 144 clinical trials but could only include data from 48 clinical trials. We found that increasing the dose of inhaled steroids to a medium dose and adding a medicine called long-acting β_2-agonist was most likely to reduce the chance of getting an asthma attack and improve the amount of air that can be forced from the lungs in 1 second (forced expiratory volume in 1 second). We found that a medicine called leukotriene receptor antagonist is not a good option by itself.

There were no deaths recorded, hospital admissions were rare, and there were no big differences in adverse events or health-related quality of life between medicines, but we did not have much data to look at this. We could not find evidence to show whether a medicine might work better for particular groups of patients, and more research would be needed.

Our economic analysis suggests that low-dose steroid inhalers offer the best value for money, as they are less expensive than other treatment options. However, medium-dose inhaled corticosteroid (alone and + long-acting β_2-agonist) were associated with the highest number of quality-adjusted life-years, but they did not represent good value for money as their cost-effectiveness exceeded the threshold set by the National Institute for Health and Care Excellence.

Scientific summary

Background

In the UK, asthma remains a common medical condition affecting over 1 million children, one of the highest prevalence rates worldwide. Asthma is characterised by wheezing, breathlessness, chest tightness, cough and can affect the child's quality of life (QoL) by limiting daily activities and causing acute attacks. In the UK, it was estimated that one child is admitted to the hospital every 20 minutes because of an asthma attack. Following a diagnosis of asthma in a child, a stepwise approach to treatment should be taken. The initial level of treatment consists of using a low-dose inhaled corticosteroid (ICS) to prevent symptoms and a short-acting β_2-adrenoceptor agonist for relieving symptoms. However, around 10–15% of children have inadequate control of asthma symptoms with a low dose of ICS. The target of asthma management is to control the disease through complete control defined as (a) no daytime symptoms, (b) no night-time awakening due to asthma, (c) no need for rescue medication, (d) no asthma attacks, (e) no exacerbation, (f) no limitations on activity, including exercise, (g) normal lung function, (h) minimal side effects from medication. Hence, when asthma remains uncontrolled, a series of further steps are followed. These consist of a treatment step-up by including add-on preventer therapies, such as long-acting β_2-agonists (LABAs) or leukotriene receptor antagonists (LTRAs), an increase of the dose of ICS, or adding sustained-release theophylline.

Choosing the best step-up treatment becomes a crucial decision to prevent exacerbation occurrence and avoid poor asthma control, improve the QoL of patients and their families, and optimise the use of NHS resources. No clear preferential option for initial step-up exists. Moreover, there is substantial heterogeneity among individuals in the treatment response.

Objectives

The overall aim of the EINSTEIN study was to identify and synthesise all evidence from randomised controlled trials (RCTs) using individual participant data (IPD) to evaluate the clinical effectiveness of pharmacological treatments to use in children with uncontrolled asthma on ICS. A further aim was to identify and evaluate the potential for treatment effect modification to optimise treatment delivery and maximise patients' informed treatment choice. We assessed the cost-effectiveness of treatments by developing an economic model to estimate the incremental cost per quality-adjusted life-year (QALY) gained.

Methods

We carried out a systematic review and IPD network meta-analysis (NMA) – supplemented with aggregate data (AgD) – of RCTs in children (< 12 years) and adolescents (12–17 years) with asthma uncontrolled on ICS, and a Markov-based economic model. A comprehensive search strategy was developed with an information specialist. We searched MEDLINE, the Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, National Institute for Health and Care Excellence (NICE) Technology Appraisals, and the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) series for RCTs of interventions. The reference lists of existing clinical guidelines, along with included studies and relevant reviews, were checked to identify further relevant studies. Unpublished studies were located by searching across a range of clinical trial registries, including internal trial registers for pharmaceutical companies. Only articles in the English language were considered. Studies were eligible if they were parallel or crossover RCTs of any duration and level of blinding comparing at least one of the health technologies of interest; they included participants aged under 18 years with uncontrolled asthma on any dose ICS alone at the screening visit; they considered the following pharmacological treatments at any dose and with any inhaler device: ICS (beclometasone dipropionate; ciclesonide; fluticasone propionate and fluticasone furoate; budesonide; mometasone), LABA (formoterol; salmeterol; vilanterol), LTRA (zafirlukast; montelukast) and theophylline. Study screening was conducted independently by two reviewers using a consensus procedure for disagreements, and one reviewer

performed data extraction and risk-of-bias assessment (using the Cochrane Risk Of Bias tool), which was confirmed by a second reviewer for a sample of studies. We contacted the first author or sponsor of each included trial to request anonymised IPD, metadata and relevant documentation (protocol and blank case report forms) for the respective trial. When IPD was unavailable, we supplemented the missing data with AgD from publications where possible.

Primary outcomes of interest were *exacerbation* and *asthma control* measured by a validated test [asthma control test (ACT), asthma control questionnaire (ACQ)]. Secondary outcomes included *quality of life*, *mortality*, *forced expiratory volume in 1 second (FEV_1)*, *adverse events (AEs)*, *hospital admissions*, *costs*, *resource use* and *utilities* to inform the economic model. We had initially planned to include the outcome '*symptoms*'. Still, we abandoned this before conducting any analyses because it can be challenging to interpret symptoms in isolation. It was likely that many of the individual symptoms would have contributed to the asthma control outcome, with the rationale of a control score being to provide a summary of these symptoms.

We categorised ICS dose as 'Low', 'Medium' and 'High' according to Global Initiative for Asthma guidelines and conducted three separate analyses, subject to data availability: (a) comparison of treatment classes with ICS dose grouped when combined with LABA; (b) comparison of treatment classes with ICS dose stratified (Low, Medium, High) when combined with LABA; (c) comparison of individual treatment compounds. We used odds ratio (OR) as the measure of treatment effect for binary outcomes and mean difference (MD) as the measure of treatment effect for continuous outcomes.

We carried out pairwise meta-analyses (MAs), NMA and network meta-regression (NMR) analyses [fixed-effect (FE) and random-effects (REs) models] in a Bayesian framework using the R package (The R Foundation for Statistical Computing, Vienna, Austria) 'multinma' based on Stan. We examined model fit by the posterior mean of the residual deviance and the deviance information criterion to select models. Pairwise MA and NMA were also carried out with a frequentist framework using the R functions 'netmetabin' and 'netmeta'. An inverse variance model was used with a generalised methods of moments estimate of the between-studies variance. NMA models were multilevel models that combined IPD and AgD and accounted for correlation between treatment effects from multiarm trials. The between trial variance was assumed to be constant across all comparisons in the network. Inconsistency models and sensitivity analyses to explore the impact of exacerbation data collection approach and data availability bias were carried out, and we created dev–dev plots. To explore whether participant characteristics modify the treatment effects, we fitted Bayesian NMR models that included treatment by covariate interactions for the outcomes: *exacerbation*, *asthma control* and *FEV_1*. The following covariates were studied: age, sex, ethnicity, eczema, baseline severity (based on baseline FEV_1% predicted) and eosinophilia. We applied one NMR model for each outcome and covariate combination in turn.

A cost–utility analysis with a 12-month time horizon, which adopted the perspective of the NHS and Personal Social Services in the UK, was undertaken to compare alternative treatments for children with uncontrolled asthma despite ICSs. A literature review was performed to identify a suitable model structure and data requirements for a decision analysis to simulate resource use and health outcomes associated with asthma treatment. A Markov state transition model was developed, with probabilities of transitioning among four health states representing asthma being controlled, uncontrolled, asthma exacerbation and death from asthma exacerbation. Transition probabilities pertaining to low-dose ICS were adjusted by relative risks for asthma control and exacerbations for alternative treatments, derived from a NMA. Health state utilities were identified from literature sources. Costs comprised direct medical expenditures based on patients' use of primary and secondary care services and personal and social services. The model was based on weekly cycles with a half-cycle correction to account for events and transitions occurring at any point of the cycle. Cost-effectiveness was based on incremental costs per QALYs gained. One-way sensitivity analyses were conducted to assess the stability of the incremental cost-effectiveness ratio (ICER) to different assumptions or ranges of parameter estimates. A number of analyses were undertaken to assess the impact of structural uncertainty on the base-case ICER. A probabilistic sensitivity analysis was performed with Gamma distributions specified for utility scores; log-normal distributions for items of resource use and beta distributions to FE and RE Bayesian probabilities. The joint uncertainty in costs and QALYs was assessed using a Monte Carlo simulation with 10,000 replicates. A cost-effectiveness curve was generated to depict the probability of each intervention being cost-effective at different willingness-to-pay thresholds.

Results

We identified and screened 4708 publications from the search and retrieved 508 full-text articles for eligibility assessment. We confirmed 144 RCTs as meeting the eligibility criteria for this review and attempted to contact the trial owner for all studies. We could not identify a contact for 4 studies; 46 did not reply; 41 refused access to IPD; 24 agreed to provide IPD, but the legal terms of the data-sharing contract could not be agreed upon between the NIHR and the trial sponsors. We obtained IPD from 29 (20%) of the eligible trials contributing data for 5494 eligible participants and were able to extract limited AgD from a further 19 (13%) of the trials without IPD. The majority of trials included in the analyses had a low risk of bias overall.

The Bayesian NMA suggests that ICS Medium + LABA reduces the odds of exacerbation [OR 95% credibility interval (CrI): 0.44 (0.19 to 0.90); 40 studies, 8168 patients] and increases FEV_1 [MD 95% CrI: 0.71 (0.35 to 1.06); 23 studies, 2518 patients] compared to ICS Low and also compared to ICS Medium [MD 95% CrI: 0.69 (0.33 to 1.05); 23 studies, 2518 patients] and ICS High [MD 95% CrI: 0.54 (0.24 to 0.81); 23 studies, 2518 patients]. LTRA is the least preferred. We could not find clear differences between treatments for asthma control measured by the ACT/ACQ test (16 studies, 3027 patients). Sensitivity analyses did not change conclusions.

We could not conduct NMA for any other outcome due to data limitations. Direct pairwise MA of a limited subset of two trials suggests a reduction in the mean QoL score, measured by the paediatric asthma QoL questionnaire (PAQLQ), for ICS + LABA compared to ICS medium [MD 95% confidence interval (CI) −0.91 (−1.53 to −0.29)], although the upper limit of the 95% CI includes values that would not be considered clinically important. There is insufficient evidence to conclude any further differences in QoL amongst the pairs of treatment classes for which we had sufficient data available.

The hospitalisation rate due to an asthma attack ranged from 0.5% of patients to 2.7% of patients across five trials, but data were too limited to perform MA.

There was considerable heterogeneity in the recording and coding of AEs data across studies. Slightly fewer patients reported neurological disorders (graded as mild or moderate) on ICS + LABA [one patient (4.3%)] compared to ICS + LTRA [seven patients (33.3%)] in one study [OR, 95% CI: 0.09 (0.01 to 0.82)], and a greater number of patients reported neurological disorders for ICS Medium compared to placebo in three studies [OR, 95% CI: 4.8 (1.12 to 20.60)]. There were no other notable differences in AEs, but analyses were limited by data availability and heterogeneity. There were no deaths recorded in any of the trials. We did not find convincing, consistent evidence to suggest that any of the patient characteristics (*age*, *sex*, *ethnicity*, *eczema*, *eosinophilia*, *asthma severity*), which we examined in exploratory NMR analyses, would be regarded as an effect modifier that is adequately supported by robust statistical evidence and clinical rationale. We cannot rule out the possibility of data availability bias but have tried to mitigate this risk by including both IPD and AgD in analyses wherever possible.

In the base-case analysis, ICS Low was the cost-effective option; ICS Medium (alone or + LABA) were not cost-effective, with ICERs of £232,500 and £310,000 per QALY gained, respectively. ICS High, ICS + LTRA and LTRA monotherapy were dominated by alternatives which were less costly and associated with more QALYs. Sensitivity analyses indicated that changes in utilities had an inconsequential effect on the ICERs, while varying the transition probabilities associated with the controlled and exacerbation states by ± 50% concurrently for all treatments resulted in ICS Medium becoming cost-effective at £15,102 per QALY gained. When the costs of branded inhalers were reduced individually by 50%, potentially reflecting a generic alternative, the ICER for ICS Medium + LABA reduced considerably but remained non-cost-effective. All the comparators to ICS Low remained non-cost-effective in the analysis of structural uncertainty. At willingness-to-pay thresholds of £20,000 and £30,000 per QALY, ICS Low had 0.45 and 0.44 probabilities of being cost-effective, respectively. ICS Medium had lower probabilities of 0.20 at £20,000 and 0.21 at £30,000 per QALY; while ICS Medium + LABA was the least likely of being cost-effective, with probabilities of 0.07 and 0.09 at the £20,000 and £30,000 per QALY thresholds, respectively.

Conclusions

Overall, we conclude that ICS Medium + LABA would be the recommended step-up treatment for children with asthma that is not well controlled on ICS and that LTRA alone should be avoided. There is very little evidence available on which to make conclusions regarding ICS + Theophylline and insufficient evidence at this time to suggest that treatment effect is modified by patient characteristics (age, sex, ethnicity, eczema, eosinophilia, asthma severity), although further research is recommended. The economic analysis indicated that ICS Low was the most cost-effective treatment, while ICS Medium (alone and + LABA) were associated with the highest number of QALYs; however, they did not meet the criteria to be cost-effective.

Study registration

This study is registered as PROSPERO CRD42019127599.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 16/110/16) and is published in full in *Health Technology Assessment*; Vol. 29, No. 15. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

Rationale

Asthma is a common condition characterised by regular wheeze, breathlessness, chest tightness and cough, with periods of relapse and remission, often throughout the life course, from childhood into old age. The World Health Organization (WHO) reported 262 million people with asthma worldwide in 2019 and referred that asthma is the most common chronic childhood condition. Asthma is the most common long-term medical condition in young people and affects over 1 million children in the UK, one of the highest prevalence rates worldwide. Asthma can impact on a child's quality of life (QoL) by limiting daily activities, such as sleep, attending school and playing sport. One in 11 children in the UK are currently receiving asthma treatment, and 1 child is admitted to hospital every 20 minutes because of an asthma attack. The NHS spends around £1 billion a year treating and caring for people with asthma.

Asthma cannot be cured, but preventer treatment is available to control symptoms. Complete control is defined as (a) no daytime symptoms, (b) no night-time awakening due to asthma, (c) no need for rescue medication, (d) no asthma attacks, (e) no exacerbation, (f) no limitations on activity including exercise, (g) normal lung function [i.e. forced expiratory volume in 1 second (FEV_1) and/or peak expiratory flow (PEF) > 80% predicted], (h) minimal side effects from medication. The British Guidelines on the management of asthma[1] recommends that, following a diagnosis of asthma in a child, a stepwise approach to treatment using regular preventer treatment should be taken, in addition to as required reliever treatment. The initial level of preventer treatment consists of a low-dose inhaled corticosteroid (ICS) with a short-acting β_2-adrenoceptor agonist (SABA) to relieve symptoms. Nevertheless, treatment with 'ICS Low' alone fails to control asthma symptoms in around 10–15% of children. When ICS Low treatment does not control symptoms, there are further treatment options, which include either increasing the dose of ICS or the introduction of other preventer treatments, such as long-acting β_2-agonist (LABAs) or leukotriene receptor antagonists (LTRAs), or sustained-release (SR) theophylline. At present, there is no consensus as to which option is preferable. Two UK guidelines make different recommendations, and the US Global Initiative for Asthma (GINA) guideline makes recommendations that differ from those proposed by the UK guideline groups. Part of the reason for the uncertainty is that there is heterogeneity in treatment response within the population of children with asthma. The differing recommendations from guideline groups also depend on some being focused on cost–benefit while others are interested in a patient's benefit. An additional challenge to identifying a 'best' treatment recommendation when ICS Low does not provide sufficient control is that some step-up options are associated with improved control, and others are linked to reduced asthma exacerbation.

A Cochrane review considering 6381 children from 33 trials demonstrated that adding LABAs to ICSs was not associated with a significant decrease in the rate of exacerbation requiring systemic steroids. However, it showed an improved lung function, relatively to FEV_1 and PEF, compared with the same or higher doses of ICS, and adverse events (AEs) were similar in both groups. Hospital admissions were not significantly different between the two groups; however, the authors advised further treatment monitoring because of a trend towards increased risk of hospital admission with LABA independently of ICS dose.[2] An earlier Cochrane review found that combining LTRA with ICS was not associated with a reduction for rescue oral corticosteroids (OCSs) or hospital admission compared with the same or a higher dose of ICS in children and adolescents with mild to moderate asthma. However, evidence was based only on four trials with 559 children and adolescents. So, the authors cautioned that the lack of paediatric trials, the absence of data on pre-schoolers and the variability in reporting relevant clinical outcomes were a limit for firm conclusions regarding this comparison.

Several randomised controlled trials (RCTs) have compared two alternative step-up options head-to-head, but only a few individual trials have considered more than two classes head-to-head.

The BADGER trial[3] randomised 182 children, aged 6–17 with uncontrolled asthma to receive each of three blinded step-up therapies in random order for 16 weeks: (a) intermediate dose ICS (ICS step-up), (b) addition of LABA (LABA step-up) or (c) addition of LTRA (LTRA step-up). The authors found that most children 'responded' to each step-up

therapy, but LABA step-up showed as significantly more likely to provide the 'best response' than the other two step-up treatments. However, only 40% had a 'best response' to LABA, meaning that this treatment was not the best option for the majority of participants.

The MASCOT trial[4] attempted to compare increased ICS versus LABA add on versus LTRA add on but failed to recruit an adequate number of patients because of several significant challenges, the most important of which was recruiting eligible participants. Children who were uncontrolled on ICS Low were rapidly stepped up in the community before being identified, which restricted the pool of patients available for randomisation.

A network meta-analysis (NMA) is a statistical technique that allows synthesising all the available evidence comparing and ranking all treatments based on RCT results, even if treatments have not been directly compared with each other in the previous trials. A NMA would address the challenges identified by the MASCOT trial in designing a trial where multiple interventions are compared and would answer the question 'Which of these treatments is best?' by using data that are already collected, thus considerably saving time and money.

In 2012, van der Mark *et al.*[5] published a quantitative synthesis with 23 trials including 4129 patients, and although the authors had planned to conduct an NMA, they were not able to, since outcome measures were too heterogeneous and inadequately reported in trial publications. Following this, Zhao *et al.* were able to conduct a formal NMA, reported in 2015, using data from 35 RCTs and 12,010 children, although only 7 RCTs were in common across the 2 reviews. The authors suggested that combined ICS and LABA treatments were most effective in preventing exacerbation and that medium-dose or high-dose ICS, combined ICS and LTRAs, and low-dose ICS treatments seem to be equally effective. One limitation of this second NMA was that 70 relevant RCTs had been excluded because data about exacerbation or symptom-free days were not provided in trial publications. Outcome reporting bias thus represents a threat to the validity of their results if excluded studies had selectively reported results based on the statistical significance of their findings. Additionally, the interpretation and generalisability of results from this NMA are challenging because of the lack of analyses focusing on outcomes of importance and relevance to patients, and the lack of analyses comparing different drugs, doses within ICS, LABA and LTRA classes.

Need for this research

There is an inconsistency in both the UK and international guidelines for the treatment option for a child on ICS Low whose symptoms are not controlled. This clinical scenario is extremely common. The correct step-up decision can lead to improved asthma control and QoL for the child and their caregivers and reduce the risk of hospitalisation and death. In the absence of evidence, clinicians are delivering inconsistent step-up treatments, and feedback from our consultation with parents suggested that more needed to be done.

The EINSTEIN (EstablishINg the best STEp-up treatments for children with uncontrolled asthma despite ICSs) study aims to address this pressing need for an answer by seeking to include all available evidence (including unpublished data) and use robust and unbiased methods. A key strength of the EINSTEIN methodology has been using individual participant data (IPD) to assess individual participant-level characteristics in modifying the patient's response to treatment. Furthermore, an economic analysis of the treatment options provided evidence of their cost-effectiveness from the perspective of the NHS and Personal Social Services (PSS) in the UK. Results from the EINSTEIN study will provide clinicians and patients with accessible, high-quality, patient-relevant information to help make evidence-informed treatment choices. Earlier identification of the best step-up treatment for a particular child could significantly impact children's lives with more extensive benefits to society and the NHS.

Aims and objectives

The aim of the EINSTEIN study was to identify and synthesise all available evidence from RCTs to establish the clinical-effectiveness and cost-effectiveness of pharmacological treatments used for the treatment of children (< 12 years) and adolescents (12–17 years) with uncontrolled asthma on ICS alone, and explore potential treatment effect modifiers.

Specific objectives were to:

- undertake a systematic review to identify relevant RCTs of treatment for children with asthma uncontrolled with ICS
- collect IPD from all eligible trials
- conduct an NMA of IPD, supplemented with aggregate data (AgD), to identify the most effective treatment
- identify and synthesise treatment effect modifiers to establish which patients respond better to each treatment
- construct an economic model to estimate the incremental cost per quality-adjusted life-year (QALY) gained of treatment options, from the perspective of the NHS and PSS
- identify where uncertainties remain to produce recommendations to inform priorities for future research.

Chapter 2 Methods: clinical effectiveness

This chapter describes the methods and processes used for the systematic review, pairwise meta-analysis (MA), NMA, network meta-regression (NMR) analysis and the Markov-based economic model.

Protocol and statistical analysis plan

The protocol for the study was registered with PROSPERO (CRD42019127599) and published in *BMJ Open*.[6] The PRISMA-P guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols)[7] guided the drafting of the protocol, and PRISMA-NMA guidelines guided the drafting of the report.[8] A full statistical analysis plan (SAP) was developed in May 2021.

The first version of the protocol was updated twice, in September 2019 and March 2020. The first update consisted of adding some additional sections. The second update reflected decisions made at the searching and screening stages of the review that are listed in the corresponding section, with full details and accompanying rationale reported in *Table 1*. Further changes and clarifications were made at the analysis stage in the SAP and are listed in the analysis section and reported in *Table 1*.

Eligibility criteria

For inclusion in the EINSTEIN study, we selected studies according to the criteria outlined below.

Study design

We included parallel and crossover RCTs of any duration and with any level of blinding, which compared at least one of the health technologies of interest. All studies meeting our inclusion criteria were included irrespective of the outcomes reported in the publications to reduce the potential for outcome reporting bias. For crossover studies, we used only data from the first period in analyses.

Participants

We considered children (< 12 years) and adolescents (12–17 years) of any ethnicity with poor asthma control on any dose of ICS at the screening visit as defined by the study protocol. We included studies with mixed age groups where children and adolescents were eligible for inclusion and contacted the authors concerning specific data on patients under 18. Patients aged 18 or older, or with stable asthma, or using an asthma medication other than ICS, or an ICS with an add-on active (e.g. ICS/LABA) as a treatment regimen at the screening visit were not considered. Participants had to be using any dose of ICS alone at the screening visit to be eligible for inclusion.

Interventions and comparators

We considered eligible all studies where children and adolescents were randomised to at least one of the following treatments, alone or in combination with each other (where applicable):

- ICSs – beclomethasone dipropionate (BDP); ciclesonide (CIC); fluticasone propionate (FP); fluticasone furoate (FF); budesonide (BUD); mometasone furoate (MF)
- LABAs – formoterol (FORM); salmeterol (SAL); vilanterol (VI)
- LTRAs – zafirlukast; montelukast
- theophylline.

Studies had to provide a direct head-to-head comparison of at least two of these interventions against each other or at least one of these interventions against placebo. While we would not recommend designing a RCT with a placebo-only arm in this population due to the ethical implications of withholding a potentially effective treatment from children who are already uncontrolled, excluding this as a node in the network could have an important effect on the results and

TABLE 1 Protocol and SAP deviations and clarifications

Deviation or clarification	Date[a]	Review stage and change	Rationale
Protocol			
Clarification	September 2019	Informative and organisational	Section added to acknowledge funding source
Clarification	September 2019	Informative and organisational	Section added to acknowledge. Department of Health disclaimer
Clarification	September 2019	Informative and organisational	Section added to outline project start and end date
Clarification	September 2019	Informative and organisational	Section 'protocol changes' added
Deviation	September 2019	Screening: change to inclusion criteria	Indacaterol was added to the previous list of LABAs
Deviation	March 2020	Screening: change to inclusion criteria	After consultation with physicians, indacaterol was removed from the list of LABAs considered because it is not very used, and we decided not to add it to the primary search algorithm in the first instance
Clarification	March 2020	Screening: additional search	Further effect-modifiers added
Clarification	March 2020	Screening: additional search	The literature search strategy was updated
Clarification	March 2020	Informative and organisational	References were updated
SAP			
Deviation	August 2021	Analysis: change to a different software	The statistical analysis was carried out using the R package (The R Foundation for Statistical Computing, Vienna, Austria) 'multinma' based on Stan instead of WinBUGS based on Gibbs sampling (BUGS project). The first release of the R package 'multinma' was in March 2021. This package offered more flexibility and options than WinBUGS. Given the complexity of the fitted models and the data typology, we opted to use this tool as the best choice
Deviation	August 2021	Analysis: change to the analysis plan	We decided to add the frequentist approach as the second method to be compared with the Bayesian approach for the pairwise MA and NMA because the data were sparse, especially for the primary outcome 'exacerbation'
Deviation	August 2021	Analysis: change to the analysis plan	We could not carry out all the planned analyses because we could not retrieve sufficient data for a few outcomes

a Project started in March 2019.

could diminish the usefulness of the research.[9] We considered any dose of preventer treatment – oral or inhaled – and any inhaler devices used for the medicine administration, namely pressurised metered-dose inhaler (pMDI), dry powder inhaler (DPI), combination inhaler. The presence or absence of spacer devices was noted where possible. We did not consider studies with participants randomised to any asthma medication other than those listed in the inclusion criteria.

For both primary and secondary outcomes, patient outcomes were compared at the level of the following treatment classes: (a) ICS, (b) LABA, (c) LTRA, (d) theophylline and (e) placebo. For ICS, we distinguished among low, medium and high doses as defined in the GINA 2019 (*Table 2*). The age class '≤ 5 years' did not have a corresponding dosage in the classification system; therefore, we applied the dosage of the age class '6–11 years' for this group. We planned to conduct analyses with (a) ICS doses 'grouped' when in combination with other treatment (clinically less useful but presented for completeness); (b) ICS dose stratified by low, medium, high when in combination with other treatments

TABLE 2 Estimated clinical comparability daily doses (µg) of ICSs

Drug	Low dose	Medium dose	High dose
≤ 5-year-old (children)			
BDP (HFA)	100 (≥ 5 years)	N/A	N/A
BUD nebulised	500 (≥ 1 year)	N/A	N/A
BUD pMDI + spacer	N/A	N/A	N/A
FP (HFA)	50 (≥ 4 years)	N/A	N/A
MF	110 (≥ 4 years)	N/A	N/A
CIC	N/A	N/A	N/A
6- to 11-year-old (children)			
BDP (CFC)	100–200	> 200–400	> 400
BDP (HFA)	50–100	> 100–200	> 200
BUD (DPI)	100–200	> 200–400	> 400
BUD (nebules)	250–500	> 500–1000	> 1000
CIC	80	> 80–160	> 160
FF (DPI)	N/A	N/A	N/A
FP (DPI)	100–200	> 200–400	> 400
FP (HFA)	100–200	> 200–500	> 500
MF	110	≥ 220–< 440	≥ 440
≥ 12-year-old (adults and adolescents)			
BDP (CFC)	200–500	> 500–1000	> 1000
BDP (HFA)	100–200	> 200–400	> 400
BUD (DPI)	200–400	> 400–800	> 800
CIC (HFA)	80–160	> 160–320	> 320
FF (DPI)	100	N/A	200
FP (DPI)	100–250	> 250–500	> 500
FP (HFA)	100–250	> 250–500	> 500
MF	110–220	> 220–440	> 440

CFC, chlorofluorocarbon propellant (no longer used; included for comparison with older literature); HFA, hydrofluoroalkane propellant; N/A, not applicable.

(most clinically useful) – however, due to limitations with the data, we could only do this for combinations with LABA; (c) individual compounds (BDP; CIC; FP; FF; BUD; MF; FORM; SAL; VI; zafirlukast; montelukast; theophylline; 'placebo') within every treatment class; however, we could only partially complete this analysis due to insufficient data and disconnected networks.

Outcomes

This review included the outcomes that healthcare practitioners and patients identified as relevant while developing a core outcome set for trials in children with asthma. Every RCT that met the inclusion criteria was considered irrespective of the outcomes reported in the corresponding publication to reduce outcome reporting bias. Subsequently, we contacted authors or sponsors to collect IPD to analyse outcome data that had not been previously analysed or reported where possible.

The primary outcomes were as follows:

- Exacerbation defined as in American Thoracic Society (ATS)/European Respiratory Society (ERS),[10] namely '*events characterized by a change from the patient's previous status*'. We mainly defined exacerbation as an event requiring (a) the use of OCS, (b) the need for unscheduled visits with general practitioners (GPs) or at the emergency department (ED) and (c) hospitalisation. However, we could not strictly follow the reported primary definition due to the scarcity of events and considered all events classified as exacerbation by the studies' authors.
- Asthma control defined as '*the extent to which the various manifestations of asthma have been reduced or removed by treatment*'.[10] Asthma control should be measured by a validated test: asthma control test (ACT),[11] asthma control questionnaire (ACQ),[12–15] other validated tests if relevant (none were identified).

The secondary outcomes were as follows:

- physiological outcomes (FEV_1)
- symptoms
- QoL
- mortality
- AEs
- hospital admissions
- total healthcare costs (obtained by the sum-product of item of resource use and their unit cost), resource use, and utility outcomes to inform the economic model.

Timing, setting and language

We selected studies for inclusion independently of the length of follow-up of outcomes, and we did not apply restrictions by type of setting. We only included articles in the English language.

Treatment effect modifiers

A set of potential treatment effect modifiers were evaluated for both the primary and secondary outcomes. The choice of the treatment effect modifiers was based on the following:

- discussion within the research team based on existing trials
- consultation with clinicians and service users through patient and public involvement (PPI) in the local trust
- review of previous MA/NMA for asthma in children
- a targeted search of the literature (see *Appendix 1*)
- review of specific guidelines.[1,16]

The treatment modifiers of interest were as follows.

Participant demographic characteristics

- Age (at randomisation where possible).
- Gender.
- Ethnicity.

Participant clinical characteristics

- Eczema status.
- Asthma severity (based on baseline FEV_1% predicted).
- Inflammatory asthmatic phenotype (AP) mainly based on blood eosinophilia.

Information sources, identification of studies and search strategy

Review of clinical effectiveness

The search strategy used in this review identified published and unpublished studies and was built upon previously published search strategies for AgD network meta-analyses and Cochrane reviews (see *Appendix 1*; e.g., MEDLINE search). The search strategies ran from July 2014 to September 2019, adding to the previous ones completed before July 2014. The search was subsequently updated to 5 May 2023. We searched MEDLINE, the Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, National Institute for Health and Care Excellence (NICE) Technology Appraisals, and the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) series using relevant search terms. The reference list of included studies and relevant reviews, along with the reference lists of existing clinical guidelines, such as the British Thoracic Society (BTS) Guideline[1] and GINA,[16] were also scanned. Unpublished studies were located by searching across a range of clinical trial registries included within the WHO International Clinical Trials Registry Platform search portal (including ClinicalTrials.gov and International Standard Randomised Controlled Trial Number) and conference abstracts (e.g. ERS, ATS). We also searched internal clinical trial registers for pharmaceutical companies that manufacture health technologies of interest (e.g. GSK, AstraZeneca, Novartis, Merck). The search focused on identifying articles in the English language and ensured that RCTs included participants aged < 18 as a subset. Studies identified for screening of abstracts and full-text articles were managed within Covidence (www.covidence.org/home) and Rayyan (www.rayyan.ai/) and duplicate studies removed.

Review of effect modifiers

To identify potential modifiers for analysis in the NMA (and inform the assessment of the transitivity assumption), a search was first conducted in MEDLINE combining four concepts; asthma terms AND child terms AND ICS terms AND modifier terms (see *Appendix 1* for the full search strategy). As modifier details may not be identified from titles and abstracts, a second MEDLINE search was then conducted on the following concepts: asthma terms AND child terms AND ICS terms AND limit to RCTs (see *Appendix 1* for the full search strategy). All results from this search were then imported into an EndNote Library, and the full text for all RCTs were obtained. A full-text search of the PDFs was then undertaken on the following terms: modifier*, modified, differential effect, predictor*, stratified, subgroup analysis.

Study selection

Titles and abstracts were screened in the first stage of study selection followed by full-text review in the second stage. Two independent reviewers (SC, KR) screened and appraised all studies for inclusion, resolving disagreements with a consensus procedure or discussing with a third reviewer (ST, IS, CTS) when consensus was not reached; the whole process was managed inside Covidence and Rayyan. The inclusion of trials was not determined by the outcomes reported in the relative publications to minimise the impact of selective reporting. Instead, we recorded whether the outcomes of interest had been reported, formally assessed the potential for outcome reporting bias, and requested the IPD for all outcomes relevant to the review irrespective of whether these were reported in the trial publications.

Processing individual participant data

Individual participant data collection

We approached the sponsor or the corresponding author of each study eligible for inclusion via e-mail or a dedicated portal for data-sharing (e.g. Clinical Study Data Request – CSDR; Vivli; BioLINCC; EngageZone). We requested anonymised IPD, metadata, and relevant documentation, such as protocol, a blank case report form (CRF), coding and labels for variables, and SAP where possible. Furthermore, in the case of direct contact, we created a data availability form for completion by the authors specifying the availability of variables and documentation we needed. We completed any required forms and provided detailed research proposals when a specific portal was used for requesting IPD, mainly from pharmaceutical companies (e.g. GSK, AstraZeneca, Merck, Novartis). Additionally, we supplied the EINSTEIN protocol, a detailed SAP, and CVs of the investigators who managed data to support our request. After about 2 or 3 weeks from the first approach, we contacted again via e-mail all authors who did not reply, and, subsequently

sent reminders periodically. We took note of dates and authors' responses (when received) with any reasons provided for not sharing data (if any). We used AgD from publications to supplement missing IPD wherever possible.

We stored the anonymised IPD on a secure, password-protected server at the University of Liverpool (UK) with access granted to the statistical project team only. No attempt was made to reidentify participants within data sets, and the copying or transfer of data to local computers or data storage devices was strictly prohibited.

Individual participant data variables

The IPD requested from each clinical trial were at least as follows.

- Baseline characteristics – age; sex; ethnicity; eczema; height; weight; baseline severity; baseline peak expiratory flow rate; FEV_1. Where available, we also collected other variables, such as age at asthma diagnosis, asthma-related hospitalisation and exacerbation history, allergic sensitisation, parental asthma, objective indicators of asthma, such as bronchodilator reversibility or methacholine PC_{20}.
- The date of randomisation and dates of follow-up visits/interval between randomisation and follow-up.
- Treatment details including inhalation device and dose.
- Adherence data if available.
- Data for the review outcomes along with details of their definitions and measurement tools used – symptoms; exacerbation; asthma control; mortality; QoL; growth; physiological outcomes: FEV_1; hospital admissions.
- Cost, resource use and utility outcomes to inform the economic model.

Individual participant data cleaning

A range of standard quality and consistency checks of the data were conducted, cross-checking the reanalysed IPD against previously published results to highlight inconsistencies or possible errors. To this aim, we created a specific form with several sections concerning data-check and cleaning (see *Appendix 2*). We reported information, notes, calculations and inconsistencies (if any) to be investigated with the data providers for every study. Queries were raised with the original trialists wherever possible. The main steps were as follows:

- checks of the supplied data and accompanying documents
- documentation list
- usability of provided files
- data sets
- actions
- general checks on data content
- patient identifier (ID) variables
- missing values/errors in data
- comparison to published data where possible (recognising that differences may be explained by data anonymisation methods)
- actions.

Individual participant data standardisation

For each eligible study, we created a new data set to collate relevant study-level data and standardised IPD using a pre-specified variable dictionary (see *Appendix 3*), which was developed to ensure a standardised approach across all studies. Study-level data were extracted by one reviewer (SC) and checked for consistency and correctness by a second reviewer (CTS). Discrepancies were resolved through a consensus procedure.

Patients were eligible if (a) they were children (< 12 years) or adolescents (12–17 years); (b) they were using any dose of ICS alone at the screening visit. The availability of IPD allowed us to select the patients that exactly met these eligibility criteria where possible. Many studies included patients using different treatment regimens at the screening visit, for instance, ICS + LABA, ICS + LTRA, SABA alone, or other medicines. In a few studies, there was a very small proportion of the included patients that could not be confirmed as taking ICS alone at screening but could not be isolated from the remaining patients that were taking ICS alone at screening. In this case, we made a pragmatic decision to include all

patients rather than exclude the whole study; any impact on results would likely be negligible and patients of unknown ICS status would likely be balanced across treatment groups due to randomisation.

For the primary outcome 'asthma exacerbation', we considered any event requiring (a) the use of OCS, (b) the need for unscheduled visits with GPs or the ED, and (c) hospitalisation, or (d) classified as exacerbation by the study author. The primary focus was to create a variable indicating whether the event occurred between the date of randomisation and the date of the last follow-up (binary variable: 0 = no event; 1 = event). We also considered the data relating to the number of exacerbations and the time between randomisation and first exacerbation. However, we only analysed the binary outcome variable as this was the most consistently available data across studies. Most of the studies provided a dedicated data set where exacerbation data had been consistently collected as a specific outcome. However, in a few cases, the exacerbation data were only mentioned within the AE data set, and we explored the potential impact of this differential data collection approach using sensitivity analyses.

Asthma control, as measured by a validated test (ACT,[11] ACQ,[12–15] other validated tests if applicable), was defined as an individual-level binary variable (poor control; good/total control) (*Table 3*). We did not find any studies reporting results of any validated tests other than ACT and ACQ. We considered the measurement taken at the last time point during follow-up as the best clinically relevant time point. If both ACT and ACQ measurements were available for a specific trial, we used the ACT measurement in our outcome derivation.

Quality of life was mainly measured with the asthma QoL questionnaire (AQLQ) or paediatric asthma QoL questionnaire (PAQLQ), and no further modification was required.

After consulting clinicians, we decided to consider only FEV_1 (l/1s) as the most reliable physiological parameter and the last collected test measure as the best clinically relevant time point. Most of the studies provided FEV_1 in l/1s, but for the few that considered a different measuring unit, we were able to standardise into l/1s.

We took note of the relevant AEs reported across the studies, such as infections/infestations, neurological disorders, oral candidiasis, pneumonia, cardiac disorders, clinically relevant electrocardiogram (ECG) changes and heart rate (HR) change (last visit vs. baseline).

For the outcome 'hospital admissions', we looked for evidence, such as dates of hospitalisation, AEs indicating admission occurred, and variables directly reporting hospitalisation between the randomisation visit and the end of the follow-up.

Covariates selected as potential effect modifiers of the relationship between asthma and treatment and used in the analysis were as follows.

Participants' demographic characteristics

- Age: considered a continuous individual-level numerical variable (years).

TABLE 3 Categorisation of the asthma control outcome based on ACT/ACQ scores

Test	Total score	Asthma control
ACT 4–11 (years)	Score ≤ 19 Score = 20–27	0 = poor control 1 = good/total control
ACT 12 + (years)	Score ≤ 19 Score = 20–25	0 = poor control 1 = good/total control
ACQ	Score > 1 Score ≤ 1	0 = poor control 1 = good/total control
Others	To be evaluated on an individual case by case basis	0 = poor control 1 = good/total control

- Sex: considered a categorical individual-level numerical variable (M = 0, F = 1).
- Ethnicity: considered a categorical individual-level character numerical variable (Hispanic or Latino = 0, Not Hispanic or Latino = 1). We created another categorical individual-level character variable for the race but could not be used in the analysis due to lack of data.

Participants' clinical characteristics

- Eczema: considered a categorical individual-level numerical variable (no eczema = 0, eczema = 1).
- Asthma severity: we used the per cent predicted normal FEV_1 [FEV_1(%)] index at the baseline to establish the level of asthma severity in the following way: 'mild' for FEV_1(%) > 80%, 'moderate' for FEV_1(%) between 60% and 80%, and 'severe' for FEV_1(%) < 60%. Asthma severity was considered a categorical individual-level numerical variable (mild = 0, moderate = 1, severe = 2).
- Inflammatory asthmatic background: considered a categorical individual-level numerical variable (non-eosinophilic = 0, eosinophilic = 1). We used three methods to evaluate AP based on clinical experience and guidance from the literature,[17–19] namely, (1) the baseline blood count of eosinophils (cells/μl): 'eosinophilic' for cells/μl ≥ 370, 'non-eosinophilic' for cells/μl < 370, (2) the blood percentage of eosinophils (%): 'eosinophilic' for a percentage of ≥ 5%, 'non-eosinophilic' for a percentage of < 5%, and (3) the baseline value of exhaled nitric oxide (eNO) (ppb): 'eosinophilic' for eNO ≥ 30, 'non-eosinophilic' for eNO < 30. Where possible, the preferential method was that based on blood eosinophils as cells/μl.

Aggregate data extraction

For eligible studies without IPD, we extracted relevant aggregate outcome and treatment effect modifier data from text, tables and graphical summaries, to allow inclusion in analyses wherever possible. For binary outcomes, we extracted the number of events and number of randomised patients in each treatment group. For continuous outcomes, we extracted the number of patients randomised in each treatment group, mean response and standard deviation (SD) [or other data to allow calculation of SD, e.g. confidence interval (CI) or standard error of the mean[20]].

Risk-of-bias assessment in individual studies

One reviewer (SC) used the Cochrane Risk of Bias tool to record the risk of bias concerning: (a) randomisation method, (b) allocation concealment, (c) blinding, (d) incomplete outcome data, (e) selective reporting. The assessment was done at the study level. Concerns were resolved through discussion with a second reviewer (CTS).

Synthesis methods

This review used pairwise MA, NMA and Bayesian multilevel network meta-regression (ML-NMR) supplemented (if possible) with AgD when IPD were not available to synthesise evidence. Both fixed-effect (FE) and random-effects (REs) models were applied. An 'available case' approach was taken for all analyses.

We used odds ratio (OR) as the measure of treatment effect for binary outcomes (exacerbation, asthma control, AEs) and mean difference (MD) as the measure of treatment effect for continuous outcomes (FEV_1, QoL). Pairwise MA and NMA were performed using both the frequentist approach (NMA results not shown) and the Bayesian approach. Frequentist MAs were carried out using the R functions 'netmetabin' and 'netmeta'. An inverse variance (IV) model was used with a generalised methods of moments estimate of the between-studies variance. NMA models were multilevel models that combined IPD and AgD from studies for which IPD was unavailable (i.e. event rates or means and variances for each trial arm, and the average covariate value for each trial).[21,22] A logit link function was used for binary outcomes (*exacerbation* and *asthma control*) and an identity link function for normally distributed continuous outcomes (FEV_1). Models accounted for correlation between treatment effects from multiarm trials. The between trial variance was assumed to be constant across all comparisons in the network.

To explore whether patient characteristics (i.e. covariates) modify the treatment effects, Bayesian ML-NMR models that include independent treatment by covariate interactions for the outcomes *exacerbation*, *asthma control* and *FEV*$_1$ were fitted. The following covariates were studied: *age* (years); *sex* (female vs. male); *ethnicity* (non-Hispanic or non-Latino vs. Hispanic or Latino); *eczema* (present vs. absent); *eosinophilia* (eosinophilic vs. non-eosinophilic); and *baseline severity* (mild, moderate, severe). All ML-NMR models for FEV$_1$ were adjusted for FEV$_1$ at baseline; hence, the treatment interactions for the covariate 'baseline severity', which is based on baseline FEV$_1$% predicted, were not explored for this outcome. One ML-NMR model was applied for each outcome and covariate combination in turn. The model specification is provided in Phillippo *et al.*[21,22] The models assumed independent treatment by covariate interactions, that is, the covariate can modify each treatment effect differently. The regression coefficients were considered to be fixed rather than random, which is conventional in meta-regression models. Treatment effect modifiers can invalidate the underlying assumption of transitivity in NMA if there is variation in the covariate distribution across comparisons. This was assessed using descriptive summaries of covariates that were thought to be effect modifiers along with results of the ML-NMR models (see *Chapter 7*).

The software R (package 'multinma') was used to construct all plots and fit models in a framework based on the Stan language. The Markov Chain Monte Carlo (MCMC) algorithm with four chains was run for each model until convergence was achieved; 50% of iterations were discarded as the warmup period. Convergence was assessed using the Gelman-Rubin R hat statistic. For exacerbation and asthma control, chains ran for 10,000 iterations for models including age or sex; and for 7000 iterations for the other covariates. For FEV$_1$, chains ran for 2000 iterations for sex, age and ethnicity; for 5000 iterations for eosinophilia and baseline severity; and for 10,000 iterations for eczema. Bulk-effective samples size (ESS) and tail-ESS were used as diagnostics for the sampling efficiency in the bulk of the posterior and in the tails of the posterior, respectively; both should be at least 100 (approximately) per chain to be reliable. The number of iterations were increased when the bulk-ESS and tail-ESS were too low; when increasing the number of iterations did not resolve the issue, analyses were based on IPD alone. QR decomposition was used to improve sampling efficiency. Normal prior distributions were used for model parameters (i.e. trial-specific event rate or mean, log OR or MD, and regression coefficients for covariate terms), except for the between-trial SD, for which a half-Normal prior distribution was used. The deviance information criterion (DIC) was used to compare the model fit and complexity of models (e.g. FE and REs; or models with and without interaction terms). If the difference in DIC was > 5, we deemed the model with the lowest DIC to be favourable to draw clinical conclusions. For the ML-NMR models, we also examined the credibility interval (CrI) of the interaction regression coefficients and highlighted potential effect modifiers when the CrI excluded the null value, in which case the full table of treatment effects (ORs or MDs) and CrI was presented for each subgroup of participants. Our investigation examined the overlap of CrI results for different levels of the covariate obtained from the fitted model to qualitatively assess whether the results were different.

For the frequentist pairwise MA, we summarised statistical heterogeneity using Q-test, I^2, and τ^2 and created forest plots. For Bayesian NMA, we also ran models of inconsistency based on unrelated mean effects (UMEs) to assess the consistency assumption and created dev–dev plots to evaluate the agreement of direct and indirect evidence in the treatment networks studied. Posterior treatment rankings and rank probabilities were obtained from fitted NMA models for every outcome using '*posterior_ranks*' and '*posterior_rank_probs*' commands in the package '*multinma*'.

For every outcome variable and fitted model of NMA or ML-NMR, we investigated the geometry of the treatment network under the study and potential biases related using network diagrams that include the treatment classes and the number of studies for every comparison.

Table 4 displays the specific prior distributions used; increasingly more informative prior distributions were used when the data would not permit use of the following prior distributions: Normal(0,100^2) and half-Normal(2.5^2). Divergent transitions were handled by choosing appropriate priors (weakly informative or informative) and/or increasing the target average proposal acceptance probability during Stan's adaptation period. Models were fitted using a tree depth of 15.

TABLE 4 Prior distributions used in Bayesian NMA and ML-NMR models

Outcome	Model	Prior distribution	
		FE model	REs model
Exacerbation	NMA 1 NMA 2	Intercept, trt ~ Normal(0,100^2)	Intercept, trt ~ Normal(0,100^2) het ~ half-Normal(2.5^2)
	ML-NMR All covariates	Intercept, trt, reg ~ Normal(0,100^2)	Intercept, trt, reg ~ Normal(0,100^2) het ~ half-Normal(2.5^2)
Asthma control	NMA 1 NMA2 NMA 3	Intercept, trt ~ Normal(0,10^2)	Intercept, trt ~ Normal(0,100^2) het ~ half-Normal(2.5^2)
	ML-NMR Age Sex Ethnicity Baseline severity	Intercept, trt, reg ~ Normal(0,100^2)	Intercept, trt, reg ~ Normal(0,100^2) het ~ half-Normal(2.5^2)
	Eczema	Intercept, trt, reg ~ Normal(0,100^2)	Intercept ~ Normal(0,5^2) trt, reg ~ Normal(0,3^2) het ~ half-Normal(0.5^2)
	Eosinophilia	Intercept, trt, reg ~ Normal(0,100^2)	Intercept, trt, reg ~ Normal(0,100^2) het ~ half-Normal(1.5^2)
FEV_1	NMA 1	intercept ~ Normal(0,10^2) trt, aux ~ Normal(0, 5^2)	intercept ~ normal(scale ~ 100) trt ~ normal(scale ~ 10) het ~ half_normal(scale ~ 1.5) aux ~ normal(scale ~ 10)
	NMA 2	intercept ~ Normal(0,10^2) trt, aux ~ Normal(0, 5^2)	intercept ~ normal(scale ~ 100) trt ~ normal(scale ~ 10) het ~ half_normal(scale ~ 1) aux ~ normal(scale ~ 10)
	NMA 3	intercept ~ Normal(0,100^2) trt, aux ~ Normal(0,10^2)	intercept ~ normal(scale ~ 100) trt ~ normal(scale ~ 10) het ~ half_normal(scale ~ 1.5) aux ~ normal(scale ~ 10)
	NMR 1[a] NMR 2[a]	Intercept, reg ~ Normal(0,10^2) trt, aux ~ Normal(0,5^2)	intercept ~ normal(scale ~ 10) trt ~ normal(scale ~ 3) reg ~ normal(scale ~ 3) het ~ half_normal(scale ~ 1) aux ~ normal(scale ~ 3)
	NMR 3[a]	Intercept, trt ~ Normal(0,10^2) trt, aux ~ Normal(0, 5^2)	intercept ~ normal(scale ~ 10) trt ~ normal(scale ~ 2) reg ~ normal(scale ~ 2) het ~ half_normal(scale ~ 1) aux ~ normal(scale ~ 2)
	ML-NMR		
	Age Ethnicity	Intercept, aux ~ Normal(0,10^2) trt, reg ~ Normal(0,5^2)	Intercept ~ Normal(0,100^2) trt, reg, aux ~ Normal(0,3^2) het ~ half-Normal(1^2)
	Sex		Intercept ~ Normal(0,100^2) trt, reg, ~ Normal(0,5^2) aux ~ Normal(0,10^2) het ~ half-Normal(1.5^2)
	Eczema	intercept ~ Normal(0,100^2) trt, reg, aux ~ Normal(0,10^2)	intercept ~ Normal(0,10^2) trt, reg, aux ~ Normal(0,2^2) het ~ half-Normal(0.1^2)

continued

TABLE 4 Prior distributions used in Bayesian NMA and ML-NMR models (*continued*)

Outcome	Model	Prior distribution	
		FE model	REs model
	Eosinophilia	intercept ~ Normal(0,100^2) trt, reg, aux ~ Normal(0,5^2)	intercept ~ Normal(0,5^2) trt, reg, aux ~ Normal(0,2^2) het ~ half-Normal(0.5^2)

NMA 1, analysis with grouped ICS + LABA; NMA 2, analysis with stratified ICS dose + LABA; NMA 3, analysis of individual compounds.
a The same models as NMA but adjusted for FEV_1 at baseline.

Note
The 'intercept' represents the log odds of an event in the baseline group, 'trt' represents the treatment effects, 'reg' represents the regression coefficients for the interaction, 'het' represents the between trial SD, 'aux' represents the arm-level SDs.

Sensitivity analysis

We conducted sensitivity analyses to explore the impact of the exacerbation data collection approach by excluding trials that had recorded exacerbation data only through AE data collection and may not have captured all events systematically. Data availability bias could impact on the results of the IPD NMA if the availability of IPD from included trials is related to the trial results. We attempted to overcome this by including AgD wherever possible in primary analyses and explored whether results and conclusions were different in sensitivity analyses that excluded AgD. We also compared risk of bias, patient and trial characteristics between IPD trials, and trials with no IPD wherever possible.

Chapter 3 Methods: economic evaluation

The aim of the economic analysis of the EINSTEIN study was to assess the cost-effectiveness of treatments in children who have poor asthma control, despite therapy with ICS. The primary objective was to estimate the incremental cost per QALY gained (ICER) using a decision-analytic model[23] and by adopting the perspective of the NHS and PSS in the UK, in accordance with NICE guidelines.

A cost–utility analysis was performed to compare the incremental costs and incremental QALYs of alternative treatments for the management of paediatric asthma in patients < 18 years who are not well controlled by ICS. A literature review was undertaken to identify a suitable model structure and data requirements for a decision analysis to simulate resource use and health outcomes and investigate the impact of alternative treatment regimens including ICS, LABA and LTRA. A Markov state transition model was developed, with probabilities of transitioning among four health states representing asthma being controlled, uncontrolled, asthma exacerbation, and death from asthma exacerbation. Health state utilities were specified, and costs comprised direct medical expenditures based on patients' use of primary and secondary care services and personal and social services. The cost–utility analysis adopted a 1-year time horizon, with the model having weekly cycles and a half-cycle correction to account for events and transitions occurring at any point of the cycle and not necessarily at the beginning or end.[24] The primary outcome of the economic evaluation was the incremental cost-effectiveness ratio (ICER). The economic analysis is reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards.

Study population and treatments

The study considered a paediatric population of children aged < 18 years old of both sexes and of any ethnicity who were prescribed ICS and had poor asthma control. The treatment comparators in the analysis were ICSs – beclometasone dipropionate, CIC, FP, FF, BUD, mometasone; alone or in combination with (1) LABA – FORM, SAL, VI; or (2) leukotriene receptor (cysteinyl leukotriene receptor 1) antagonists (LTRAs) – zafirlukast, montelukast; or theophylline.

Inhaled corticosteroids were categorised as being low, medium and high dose, in accordance with the GINA strategy.

Model structure: Markov health states

To inform the development of the economic model, a literature search was conducted across five electronic databases (PubMed, Ovid MEDLINE, EMBASE, Cochrane library, BMJ) from January 2000 up to September 2020. The aims of the search were to identify economic models used in previous evaluations of asthma treatments, to define relevant health states, and transition probabilities among these health states. The search strategy included medical subject headings and free-text words combined with Boolean operators: 'asthma' and ('children' or 'paediatric' or 'adolescents') and ('decision analytic model' or 'Markov model' or 'decision tree') and ('qaly' or 'utilities') and ('cost' or 'costs'). Titles and abstracts were screened, and studies were selected for further scrutiny based on their reference to 'Markov', 'health states' and 'decision analysis'.

The search returned 48 papers in PubMed database, 181 in Ovid MEDLINE, 8 in EMBASE, 9 in BMJ and 5 in the Cochrane library. Of these, nine economic models were identified, which considered potentially suitable health states. These were presented to the clinical coinvestigators to agree on a clinically meaningful structure that represented disease progression with mutually exclusive health states. Their views on the expected direction of transitions between health states were also sought.

The four Markov health states were 'controlled asthma with treatment', 'uncontrolled asthma', 'asthma exacerbation' and 'death from asthma exacerbation'. Patients reside in the controlled asthma health state if they manage day-to-day asthma symptoms by taking a maintenance treatment in the form of ICS. Patients in the uncontrolled asthma state

experience mild events of exacerbation, despite taking inhaler corticosteroids. These are characterised by typically requiring extra consultations with the GP or nurse and, on occasion, with healthcare professionals from secondary care setting. The asthma exacerbation state includes patients who – following a severe deterioration of the asthma symptoms – need to consult a healthcare professional in a primary healthcare setting, ED, and/or to be admitted to a hospital. The model also considers a death state, which captures deaths due to acute asthma exacerbation. The Markov model is represented in *Figure 1*.

Transition probabilities

Transition probabilities pertaining to ICS were based on those identified from published economic evaluations. These were modified for the alternative treatments based on their relative risks (RRs), versus ICS, of asthma control and exacerbation, derived from the NMA. For ICS, the transition probabilities were associated with the comparator group of studies that tested different dosing strategies in children with persistent asthma – specifically, patients who were randomised to continuous ICS therapy. Rodriguez-Martinez *et al.* (2015, 2016)[25,26] calculated transition probabilities associated with three health states: (1) 'no symptoms', which was associated with a GP consultation, paediatrician consultation, spirometry, BDP via pMDI; (2) 'suboptimal control, no exacerbation', which was associated with GP consultation, paediatrician consultation, spirometry, BDP and salbutamol via pMDI and (3) 'asthma exacerbation', which involved a GP consultation, paediatrician consultation, spirometry, BDP and salbutamol via pMDI, treatment in the ED, hospitalisation for asthma exacerbation, oral prednisolone, and radiology procedures, laboratory tests, ambulance.

The probabilities calculated by Rodriguez-Martinez *et al.* (2015, 2016)[25,26] were based on data extracted from a systematic review, which they had performed, of published trials that (1) included children and young persons < 18 years of age with recurrent wheezing or mild asthma; (2) compared continuous daily, versus intermittent ICS; and (3) reported the percentage of symptom-free days or the probability of exacerbation during the observed period. Four studies informed the transition probabilities from the 'suboptimal control, no exacerbation' to the 'asthma exacerbation' state; from the 'suboptimal control, no exacerbation' to the 'no symptoms' state; and from the 'no symptoms' to the 'no

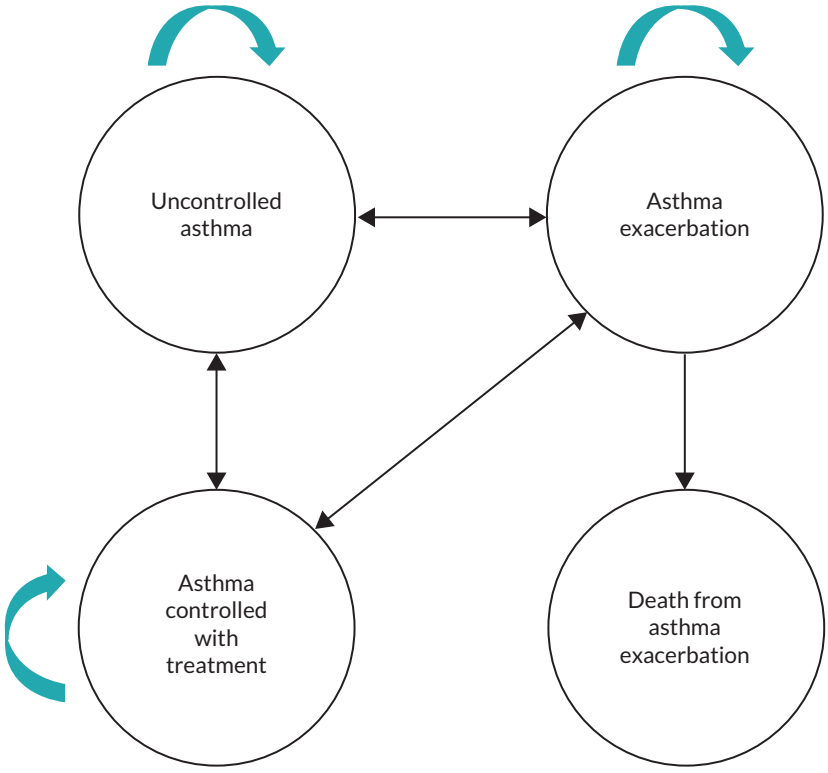

FIGURE 1 Schematic representation of the Markov economic model. Illustrating possible transitions among mutually exclusive health states for paediatric patients with asthma. Arrows depict the direction of patients' movement among health states.

symptoms' and to the 'asthma exacerbation' states. A previous study by Rodriguez-Martinez *et al.* (2013)[27] informed the transition probabilities from the 'asthma exacerbation' state to the 'no symptoms' state. A review of these studies was undertaken to establish their generalisability to the EINSTEIN population.

Zeiger *et al.* (2011)[28] included a population of 278 children, aged 58 months to 12 years, who had positive values on the modified asthma predictive index, recurrent wheezing episodes, and at least one exacerbation in the previous year but a low degree of impairment. Participants were randomised to receive a BUD inhalation suspension for 1 year as (1) intermittent high-dose regimen or (2) daily low dose. Martinez *et al.* (2011)[29] randomised a paediatric population aged 5–18 years with persistent asthma to one of the four interventions: (1) twice daily beclomethasone with beclomethasone + salbutamol as rescue; (2) twice daily beclomethasone with placebo + salbutamol as rescue; (3) twice daily placebo with beclomethasone + salbutamol as rescue and (4) twice daily placebo with placebo + salbutamol as rescue. Papi *et al.* (2009)[30] included a population of 276 symptomatic children with frequent wheeze, aged 1–4 years, who were randomly assigned to one of three groups for a 3-month nebulised treatment: (1) twice daily 400 µg beclomethasone + 2500 µg salbutamol prn; (2) twice daily placebo + 800 µg beclomethasone/1600 µg salbutamol combination prn or (3) twice daily placebo + 2500 µg salbutamol prn. Turpeinen *et al.* (2008)[31] randomised 176 children aged 5–10 years with newly detected asthma to three treatment groups: (1) continuous BUD (400 µg twice daily for 1 month, 200 µg twice daily for months 2–6, 100 µg twice daily for months 7–18); (2) BUD, identical treatment to group 1 during months 1–6, then BUD for exacerbation as needed for months 7–18; or (3) disodium cromoglycate 10 mg three times daily for months 1–18. Exacerbation was treated with BUD 400 µg twice daily for 2 weeks.

The description of health states, and data sources that informed the transition probabilities matrix relating to continuous ICS in the Rodriguez-Martinez *et al.* (2015) study were considered to be appropriate for the EINSTEIN model. However, there were caveats that were addressed by (1) adding a state for asthma-specific death; (2) assuming all patients entered the model in the 'uncontrolled asthma' state and (3) assuming in the base-case analysis that the probabilities were related to ICS Low.

All transition probabilities were from Rodriguez-Martinez *et al.* (2015) with the exception of death from asthma exacerbation, which was calculated as the average of the probably of dying from asthma exacerbation for children under 5 years old and children aged 5–17 years, weighted by the proportion of children in each age category. These were converted to weekly probabilities, assuming a constant hazard function, to align with the model cycle length (Equation 1).

$$D_p = \frac{t+z}{T(N_t+N_z)}, \quad (1)$$

where *Dp* is the probability of death from asthma exacerbation, *t* is the number of children who died in the under 5-year-old group, *z* is the number of children who died in the 5- to 17-year-old group, *Nt* and *Nz* are the populations of each group and *T* is equal to 52, being the number of weeks in a year. Deaths were not assumed to occur from other health states.

The remaining transition probabilities were calculated as one minus the sum of the probabilities in the same row. The transition probability matrix for ICS Low is presented in *Table 5*.

Treatment effect

The effects of alternative treatments relative to ICS Low were incorporated into the model based on their RRs in achieving unfavourable (unwanted/undesirable) effects (asthma exacerbation); or favourable effects (asthma control). RRs for the base case were calculated as the mean probability of asthma control or exacerbation for the alternative treatment divided by the probability of asthma control or exacerbation for ICS Low (*Tables 6* and *7*). These were based on the Bayesian FE NMA analysis reported in *Chapter 5*.

To model the effect of each treatment, the transition probabilities of the referent treatment were adjusted by the RRs for the alternative treatments according to the calculations in *Tables 8* and *9*.

TABLE 5 Transition probabilities relating to the weekly rate at which paediatric patients transit among health states in the base case

	Transition to			
Transition from	**Asthma controlled**	**Asthma uncontrolled**	**Asthma exacerbation**	**Death from asthma exacerbation**
Asthma controlled	0.93300	0.05800	0.00900	0.00000
Asthma uncontrolled	0.88700	0.09700	0.01600	0.00000
Asthma exacerbation	0.25500	0.73300	0.01200	1.92×10^{-6}
Death from asthma exacerbation	0.00000	0.00000	0.00000	1.00000

TABLE 6 Bayesian FE mean predicted probabilities and RRs for controlled asthma for the base case

	Probability		RR		
Treatment	**Mean**	**SD**	**Mean**	**Lower 95% CI**	**Upper 95% CI**
ICS Low	0.7520	0.0190	1.0000	–	–
ICS Medium	0.7593	0.0598	1.0097	0.8988	1.1397
ICS High	0.6921	0.0702	0.9203	0.7278	1.0876
ICS + LTRA	0.7554	0.1504	1.0045	0.5434	1.2999
LTRA	0.4255	0.1734	0.5658	0.1538	1.0259
ICS Low + LABA	0.7772	0.0344	1.0335	0.9358	1.1355
ICS Medium + LABA	0.7666	0.0585	1.0194	0.8533	1.1701
ICS High + LABA	0.8126	0.0542	1.0806	0.9158	1.2227

TABLE 7 Bayesian FE predicted probabilities and RRs for asthma exacerbation for the base case

	Probability		RR		
Treatment	**Mean**	**SD**	**Mean**	**Lower 95% CI**	**Upper 95% CI**
ICS Low	0.0595	0.0054	1.0000	–	–
ICS Medium	0.0455	0.0105	0.7647	0.4469	1.1902
ICS High	0.0469	0.0163	0.7882	0.3408	1.4426
ICS + LTRA	0.0785	0.0365	1.3193	0.3835	2.8584
LTRA	0.2107	0.1265	3.5412	0.4746	8.6728
ICS Low + LABA	0.0486	0.0095	0.8168	0.5130	1.2123
ICS Medium + LABA	0.0340	0.0086	0.5714	0.3077	0.9280
ICS High + LABA	0.0592	0.0209	0.9950	0.4207	1.8357

Identification of costs and utilisation of resources

A purposive search of the health economics and the medical literature was performed to identify resource use data to parameterise the economic model. First, a citation search of 29 studies that were included in the NMA was undertaken to establish whether any of these trials had separate reports of cost or economic data. This search yielded 2240 publications, which were screened for health economic analyses, data on resource use and costs. Three studies were selected for a full review but were discarded as they referred to mixed populations (children and adults).

TABLE 8 Calculations for the transition probability matrix

Transition from	Transition to			
	Asthma controlled	Asthma uncontrolled	Asthma exacerbation	Death from asthma exacerbation
Asthma controlled	1 – (Σ remainder)	$AC/AU_{Referent}$	$AC/AE_{Referent} \times RR_{AE}$	0
Asthma uncontrolled	$AU/AC_{Referent} \times RR_{AC}$	1 – (Σ remainder)	$AU/AE_{Referent} \times RR_{AE}$	0
Asthma exacerbation	$AE/AC_{Referent} \times RR_{AC}$	$AE/AU_{Referent}$	1 – (Σ remainder)	Pr (asthma death) × RR_{AE}
Death from asthma exacerbation	0	0	0	1

Note
State 1/State $2_{Referent}$ are the transition probabilities for the referent (ICS Low; *Table 1*), RR_{AE} and RR_{AC} are the RRs (for any given treatment) of 'asthma exacerbation' and 'asthma controlled', respectively.

TABLE 9 Transition probability matrices by treatment for the base-case analysis

Transition from	Transition to			
	Asthma controlled	Asthma uncontrolled	Asthma exacerbation	Death from asthma exacerbation
ICS Medium				
Asthma controlled	0.93512	0.05800	0.00688	0.00000
Asthma uncontrolled	0.89561	0.09215	0.01224	0.00000
Asthma exacerbation	0.25748	0.73300	0.00952	1.5×10^{-6}
Death from asthma exacerbation	0.00000	0.00000	0.00000	1.00000
ICS High				
Asthma controlled	0.93491	0.05800	0.00709	0.00000
Asthma uncontrolled	0.81635	0.17104	0.01261	0.00000
Asthma exacerbation	0.23469	0.73300	0.03231	1.5×10^{-6}
Death from asthma exacerbation	0.00000	0.00000	0.00000	1.00000
ICS + LTRA				
Asthma controlled	0.93013	0.05800	0.01187	0.00000
Asthma uncontrolled	0.89101	0.08788	0.02111	0.00000
Asthma exacerbation	0.25615	0.73300	0.01084	2.5×10^{-6}
Death from asthma exacerbation	0.00000	0.00000	0.00000	1.00000
LTRA				
Asthma controlled	0.91013	0.05800	0.03187	0.00000
Asthma uncontrolled	0.50189	0.44145	0.05666	0.00000
Asthma exacerbation	0.14429	0.73300	0.12271	6.8×10^{-6}
Death from asthma exacerbation	0.00000	0.00000	0.00000	1.00000
ICS Low + LABA				
Asthma controlled	0.93465	0.05800	0.00735	0.00000
Asthma uncontrolled	0.91672	0.07021	0.01307	0.00000

continued

TABLE 9 Transition probability matrices by treatment for the base-case analysis (*continued*)

	Transition to			
Transition from	**Asthma controlled**	**Asthma uncontrolled**	**Asthma exacerbation**	**Death from asthma exacerbation**
Asthma exacerbation	0.26355	0.73300	0.00345	1.6×10^{-6}
Death from asthma exacerbation	0.00000	0.00000	0.00000	1.00000
ICS Medium + LABA				
Asthma controlled	0.93686	0.05800	0.00514	0.00000
Asthma uncontrolled	0.90422	0.08664	0.00914	0.00000
Asthma exacerbation	0.25995	0.73300	0.00705	1.1×10^{-6}
Death from asthma exacerbation	0.00000	0.00000	0.00000	1.00000
ICS High + LABA				
Asthma controlled	0.93305	0.05800	0.00895	0.00000
Asthma uncontrolled	0.95848	0.02560	0.01592	0.00000
Asthma exacerbation	0.27000	0.71824	0.01176	1.9×10^{-6}
Death from asthma exacerbation	0.00000	0.00000	0.00000	1.00000

A search of the PubMed, Ovid MEDLINE, EMBASE, EconLit and Cochrane databases was conducted subsequently to identify relevant sources of data on resource utilisation and costs. The search was limited to studies published in the English language between January 2000 and October 2021 and filtered for a population aged < 18 years. The search criteria employed a combination of terms connected by the Boolean operator AND: 'asthma', 'children', 'inhaled corticosteroids', 'health economics', 'cost effectiveness OR cost-effectiveness', 'healthcare costs', 'economic burden', 'cost benefit analysis', 'drug cost', 'cost of illness', 'quality of life', 'cost analysis', 'paediatric asthma', 'asthma exacerbation', 'asthma hospital costs', 'asthma medicines', 'asthma therapy'.

The search returned 3471 results in PubMed, 10 in Ovid MEDLINE, 3316 in EMBASE, 0 in EconLit, 1 in ScHARR-HUD and 12 in the Cochrane database. The full-text publication of 85 studies were examined, however, after careful consideration and detailed discussions with the clinical team, consensus was reached on utilising data pertaining to the control arm (standard treatment) of a paediatric clinical trial (RAACENO, Reducing Asthma Attacks in Children using eNO, ISRCTN67875351) as the basis for estimating all resource use, other than the study treatments. Twelve-month health service resource use in RAACENO that were not associated with an exacerbation were assumed to apply to the asthma controlled and uncontrolled health states in EINSTEIN; the difference between the two being the inclusion of emergency and secondary care costs in the uncontrolled health state (*Table 10*). Total costs relating to these states were adjusted proportionally to weekly costs, to correspond with the cycle length of the EINSTEIN economic model.

Resource use associated with each exacerbation as reported by the RAACENO trial were applied to the weekly cycle attributed to the asthma exacerbation health state in EINSTEIN (*Table 10*). To estimate prescription items for treatments, we assumed a 1-week utilisation of a 200-dose inhaler with a regimen of two puffs administered twice daily. A SD of 0.1 was assumed, to account for variability in usage.

Unit costs

Unit costs were assigned to each item of resource use, based on a 2019–20 cost year and expressed in pounds sterling (£GBP). Healthcare Resource Group (HRG) codes were identified for ED attendances, hospital outpatient clinic visits, day case consultation, and inpatient stays and costed using the NHS National Schedule of Reference Costs 2018–9 (*Table 11*). Unit costs of primary care GP consultations were sourced from the Compendium of Unit Costs of Health and Social Care 2019. Costs were inflated, where applicable, using the NHS cost inflation index.

TABLE 10 Resource use numbers by health state, per year. Values are means (SDs)

Items of resource use	Health state		
	Asthma controlled (per annum)	Asthma uncontrolled (per annum)	Asthma exacerbation (per exacerbation)
Prescription items for comparator treatments (inhalers, pack of 28 tablets)	12 (2)	12 (2)	0.14 (0.1)
GP	0.75(1.65)	0.75 (1.65)	0.79 (0.87)
Consultations with nurse	0.15 (0.54)	0.15 (0.54)	0.11 (0.43)
Walk-in consultations	0.05 (0.27)	0.05 (0.27)	0.05 (0.24)
NHS 24/111 calls	0.09 (0.51)	0.09 (051)	0.09 (0.42)
Out of hours GP consultations	0.04 (0.21)	0.04 (0.21)	0.05 (0.23)
Pharmacist	0.01 (0.10)	0.01 (0.10)	0
Reliever	1 (0.20)	1 (0.20)	0.02 (0.2)
ED visits	0	0.09 (0.32)	0.2 (0.45)
Hospital inpatient stays	0	0.02 (0.15)	0.14 (0.38)
Hospital outpatient clinic attendance	0	0.25 (0.92)	0.03 (0.17
Day case	0	0	0.00 (0.06)
Bronchoscopy	0	0.01 (0.1)	0
Ambulance	0	0.01 (011)	0.03 (0.20)
Other (physiotherapist/psychologist/ speech and language therapist)	0	0.01 (0.14)	0

TABLE 11 Unit costs

Item of resource use	Cost per item/episode (£)	Reference
GP visit	39.65	Curtis *et al.* (2019)[32]
ED [HRG code VB09Z – VB09Z Emergency medicine, category 1 investigation with category 1–2 treatment (type 1 non-admitted)]	133.00	National Schedule of Reference cost
ED (HRG codes VB06Z and VB04Z weighted average by severity of admission)	264.00	National Schedule of Reference cost
Nurse consultation	24.00	Curtis *et al.* (2019)[32]
Walk-in consultation (Weighted average of T04 A and T04NA – excluding emergency dental)	45.71	Curtis *et al.* (2019);[32] National Schedule of Reference costs
NHS 24/111 call	12.96	Pope *et al.* (2017)
Out of hours GP (Weighted average of T03 A and T03NA – excluding emergency dental)	74.02	National Schedule of Reference cost
Hospital short stay (admitted for ≤ 1 night) (Weighted average of PD12 Paediatric, Asthma or Wheezing)	594.00	National Schedule of Reference cost
Hospital long stay [admitted for ≤ 4 days and > 1 night (Weighted average of PD12 Paediatric, Asthma or Wheezing)]	1913.00	National Schedule of Reference cost; Curtis *et al.* (2019)[32]

continued

TABLE 11 Unit costs (*continued*)

Item of resource use	Cost per item/episode (£)	Reference
Excess bed-days (Weighted average of PD12 Paediatric, Asthma or Wheezing)	575.00	National Schedule of Reference cost; Curtis *et al.* (2019)[32]
Hospital day case (Weighted average of PD12 Paediatric, Asthma or Wheezing)	394.00	National Schedule of Reference cost
Bronchoscopy (DZ69B Diagnostic Bronchoscopy, 18 years and under, combined day case/ordinary elective spell tariff)	952.00	NHS Improvement. National Tariff
Ambulance (see and treat)	209.00	AMB ASS01
Ambulance (see and convey)	257.00	AMB ASS01
Clinical psychologist	54.00	Curtis *et al.* (2019)[32]
Physiotherapist	57.00	Curtis *et al.* (2019)[32]
Speech and language therapist	34.00	Curtis *et al.* (2019)[32]

Cost of medicines

As there are several formulations of ICSs and LABA and they all differ in costs, we tried to identify which would be the most commonly prescribed by analysing the prescription cost analysis data.[33] However, as these data do not distinguish between adult and paediatric prescriptions, expert opinion was sought from the clinical coinvestigators. The asthma medicines used in the analysis are listed in *Table 12* and their unit costs were taken from the *British National Formulary*.[34] The weekly cost of inhaler devices was estimated by calculating the daily cost of a medicine, based on the prescribed

TABLE 12 Unit costs of asthma medicines

Medication	Formulation	Active ingredients	Unit size	Cost per unit (£)
ICS Low	Clenil Modulite 100 µg/dose inhaler (Chiesi Ltd)	Beclometasone dipropionate 100 µg per 1 dose	200 puffs	7.42
ICS Medium	Clenil Modulite 200 µg/dose inhaler (Chiesi Ltd)	Beclometasone dipropionate 200 µg per 1 dose	200 puffs	16.17
ICS Medium + LABA	Symbicort 200/6 Turbohaler (AstraZeneca UK Ltd)	BUD 200 µg per 1 dose; and FORM fumarate dihydrate 6 µg per 1 dose	120 puffs	28
ICS + LTRA	Clenil Modulite 200 µg/dose inhaler (Chiesi Ltd)	Beclometasone dipropionate 200 µg per 1 dose	200 puffs	16.17
	Montelukast 10 mg tablets (A A H Pharmaceuticals Ltd)	Montelukast (as Montelukast sodium) 10 mg	28 tablets	1.7
ICS High	Flixotide 250 µg/dose Evohaler (GlaxoSmithKline UK Ltd)	FP 250 µg per 1 dose	120 puffs	36.14
LTRA	Montelukast 5 mg chewable tablets sugar free (A A H Pharmaceuticals Ltd)	Montelukast (as Montelukast sodium) 5 mg	28 tablets	1.45
ICS Low + LABA	Seretide 50 Evohaler (GlaxoSmithKline UK Ltd)	FP 50 µg per 1 dose; and SAL (as SAL xinafoate) 25 µg per 1 dose	120 puffs	17.46
ICS High + LABA	AirFluSal 25 µg/dose/250 µg/dose inhaler (Sandoz Ltd)	FP 250 µg per 1 dose; and SAL (as SAL xinafoate) 25 µg per 1 dose	120 puffs	29.32
SABA	Airomir 100 µg/dose inhaler (Teva UK Ltd)	Salbutamol (as salbutamol sulphate) 100 µg per 1 dose	200 puffs	1.5

dose (e.g. two inhalations twice a day), and dividing by the number of actuations per inhaler device and multiplying by seven.

Identification and valuation of outcome

In order to calculate the number of QALYs experienced by patients, health utilities in paediatric asthma were sourced by updating a previously published systematic review of the literature conducted until 6 July 2014.[35] Searched databases were Ovid MEDLINE, EMBASE, PubMed, ScHARR-Hud and the Cochrane Library. The literature review was filtered for the English language and human studies published from 6 July 2014 to October 2021.

The search strategy mirrored those of Kua *et al.* (2016)[35] and employed a combination of terms using Boolean operators: ('child', 'adolescent', 'teenager', 'preteen', 'young', 'youth'), ('asthma', 'asthma exacerbation' or 'asthma$' adj 'exacerbate'), ('quality of life', 'quality adjusted life year', 'qaly', 'health status indicators', 'euroqol', 'eq-5d', 'eq5d', 'health utility', 'sf36', 'sf 36', 'short form 36', 'shortform 36', 'sf thirtysix', 'sf thirty six', 'shortform thirtysix', 'shortform thirty six', 'short form thirtysix', 'short form thirty six'), ('eq5d child$', 'eq 5d child$', 'eq5d-youth', 'eq-5d-y', 'EuroQol 5DYouth', 'EQ-5D Youth', 'eq 5d youth'), ('chu-9d', 'chu9d', 'Child Health Utility Index 9D'), ('asui', 'Asthma Symptom Utility Index'), ('hql', 'hqol', 'h qol', 'HRQoL', 'hr qol'), ('health$ year$ equivalent$'), ('health utilit$'), ('hui', 'hui1', 'hui2', 'hui3'), ('quality of wellbeing', 'qwb'), ('willingness to pay'), ('standard gamble$'), ('time trade off', 'tto'), ('preference-based', 'preference based').

In addition to the 927 studies identified previously, the search returned 2615 publications in PubMed, 2 in Ovid MEDLINE, 135 in EMBASE, 81 reviews in the Cochrane databases and none in ScHARR-Hud. Titles were screened and duplicates eliminated, resulting in 86 articles that were retrieved for full-text reviewing. Studies that reported utility scores using the EuroQol-5 Dimensions (EQ-5D) generic measure in line with NICE's preferred health utility instrument were selected.[36]

For patients with controlled asthma, a utility weight of 0.96 was applied, based on the standard of care group of a RCT conducted in the Netherlands by Willems *et al.* (2007),[37] involving a population of adults and children with mild to moderate asthma in which they used the UK valuation set of EQ-5D.[38]

For the 'asthma uncontrolled' and 'asthma exacerbation' health states, disutilities of 0.10 and 0.20 were applied (as deductions from 0.96[39]), respectively. These values were sourced from a population of adult patients with moderate or severe asthma (BTS rating: 4/5) enrolled in a prospective observational study, who had experienced one exacerbation requiring oral steroid treatment (without hospitalisation) in the previous 4 weeks. This follows the same assumption as in the economic evaluations of a public health intervention for children with asthma,[40] and of as-needed ICS/LABA versus low-dose ICS maintenance therapy in patients (≥ 12 years) with mild asthma in the UK.[41] These utility values are also consistent with the NICE technology appraisal of ICSs for the treatment of chronic asthma in children under the age of 12,[42] which sourced utility values of 0.97 for 'symptoms free' and 0.85 for 'with symptoms' from adults enrolled in the GOAL study.[43] All health state utilities were assumed a SD of 0.2.[43]

Cost-effectiveness analysis

Base-case analysis

The base-case analysis assumed the transition probabilities computed by Rodriguez-Martinez *et al.* (2015) applied to ICS Low. RRs were applied to these probabilities for the calculation of transition probabilities for comparator treatments, based on the FE Bayesian probabilities of controlled asthma and asthma exacerbation. Individuals entered the model in the 'asthma uncontrolled' state, from which they could transition to the other health states following weekly cycles. A half-cycle correction was applied.

Total costs and QALYs were calculated for each treatment. Treatments were ranked in order of decreasing QALYs, and an incremental analysis was undertaken by removing dominated and extendedly dominated treatments, and calculating the ICER, for the remaining treatments, according to Equation 2:

$$\text{ICER} = \Delta\text{Costs}/\Delta\text{QALY} \quad (2)$$

where, ΔCosts is the difference in mean total costs, and ΔQALY is the difference in mean total QALYs, between any two treatments.

Analysis of parameter uncertainty

One-way sensitivity analyses were conducted to assess the stability of the ICER to different assumptions or ranges of parameter estimates. The ranges were chosen based on CIs, where available, otherwise based on assumed plausible limits. These following variables were considered:

1. varying point estimate utility values within ± 0.05, and between the lower and upper bounds of their 95% CIs, to assess the robustness of the cost-effectiveness results and assess the dependency of the findings on specific utility estimates;
2. reducing the cost of branded inhaler products by 50% to simulate the potential introduction in the market of generic alternatives, typically priced lower than their branded counterparts, to evaluate how cost savings from generic inhalers would affect the overall cost-effectiveness of asthma treatments;
3. increasing the transition probability of 'asthma exacerbation' by 50% concurrently for all treatments, while compensating with a reduction in transition probabilities for 'asthma controlled' (assumed plausible range). This allows us to investigate the impact of higher exacerbation rates on the cost-effectiveness of treatments and test the robustness of the results under worse-case clinical conditions.

Analysis of structural uncertainty

A number of sensitivity analyses were undertaken to assess the impact of structural uncertainty on the base-case ICER. The following changes to the base case were made:

1. applying REs Bayesian probabilities for the calculation of RRs of transition probabilities relating to 'asthma controlled' and 'asthma exacerbation' as alternatives to the Bayesian FE NMA probabilities used in the base-case economic model. REs NMA models assume that the between-study heterogeneity is the same across all comparisons;
2. assuming that transition probabilities from Rodriguez-Martinez *et al.* (2015) applied to ICS Medium, based on the observation that some studies included ICS Medium, which might exhibit different efficacy and safety profiles compared to ICS Low. This adjustment ensures that our ICER estimates are robust and reflective of the broader clinical setting;
3. applying REs Bayesian probabilities for the calculation of RRs of transition probabilities relating to 'asthma controlled' and 'asthma exacerbation', and, with ICS Medium as a referent, addressing multiple sources of structural uncertainty simultaneously. This broad adjustment allows us to assess how sensitive the base-case ICER is to variations in both the probability estimation method and the choice of reference treatment;
4. categorising the ICS into low and high doses when combined with LABA, to reflect clinical practice of combination therapy. This categorisation allows the model to differentiate between the varying effects and costs associated with different dose level, which can significantly impact treatment outcomes and cost-effectiveness.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken using a Monte Carlo simulation with 10,000 replicates, where each parameter was fitted using the method of moments and sampled simultaneously within their parametric distribution.[44] Utility values (U) were transformed ($1 - U$), and the parameters of a gamma distribution (α, β) were estimated assuming a fixed SD of 0.2. Items of resource use were assumed to log-normally distributed according to the mean and SDs presented in *Table 10*. Drawn samples were multiplied by their respective (fixed) average unit costs as provided in the National Cost Collection for the NHS. Beta-distributions were fitted to fixed and REs Bayesian probabilities (*Table 13*).

TABLE 13 Base-case model inputs used in the probabilistic sensitivity analysis

Parameter	Point estimate	Distribution (distribution parameters)
Bayesian predicted probabilities for 'asthma controlled'		
ICS Low	0.7520	~ Beta (391.8602, 129.2305)
ICS Medium	0.7690	~ Beta (78.9320, 23.7104)
ICS High	0.6867	~ Beta (32.5213, 14.8375)
ICS Medium + LABA	0.7798	~ Beta (123.6820, 34.9253)
ICS + LTRA	0.7576	~ Beta (5.4341, 1.7387)
LTRA	0.4222	~ Beta (3.0072, 4.1155)
Bayesian predicted probabilities for 'asthma exacerbation'		
ICS Low	0.0594	~ Beta (113.7532, 1801.2838)
ICS Medium	0.0551	~ Beta (21.2642, 364.6560)
ICS High	0.0439	~ Beta (11.7487, 255.8770)
ICS Medium + LABA	0.0479	~ Beta (26.3318, 523.3937)
ICS + LTRA	0.0849	~ Beta (4.5314, 48.8427)
LTRA	0.2099	~ Beta (1.9551, 7.3595)
Health state utility		
Asthma controlled	0.96	1-U ~ Gamma (0.0400, 1)
Asthma uncontrolled	0.86	1-U ~ Gamma (0.4900, 0.2857)
Asthma exacerbation	0.76	1-U ~ Gamma (1.4400, 0.1666)

Expected QALYs and costs associated with each treatment option were combined to estimate the probability of cost-effectiveness at different thresholds of willingness-to-pay (£20,000 and £30,000 per QALY). The joint uncertainty in incremental costs and QALYs was represented as a cost-effectiveness curve, illustrating the probability of each intervention being cost-effective over a wide range of willingness-to-pay thresholds.

Value of information analysis

A value of information analysis was conducted to quantify the expected value of research to reduce decision uncertainty and advise whether there would be value in undertaking further research to reduce the decision uncertainty.[45] The expected value of perfect information (EVPI) and the expected value of perfect parameter information were calculated on both per-patient and population levels using the Sheffield Accelerated Value of Information approximation.[46] Estimates were based on 5996 patients per annum, a figure obtained from a historical cohort study of children aged > 4 years for whom standard doses of ICSs failed to control asthma symptoms. This study identified a population of 10,793 from the Clinical Practice Research Datalink and Optimum Patient Care Research Database, representing 15% of the asthma population in England, over a period of 12 years. The value of information analysis assumed, conservatively, that the decision would have clinical relevance for 10 years. Both costs and QALYs were discounted at an annual rate of 3.5%.

Chapter 4 Results: systematic review and data collection

Studies included in the review

The overall flow diagram based on PRISMA is shown in *Figure 2*. A total of 4708 studies were screened (3343 from the primary searches and 1365 from the update to 5 May 2023). Of these, we retrieved 508 full-text studies (433 from the primary searches and 75 from the update to 5 May 2023) for further appraisal, and we identified 144 studies as eligible for inclusion. However, we only sought the IPD for 140 of these studies because it was not possible to find the contact details of the authors or sponsors for four studies. The full list of included studies can be found in *Appendix 4* and *Appendix 5*. Twenty-nine studies provided IPD for a total of 5494 participants [Bateman (2014),[47] Bernstein (2015),[48] Bleecker (2012),[49] Bleecker (2014),[50] Carroll (2010),[51] de Blic (2009),[52] Fitzpatrick (2016),[53] Gappa (2009),[54] Lemanske (2010),[3] Li (2010),[55] Lotvall (2014),[56] Lotvall (2014),[57] Martin (2020),[58] Murray (2010),[59] Murray (2011),[60] O'Byrne (2014),[61] Oliver (2016),[62] Oliver (2016),[63] Pearlman (2009),[64] Scott (2005),[65] Sorkness (2007),[66] Stempel (2016),[67] Stempel (2016),[68] Thomas (2014),[69] Vaessen-Verberne (2010),[70] Verberne (1998),[71] Wechsler (2019),[72] Woodcock (2013),[73] Woodcock (2014)[74]]. We could not retrieve the IPD for 111 of the studies sought: 24 because of issues with the data-sharing agreement; 46 did not reply (two of which had originally agreed to provide data but did not reply to our subsequent contact); 41 did not want to share data. Of the 115 eligible studies without IPD (including the 4 studies not sought), we were able to extract AgD for at least one outcome from 19 studies [Akpinarli (1999),[75] Berger (2006),[76] Bisgaard (2006),[77] Buchvald (2003),[78] Everden (2004),[79] Heuck (2000),[80] Jat (2006),[81] Kondo (2006),[82] Lenney (2013),[4] Malone (2005),[83] Morice (2008),[84] Russell (1995),[85] Shapiro (2001),[86] Simons (2001),[87] Strauch (2003),[88] Tal (2002),[89] Vermeulen (2007),[90] Visitsunthorn (2011),[91] Zimmerman (2004)[92]]. The majority of remaining studies did not report adequate AgD on the subset of patients who were eligible for inclusion in our analysis (e.g. study may have included adults and children but did not report adequate AgD on the subset of children eligible for our analysis). Full details of the 96 eligible studies without IPD or AgD are summarised in *Appendix 5* [Abbas (2016),[93] Amar (2017),[94] Arama (2016),[95] Arsovski (2016),[96] Bensch (2002),[97] Berger (2010),[98] Berger (2014),[99] Bernstein (2011),[100] Bernstein (2017),[101] Bernstein (2019),[102] Bose (1987),[103] Botan (2019),[104] Byrnes (2000),[105] D'Alonzo (1994),[106] D'Urzo (2005),[107] Emeryk (2016),[108] Farzan (2017),[109] Fitzgerald (2003),[110] Gelfand (2006),[111] Gustafsson (1993),[112] Hampel (2017),[113] Ikeda (2015),[114] Ilowite (2004),[115] Jamaati (2015),[116] Jehan (2014),[117] Kerwin (2017),[118] Knorr (1998),[119] Knorr (2001),[120] Kunoe (2016),[121] Langton Hewer (1995),[122] Lin (2015),[123] Lin (2016),[124] Mallol (2016),[125] Mansfield (2017),[126] Maspero (2010),[127] McIver (2011),[128] Meltzer (2012),[129] Meltzer (2019),[130] Miller (2016),[131] Murphy (2015),[132] Nathan (2010),[133] Nielsen (2000),[134] Pearlman (2011),[135] Pearlman (2017),[136] Pearlman (2019),[137] Peden (1998),[138] Pedersen (2009),[139] Pedersen (2017),[140] Pertseva (2012),[141] Peters (2016),[142] Petnak (2016),[143] Philip (2011),[144] Phipatanakul (2003),[145] Płoszczuk (2018),[146] Pohunek (2006),[147] Pohunek (2014),[148] Rani (2016),[149] Raphael (2018),[150] Saeed (2018),[151] Shapiro (1998),[152] Shatalina (2017),[153] Sher (2017),[154] Skoner (2008),[155] Steinfeld (2015),[156] Strunk (2008),[157] Suessmuth (2003),[158] van Adelsberg (2005),[159] Vandewalker (2017),[160] Venugopal (2019),[161] Verini (2007),[162] von Berg (1998),[163] Weinstein (1998),[164] Weinstein (2010),[165] Weiss (2010),[166] Zangrilli (2001)[167]].

Of the 48 studies with IPD or AgD, 40 could be included in the analysis of exacerbation outcome (39 in the ICS grouped analysis), 16 in the analysis of asthma control outcome (15 in the ICS grouped analysis), and 23 in the analysis of FEV_1 outcome (22 in the ICS grouped analysis). Characteristics of the 48 studies with IPD or AgD are shown in *Appendix 4*, *Tables 46* and *47*: the majority of studies were parallel group trials [40 (83%)] and were double-blind [45 (94%)]; studies were conducted globally with [23 (48%)] multicountry studies and [25 (52%)] single country studies; year of publication ranged between 1995 and 2020, with the majority of AgD studies published before 2009 [17 (89%)], and the majority of IPD studies published in 2009 or later; the follow-up in the IPD studies ranged between 2 and 54 weeks with median [interquartile range (IQR)] follow-up of 12 (8, 24) weeks.

Risk of bias for eligible studies included in network meta-analysis

Risk of bias was assessed for the 29 studies with IPD and 19 studies with AgD (*Table 14*). Overall, the majority of studies [32 (67%)] were considered as low risk of bias across all domains; [12 (25%)] studies had one domain classed as high risk, [2 (4%)] studies had two domains classed as high risk, and [2 (4%)] had three domains classed as high risk; however, there were no major concerns regarding risk of bias.

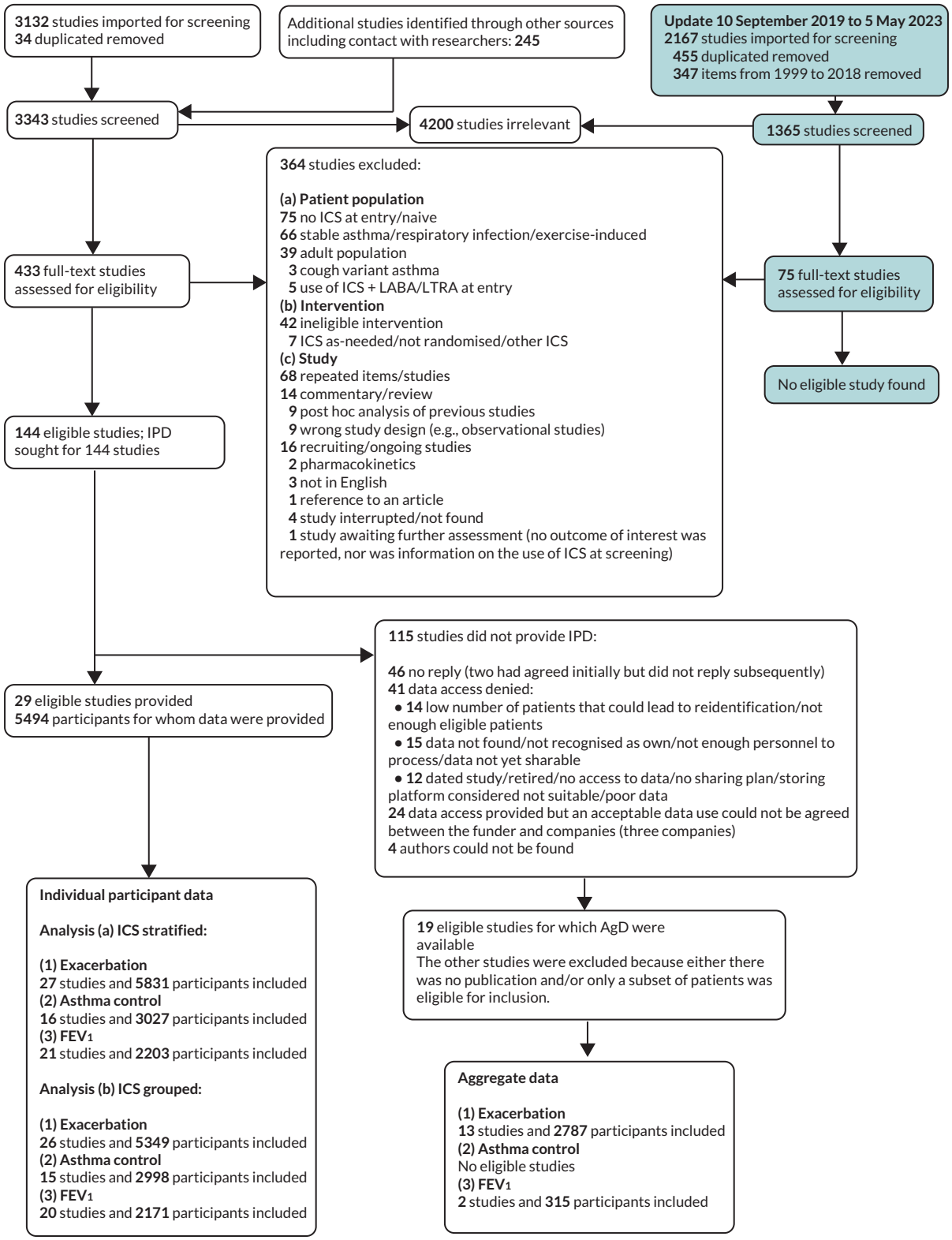

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses IPD flow diagram.

TABLE 14 Risk of bias for included studies with IPD or AgD

Study	Data	Treatment classes	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Akpinarli (1999)[75]	AgD	ICS + LABA	Unclear	Unclear	Unclear	Low	Unclear	Low	Low
		ICS High							
Bateman (2014)[47]	IPD	ICS Low	Low	Low	Low	Low	Low	Low	Low
		ICS + LABA							
Berger (2006)[76]	AgD	ICS Low	Low	Unclear	Unclear	High[a]	Unclear	Low	Low
		placebo							
Bernstein (2015)[48]	IPD	ICS Low	Low	Low	Low	Low	Low	Low	Low
		ICS + LABA							
Bisgaard (2006)[77]	AgD	ICS Medium	Low	Low	Low	Low	Low	Low	Low
		ICS + LABA							
Bleecker (2012)[49]	IPD	ICS High	Low	Low	Low	Low	Low	Low	Low
		ICS Low							
		ICS Medium							
		Placebo							
Bleecker (2014)[50]	IPD	ICS Low	Low	Low	Low	Low	Low	Low	Low
		ICS + LABA							
		Placebo							
Buchvald (2003)[78b]	AgD	ICS Medium	Low	Unclear	Unclear	Low	Low	Low	Unclear
		ICS + LABA							
		ICS + LTRA							
Carroll (2010)[51]	IPD	ICS Low	Unclear	Unclear	Low	Low	Low	Low	Low
		ICS + LABA							

TABLE 14 Risk of bias for included studies with IPD or AgD (*continued*)

Study	Data	Treatment classes	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
de Blic (2009)[52]	IPD	ICS Medium ICS + LABA	Low	Low	Low	Low	Low	Low	Low
Everden (2004)[79]	AgD	ICS + LABA (SAL) ICS + LABA (FORM)	Low	High[c]	High[c]	High[c]	Low	Low	Unclear
Fitzpatrick (2016)[53]	IPD	ICS Low LTRA	Low	Low	Low	Low	High	Low	High[d]
Gappa (2009)[54]	IPD	ICS Medium ICS + LABA	Low	Low	Low	Low	Low	Low	Low
Heuck (2000)[80]	AgD	ICS + LABA ICS Medium	Low	Low	Unclear	Low	High[e]	Low	Low
Jat (2006)[81]	AgD	ICS + LTRA ICS Medium	Unclear	Unclear	Unclear	Low	High[f]	Low	Low
Kondo (2006)[82]	AgD	ICS + LTRA ICS + theophylline	Low	Unclear	High	Low	Low	Unclear	Low
Lemanske (2010)[3]	IPD	ICS Medium ICS + LABA ICS + LTRA	Low	Low	Low	Low	Low	Low	High[g]
Lenney (2013)[4]	AgD	ICS Low ICS + LABA ICS + LTRA	Low	Low	Low	Low	High	Low	Low
Li (2010)[55]	IPD	ICS Low ICS + LABA	Low	Low	Low	Low	Low	Low	Low
Lötvall (2014)[56h]	IPD	ICS Low ICS Medium ICS + LABA	Low	Low	Low	Low	Low	Low	Low

continued

TABLE 14 Risk of bias for included studies with IPD or AgD (*continued*)

Study	Data	Treatment classes	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Lötvall (2014)[57]	IPD	ICS Low ICS Medium Placebo	Low	Low	Low		Low	Low	Low
Malone (2005)[83]	AgD	ICS Low ICS + LABA	Low	Low	Low	Low	Low	Low	Low
Martin (2020)[58]	IPD	ICS Medium ICS + LABA	Low	Low	Low	Low	Low	Low	High[g]
Morice (2008)[84]	AgD	ICS Low ICS + LABA	Low	Unclear	Unclear	Low	Low	Low	Low
Murray (2010)[59]	IPD	ICS Medium ICS + LABA	Low	Low	Low	Low	Low	Low	Low
Murray (2011)[60]	IPD	ICS Low ICS + LABA	Low	Low	Low	Low	Low	Low	Low
O'Byrne (2014)[61]	IPD	ICS High ICS + LABA	Low	Low	Low	Low	Low	Low	Low
Oliver (2016)[63]	IPD	ICS Low ICS + LABA	Low	Low	Low	Low	Low	Low	Low
Pearlman (2009)[64]	IPD	ICS Low ICS + LABA	Low	Low	Low	Low	Low	Low	Low
Russell (1995)[85]	AgD	ICS + LABA ICS High	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Scott (2005)[65]	IPD	ICS Low ICS + LABA	Low	Low	Low	Low	Low	Unclear	High[i]
Shapiro (2001)[86]	AgD	ICS Low ICS Medium Placebo	Unclear	Unclear	Low	Low	Unclear	Low	Low

TABLE 14 Risk of bias for included studies with IPD or AgD (*continued*)

Study	Data	Treatment classes	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Simons (2001)[87b]	AgD	ICS Medium	Unclear	Unclear	Low	Low	Low	Low	High[d]
		ICS + LTRA							
Sorkness (2007)[66]	IPD	ICS Low	Low	Low	Low	Low	Low	Low	Low
		ICS + LABA							
		LTRA							
Stempel (2016)[67]	IPD	ICS Medium	Low	Low	Unclear	Low	Low	Low	Unclear
		ICS + LABA							
Stempel (2016)[68]	IPD	ICS High	Low	Low	Unclear	Low	Low	Low	Unclear
		ICS Low							
		ICS Medium							
		ICS + LABA							
Strauch (2003)[88]	AgD	ICS High	Unclear	Unclear	Low	Low	Low	Low	Low
		ICS + LTRA							
Tal (2002)[89]	AgD	ICS Low	Low	Low	Low	Low	Low	Low	Low
		ICS + LABA							
Thomas (2014)[69]	IPD	ICS Medium	High[i]	High[i]	High[i]	Low	Low	Low	Unclear
		ICS + LABA							
		ICS + LTRA							
Vaessen-Verberne (2010)[70]	IPD	ICS Medium ICS + LABA	Low	Low	Unclear	Low	Low	Low	High[j]
Verberne (1998)[71]	IPD	ICS High	Low	Low	Low	Low	High[k]	Low	High[k]
		ICS + LABA							
Vermeulen (2007)[90]	AgD	ICS Medium (CIC)	Low	Low	Unclear	Low	Low	Low	Low
		ICS Medium (BUD)							

continued

TABLE 14 Risk of bias for included studies with IPD or AgD (*continued*)

Study	Data	Treatment classes	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Visitsunthorn (2011)[91]	AgD	ICS unknown dose	Unclear	Unclear	Unclear	Low	Low	Low	High[g]
		ICS + LTRA							
Wechsler (2019)[72]	IPD	ICS High	Low	Low	Low	Low	Low	Low	High[g]
		ICS Low							
		ICS + LABA							
Woodcock (2013)[73]	IPD	ICS Low + LABA	Low	Low	Low	Low	Low	Low	Low
		ICS Medium + LABA							
Woodcock (2014)[74]	IPD	ICS High	Low	Low	Low	Low	Low	Low	Low
		ICS Low							
Zimmerman (2004)[92]	AgD	ICS Medium ICS + LABA	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

a Response to therapy was assessed by the physician or a designee by comparing the current level of symptoms with those noted at the baseline visit using a 5-point scale. The method can be affected by subjectivity.
b Data could not be included in analyses as insufficient data reported for the first period of crossover.
c Study medication was sourced from commercially available stock and was repackaged and administered according to a computer-generated randomisation scheme provided by the sponsor. No further details.
d Crossover trial with no wash-out period.
e Only 24 of 27 children were included in the analysis (11% of missing outcome data). These three withdrawn children were all in the BUD-placebo group, and two had an exacerbation requiring OCS.
f 8 (11.3%) of 71 randomised patients were dropped out in the first 2 weeks and were not included in the analysis. Patients dropped out were four for each group, and no reasons were provided.
g Possible carry-over effect.
h Lötvall (2014)[56] was included in analyses as two separate studies.
i No peer reviewed publication.
j No methods reported. No protocol was provided by the author.
k Possible bias as discrepancy identified between data and publication that could not be verified due to age of trial and lack of documentation.

Chapter 5 Clinical effectiveness results: primary outcomes

In this chapter, we report the Bayesian NMA results for the primary clinical outcomes of (1) exacerbation and (2) asthma control. The main analyses include the most complete data incorporating both IPD, if available, and AgD otherwise. When only one study was available for a particular pairwise comparison, we estimated the direct treatment effect and CrI using Bayesian logistic regression and conducted Bayesian MA if at least two studies had data available. Full results from both FE and REs NMA are provided in *Appendix 6*, but we focus on results from the best fitting model in the main body of the report. We also conducted the frequentist analyses (logistic regression, IV and MH MA) for comparison but focus on the Bayesian results as pre-specified in our analysis plan. A qualitative and quantitative assessment of potential effect modifiers (see *Chapter 7*) suggested that, on average, there were no important concerns regarding the transitivity assumption for the NMA of exacerbation or asthma control.

Exacerbation network meta-analysis

Inhaled corticosteroid grouped when combined with long-acting β_2-agonist

A total of 39 studies with 8136 patients had data available for the 'exacerbation' outcome. We had IPD for 5349 patients from 26 studies and could extract AgD for 2787 patients from 13 trials. The studies with data available for the NMA provided evidence for 8 treatment classes [ICS Low (23 trials); ICS Medium (15 trials); ICS High (8 trials); ICS + LABA (30 trials); ICS + LTRA (3 trials); LTRA (1 trial); ICS + theophylline (1 trial); placebo (6 trials)] as shown in the network plot (*Figure 3*). For this analysis, where all doses of ICS were grouped together when added to LABA (*Figure 3*; *Tables 15* and *16*), the difference in DIC between the FE and REs NMA is < 5, and we therefore focus the main interpretation of results on the simplest, FE model (*Table 16*).

The direct OR could be estimated for 13 pairwise comparisons (*Table 15*). Overall, for each direct pairwise comparison, there is little difference between results of analyses based on different analytic approaches (*Table 15*). Focusing on the Bayesian FE results, the only direct comparison with a reasonable level of certainty of evidence in terms of magnitude and precision is the comparison ICS Low versus placebo [6 studies, 899 patients, 105 events, OR (95% CrI): 0.41

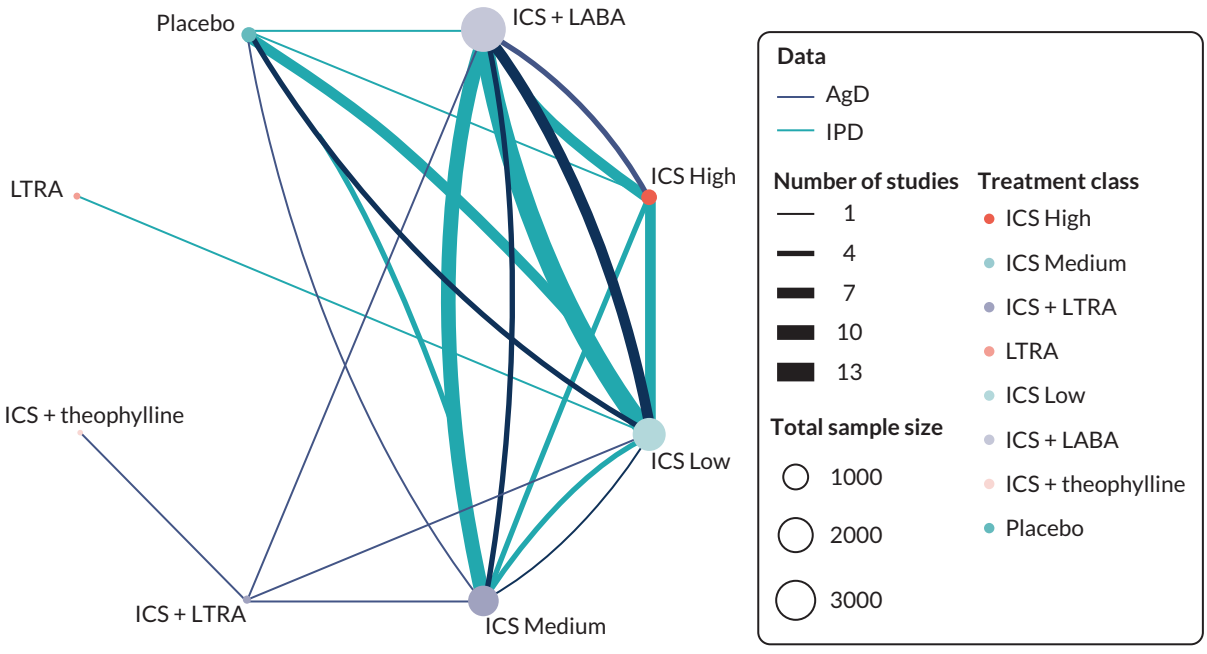

FIGURE 3 Network diagram (IPD and AgD) for exacerbation (a) ICS grouped when combined with LABA.

TABLE 15 Pairwise MA results (IPD and AgD) for exacerbation (a) ICS grouped when combined with LABA

Direct comparison (Treatment 1 vs. Treatment 2)[a]	Data [b]	Author (year) (participants on each treatment)	Studies (*N*)	Participants (*N*)	Events (*N*)	Statistical approach	Heterogeneity	FE model OR (95% CI or CrI)	REs model OR (95% CI or CrI)
ICS L vs. ICS M	IPD AgD	Bleecker (2012)[49] (14 vs. 13) Lötvall (2014)[57] (17 vs. 11) Shapiro (2001)[86] (90 vs. 93) Stempel (2016)[68] (15 vs. 50)	4	136 vs. 167	10 vs. 10	IV MH Bayesian	I^2 = 0%; τ^2 = 0; p = 0.69 I^2 = 0%; τ^2 = 0; p = 0.79 Not provided	1.18 (0.44 to 3.17) 1.20 (0.49 to 2.95) 1.19 (0.46 to 3.03)	1.18 (0.44 to 3.17) 1.20 (0.48 to 2.99) 1.13 (0.00 to 1451.00)
ICS H vs. ICS L	IPD	Bleecker (2012)[49] (29 vs. 14) Stempel (2016)[68] (40 vs. 15) Wechsler (2019)[72] (45 vs. 33) Woodcock (2014)[74] (6 vs. 7)	4	120 vs. 69	8 vs. 11	IV MH Bayesian	I^2 = 0%; τ^2 = 0; p = 0.70 I^2 = 0%; τ^2 = 0; p = 0.55 Not provided	0.33 (0.10 to 1.07) 0.43 (0.17 to 1.10) 0.40 (0.14 to 1.11)	0.33 (0.10 to 1.07) 0.39 (0.14 to 1.08) 0.17 (0.00 to 102.51)
ICS H vs. ICS M	IPD	Bleecker (2012)[49] (29 vs. 13)[c] Stempel (2016)[68] (40 vs. 50)	2	69 vs. 63	3 vs. 2	IV MH Bayesian	I^2 = N/A; τ^2 = N/A; p = N/A I^2 = N/A; τ^2 = N/A; p = N/A Not provided	1.95 (0.31 to 12.25) 1.95 (0.31 to 12.25) 1.92 (0.28 to 15.03)	1.95 (0.31 to 12.25) 1.95 (0.31 to 12.25) 2.03 (0.00 to 28853.89)
ICS L vs. ICS + LABA	IPD AgD	Bateman (2014)[47] (102 vs. 111) Bernstein (2015)[48] (17 vs. 25)[c] Bleecker (2014)[50] (19 vs. 19)[c] Carroll (2010)[51] (17 vs. 22) Lenney (2013)[4] (19 vs. 23) Li (2010)[55] (177 vs. 173) Lötvall (2014)[56] (5 vs. 15)[c] Malone (2005)[83] (102 vs. 101) Morice (2008)[84] (207 vs. 415) Murray (2011)[60] (117 vs. 113) Oliver (2016)[62] (115 vs. 341) Pearlman (2009)[64] (124 vs. 124) Scott (2005)[65] (100 vs. 99) Stempel (2016)[68] (15 vs. 117) Tal (2002)[89] (138 vs. 148) Wechsler (2019)[72] (33 vs. 94)	16	1307 vs. 1940	60 vs. 80	IV MH Bayesian	I^2 = 15%; τ^2 = 0.096; p = 0.29 I^2 = 17%; τ^2 = 0.109; p = 0.27 Not provided	1.37 (0.94 to 2.02) 1.27 (0.89 to 1.82) 1.25 (0.87 to 1.79)	1.33 (0.85 to 2.06) 1.28 (0.82 to 1.98) 1.14 (0.59 to 1.93)

TABLE 15 Pairwise MA results (IPD and AgD) for exacerbation (a) ICS grouped when combined with LABA (*continued*)

Direct comparison (Treatment 1 vs. Treatment 2)[a]	Data [b]	Author (year) (participants on each treatment)	Studies (*N*)	Participants (*N*)	Events (*N*)	Statistical approach	Heterogeneity	FE model OR (95% CI or CrI)	REs model OR (95% CI or CrI)
ICS M vs. ICS + LABA	IPD AgD	Bisgaard (2006)[77] (106 vs. 235) de Blic (2009)[52] (153 vs. 150) Gappa (2009)[54] (133 vs. 129) Heuck (2000)[80] (10 vs. 14) Lötvall (2014)[56] (9 vs. 17) Martin (2020)[58] (5 vs. 6) Murray (2010)[59] (7 vs. 6) Stempel (2016)[67] (813 vs. 818) Stempel (2016)[68] (50 vs. 117) Vaessen-Verberne (2010)[70] (78 vs. 80) Zimmerman (2004)[92] (101 vs. 201)	11	1465 vs. 1773	136 vs. 16w3	IV MH Bayesian	I^2 = 0%; τ^2 = 0; p = 0.80 I^2 = 0%; τ^2 = 0; p = 0.72 Not provided	1.16 (0.90 to 1.50) 1.18 (0.92 to 1.51) 1.19 (0.92 to 1.52)	1.16 (0.90 to 1.50) 1.18 (0.92 to 1.52) 1.26 (0.85 to 2.12)
ICS H vs. ICS + LABA	IPD AgD	Akpinarli (1999)[75] (16 vs. 16)[c] O' Byrne (2014)[61] (7 vs. 3)[c] Russell (1995)[85] (107 vs. 99) Stempel (2016)[68] (40 vs. 117) Verberne (1998)[71] (117 vs. 60) Wechsler (2019)[72] (45 vs. 94)	6	332 vs. 389	50 vs. 48	IV MH Bayesian	I^2 = 0%; τ^2 = 0; p = 0.92 I^2 = 0%; τ^2 = 0; p = 0.92 Not provided	0.95 (0.60 to 1.51) 0.95 (0.60 to 1.51) 0.96 (0.61 to 1.52)	0.95 (0.60 to 1.51) 0.95 (0.60 to 1.51) 0.94 (0.39 to 2.25)
ICS L vs. ICS + LTRA	AgD	Lenney (2013)[4] (19 vs. 21)	1	19 vs. 21	4 vs. 3	Frequentist logistic regression: 1.60 (0.31 to 9.21) Bayesian logistic regression (Stan): 1.49 (0.32 to 8.85)			
LTRA vs. ICS L	IPD	Fitzpatrick (2016)[53] (30 vs. 30)	1	30 vs. 30	8 vs. 3	Frequentist logistic regression: 3.29 (0.84 to 16.28) Bayesian logistic regression (Stan): 3.32 (0.86 to 13.30)			
ICS M vs. ICS + LTRA	AgD	Jat (2006)[81] (33 vs. 30)	1	33 vs. 30	3 vs. 10	Frequentist logistic regression: **0.20 (0.04** to **0.75)** Bayesian logistic regression (Stan): **0.22 (0.05** to **0.76)**			
ICS + LTRA vs. ICS + LABA	AgD	Lenney (2013)[4] (23 vs. 21)	1	23 vs. 21	3 vs. 7	Frequentist logistic regression: 0.38 (0.07 to 1.62) Bayesian logistic regression (Stan): 0.41 (0.07 to 1.58)			
ICS + theophylline vs. ICS + LTRA	AgD	Kondo (2006)[82] (36 vs. 39)	1	36 vs. 39	1 vs. 1	Frequentist logistic regression: 1.09 (0.04 to 28.22) Bayesian logistic regression (Stan): 1.11 (0.10 to 13.60)			

continued

TABLE 15 Pairwise MA results (IPD and AgD) for exacerbation (a) ICS grouped when combined with LABA (*continued*)

Direct comparison (Treatment 1 vs. Treatment 2)[a]	Data [b]	Author (year) (participants on each treatment)	Studies (*N*)	Participants (*N*)	Events (*N*)	Statistical approach	Heterogeneity	FE model OR (95% CI or CrI)	REs model OR (95% CI or CrI)
ICS L vs. placebo	IPD AgD	Berger (2006)[76] (197 vs. 99) Bleecker (2012) (14 vs. 13)[49] Lötvall (2014)[57] (17 vs. 18) Bleecker (2014)[50] (19 vs. 23)[c] Oliver (2016)[63] (253 vs. 65) Shapiro (2001)[86] (90 vs. 91)	6	590 vs. 309	50 vs. 55	IV MH Bayesian	I^2 = 40%; τ^2 = 0.337; p = 0.16 I^2 = 44%; τ^2 = 0.350; p = 0.13 Not provided	**0.42 (0.26** to **0.66)** **0.43 (0.28** to **0.67)** **0.41 (0.26** to **0.64)**	**0.41 (0.17** to **0.99)** 0.45 (0.19 to 1.04) 0.38 (0.02 to 8.17)
ICS M vs. placebo	IPD AgD	Bleecker (2012)[49] (13 vs. 13)[c] Lötvall (2014)[57] (11 vs. 18) Shapiro (2001)[86] (93 vs. 91)	3	117 vs. 122	8 vs. 11	IV MH Bayesian	I^2 = 0%; τ^2 = 0; p = 0.61 I^2 = 0%; τ^2 = 0; p = 0.82 Not provided	0.74 (0.28 to 1.96) 0.73 (0.29 to 1.87) 0.72 (0.27 to 1.90)	0.74 (0.28 to 1.96) 0.74 (0.29 to 1.88) 0.14 (0.00 to 108.85)
ICS H vs. placebo	IPD	Bleecker (2012)[50] (13 vs. 13)[c]	1	13 vs. 13	0 vs. 0	Frequentist logistic regression: Not estimable Bayesian logistic regression (Stan): Not estimable			
ICS + LABA vs. placebo	IPD	Bleecker (2014)[50] (19 vs. 23)[c]	1	19 vs. 23	0 vs. 0	Frequentist logistic regression: Not estimable Bayesian logistic regression (Stan): Not estimable			

H, high; IV, inverse variance; L, low; M, medium; MH, Mantel–Haenszel; N/A, not available.
a OR > 1 favours treatment 2 (the probability of having exacerbation was modelled). Results with CrIs or CIs that exclude the OR value of 1 are highlighted in bold.
b All available data included (IPD and AgD wherever available).
c Studies with no events in both arms.

TABLE 16 Bayesian NMA (FE) results (IPD and AgD) for exacerbation (a) ICS grouped when combined with LABA

	TRT 2							
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS + LABA**	**ICS + LTRA**	**LTRA**	**ICS + theophylline**	**Placebo**
ICS Low	○	1.11 (0.75; 1.63) *1.19 (0.46; 3.03)*	1.42 (0.84; 2.46) *2.48 (0.90; 7.10)*	1.27 (0.90; 1.79) *1.25 (0.87; 1.79)*	0.75 (0.30; 1.90) *1.49 (0.32; 8.85)*[a]	0.28 (0.05; 1.17) *0..33 (0.07; 1.23)*[a]	0.74 (0.02; 27.66)	**0.43** **(0.28; 0.66)** ***0.41 (0.26; 0.64)***
ICS Medium	0.90 (0.61; 1.34) *0.84 (0.33; 2.18)*	○	1.30 (0.78; 2.14) *0.52 (0.07; 3.60)*	1.15 (0.90; 1.48) *1.19 (0.92; 1.52)*	0.68 (0.28; 1.65) ***0.22 (0.05;0.76)***[a]	0.25 (0.05; 1.12)	0.68 (0.02; 24.53)	**0.39** **(0.22; 0.66)** *0.72 (0.27; 1.90)*
ICS High	0.70 (0.41; 1.20) *0.40 (0.14; 1.11)*	0.77 (0.47; 1.28) *1.92 (0.28; 15.03)*	○	0.90 (0.57; 1.40) *0.96 (0.61; 1.52)*	0.52 (0.19; 1.45)	**0.20** **(0.04; 0.92)**	0.52 (0.01; 19.69)	**0.30** **(0.15; 0.58)** *Not estimable*[b]
ICS + LABA	0.79 (0.56; 1.11) *0.80 (0.56; 1.15)*	0.87 (0.68; 1.11) *0.84 (0.66; 1.08)*	1.12 (0.71; 1.77) *1.04 (0.66; 1.65)*	○	0.58 (0.24; 1.45) *2.46 (0.59; 12.18)*[a]	**0.22** **(0.04; 0.95)**	0.58 (0.02; 21.76)	**0.33** **(0.20; 0.56)** *Not estimable*[b]
ICS + LTRA	1.64 (0.53; 3.35) *0.67 (0.13; 3.22)*[a]	1.48 (0.61; 3.60) ***4.48 (1.30; 21.12)***[a]	1.92 (0.69; 5.16)	1.72 (0.69; 4.14) *0.41 (0.07; 1.58)*[a]	○	0.37 (0.06; 2.08)	1.00 (0.03; 32.14) *1.00 (0.08; 12.55)*[a]	0.57 (0.21; 1.54)
LTRA	3.60 (0.85; 18.36) *3.32 (0.86; 13.30)*[a]	3.97 (0.90; 21.33)	**5.10** **(1.08; 28.50)**	**4.57** **(1.05; 24.29)**	2.69 (0.48; 16.78)	○	2.66 (0.05; 135.95)	1.54 (0.33; 8.33)
ICS+ theophylline	1.35 (0.04; 49.40)	1.48 (0.04; 54.60)	1.92 (0.05; 72.97)	1.72 (0.05; 64.07)	1.00 (0.03; 33.45) *1.11 (0.10; 13.60)*[a]	0.38 (0.01; 18.73)	○	0.57 (0.02; 21.76)
Placebo	**2.34** **(1.52; 3.63)** ***2.46 (1.55; 3.86)***	**2.59** **(1.51; 4.48)** *1.39 (0.53; 3.74)*	**3.35** **(1.72; 6.55)** *Not estimable*[b]	**3.00** **(1.79; 5.05)** *Not estimable*[b]	1.75 (0.65; 4.81)	0.65 (0.12; 3.00)	1.75 (0.05; 66.02)	○

a Estimates from Bayesian logistic regression models (Stan) (one study).
b Not estimable: zero events in both arms.

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
39 studies, 8136 patients, 649 events — reference treatment is ICS + LABA, DIC: 2296.3, residual deviance: 2254.1 (on 5377 data points).
OR > 1 favours TRT 2 (the probability of having exacerbation was modelled). Results with CrIs that exclude the OR value of 1 are highlighted in bold.
Direct results, where applicable, are in italic.

(0.26 to 0.64)], which suggests an advantage for ICS Low. The direct evidence also suggests an advantage to ICS Medium compared to ICS + LTRA [0.22 (0.05 to 0.76)], but this evidence comes from one small study (13 events out of 66 randomised).

For the FE NMA (*Table 16*), there is strong evidence in favour of ICS Low [0.43 (0.28 to 0.66)], ICS medium [0.39 (0.22 to 0.66)], ICS High [0.30 (0.15 to 0.58)], ICS + LABA [0.33 (0.20 to 0.56)] when compared against placebo. There is also evidence in favour of ICS High [0.20 (0.04 to 0.92)] and ICS + LABA [0.22 (0.04 to 0.95)] when compared against LTRA and to a lesser extent in favour of ICS Low [0.28 (0.06 to 1.17)] and ICS Medium [0.25 (0.05 to 1.12)] albeit with both these CrIs including unity. For all other comparisons, the 95% CrIs for the OR are very wide and include unity, making it difficult to be confident about the direction of the effect.

The posterior ranking (*Figure 4*) shows ICS High and ICS + LABA are most likely to have the best ranking for exacerbation [median (IQR) ranking: 2 (1,3) for ICS High; 2 (2,3) for ICS + LABA], while LTRA [8 (7,8)] and placebo [7 (6,7)] appear appreciably less attractive than other treatments. However, there is uncertainty around these posterior ranks, particularly for ICS + theophylline, as seen by the wide intervals (*Figure 4*) that overlap for many of the treatment classes.

Comparison of the deviance and DIC statistics of the consistency and inconsistency models provides a global test of consistency. We compared residual deviance and DIC between the NMA model that assumes consistency [residual deviance: 2254.1 (on 5377 data points); DIC: 2296.3] and the UME model [residual deviance: 2245.3 (on 5377 data points); DIC: 2289.9]. The difference in DIC is > 5 (difference is 6.4), and the residual deviance is lower for the UME model, suggesting that there is disagreement between the direct and indirect evidence that is used to estimate the ORs; therefore, results from the NMA consistency model (*Table 16*) should be viewed cautiously. The estimated treatment effects (log ORs) are reasonably similar for both models (see *Appendix 7*, *Table 52*), in that there is overlap in the 95% CrIs for all comparisons. Similar inferences can be drawn regarding the effectiveness of treatments from pairwise MA (i.e. the direct evidence) and the NMA (i.e. from *Table 16* direct and indirect evidence combined); therefore, although inconsistency exists, it does not appear to be substantial enough to affect treatment recommendations for patients.

Inhaled corticosteroid stratified by dose when combined with long-acting β_2-agonist

A total of 40 studies with 8168 patients had data available for the 'exacerbation' outcome where we could include ICS dose stratified as Low, Medium, High when combined with LABA. We had IPD for 5381 patients (328 events) from 27 trials and AgD for 2787 patients (321 events) from 13 trials. Compared to analysis (a), we could include one additional trial [Woodcock (2013)],[73] which randomised patients between ICS Low + LABA and ICS Medium + LABA; therefore, it could not be included in analysis (a) as both arms contributed to the ICS + LABA group. The studies with data available for the NMA provided evidence for 10 treatment classes [ICS Low (23 trials); ICS Medium (15 trials); ICS High (8 trials); ICS Low + LABA (24 trials); ICS Medium + LABA (8 trials); ICS High + LABA (7 trials); ICS + LTRA (3 trials); LTRA (1 trial); ICS + theophylline (1 trial); placebo (6 trials)] as shown in the network plot (*Figure 5*). The difference in DIC between the FE model and REs model is > 5, and we focus the interpretation of results on the REs model (*Table 17*).

The NMA provides further support for the beneficial effect of ICS Low [0.42 (0.18 to 0.91)], ICS Medium [0.33 (0.13 to 0.82)], ICS High [0.31 (0.09 to 0.98)], ICS Low + LABA [0.35 (0.14 to 0.84)], ICS Medium + LABA [0.18 (0.06 to 0.49)] compared to placebo (*Table 17*). There is evidence that ICS Medium + LABA is better than ICS Low [0.44 (0.19 to 0.90)], and LTRA [0.12 (0.01 to 0.84)], and to a lesser extent compared to ICS Medium [0.56 (0.27 to 1.04)] and ICS Low + LABA [0.52 (0.23 to 1.05)].

In support of these results, the posterior ranking suggests that ICS Medium + LABA [rank median (IQR): 1 (1,2)] is the most likely treatment to be best for exacerbation, while LTRA [9 (8,10)] and placebo [9 (8,9)] would be least preferred (*Figure 6*). In between these extremes, there are similar posterior rankings across the four treatment classes of ICS Low + LABA [rank medium (IQR): 4 (3,6)], ICS Medium [rank medium (IQR): 4 (3,5)], ICS High [rank medium (IQR): 4 (2, 5)] and ICS High + LABA [rank medium (IQR): 5 (4,7)] with a slightly higher rank (less favourable treatment) for ICS Low [rank medium (IQR): 6 (5,7)], ICS + LTRA [7 (5,8)] and ICS + theophylline [7 (1,10)]. However, we cannot be certain about the ranking of every treatment in the network, as shown by the wide and overlapping intervals (*Figure 6*).

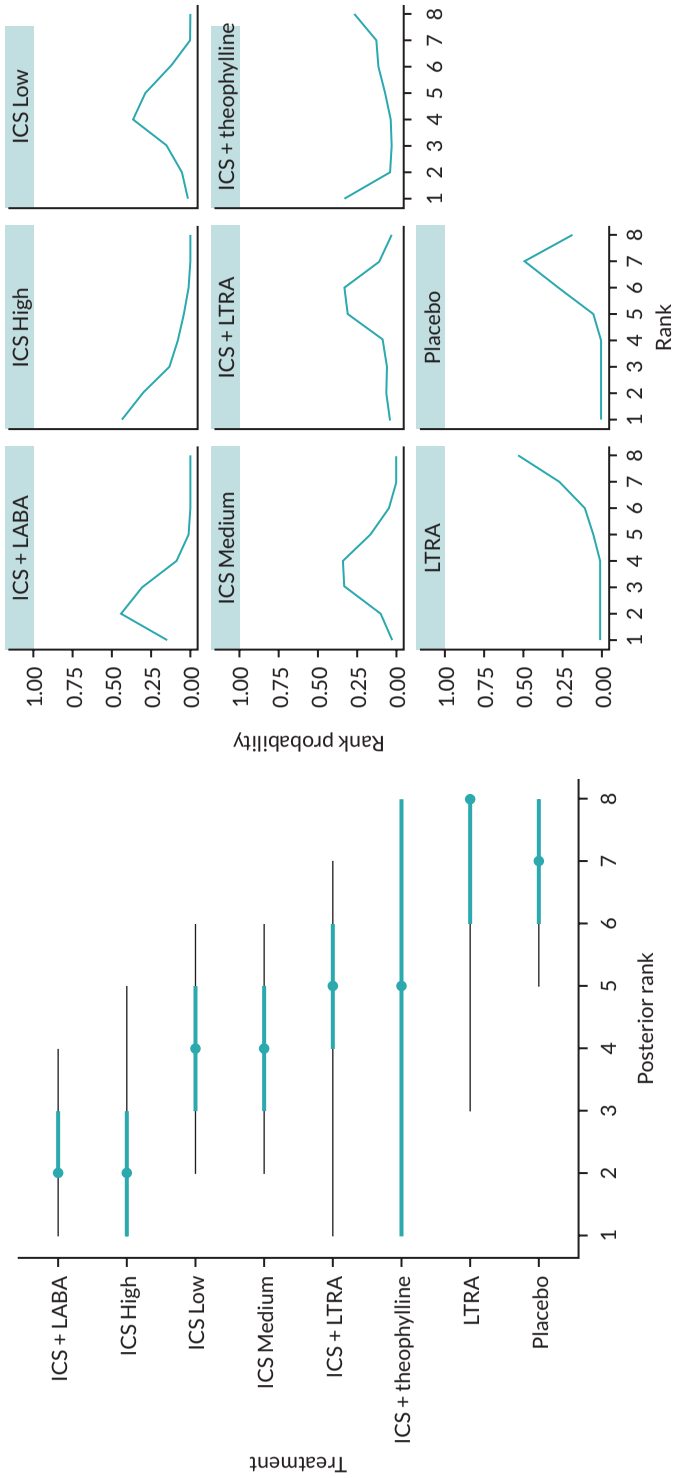

FIGURE 4 Ranks for the FE NMA (ICS grouped when combined with LABA) for exacerbation outcome. (a) Posterior treatment rankings from fitted NMA model. (b) Rank probability plots from fitted NMA model. Note: Rank median (point), IQR (bold line), 95% interval (thin line). Lower rank is better.

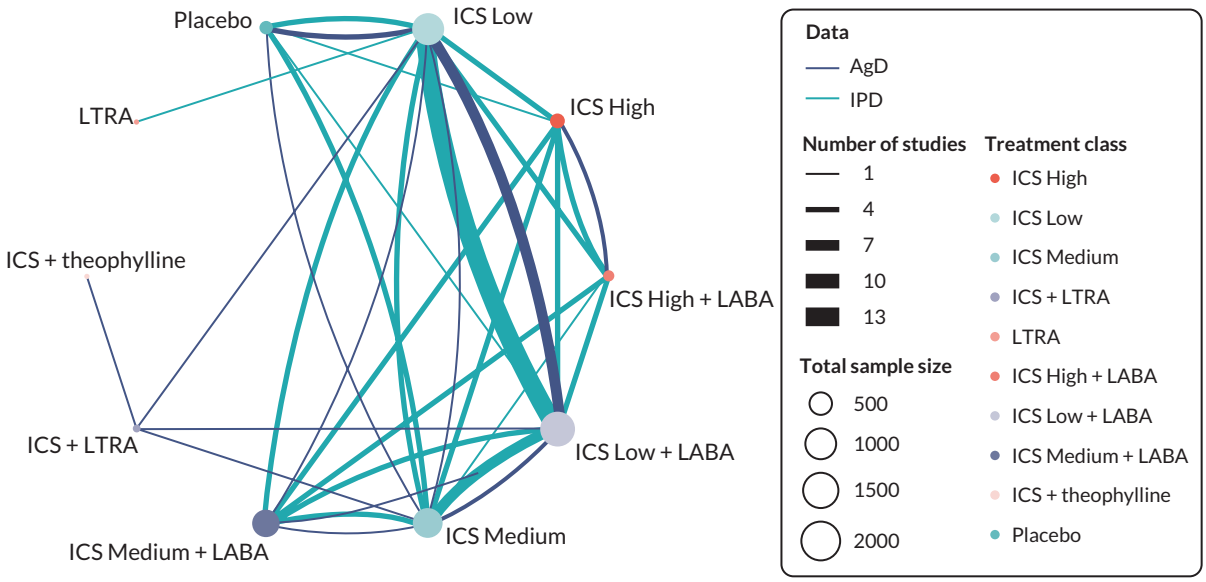

FIGURE 5 Network diagram (IPD and AgD) for exacerbation (b) ICS stratified by dose when combined with LABA.

There is little difference in residual deviance and DIC between the NMA consistency model [residual deviance: 2234.8 (on 5410 data points); DIC: 2290.6] and the UME model [residual deviance: 2233.1 (on 5410 data points); DIC: 2291.5] supporting the use of the consistency model. For each comparison, there is considerable overlap of the 95% CrIs of the treatment effect estimated by each model (see *Appendix 7*, *Table 53*), and the clinical conclusions drawn from each model in terms of effectiveness are analogous. Therefore, there is no evidence of inconsistency in the network.

Analysis of individual compounds

We attempted to conduct a NMA for individual compounds, but reliable estimates could not be obtained due to the sparse nature of the network with few studies and exacerbation events contributing data to particular nodes in the network.

Sensitivity analysis – exacerbation definition

Our primary analyses included exacerbation data that had been collected within the trials using different approaches: trials with a well-defined pre-specified outcome measure of exacerbation (systematic data collection) as well as trials which had measured exacerbation as part of AE data collection. We conducted two sensitivity analyses to assess whether results were robust to the data collection approach and excluded 11 trials (2163 patients, 130 events), for which exacerbation data had been identified in data sets of AEs rather than as a pre-defined outcome measure for the trial. For the first sensitivity analysis (a) ICS grouped when combined with LABA, similar results in magnitude and direction of effect estimates with overlapping CrIs are seen for most comparisons (*Table 18*) compared to the corresponding full analysis (*Table 16*) lending support to the robustness of the results and conclusions drawn from the full analysis. For the second sensitivity analysis (b) with ICS stratified by dose when combined with LABA, we again see similar results in the direction of the effect (*Table 19*) for most comparisons compared to the corresponding full analysis (*Table 17*), but some effect estimates are more extreme, and CrIs do not include unity for the comparison of ICS Medium + LABA to ICS Low + LABA [OR (95% CrI) 0.33 (0.09 to 0.90)] and ICS Medium + LABA to ICS High + LABA [0.31 (0.08 to 0.98)]. The clinical conclusions from the sensitivity analysis lend further support to the inference that ICS Medium + LABA is more effective than ICS Low + LABA or ICS High + LABA.

Data availability bias

To explore the potential for data availability bias, we compared OR estimates and 95% CrI from the primary analyses that included all available IPD and AgD (*Tables 16* and *17*) against the corresponding sensitivity analysis excluding 13 trials (2787 participants and 321 events) with only AgD (*Tables 20* and *21*). Where a comparison can be made, the conclusions are consistent. However, the OR estimates for comparisons against placebo are more extreme from the IPD only analyses (*Tables 20* and *21*), a trend which might be expected if IPD was more likely to be provided when

TABLE 17 Bayesian REs NMA results (IPD and AgD) for exacerbation (b) ICS stratified by dose when combined with LABA

	TRT 2									
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS Low + LABA**	**ICS Medium + LABA**	**ICS High + LABA**	**ICS + LTRA**	**LTRA**	**ICS + theophylline**	**Placebo**
ICS Low	○	1.28 (0.67; 2.44)	1.35 (0.54; 3.39)	1.20 (0.73; 1.95)	**2.29 (1.11; 5.21)**	1.06 (0.41; 2.77)	0.80 (0.23; 2.75)	0.28 (0.04; 1.68)	0.74 (0.01; 41.26)	**0.42 (0.18; 0.91)**
ICS Medium	0.78 (0.41; 1.49)	○	1.05 (0.41; 2.72)	0.93 (0.53; 1.67)	1.79 (0.96; 3.74)	0.83 (0.33; 2.18)	0.63 (0.19; 2.10)	0.21 (0.03; 1.45)	0.58 (0.01; 30.88)	**0.33 (0.13; 0.82)**
ICS High	0.74 (0.30; 1.84)	0.95 (0.37; 2.44)	○	0.89 (0.35; 2.18)	1.70 (0.68; 4.62)	0.79 (0.36; 1.72)	0.59 (0.14; 2.53)	0.20 (0.02; 1.52)	0.55 (0.01; 32.46)	**0.31 (0.09; 0.98)**
ICS Low + LABA	0.84 (0.51; 1.38)	1.07 (0.60; 1.90)	1.13 (0.46; 2.83)	○	1.92 (0.95; 4.31)	0.89 (0.35; 2.27)	0.67 (0.20; 2.27)	0.23 (0.03; 1.51)	0.63 (0.01; 35.16)	**0.35 (0.14; 0.84)**
ICS Medium + LABA	**0.44 (0.19; 0.90)**	0.56 (0.27; 1.04)	0.59 (0.22; 1.46)	0.52 (0.23; 1.05)	○	0.46 (0.17; 1.17)	0.35 (0.09; 1.27)	**0.12 (0.01; 0.84)**	0.32 (0.01; 18.17)	**0.18 (0.06; 0.49)**
ICS High + LABA	0.94 (0.36; 2.41)	1.21 (0.46; 3.03)	1.27 (0.58; 2.80)	1.13 (0.44; 2.83)	2.16 (0.85; 5.87)	○	0.76 (0.18; 3.25)	0.26 (0.03; 1.99)	0.70 (0.01; 40.85)	0.39 (0.12; 1.26)
ICS + LTRA	1.25 (0.36; 4.35)	1.60 (0.48; 5.26)	1.68 (0.39; 7.17)	1.49 (0.44; 4.90)	2.86 (0.79; 10.91)	1.32 (0.31; 5.58)	○	0.34 (0.03; 3.03)	0.93 (0.02; 41.26)	0.53 (0.12; 2.14)
LTRA	3.63 (0.59; 24.78)	4.66 (0.69; 36.97)	4.90 (0.66; 42.95)	4.35 (0.66; 32.14)	**8.33 (1.20; 69.41)**	3.86 (0.50; 34.12)	2.92 (0.33; 28.79)	○	2.72 (0.03; 230.44)	1.52 (0.21; 12.18)
ICS + theophylline	1.35 (0.02; 74.44)	1.72 (0.03; 95.58)	1.82 (0.03; 109.95)	1.60 (0.03; 86.49)	3.10 (0.06; 181.27)	1.42 (0.02; 84.77)	1.07 (0.02; 47.94)	0.37 (0.00; 29.67)	○	0.57 (0.01; 31.82)
Placebo	**2.39 (1.09; 5.42)**	**3.03 (1.22; 7.77)**	**3.22 (1.02; 10.70)**	**2.86 (1.19; 7.10)**	**5.47 (2.03; 17.12)**	2.53 (0.79; 8.58)	1.90 (0.47; 8.17)	0.66 (0.08; 4.71)	1.77 (0.03; 100.48)	○

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
OR (95% CrI) (40 studies, 8168 participants, 649 events). Reference treatment: ICS Low – DIC: 2290.6; residual deviance: 2234.8 (on 5410 data points). OR > 1 favours TRT 2 (the probability of having exacerbation was modelled). Results with CrIs that exclude the OR value of 1 are highlighted in bold.

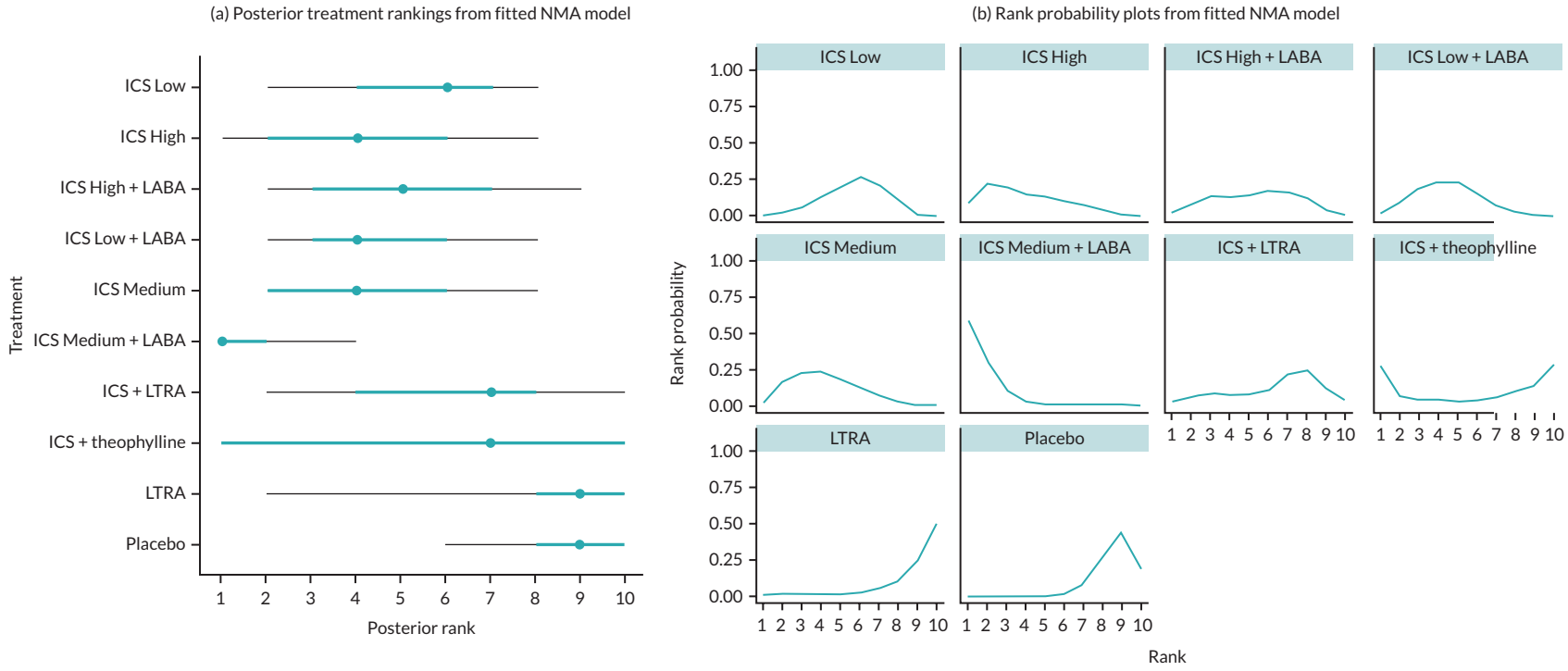

FIGURE 6 Ranks for the REs NMA (b) ICS stratified by dose when combined with LABA for exacerbation. (a) Posterior treatment rankings from fitted NMA model. (b) Rank probability plots from fitted NMA model. Note: Rank median (point), IQR (bold line), 95% interval (thin line). Lower rank is better.

TABLE 18 Sensitivity analysis (a) excluding exacerbation events identified from AE data: Bayesian NMA (FE) results (IPD and AgD) for the exacerbation outcome (ICS grouped when combined with LABA)

	TRT 2							
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS + LABA**	**ICS + LTRA**	**LTRA**	**ICS + theophylline**	**Placebo**
ICS Low	○	1.36 (0.83; 2.23)	1.73 (0.90; 3.32)	1.39 (0.90; 2.16)	0.83 (0.32; 2.18)	N/A	N/A	**0.32 (0.19; 0.53)**
ICS Medium	0.73 (0.45; 1.21)	○	1.27 (0.70; 2.32)	1.02 (0.79; 1.32)	0.61 (0.24; 1.51)	N/A	N/A	**0.24 (0.12; 0.48)**
ICS High	0.58 (0.30; 1.11)	0.79 (0.43; 1.42)	○	0.80 (0.46; 1.38)	0.48 (0.17; 1.35)	N/A	N/A	**0.19 (0.08; 0.42)**
ICS + LABA	0.72 (0.46; 1.11)	0.98 (0.76; 1.27)	1.25 (0.73; 2.16)	○	0.59 (0.24; 1.48)	N/A	N/A	**0.23 (0.12; 0.44)**
ICS + LTRA	1.21 (0.46; 3.13)	1.63 (0.66; 4.14)	2.10 (0.74; 6.05)	1.68 (0.68; 4.18)	○	N/A	N/A	0.39 (0.13; 1.15)
LTRA	N/A	N/A	N/A	N/A	N/A	○	N/A	N/A
ICS + theophylline	N/A	N/A	N/A	N/A	N/A	N/A	○	N/A
Placebo	**3.10 (1.88; 5.16)**	**4.18 (2.10; 8.50)**	**5.37 (2.36; 12.18)**	**4.31 (2.25; 8.33)**	2.56 (0.87; 7.61)	N/A	N/A	○

N/A, not available.

Notes

The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).

28 studies, 5973 patients, 519 events – reference treatment is ICS + LABA, DIC: 2160.7; residual deviance: 2132.2 (on 4988 data points); OR > 1 favours TRT 2 (the probability of having exacerbation was modelled). Results with CrIs that exclude the OR value of one are highlighted in bold.

TABLE 19 Sensitivity analysis (b) excluding exacerbation events identified from AE data: Bayesian REs NMA results (IPD and AgD) for exacerbation (ICS stratified by dose when combined with LABA)

	TRT 2									
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS Low + LABA**	**ICS Medium + LABA**	**ICS High + LABA**	**ICS + LTRA**	**LTRA**	**ICS + theophylline**	**Placebo**
ICS Low	○	2.34 (0.96; 6.36)	1.93 (0.64; 5.93)	1.34 (0.70; 2.53)	**4.10 (1.36; 15.03)**	1.26 (0.41; 4.18)	1.11 (0.28; 4.76)	N/A	N/A	**0.25 (0.07; 0.77)**
ICS Medium	0.43 (0.16; 1.04)	○	0.83 (0.25; 2.59)	0.58 (0.23; 1.21)	1.75 (0.69; 5.05)	0.54 (0.16; 1.75)	0.47 (0.12; 1.88)	N/A	N/A	**0.11 (0.02; 0.43)**
ICS High	0.52 (0.17; 1.55)	1.21 (0.39; 4.01)	○	0.70 (0.23; 1.97)	2.12 (0.68; 7.92)	0.66 (0.23; 1.93)	0.58 (0.11; 3.03)	N/A	N/A	**0.13 (0.02; 0.59)**
ICS Low + LABA	0.75 (0.39; 1.42)	1.73 (0.83; 4.26)	1.43 (0.51; 4.44)	○	**3.06 (1.11; 10.80)**	0.94 (0.32; 3.03)	0.83 (0.22; 3.35)	N/A	N/A	**0.19 (0.05; 0.68)**
ICS Medium + LABA	**0.24 (0.07; 0.73)**	0.57 (0.20; 1.45)	0.47 (0.13; 1.48)	**0.33 (0.09; 0.90)**	○	**0.31 (0.08; 0.98)**	0.27 (0.05; 1.30)	N/A	N/A	**0.06 (0.01; 0.29)**
ICS High + LABA	0.79 (0.24; 2.44)	1.84 (0.57; 6.17)	1.52 (0.52; 4.35)	1.06 (0.33; 3.10)	**3.22 (1.02; 12.06)**	○	0.88 (0.17; 4.81)	N/A	N/A	**0.20 (0.04; 0.95)**
ICS + LTRA	0.90 (0.21; 3.56)	2.12 (0.53; 8.58)	1.73 (0.33; 9.03)	1.21 (0.30; 4.53)	3.71 (0.77; 20.29)	1.14 (0.21; 6.05)	○	N/A	N/A	0.23 (0.03; 1.34)
LTRA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	○	N/A	N/A
ICS + theophylline	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	○	N/A
Placebo	**3.94 (1.30; 13.60)**	**9.12 (2.34; 45.15)**	**7.54 (1.68; 40.45)**	**5.26 (1.48; 20.91)**	**15.96 (3.46; 98.49)**	**4.95 (1.05; 28.50)**	4.35 (0.75; 29.08)	N/A	N/A	○

N/A, not available.

Notes

The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).

OR (95% CrI) (29 studies, 6005 participants, 519 events). Reference treatment: ICS Low – DIC: 2152.5; residual deviance: 2113 (on 5020 data points). OR > 1 favours TRT 2 (the probability of having exacerbation was modelled). Results with CrIs that exclude the OR value of one are highlighted in bold.

TABLE 20 Sensitivity analysis to explore data availability bias: Bayesian FE NMA results for the exacerbation outcome (including ICS grouped when combined with LABA) IPD trials only

	TRT 2							
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS + LABA**	**ICS + LTRA**	**LTRA**	**ICS + theophylline**	**Placebo**
ICS Low	○	1.09 (0.61; 1.93)	1.54 (0.79; 3.03)	1.23 (0.75; 1.99)	N/A	0.28 (0.05; 1.17)	N/A	**0.12 (0.02; 0.59)**
ICS Medium	0.91 (0.52; 1.63)	○	1.40 (0.76; 2.59)	1.13 (0.84; 1.52)	N/A	0.25 (0.05; 1.21)	N/A	**0.11 (0.02; 0.57)**
ICS High	0.65 (0.33; 1.27)	0.71 (0.39; 1.31)	○	0.80 (0.47; 1.36)	N/A	**0.18 (0.03; 0.90)**	N/A	**0.08 (0.01; 0.44)**
ICS + LABA	0.81 (0.50; 1.34)	0.89 (0.66; 1.20)	1.25 (0.73; 2.14)	○	N/A	0.23 (0.04; 1.03)	N/A	**0.09 (0.01; 0.50)**
ICS + LTRA	N/A	N/A	N/A	N/A	○	N/A	N/A	N/A
LTRA	3.60 (0.85; 18.36)	3.97 (0.83; 22.20)	**5.53 (1.11; 31.50)**	4.44 (0.97; 24.05)	N/A	○	N/A	0.42 (0.04; 4.18)
ICS + theophylline	N/A	N/A	N/A	N/A	N/A	N/A	○	N/A
Placebo	**8.58 (1.68; 52.46)**	**9.39 (1.75; 60.95)**	**13.20 (2.29; 88.23)**	**10.59 (1.99; 67.36)**	N/A	2.36 (0.24; 23.57)	N/A	○

N/A, not available.

Notes

The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
OR (95% CrI) (26 studies, 5349 participants, 328 events). Reference treatment: ICS Low – DIC: 2243.4; residual deviance: 2215.5 (on 5349 data points).
OR > 1 favours TRT 2 (the probability of having exacerbation was modelled). Results with CrIs that exclude the OR value of one are highlighted in bold.

TABLE 21 Sensitivity analysis to explore data availability bias: Bayesian FE NMA results for exacerbation (ICS stratified by dose when combined with LABA) IPD trials only

	TRT 2									
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS Low + LABA**	**ICS Medium + LABA**	**ICS High + LABA**	**ICS + LTRA**	**LTRA**	**ICS + theophylline**	**Placebo**
ICS Low	○	1.82 (0.87; 3.78)	1.67 (0.76; 3.63)	1.32 (0.79; 2.20)	**2.32 (1.08; 4.90)**	1.04 (0.47; 2.29)	N/A	0.28 (0.06; 1.21)	N/A	**0.12 (0.02; 0.59)**
ICS Medium	0.55 (0.26; 1.15)	○	0.91 (0.44; 1.93)	0.73 (0.39; 1.35)	1.27 (0.90; 1.77)	0.57 (0.27; 1.22)	N/A	**0.15 (0.03; 0.79)**	N/A	**0.07 (0.01; 0.38)**
ICS High	0.60 (0.28; 1.31)	1.09 (0.52; 2.29)	○	0.79 (0.38; 1.65)	1.39 (0.67; 2.92)	0.63 (0.34; 1.16)	N/A	**0.17 (0.03; 0.88)**	N/A	**0.07 (0.01; 0.42)**
ICS Low + LABA	0.76 (0.45; 1.26)	1.38 (0.74; 2.53)	1.26 (0.61; 2.61)	○	1.75 (0.91; 3.32)	0.79 (0.37; 1.65)	N/A	**0.21 (0.04; 0.98)**	N/A	**0.09 (0.01; 0.49)**
ICS Medium + LABA	**0.43 (0.20; 0.92)**	0.79 (0.57; 1.11)	0.72 (0.34; 1.49)	0.57 (0.30; 1.09)	○	**0.45 (0.21; 0.96)**	N/A	**0.12 (0.02; 0.64)**	N/A	**0.05 (0.01; 0.30)**
ICS High + LABA	0.96 (0.44; 2.12)	1.75 (0.82; 3.74)	1.60 (0.86; 2.97)	1.27 (0.61; 2.69)	**2.23 (1.04; 4.71)**	○	N/A	0.27 (0.04; 1.42)	N/A	**0.11 (0.02; 0.68)**
ICS + LTRA	N/A	N/A	N/A	N/A	N/A	N/A	○	N/A	N/A	N/A
LTRA	3.60 (0.83; 18.17)	**6.55 (1.26; 39.25)**	**5.99 (1.14; 36.23)**	**4.81 (1.02; 26.05)**	**8.33 (1.55; 50.40)**	3.74 (0.70; 22.65)	N/A	○	N/A	0.43 (0.04; 4.22)
ICS + Theophylline	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	○	N/A
Placebo	**8.41 (1.70; 52.98)**	**15.33 (2.66; 109.95)**	**14.01 (2.39; 100.48)**	**11.13 (2.05; 75.94)**	**19.49 (3.35; 141.17)**	**8.76 (1.48; 62.18)**	N/A	2.34 (0.24; 23.57)	N/A	○

N/A, not available.

Notes

The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).

OR (95% CrI) (27 studies, 5381 patients, 328 events). Reference treatment: ICS Low – DIC: 2242.3; residual deviance: 2212.7 (on 5381 data points). OR > 1 favours TRT 2 (the probability of having exacerbation was modelled). Results with CrIs that exclude the OR value of 1 are highlighted in bold.

results were more strongly in favour of an active treatment compared to placebo. We compared risk of bias and characteristics between trials that provided IPD and trials with only AgD but could not ascertain any clear differences. Assessment of risk of bias in the trials with only AgD was more often 'unclear' than in the IPD studies. We cannot rule out the possibility of data availability bias but have tried to mitigate this risk by including both IPD and AgD in the primary analysis.

Asthma control network meta-analysis

Inhaled corticosteroid grouped when combined with long-acting β_2-agonist

A total of 15 studies with 2998 patients had data available for the 'asthma control' outcome with a total of 2433 patients experiencing good/total asthma control at their last follow-up visit according to the ACT/ACQ test (these counted as events, representing a favourable outcome for the patient, in the analysis). All data for this analysis came from studies that had provided IPD, as none of the publications provided usable AgD for this outcome. The studies with data available for the NMA provided evidence for seven treatment classes (ICS Low; ICS Medium; ICS High; ICS + LABA; ICS + LTRA; LTRA; placebo), as shown in the network plot (*Figure 7*), with treatment effects estimable for 13 pairwise comparisons using direct head-to-head evidence, although for five of these the evidence comes from only one study. The treatment class ICS + theophylline could not be included in the network. For this analysis, where all doses of ICS were grouped together when added to LABA (*Figure 7*; *Tables 22* and *23*), the difference in DIC between the FE and REs NMA is < 5 and, therefore, we focus the main interpretation of results on the simplest, FE model.

For the pairwise comparisons (*Table 22*) where it was possible to perform a MA, there is good agreement between FE and REs results and between the different analytic approaches (IV, MH, Bayesian). However, there is evidence of moderate heterogeneity across trials (tau^2 = 0.65; I^2 = 60%, IV analysis) for the comparison of ICS High versus ICS + LABA, and, thus the 95% CrI from the FE analysis excludes unity [0.53 (0.30; 0.96)], whereas the 95% CrI from the REs analysis is considerably wider and includes unity [0.28 (0.001; 13.07)]. Nevertheless, there is agreement in the direction of the effect in favour of ICS + LABA and the overlap of the CrIs.

The NMA (*Table 23*) suggests an increase in odds of good/total asthma control for ICS + LABA when compared to LTRA [5.16 (1.08; 26.58)] and to a lesser extent when compared to ICS High [1.60 (0.93; 2.72)]. There is also an increase in odds of good/total asthma control with ICS Medium [4.85 (1.00; 25.28)] and to a lesser extent for ICS Low [4.35

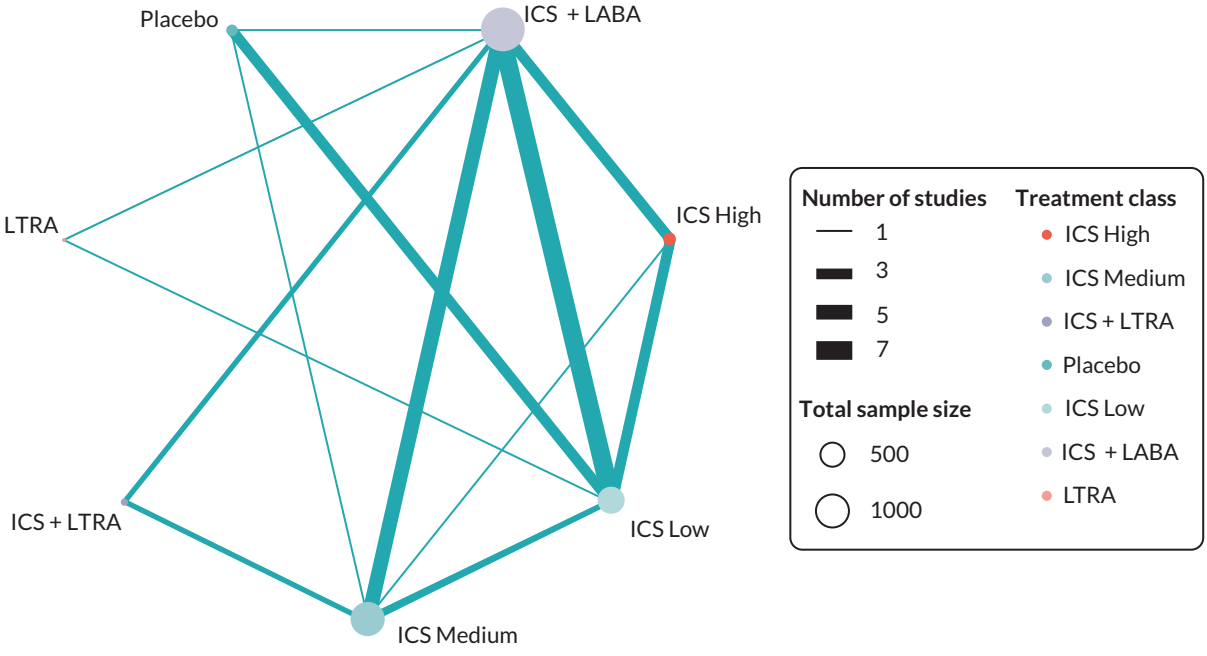

FIGURE 7 Network diagram (IPD and AgD) for asthma control (a) ICS grouped when combined with LABA.

TABLE 22 Pairwise MA results (IPD only) for asthma control (a) ICS grouped when combined with LABA

Direct comparison (Treatment 1 vs. Treatment 2)[a]	Data[b]	Author (year) (participants on each treatment)	Studies (*N*)	Participants (*N*)	Events (*N*)	Statistical approach	Heterogeneity	FE model OR (95% CI or CrI)	REs model OR (95% CI or CrI)
ICS L vs. ICS M	IPD	Lötvall (2014)[57] (17 vs. 11) Stempel (2016)[68] (13 vs. 48)	2	30 vs. 59	19 vs. 45	IV MH Bayesian	I^2 = 0%; tau^2 = 0; p = 0.73 I^2 = 0%; tau^2 = 0; p = 0.73 Not provided	0.55 (0.20 to 1.53) 0.55 (0.20 to 1.55) 0.54 (0.18 to 1.54)	0.55 (0.20 to 1.53) 0.55 (0.20 to 1.53) 0.56 (0.005 to 66.69)
ICS H vs. ICS L	IPD	Stempel (2016)[68] (40 vs. 13) Wechsler (2019)[72] (45 vs. 33) Woodcock (2014)[74] (6 vs. 7)	3	91 vs. 53	63 vs. 35	IV MH Bayesian	I^2 = 0%; tau^2 = 0; p = 0.86 I^2 = 0%; tau^2 = 0; p = 0.86 Not provided	1.25 (0.58 to 2.69) 1.25 (0.58 to 2.68) 1.25 (0.58 to 2.72)	1.25 (0.58 to 2.69) 1.25 (0.58 to 2.69) 1.20 (0.13 to 9.78)
ICS M vs. ICS H	IPD	Stempel (2016)[68] (48 vs. 40)	1	48 vs. 40	37 vs. 24	Frequentist logistic regression: 2.24 (0.90 to 5.75) Bayesian logistic regression (Stan): 2.23 (0.88 to 5.53)			
ICS L vs. ICS + LABA	IPD	Bateman (2014)[47] (97 vs. 104) Bernstein (2015)[48] (16 vs. 24) Bleecker (2014)[50] (14 vs. 15) Oliver (2016)[62] (98 vs. 294) Sorkness (2007)[66] (24 vs. 11) Stempel (2016)[68] (13 vs. 109) Wechsler (2019)[72] (33 vs. 92)	7	295 vs. 649	218 vs. 489	IV MH Bayesian	I^2 = 13%; tau^2 = 0; p = 0.33 I^2 = 13%; tau^2 = 0; p = 0.33 Not provided	0.90 (0.64 to 1.25) 0.90 (0.65 to 1.25) 0.90 (0.64 to 1.26)	0.90 (0.64 to 1.25) 0.90 (0.64 to 1.25) 0.80 (0.38 to 1.39)
ICS M vs. ICS + LABA	IPD	Lemanske (2010)[3] (7 vs. 10) Martin (2020)[58] (5 vs. 6) Stempel (2016)[67] (753 vs. 754) Stempel (2016)[68] (48 vs. 109) Thomas (2014)[69] (11 vs. 11)	5	824 vs. 890	712 vs. 774	IV MH Bayesian	I^2 = 0%; tau^2 = 0; p = 0.65 I^2 = 0%; tau^2 < 0.0001; p = 0.50 Not provided	0.89 (0.67 to 1.18) 0.92 (0.69 to 1.22) 0.91 (0.69 to 1.22)	0.89 (0.67 to 1.18) 0.91 (0.69 to 1.20) 1.02 (0.43 to 3.46)
ICS H vs. ICS + LABA	IPD	O'Byrne (2014)[61] (7 vs. 3) Stempel (2016)[68] (40 vs. 109) Wechsler (2019)[72] (45 vs. 92)	3	92 vs. 204	65 vs. 166	IV MH Bayesian	I^2 = 60%; tau^2 = 0.6499; p = 0.08 I^2 = 58%; tau^2 = 0.5060; p = 0.09 Not provided	**0.54 (0.30** to **0.97)** **0.55 (0.31** to **0.97)** **0.53 (0.30** to **0.96)**	0.54 (0.15 to 1.89) 0.54 (0.18 to 1.61) 0.28 (0.001 to 13.07)
LTRA vs. ICS L	IPD	Sorkness (2007)[66] (14 vs. 24)	1	14 vs. 24	9 vs. 21	Frequentist logistic regression: 0.26 (0.04 to 1.27) Bayesian logistic regression (Stan): 0.27 (0.06 to 1.27)			

TABLE 22 Pairwise MA results (IPD only) for asthma control (a) ICS grouped when combined with LABA (*continued*)

Direct comparison (Treatment 1 vs. Treatment 2)[a]	Data[b]	Author (year) (participants on each treatment)	Studies (*N*)	Participants (*N*)	Events (*N*)	Statistical approach	Heterogeneity	FE model OR (95% CI or CrI)	REs model OR (95% CI or CrI)
ICS M vs. ICS + LTRA	IPD	Lemanske (2010)[3] (7 vs. 14) Thomas (2014)[69] (11 vs. 11)	2	18 vs. 25	18 vs. 22	IV MH Bayesian	I^2 = N/A; tau^2 = N/A; p = N/A I^2 = N/A; tau^2 = N/A; *p* = N/A Not provided	Not estimable Not estimable Not estimable	Not estimable Not estimable Not estimable
ICS + LABA vs. ICS + LTRA	IPD	Lemanske (2010)[3] (10 vs. 14) Thomas (2014)[69] (11 vs. 11)	2	21 vs. 25	17 vs. 22	IV MH Bayesian	I^2 = 0%; tau^2 = 0; *p* = 0.57 I^2 = 0%; tau^2 = 0; *p* = 0.70 Not provided	0.57 (0.09 to 3.52) 0.52 (0.11 to 2.58) 0.43 (0.06 to 2.56)	0.57 (0.09 to 3.52) 0.53 (0.11 to 2.70) 0.08 (0.00 to 97.51)
LTRA vs. ICS + LABA	IPD	Sorkness (2007)[66] (14 vs. 11)	1	14 vs. 11	9 vs. 10	Frequentist logistic regression: 0.18 (0.01 to 1.40) Bayesian logistic regression (Stan): 0.22 (0.02 to 1.54)			
ICS L vs. placebo	IPD	Bleecker (2014)[50] (14 vs. 21) Lötvall (2014)[57] (17 vs. 15) Oliver (2016)[63] (201 vs. 37)	3	232 vs. 73	178 vs. 48	IV MH Bayesian	I^2 = 4%; tau^2 = 0.0160; *p* = 0.35 I^2 = 4%; tau^2 = 0.0162; *p* = 0.35 Not provided	1.18 (0.62 to 2.26) 1.17 (0.62 to 2.21) 1.16 (0.59 to 2.20)	1.18 (0.60 to 2.30) 1.18 (0.60 to 2.30) 1.13 (0.09 to 13.46)
placebo vs. ICS M	IPD	Lötvall (2014)[57] (15 vs. 11)	1	15 vs. 11	12 vs. 8	Frequentist logistic regression: 1.50 (0.23 to 10.07) Bayesian logistic regression (Stan): 1.35 (0.23 to 8.08)			
placebo vs. ICS + LABA	IPD	Bleecker (2014)[50] (21 vs. 15)	1	21 vs. 15	8 vs. 13	Frequentist logistic regression: **0.09 (0.01** to **0.46)** Bayesian logistic regression (Stan): **0.11 (0.02** to **0.50)**			

H, high; L, low; M, medium; MH, Mantel–Haenszel; Bayesian: framework using Stan.
a OR > 1 favours treatment 1 (the probability of having good/total asthma control was modelled). Results with CrIs that exclude the OR value of one are highlighted in bold.
b All available data included (IPD only).

TABLE 23 Bayesian FE NMA (IPD only) for asthma control (a) ICS grouped when combined with LABA

	TRT 2							
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS + LABA**	**ICS + LTRA**	**LTRA**	**ICS + theophylline**	**Placebo**
ICS Low	○	0.90 (0.59; 1.36) *0.54 (0.18; 1.54)*	1.36 (0.76; 2.44) *0.80 (0.37; 1.73)*	0.85 (0.62; 1.17) *0.90 (0.64; 1.26)*	0.81 (0.14; 4.76)	4.35 (0.93; 21.98) *3.32 (0.73; 18.17)*[a]	N/A	1.42 (0.77; 2.56) *1.16 (0.59; 2.20)*
ICS Medium	1.12 (0.73; 1.68) *1.86 (0.65; 5.42)*	○	1.51 (0.84; 2.69) *2.23 (0.88; 5.53)*[a]	0.94 (0.72; 1.25) *0.91 (0.69; 1.22)*	0.90 (0.15; 5.10) *Not estimable*	4.85 (1.00; 25.28)	N/A	1.58 (0.79; 3.13) *0.67 (0.12; 4.01)*[a]
ICS High	0.73 (0.41; 1.31) *1.25 (0.58; 2.72)*	0.66 (0.37; 1.19) *0.45 (0.18; 1.16)*[a]	○	0.63 (0.37; 1.07) ***0.53 (0.30; 0.96)***	0.59 (0.09; 3.63)	3.19 (0.62; 17.99)	N/A	1.04 (0.46; 2.36)
ICS + LABA	1.17 (0.85; 1.62) *1.12 (0.79; 1.55)*	1.06 (0.80; 1.39) *1.09 (0.82; 1.45)*	1.60 (0.93; 2.72) ***1.88 (1.04; 3.39)***	○	0.95 (0.16; 5.37) *0.43 (0.06; 2.56)*	**5.16** **(1.08; 26.58)** *4.48 (0.70; 53.52)*[a]	N/A	1.67 (0.88; 3.22) ***9.97 (2.01; 59.15)***[a]
ICS + LTRA	1.23 (0.21; 7.39)	1.12 (0.20; 6.62) *Not estimable*	1.68 (0.28; 10.80)	1.05 (0.19; 6.23) *2.34 (0.39; 15.49)*	○	5.42 (0.52; 60.95)	N/A	1.75 (0.28; 11.36)
LTRA	0.23 (0.05; 1.07) *0.27 (0.06; 1.27)*[a]	0.21 (0.04; 1.00)	0.31 (0.10; 1.62)	**0.19** **(0.04; 0.92)** *0.22 (0.02; 1.54)*[a]	0.18 (0.02; 1.93)	○	N/A	0.33 (0.06; 1.68)
ICS + theophylline	N/A	N/A	N/A	N/A	N/A	N/A	○	N/A
Placebo	0.70 (0.39; 1.30) *0.86 (0.45; 1.68)*	0.63 (0.32; 1.26) *1.35 (0.23; 8.08)*[a]	0.96 (0.42; 2.18)	0.60 (0.31; 1.14) ***0.11 (0.02; 0.50)***[a]	0.57 (0.09; 3.60)	3.06 (0.59; 17.46)	N/A	○

N/A, not available.
a Estimates from Bayesian logistic regression models (Stan) (one study).

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
15 studies, 2998 patients, 2433 events. Reference treatment: ICS + LABA – DIC: 2822.5; residual deviance: 2801.3 (on 2998 data points).
OR > 1 favours TRT 1 (the probability of having good/total asthma control was modelled). Direct results, where applicable, are in Italic. Results with CrIs that exclude the OR value of one are highlighted in bold.

(0.93; 21.98)] when compared with LTRA. For all other comparisons, there is substantial uncertainty with wide CrIs that include estimates indicative of both benefit and harm (*Table 23*).

The rank probabilities suggest the ICS + LABA combination is ranked as most favourable [rank medium (IQR): 2 (2,3)], followed by ICS Medium [3 (2,3)], ICS Low [4 (3,4)], ICS High [5 (4,6)]. The rank median is low for ICS + LTRA, but there is much more uncertainty [2 (1,5)]. Placebo [5 (5,6)] and LTRA [7 (7,7)] are ranked at the higher end, indicating a less favourable treatment (*Figure 8*).

The residual deviance and DIC of the NMA consistency model [residual deviance: 2801.3 (on 2998 data points); DIC: 2822.5] and UME model [residual deviance: 2800.3 (on 2998 data points); DIC: 2825.1] are similar; therefore, the consistency model is the preferred model. Additionally, there is considerable overlap of the 95% CrIs of treatment effects estimated by each model (see *Appendix 7*, *Table 54*). Furthermore, similar clinical inferences can be drawn from each model in terms of effectiveness. Overall, there is no evidence of inconsistency in the network.

Inhaled corticosteroid stratified when combined with long-acting β_2-agonist

A total of 16 studies with 3027 participants had data available for the secondary analysis of 'asthma control' outcome with a total of 2453 patients experiencing good/total asthma control at their last follow-up visit according to the ACT/ACQ test (these counted as events, representing a favourable outcome for the patient, in the analysis). All data for this analysis came from studies that had provided IPD, as none of the publications provided usable AgD for this outcome. The studies with data available for the NMA provided evidence for nine treatment classes (ICS Low; ICS Medium; ICS High; ICS Low + LABA; ICS Medium + LABA; ICS High + LABA; ICS + LTRA; LTRA; placebo), as shown in the network plot (*Figure 9*). The treatment class ICS + theophylline could not be included in the network. For this secondary analysis, where doses of ICS were stratified as Low, Medium, High when added to LABA (*Figure 9*; *Table 24*), the difference in DIC between the FE and REs NMA is < 5, and, therefore, we focus the main interpretation of results on the simplest, FE model (*Table 24*), which suggests an advantage for both ICS Low + LABA [5.00 (1.04 to 25.53)] and ICS High + LABA when compared with LTRA [6.36 (1.17 to 35.87)]. However, for all other pairwise comparisons in *Table 24*, the 95% CrI includes values for the OR that could indicate benefit for either treatment being compared, as well as both being identical. There is too much uncertainty to make any firm conclusions, and this is supported by the overlapping intervals for the rank probabilities (*Figure 10*).

There is little difference in residual deviance and DIC between the NMA consistency model [residual deviance: 2839.7 (on 3027 data points); DIC: 2864.1] and the UME model [residual deviance: 2838.5 (on 3027 data points); DIC: 2867.3], supporting the consistency model. Additionally, practically the same inferences would be drawn regarding the log ORs for both models, and there is considerable overlap in the 95% CrIs (see *Appendix 7*, *Table 55*) estimated for the treatment effects from each model, indicating there is no important inconsistency in the network.

Individual compounds

The Bayesian REs NMA for individual compounds (FF; FF + VI; FP; FP + Montelukast; FP + SAL; FP + VI; montelukast; placebo) for the asthma control outcome includes 15 studies, 3014 participants, 2447 events (*Figure 11*; *Table 25*). Results suggest an increased odds of asthma control on FF + VI compared to montelukast [OR 16.28 (95% CrI) (1.52 to 212.72)] with FF + VI ranked as the best treatment (*Figure 12*) in this network. However, not all compounds are represented in the network, and there is considerable uncertainty about the effectiveness and ranking of other treatments. The residual deviance and DIC of the NMA consistency model [residual deviance: 2808.4 (on 3014 data points); DIC: 2836.9] and UME model [residual deviance: 2809.3 (on 3014 data points); DIC: 2838.7] are comparable, supporting the use of the consistency model. Furthermore, for each model, practically the same inferences would be drawn regarding the effectiveness of treatments, and the 95% CrIs overlap (see *Appendix 7*, *Table 56*) for all treatment comparisons, indicating there is no substantial inconsistency in the network.

Conclusions for the analysis of primary outcomes

For exacerbation, the NMA suggests that ICS Low, ICS Medium, ICS High, ICS + LABA (specifically ICS Low + LABA and ICS Medium + LABA when considering dose of ICS) are more effective than placebo; ICS High and ICS + LABA,

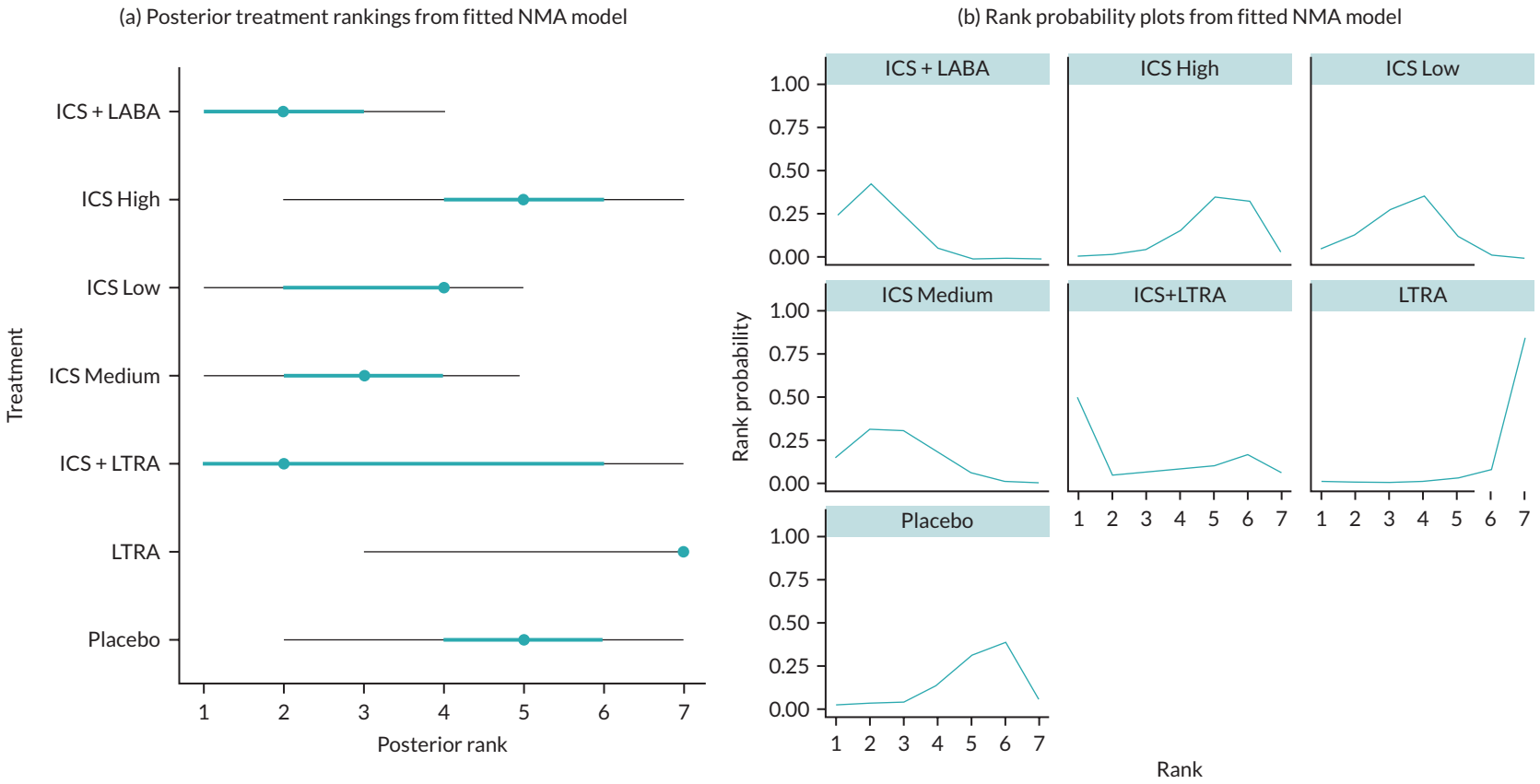

FIGURE 8 Ranks for the FE NMA (ICS grouped when combined with LABA) for asthma control. (a) Posterior treatment rankings from fitted NMA model. (b) Rank probability plots from fitted NMA model. Note: Rank median (point), IQR (bold line), 95% interval (thin line). Lower rank is better.

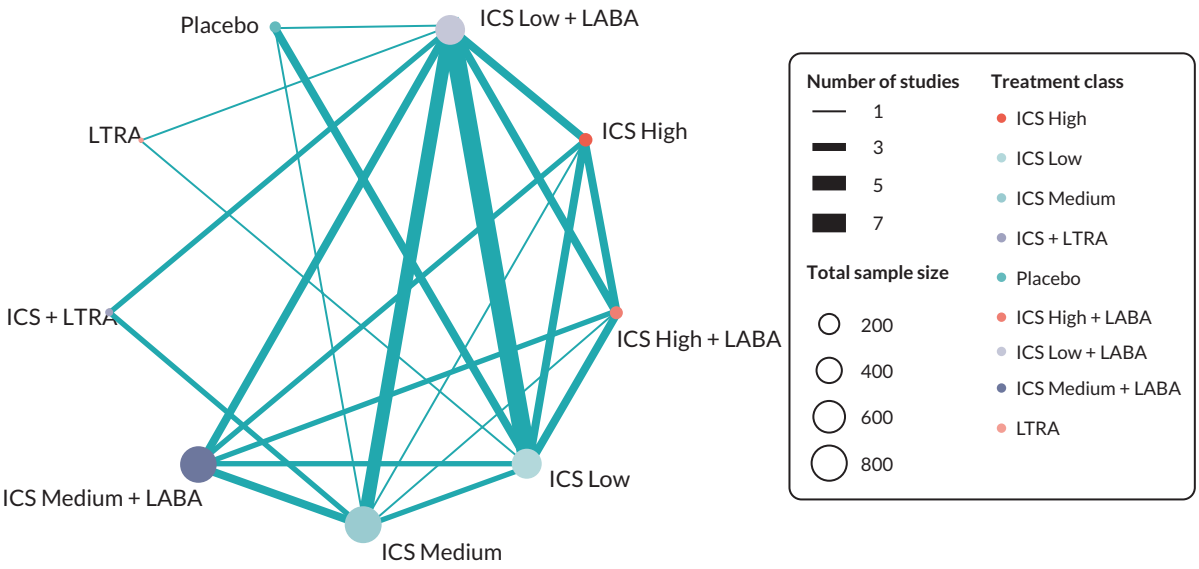

FIGURE 9 Network diagram (IPD only) for asthma control (b) ICS stratified when combined with LABA.

and to a lesser extent ICS Low and ICS Medium are more effective than LTRA. ICS + LABA suggested to be slightly more effective than ICS Low and ICS Medium (although CrI includes unity), whereas it is more difficult to establish a preference between ICS + LABA and ICS High, as the CrI includes values that could favour either treatment class. When ICS is stratified according to dose, the ICS Medium + LABA is the preferred treatment class over ICS Low and LTRA, and to a lesser extent over ICS Medium and ICS Low + LABA. There is very little evidence available on which to make conclusions regarding ICS + Theophylline. The evidence available for the asthma control outcome is less compelling than exacerbation but does suggest that ICS + LABA is more effective than LTRA. Overall, we conclude that ICS + LABA (with ICS at medium dose), would be recommended, and LTRA should be avoided.

TABLE 24 Bayesian FE NMA (IPD only) for asthma control (b) ICS stratified when combined with LABA

	TRT 2									
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS Low + LABA**	**ICS Medium + LABA**	**ICS High + LABA**	**ICS + LTRA**	**LTRA**	**ICS + theophylline**	**Placebo**
ICS Low	○	0.94 (0.50; 1.73)	1.32 (0.70; 2.46)	0.86 (0.62; 1.21)	0.90 (0.49; 1.67)	0.68 (0.34; 1.31)	0.82 (0.13; 4.71)	4.31 (0.90; 21.54)	N/A	1.42 (0.78; 2.56)
ICS Medium	1.06 (0.58; 1.99)	○	1.42 (0.73; 2.72)	0.92 (0.50; 1.68)	0.96 (0.73; 1.27)	0.72 (0.35; 1.43)	0.87 (0.14; 4.95)	4.57 (0.87; 25.28)	N/A	1.52 (0.66; 3.42)
ICS High	0.76 (0.41; 1.43)	0.70 (0.37; 1.36)	○	0.65 (0.35; 1.22)	0.68 (0.35; 1.30)	0.51 (0.25; 1.03)	0.62 (0.09; 3.74)	3.25 (0.61; 18.17)	N/A	1.07 (0.46; 2.48)
ICS Low + LABA	1.16 (0.83; 1.62)	1.08 (0.59; 1.99)	1.54 (0.82; 2.86)	○	1.04 (0.57; 1.92)	0.78 (0.39; 1.51)	0.95 (0.15; 5.31)	**5.00 (1.04; 25.53)**	N/A	1.65 (0.86; 3.16)
ICS Medium + LABA	1.12 (0.60; 2.05)	1.04 (0.79; 1.38)	1.48 (0.77; 2.83)	0.96 (0.52; 1.75)	○	0.75 (0.36; 1.49)	0.90 (0.14; 5.21)	4.76 (0.91; 26.05)	N/A	1.58 (0.69; 3.60)
ICS High + LABA	1.48 (0.76; 2.94)	1.39 (0.70; 2.86)	1.97 (0.97; 4.01)	1.28 (0.66; 2.53)	1.34 (0.67; 2.75)	○	1.21 (0.18; 7.46)	**6.36 (1.17; 35.87)**	N/A	2.12 (0.87; 5.16)
ICS + LTRA	1.22 (0.21; 7.61)	1.15 (0.20; 7.10)	1.62 (0.27; 10.59)	1.05 (0.19; 6.69)	1.11 (0.19; 6.96)	0.83 (0.13; 5.53)	○	5.26 (0.52; 60.34)	N/A	1.75 (0.28; 11.82)
LTRA	0.23 (0.05; 1.11)	0.22 (0.04; 1.15)	0.31 (0.06; 1.63)	**0.20 (0.04; 0.96)**	0.21 (0.04; 1.09)	**0.16 (0.03; 0.85)**	0.19 (0.02; 1.93)	○	N/A	0.33 (0.06; 1.75)
ICS + theophylline	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	○	N/A
Placebo	0.70 (0.39; 1.28)	0.66 (0.29; 1.51)	0.93 (0.40; 2.16)	0.61 (0.32; 1.16)	0.63 (0.28; 1.45)	0.47 (0.19; 1.15)	0.57 (0.08; 3.53)	3.00 (0.57; 16.61)	N/A	○

N/A, not available.

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
16 studies, 3027 participants, 2453 events. Reference treatment: ICS Low + LABA – DIC: 2864.1; residual deviance: 2839.7 (on 3027 data points). OR > 1 favours TRT 1 (the probability of having good/total asthma control was modelled). Results with CrIs that exclude the OR value of 1 are highlighted in bold.

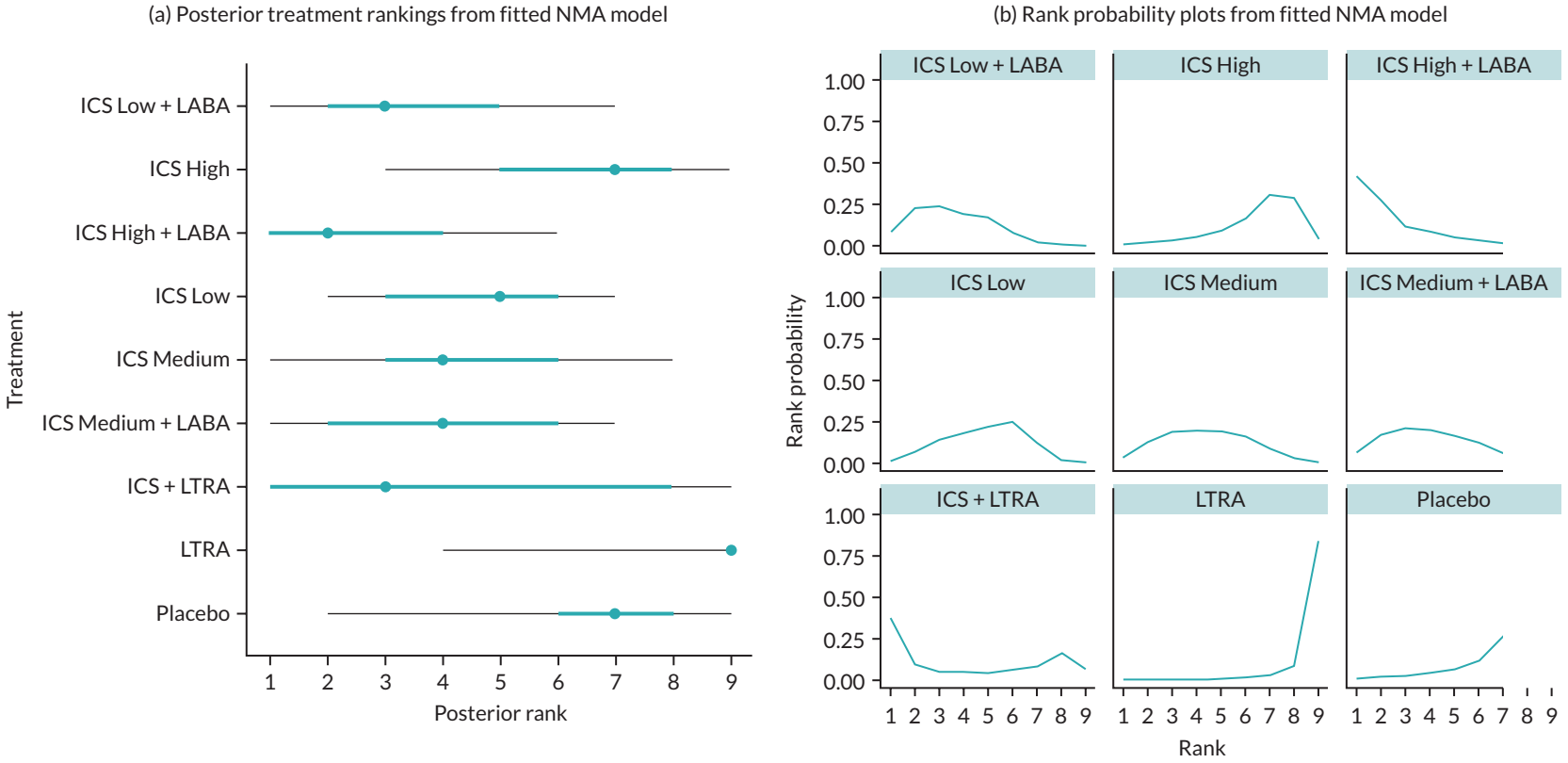

FIGURE 10 Ranks for the FE NMA (b) ICS stratified when combined with LABA for asthma control. (a) Posterior treatment rankings from fitted NMA model. (b) Rank probability plots from fitted NMA model. Note: Plot displays rank median (point), IQR (bold line), 95% interval (thin line). A lower rank indicates better treatment.

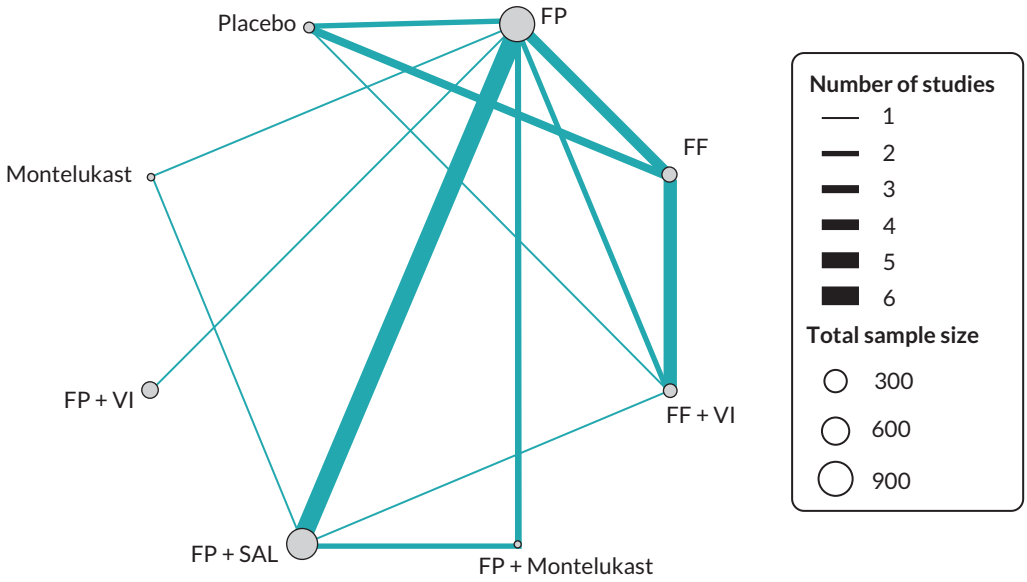

FIGURE 11 Network diagram (IPD only) for asthma control (individual compounds).

TABLE 25 Bayesian REs NMA (IPD only) for asthma control (individual compounds)

	TRT 2							
TRT 1	**FF**	**FF + VI**	**FP**	**FP + montelukast**	**FP + SAL**	**FP + VI**	**Montelukast**	**Placebo**
FF	○	0.51 (0.16; 1.26)	1.63 (0.53; 5.00)	1.58 (0.13; 18.36)	1.73 (0.50; 7.32)	1.68 (0.22; 12.81)	8.17 (0.78; 94.63)	1.54 (0.50; 4.57)
FF + VI	1.97 (0.79; 6.42)	○	3.25 (0.97; 12.55)	3.13 (0.26; 43.82)	3.46 (0.93; 18.54)	3.32 (0.45; 31.82)	**16.28 (1.52; 212.72)**	3.03 (0.88; 13.20)
FP	0.61 (0.20; 1.90)	0.31 (0.08; 1.03)	○	0.96 (0.10; 9.03)	1.06 (0.50; 2.91)	1.02 (0.19; 5.58)	5.00 (0.61; 44.70)	0.93 (0.25; 3.35)
FP + montelukast	0.63 (0.05; 7.46)	0.32 (0.02; 3.78)	1.04 (0.11; 9.97)	○	1.11 (0.13; 10.59)	1.06 (0.06; 16.61)	5.21 (0.25; 108.85)	0.97 (0.08; 12.68)
FP + SAL	0.58 (0.14; 2.01)	0.29 (0.05; 1.07)	0.94 (0.34; 2.01)	0.90 (0.09; 7.77)	○	0.96 (0.12; 5.70)	4.71 (0.51; 40.45)	0.88 (0.17; 3.56)
FP + VI	0.59 (0.08; 4.62)	0.30 (0.03; 2.20)	0.98 (0.18; 5.31)	0.94 (0.06; 15.80)	1.04 (0.18; 8.00)	○	4.90 (0.36; 75.19)	0.91 (0.11; 7.54)
Montelukast	0.12 (0.01; 1.28)	**0.06 (0.00; 0.66)**	0.20 (0.02; 1.63)	0.19 (0.01; 3.97)	0.21 (0.02; 1.95)	0.20 (0.01; 2.80)	○	0.19 (0.01; 2.16)
Placebo	0.65 (0.22; 2.01)	0.33 (0.08; 1.14)	1.07 (0.30; 3.94)	1.03 (0.08; 13.20)	1.14 (0.28; 5.75)	1.09 (0.13; 9.30)	5.37 (0.46; 70.11)	○

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
OR (95% CrI) (15 studies, 3014 participants, 2447 events). Reference treatment: FP – DIC: 2836.9; residual deviance: 2808.4 (on 3014 data points).
OR > 1 favours TRT 1 (the probability of having good/total asthma control was modelled).
Results with CrIs that exclude the OR value of 1 are highlighted in bold.

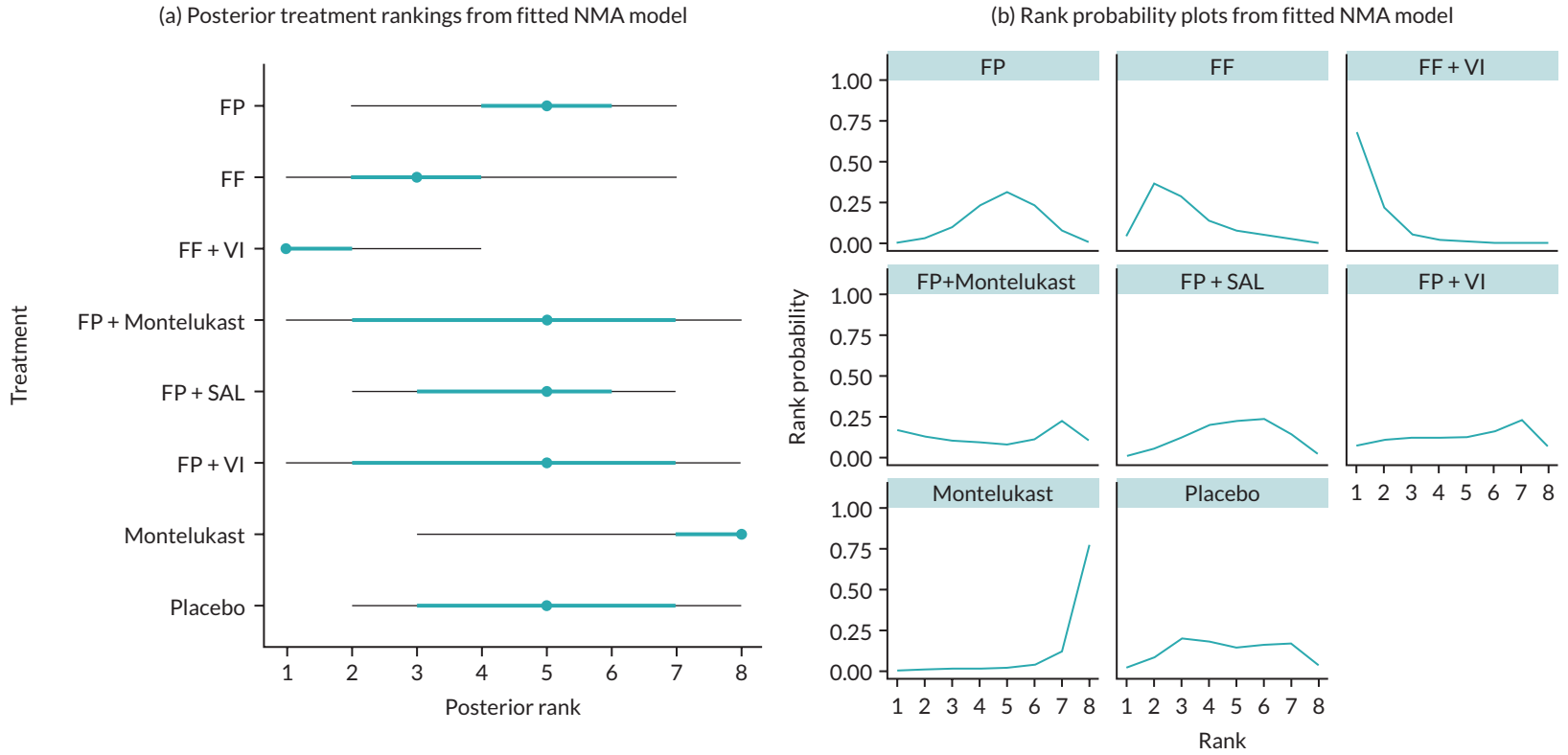

FIGURE 12 Ranks for the REs NMA (c) individual compounds for asthma control. (a) Posterior treatment rankings from fitted NMA model. (b) Rank probability plots from fitted NMA model. Note: Rank median (point), IQR (bold line), 95% interval (thin line). Lower rank is better.

Chapter 6 Clinical effectiveness results: secondary outcomes

In this chapter, we report the clinical effectiveness results, including Bayesian NMA where possible, for the secondary clinical outcomes (FEV_1; symptoms; QoL; mortality; hospital admissions; AEs). The main analyses include the most complete data incorporating both IPD, if available, and AgD otherwise. When only one study was available for a particular pairwise comparison, we estimated the direct treatment effect and CrI using Bayesian regression and conducted Bayesian MA if at least two studies had data available. Full results from both FE and REs NMA are provided in *Appendix 6*, but we focus on results from the best fitting model in the main body of the report. We also conducted the frequentist analyses (results not shown) for comparison but focus on the Bayesian results as pre-specified in the analysis plan. A qualitative and quantitative assessment of potential effect modifiers (see *Chapter 7*) suggested that, on average, there were no important concerns regarding the transitivity assumption for the NMA of FEV_1.

Forced expiratory volume in 1 second

Inhaled corticosteroid grouped when combined with long-acting β_2-agonist

A total of 22 studies with 2486 patients had data available for the 'FEV_1' outcome. We had IPD for 2171 patients from 20 studies and could extract AgD for 315 patients from two trials. The studies with data available for the NMA provide evidence for eight treatment classes (ICS unknown dose; ICS Low; ICS Medium; ICS High; ICS + LABA; ICS + LTRA; LTRA; placebo) as shown in the network plot (*Figure 13*). For this primary analysis, where all doses of ICS were grouped together when added to LABA (*Figure 13*; *Tables 26* and *27*), the difference in DIC between the FE and REs NMA is > 5; therefore, we focus the main interpretation of results on the REs model (*Table 27*).

The direct MD could be estimated for 11 pairwise comparisons (*Table 26*). Overall, for each direct pairwise comparison, there is little difference between the results of analyses based on different analytic approaches (IV vs. Bayesian) and between FE and REs analyses (*Table 26*) apart from two pairwise comparisons (ICS High vs. ICS + LABA; ICS Medium

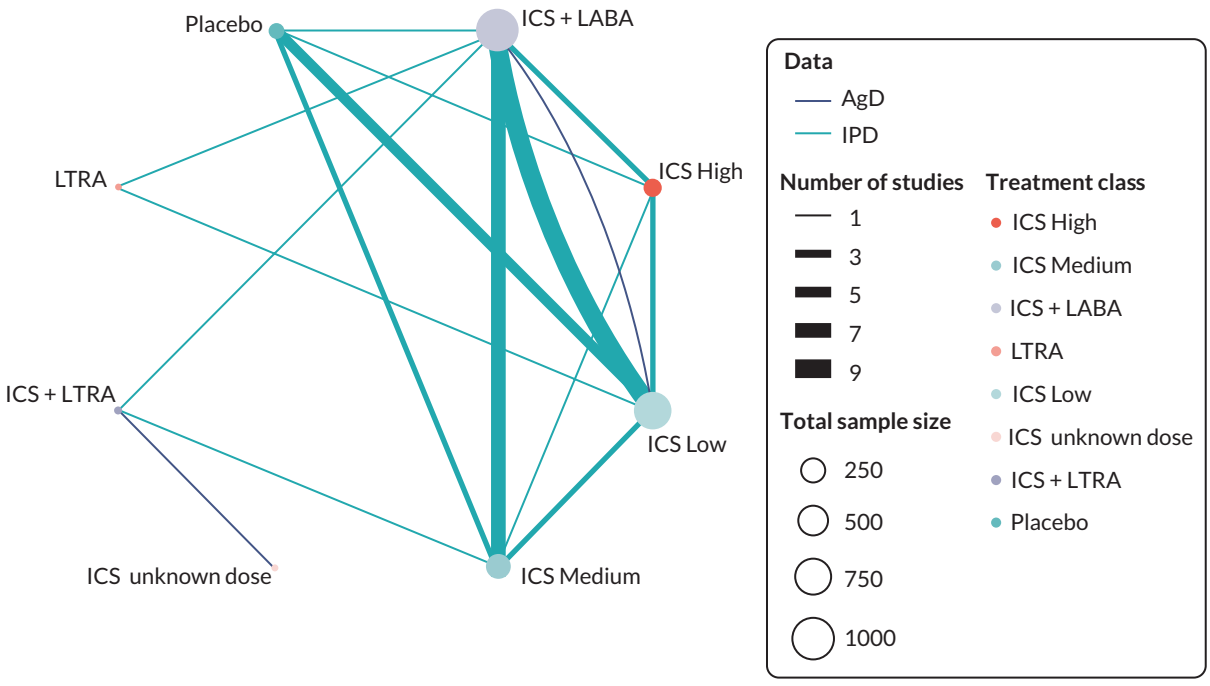

FIGURE 13 Network diagram (IPD and AgD) for FEV_1 (a) ICS grouped when combined with LABA.

TABLE 26 Pairwise MA results (IPD and AgD) for FEV_1 (a) ICS grouped when combined with LABA

Direct comparison (TRT1 vs. TRT2) [a]	Data	Author (year) (participants on each treatment)	Trial level MD (95% CI)	Statistical approach	Heterogeneity	Fixed-effect model MD (95% CI or CrI)	Random-effects model MD (95% CI or CrI)
ICS L vs. ICS M	IPD	Bleecker (2012)[49] (13 vs. 13)	−0.25 (−0.76 to 0.26)	IV	I^2 = 23%,	−0.03 (−0.37 to 0.31)	−0.04 (−0.42 to 0.35)
		Lötvall (2014)[57] (17 vs. 11)	0.14 (−0.31 to 0.60)	Bayesian	tau² = 0.0179,	−0.04 (−0.42 to 0.35)	−0.06 (−1.64 to 1.47)
					p = 0.26		
					Not provided		
ICS H vs. ICS L	IPD	Bleecker (2012)[49] (28 vs. 13)	0.42 (0.00 to 0.84)	IV	I^2 = 0%, tau² = 0,	**0.41 (0.03 to 0.80)**	**0.41 (0.03 to 0.80)**
		Woodcock (2014)[74] (6 vs. 7)	0.37 (−0.58 to 1.32)	Bayesian	*p* = 0.92	0.41 (−0.01 to 0.83)	0.38 (−2.08 to 2.77)
					Not provided		
ICS M vs. ICS H	IPD	Bleecker (2012)[49] (13 vs. 28)	−0.17 (−0.61 to 0.27)	Frequentist linear regression model: −0.17 (−0.61 to 0.27) Bayesian linear regression model (Stan): −0.17 (−0.64 to 0.28)			
ICS L vs. ICS + LABA	IPD	Bateman (2014)[47] (102 vs. 110)	−0.03 (−0.24 to 0.17)	IV	I^2 = 0%, tau² = 0,	−0.01 (−0.09 to 0.06)	−0.01 (−0.09 to 0.06)
	AgD	Bernstein (2015)[48] (17 vs. 24)	0.07 (−0.43 to 0.57)	Bayesian	*p* = 0.49	−0.02 (−0.10 to 0.06)	0.00 (−0.12 to 0.17)
		Bleecker (2014)[50] (19 vs. 19)	−0.01 (−0.44 to 0.43)		Not provided		
		Carroll (2010)[51] (16 vs. 21)	0.37 (−0.20 to 0.94)				
		Lötvall (2014)[56] (5 vs. 15)	0.72 (0.01 to 1.44)				
		Oliver (2016)[62] (96 vs. 277)	−0.02 (−0.12 to 0.09)				
		Scott (2005)[65] (77 vs. 74)	−0.08 (−0.23 to 0.06)				
		Sorkness (2007)[66] (24 vs. 11)	0.15 (−0.27 to 0.57)				
		Tal (2002)[89] (138 vs. 148)	−0.10 (−3.80 to 3.60)				
ICS M vs. ICS + LABA	IPD	Bisgaard (2006)[77]	−0.020	IV	I^2 = 60%,	−0.01 (−0.10 to 0.08)	0.02 (−0.19 to 0.24)
	AgD[b]	(106 vs. 235)[b]	−0.020 (−0.132 to 0.093)	Bayesian	tau² = 0.03,	−0.02 (−0.11 to 0.08)	0.01 (−0.30 to 0.38)
		de Blic (2009)[52] (153 vs. 150)	−0.026 (−0.214 to 0.162)		*p* = 0.03		
		Gappa (2009)[54] (131 vs. 127)	0.788 (0.061 to 1.516)		Not provided		
		Lemanske (2010)[3] (7 vs. 10)	−0.207 (−0.749 to 0.335)				
		Lötvall (2014)[56] (9 vs. 17)	−0.601 (−1.220 to 0.017)				
		Martin (2020)[58] (5 vs. 6)	0.490 (−0.008 to 0.988)				
		Murray (2010)[59] (4 vs. 4)	−0.090				
		Zimmerman (2004)[92]					
		(101 vs. 201)[b]					
ICS H vs. ICS + LABA	IPD	O' Byrne (2014)[61] (7 vs. 3)	−0.98 (−1.95 to −0.01)	IV	I^2 = 77%,	0.02 (−0.21 to 0.24)	−0.34 (−1.36 to 0.67)
		Verberne (1998)[71] (106 vs. 54)	0.07 (−0.16 to 0.30)	Bayesian	tau² = 0.4283,	0.05 (−0.19 to 0.29)	−0.28 (−3.22 to 2.48)
					p = 0.04		
					Not provided		
LTRA vs. ICS L	IPD	Sorkness (2007)[66] (14 vs. 24)	0.08 (−0.38 to 0.53)	Frequentist linear regression model: 0.08 (−0.38 to 0.53) Bayesian linear regression model (Stan): 0.07 (−0.40 to 0.53)			
ICS + LTRA vs. ICS M	IPD	Lemanske (2010)[3] (7 vs. 14)	0.77 (−0.01 to 1.55)	Frequentist linear regression model: −0.77 (−1.63 to 0.09) Bayesian linear regression model (Stan): −0.78 (−1.64 to 0.14)			
ICS + LTRA vs. ICS + LABA	IPD	Lemanske (2010)[3] (14 vs. 10)	0.02 (−0.68 to 0.72)	Frequentist linear regression model: 0.02 (−0.72 to 0.75) Bayesian linear regression model (Stan): 0.02 (−0.72 to 0.77)			

TABLE 26 Pairwise MA results (IPD and AgD) for FEV_1 (a) ICS grouped when combined with LABA (*continued*)

Direct comparison (TRT1 vs. TRT2) [a]	Data	Author (year) (participants on each treatment)	Trial level MD (95% CI)	Statistical approach	Heterogeneity	Fixed-effect model MD (95% CI or CrI)	Random-effects model MD (95% CI or CrI)
LTRA vs. ICS + LABA	IPD	Sorkness (2007)[66] (14 vs. 11)	0.23 (−0.28 to 0.73)	Frequentist linear regression model: 0.23 (−0.28 to 0.73) Bayesian linear regression model (Stan): 0.22 (−0.30 to 0.73)			
ICS L vs. placebo	IPD AgD	Berger (2006)[76] (197 vs. 99)[b] Bleecker (2012)[49] (13 vs. 13) Bleecker (2014)[50] (19 vs. 23) Lötvall (2014)[57] (17 vs. 18) Oliver (2016)[63] (234 vs. 60)	0.26 −0.01 (−0.68 to 0.66) 0.23 (−0.18 to 0.63) 0.18 (−0.27 to 0.64) 0.15 (0.02 to 0.28)	IV Bayesian	I^2 = 0%, tau^2 = 0, p = 0.95 Not provided	0.15 (0.04 to 0.27) 0.15 (0.04 to 0.27)	**0.15 (0.04** to **0.27)** 0.15 (−0.17 to 0.46)
ICS M vs. placebo	IPD	Bleecker (2012)[49] (13 vs. 13) Lötvall (2014)[57] (11 vs. 18)	0.24 (−0.45 to 0.93) 0.04 (−0.42 to 0.50)	IV Bayesian	I^2 = 0%, tau^2 = 0, p = 0.63 Not provided	0.10 (−0.28 to 0.48) 0.10 (−0.32 to 0.52)	0.10 (−0.28 to 0.48) 0.12 (−1.03 to 1.29)
ICS H vs. placebo	IPD	Bleecker (2012)[49] (28 vs. 13)	0.41 (−0.12 to 0.94)	Frequentist linear regression model: 0.41 (−0.12 to 0.94) Bayesian linear regression model (Stan): 0.42 (−0.14 to 0.96)			
ICS + LABA vs. placebo	IPD	Bleecker (2014)[50] (19 vs. 23)	0.23 (−0.27 to 0.73)	Frequentist linear regression model: 0.23 (−0.27 to 0.73) Bayesian linear regression model (Stan): 0.24 (−0.29 to 0.76)			
ICS unkn vs. ICS + LTRA	AgD	Visitsunthorn (2011)[91] (15 vs. 14)	0.05 (−0.21 to 0.31)	Frequentist linear regression model: not calculated AgD only Bayesian linear regression model (Stan): not calculated AgD only			

H, high; Bayesian: framework using Stan; L, low; M, medium; NA, not available (estimates were derived from the complementary comparison to optimise models).
a MD > 0 favours treatment 1; MD < 0 favours treatment 2. Results with CrIs that exclude the MD value of zero are highlighted in bold.
b Studies without SD could not be included.

TABLE 27 Bayesian REs NMA (IPD and AgD) for FEV_1 (a) ICS grouped when combined with LABA

	TRT 2								
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS unk dose**	**ICS + LABA**	**ICS + LTRA**	**LTRA**	**ICS + theophylline**	**Placebo**
ICS Low	○	0.00 (−0.14; 0.14) *−0.06 (−1.64; 1.47)*	−0.15 (−0.37; 0.07) *−0.38 (−2.77; 2.08)*	0.30 (−0.97; 1.60)	−0.02 (−0.11; 0.08) *0.00 (−0.12; 0.17)*	0.24 (−0.58; 1.09)	−0.15 (−0.63; 0.35) *−0.10 (−0.56; 0.41)*[a]	N/A	**0.16 (0.01; 0.30)** *0.15 (−0.17; 0.46)*
ICS Medium	0.00 (−0.14; 0.14) *0.06 (−1.47; 1.64)*	○	−0.15 (−0.38; 0.09) *−0.20 (−0.64; 2.28)*[a]	0.30 (−0.96; 1.59)	−0.02 (−0.13; 0.10) *0.01 (−0.30; 0.38)*	0.24 (−0.57; 1.08) *0.76 (−0.17; 1.69)*[a]	−0.14 (−0.65; 0.36)	N/A	0.16 (−0.04; 0.35) *0.12 (−1.03; 1.29)*
ICS High	0.15 (−0.07; 0.37) *0.38 (−2.08; 2.77)*	0.15 (−0.09; 0.38) *0.20 (−0.28; 0.63)*[a]	○	0.45 (−0.83; 1.76)	0.13 (−0.08; 0.35) *−0.28 (−3.22; 2.48)*	0.39 (−0.43; 1.26)	0.01 (−0.53; 0.54)	N/A	**0.31 (0.05; 0.57)** *0.40 (−0.14; 0.96)*[a]
ICS unknown dose	−0.30 (−1.60; 0.97)	−0.30 (−1.59; 0.96)	−0.45 (−1.76; 0.83)	○	−0.32 (−1.61; 0.95)	−0.05 (−1.02; 0.91) *not calculated*	−0.44 (−1.81; 0.91)	N/A	−0.14 (−1.44; 1.13)
ICS + LABA	0.02 (−0.08; 0.11) *0.00 (−0.17; 0.12)*	0.02 (−0.10; 0.13) *0.01 (−0.38; 0.30)*	−0.13 (−0.35; 0.08) *0.28 (−2.48; 3.22)*	0.32 (−0.95; 1.61)	○	0.26 (−0.55; 1.10) *−0.02 (−0.76; 0.77)*[a]	−0.13 (−0.61; 0.36) *−0.20 (−0.74; 0.34)*[a]	N/A	0.18 (0.00; 0.34) *0.20 (−0.29; 0.76)*[a]
ICS + LTRA	−0.24 (−1.09; 0.58)	−0.24 (−1.08; 0.57) *−0.78 (−1.64; 0.14)*[a]	−0.39 (−1.26; 0.43)	0.05 (−0.91; 1.02) *not calculated*	−0.26 (−1.10; 0.55) *0.02 (−0.72; 0.77)*[a]	○	−0.39 (−1.37; 0.56)	N/A	−0.09 (−0.94; 0.73)
LTRA	0.15 (−0.35; 0.63) *0.10 (−0.40; 0.53)*[a]	0.14 (−0.36; 0.65)	−0.01 (−0.54; 0.53)	0.44 (−0.91; 1.81)	0.13 (−0.36; 0.61) *0.20 (−0.3; 0.73)*[a]	0.39 (−0.56; 1.37)	○	N/A	0.30 (−0.21; 0.81)
ICS + theophylline	N/A	N/A	N/A	N/A	N/A	N/A	N/A	○	N/A
Placebo	**−0.16 (−0.30; −0.01)** *−0.15 (−0.46; 0.17)*	−0.16 (−0.35; 0.04) *−0.12 (−1.29; 1.03)*	**−0.31 (−0.57; −0.05)** *−0.40 (−0.92; 0.12)*[a]	0.14 (−1.13; 1.44)	−0.18 (−0.34; 0.00) *−0.20 (−0.75; 0.27)*[a]	0.09 (−0.73; 0.94)	−0.30 (−0.81; 0.21)	N/A	○

N/A, not available.
a Estimates from Bayesian linear regression models (Stan).
MD > 0 favours TRT 1; MD < 0 favours TRT 2. Results with CrI that excludes the MD value of zero are highlighted in bold.

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
MD (95% CrI) from NMA with direct results in Italics; 22 studies, 2486 patients. Reference treatment: ICS + LABA; DIC; 1768.4, residual deviance: 2129.2 (on 2175 data points).

vs. ICS + LTRA) due to a high degree of heterogeneity between trials. Focusing on the Bayesian REs results, the 95% CrI includes the value of zero as well as values that favour either treatment in each pairing for all comparisons.

There is good consistency in the direction of effect between the point estimates from NMA and direct estimates, where it is possible to estimate both (*Table 27*) apart from the comparison of ICS High versus ICS + LABA. Here, the NMA suggests an advantage to ICS High [MD (95% CrI) 0.13 (−0.08 to 0.35)] whereas an advantage for ICS + LABA from the direct evidence [−0.28 (−3.22 to 2.48)] from two trials with high degree of heterogeneity. However, there is an overlap in the CrI, both of which include zero. For the REs NMA (*Table 27*), there is evidence in favour of ICS Low [MD (95% CrI): 0.16 (0.01 to 0.30)], ICS High [0.31 (0.05 to 0.57)], and slightly weaker evidence for ICS Medium [0.16 (−0.04 to 0.35)] and ICS + LABA [0.18 (0.00 to 0.34)] when compared against placebo. For all other comparisons, the 95% CrI for the MD includes zero and a range of values that could indicate an important advantage for either treatment, making it difficult to be confident about the direction of the effect.

The posterior ranking (*Figure 14*) shows ICS High is most likely to result in the best FEV_1, whereas placebo appears least attractive. There is considerable uncertainty around the posterior ranks of other treatments, as seen by the wide intervals (*Figure 14*) that overlap, making it difficult to draw firm conclusions about the order of effectiveness of treatments at improving FEV_1.

Through comparison of the deviance and DIC statistics of the consistency and UME models, the posterior means of the residual deviance are very similar, but the DIC is lower for the consistency model (1768.4) compared to the UME model (1817.1), suggesting consistency of direct and indirect evidence. Furthermore, the MDs produced by each model support the conclusion regarding the absence of important inconsistency because the results are reasonably comparable in terms of overlap of the 95% CrIs (see *Appendix 7*, *Table 57*) and the clinical inferences that can be drawn.

Inhaled corticosteroid stratified when combined with long-acting β_2-agonist

Data were available for 23 studies, 2518 participants [21 trials (2203 participants) with IPD and 2 trials (315 participants) with AgD] for the secondary analysis of FEV_1 that considered ICS at Low, Medium or High dose when combined with LABA. There are 10 treatment classes included in this network (*Figure 15*), and results for the Bayesian FE NMA (*Table 28*) suggest that ICS Low [0.15 (0.04 to 0.27)]; ICS Medium [0.17 (0.01 to 0.33)]; ICS Low + LABA [0.18 (0.04 to 0.31)] and ICS Medium + LABA [0.86 (0.49 to 1.24)] are each more effective than placebo. There is greater uncertainty for the effect of ICS High compared to placebo [0.32 (−0.01 to 0.63)] and insufficient evidence to conclude that ICS High + LABA is more effective than placebo [−0.13 (−0.50 to 0.22)].

There is evidence that ICS Medium + LABA is more effective than ICS Low 0.71 (0.35 to 1.06); ICS Medium 0.69 (0.33 to 1.05); ICS High 0.54 (0.24 to 0.81); ICS Low + LABA 0.68 (0.33 to 1.04); ICS High + LABA 0.99 (0.67 to 1.27) and ICS + LTRA 0.94 (0.07 to 1.82). There is also some evidence to suggest that ICS High is better than ICS High + LABA 0.45 (0.25 to 0.64). The rank probability plots (*Figure 16*) show that ICS Medium + LABA is likely to be the best treatment in this network, but there is considerable uncertainty around the rank probability of other treatments. To assess the inconsistency assumption, model fit statistics of the consistency and UME models were compared; the posterior means of the residual deviance are very similar, but there is difference between the DIC for the consistency model (−110.6) compared to the UME model (−98.9), favouring the consistency model. For each treatment comparison, the CrIs of the MDs from each model are overlapping (see *Appendix 7*, *Table 58*), and reasonably similar conclusions regarding effectiveness can be drawn; this indicates evidence consistency.

Individual compounds

The individual compound NMA for FEV_1 includes data from 17 trials, 1984 participants (*Figure 17*; *Table 29*) with eight treatments (FP; FF; FF + VI; FP + montelukast; FP + SAL; FP + VI; montelukast; placebo). AgD could not be included in this NMA due to issues with the convergence of the model. The Bayesian FE NMA suggests that FEV_1 is increased for FF [MD (95% CrI) 0.18 (0.05; 0.30)] and FF + VI [0.23 (0.03; 0.43)], and to a lesser extent for FP [0.11 (−0.04; 0.26)], FP + SAL [0.12 (−0.05; 0.29)] and FP + VI [0.12 (−0.06; 0.31)] when compared to placebo. There is considerable uncertainty in the ranking of treatments (*Figure 18*), as seen by overlapping intervals, and we cannot make any firm conclusions about the comparative effects of the different individual compounds.

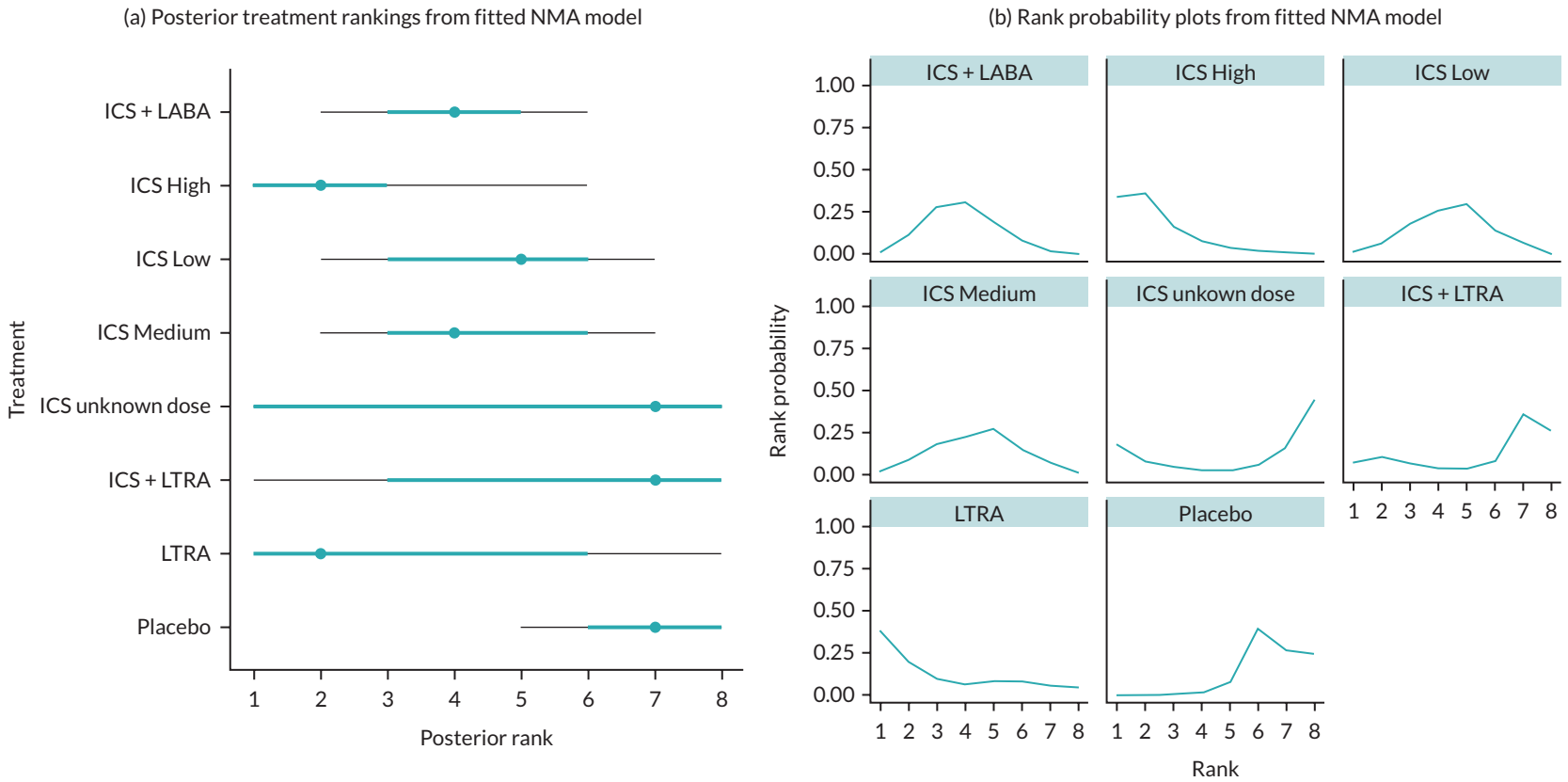

FIGURE 14 Ranks for the REs NMA (a) ICS grouped when combined with LABA for FEV_1. (a) Posterior treatment rankings from fitted NMA model. (b) Rank probability plots from fitted NMA model. Note: Rank median (point), IQR (bold line), 95% interval (thin line). Lower rank is better.

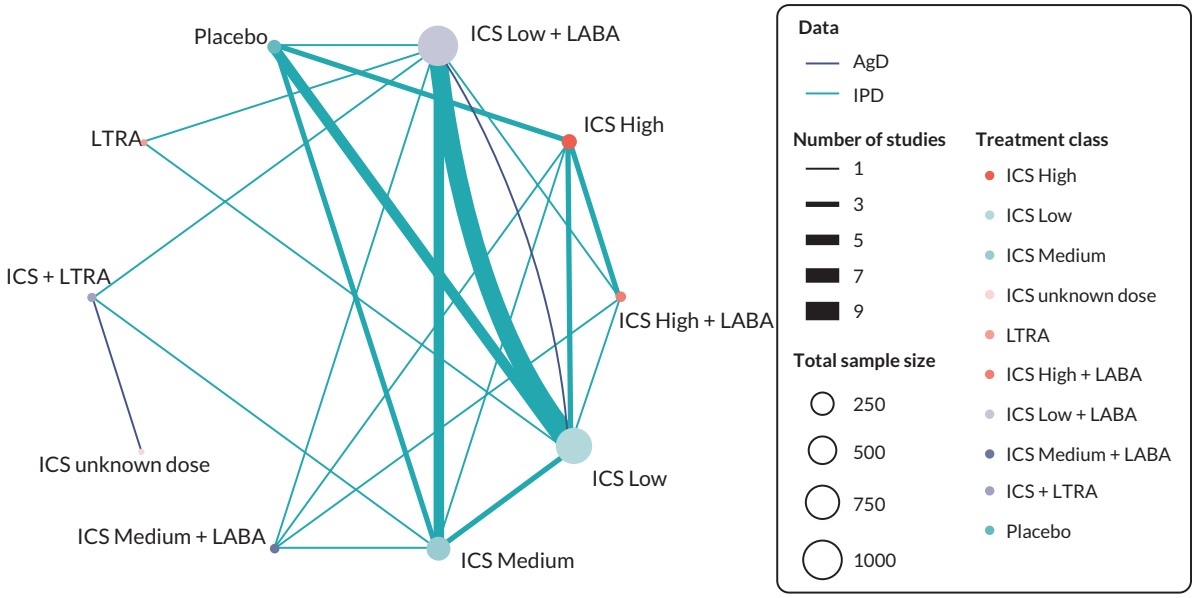

FIGURE 15 Network diagram (IPD and AgD) for FEV_1 (b) ICS stratified when combined with LABA.

Sensitivity analysis

We conducted a series of sensitivity analyses adjusting for baseline FEV_1 value in the NMA where this data was available. Although there are some differences in the number of trials and patients included in the individual sensitivity analyses (data not shown), the numerical results and conclusions are similar to the corresponding analyses that include additional trials and patients without adjustment for baseline FEV_1 (*Tables 27–29*). We explored the impact of removing trials that only had AgD (2 trials, 315 participants) and found the numerical results and conclusions were very similar to the corresponding analyses that included both IPD and AgD (*Tables 27* and *28*).

Symptoms

We had planned to conduct an analysis of 'symptoms' (recorded as an outcome in the original EINSTEIN protocol). We summarised how symptoms had been measured in each of the studies that had provided IPD (data not shown). However, following further discussion within the EINSTEIN team, we decided not to progress with this analysis, as it can be difficult to interpret symptoms in isolation, for example, coughing at night but not needing reliever medication, not missing school and not having wheeze when running around. It was likely that many of the individual symptoms would have contributed to the asthma control outcome with the rationale of a control score being to provide a summary of these symptoms. From a clinician's perspective (also the child's and parents'), those who have troublesome symptoms at night also have them by day, and these individuals are poorly controlled. Composite symptom scores are used to give a global score/perspective of control in lieu of a single symptom, which by definition gives a narrow perspective. The decision to abandon this analysis was not in any way influenced by any results or other analyses that had been completed.

Quality of life

Eleven trials provided IPD or AgD on QoL. The trials had either used the AQLQ, developed for use in adults (17–70 years), which includes 32 items each scored on a 7-point Likert scale with a score of 1 representing maximal impairment and 7 representing no impairment: symptoms (11 items), activity limitation (12 items, 5 of which are individualised), emotional function (5 items), and environmental exposure (4 items); or the PAQLQ developed for use in children (7–17 years), which includes 23 items in three domains (symptoms, activity limitation and emotional function) on a scale of 1 (severely affected) to 7 (unaffected). For both tools a minimum clinically important difference is reflected

TABLE 28 Bayesian FE NMA (IPD and AgD) for FEV_1 (b) ICS stratified when combined with LABA

	TRT 2									
TRT 1	**ICS Low**	**ICS Medium**	**ICS High**	**ICS unknown dose**	**ICS Low + LABA**	**ICS Medium + LABA**	**ICS High + LABA**	**ICS + LTRA**	**LTRA**	**Placebo**
ICS Low	○	−0.02 (−0.13; 0.09)	−0.16 (−0.46; 0.15)	0.27 (−0.95; 1.52)	−0.02 (−0.10; 0.05)	**−0.71 (−1.06; −0.35)**	0.29 (−0.05; 0.64)	0.23 (−0.56;1.04)	−0.15 (−0.63; 0.33)	**0.15 (0.04; 0.27)**
ICS Medium	0.02 (−0.09; 0.13)	○	−0.14 (−0.45; 0.16)	0.29 (−0.93; 1.53)	−0.01 (−0.10; 0.09)	**−0.69 (−1.05; −0.33)**	0.30 (−0.04; 0.66)	0.25 (−0.55; 1.05)	−0.13 (−0.63; 0.36)	**0.17 (0.01; 0.33)**
ICS High	0.16 (−0.15; 0.46)	0.14 (−0.16; 0.45)	○	0.44 (−0.83; 1.72)	0.14 (−0.17; 0.43)	**−0.54 (−0.81; −0.24)**	**0.45 (0.25; 0.64)**	0.39 (−0.46; 1.25)	0.02 (−0.55; 0.58)	0.32 (−0.01; 0.63)
ICS unknown dose	−0.27 (−1.52; 0.95)	−0.29 (−1.53; 0.93)	−0.44 (−1.72; 0.83)	○	−0.30 (−1.54; 0.92)	−0.98 (−2.27; 0.30)	0.01 (−1.27; 1.28)	−0.05 (−1.01; 0.91)	−0.42 (−1.75; 0.90)	−0.12 (−1.37; 1.11)
ICS Low +LABA	0.02 (−0.05; 0.10)	0.01 (−0.09; 0.10)	−0.14 (−0.43; 0.17)	0.30 (−0.92; 1.54)	○	**−0.68 (−1.04; −0.33)**	0.31 (−0.03; 0.66)	0.25 (−0.54; 1.06)	−0.12 (−0.61; 0.36)	**0.18 (0.04; 0.31)**
ICS Medium +LABA	**0.71 (0.35; 1.06)**	**0.69 (0.33; 1.05)**	**0.54 (0.24; 0.81)**	0.98 (−0.30; 2.27)	**0.68 (0.33; 1.04)**	○	**0.99 (0.67; 1.27)**	**0.94 (0.07; 1.82)**	0.56 (−0.04; 1.15)	**0.86 (0.49; 1.24)**
ICS High +LABA	−0.29 (−0.64; 0.05)	−0.30 (−0.66; 0.04)	**−0.45 (−0.64; −0.25)**	−0.01 (−1.28; 1.27)	−0.31 (−0.66; 0.03)	**−0.99 (−1.27; −0.67)**	○	−0.06 (−0.92; 0.81)	−0.43 (−1.02; 0.15)	−0.13 (−0.50; 0.22)
ICS + LTRA	−0.23 (−1.04; 0.56)	−0.25 (−1.05; 0.55)	−0.39 (−1.25; 0.46)	0.05 (−0.91; 1.01)	−0.25 (−1.06; 0.54)	**−0.94 (−1.82; −0.07)**	0.06 (−0.81; 0.92)	○	−0.38 (−1.31; 0.55)	−0.07 (−0.90; 0.72)
LTRA	0.15 (−0.33; 0.63)	0.13 (−0.36; 0.63)	−0.02 (−0.58; 0.55)	0.42 (−0.90; 1.75)	0.12 (−0.36; 0.61)	−0.56 (−1.15; 0.04)	0.43 (−0.15; 1.02)	0.38 (−0.55; 1.31)	○	0.30 (−0.19; 0.80)
Placebo	**−0.15 (−0.27; −0.04)**	**−0.17 (−0.33; −0.01)**	−0.32 (−0.63; 0.01)	0.12 (−1.11; 1.37)	**−0.18 (−0.31; −0.04)**	**−0.86 (−1.24; −0.49)**	0.13 (−0.22; 0.50)	0.07 (−0.72; 0.90)	−0.30 (−0.80; 0.19)	○

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
MD (95% CrI) (23 studies, 2518 participants). Reference treatment: ICS Low + LABA — DIC: −110.6; residual deviance: 2157.3 (on 2207 data points); MD > 0 favours TRT 1; MD < 0 favours TRT 2. Results with CrI that excludes the MD value of zero are highlighted in bold.

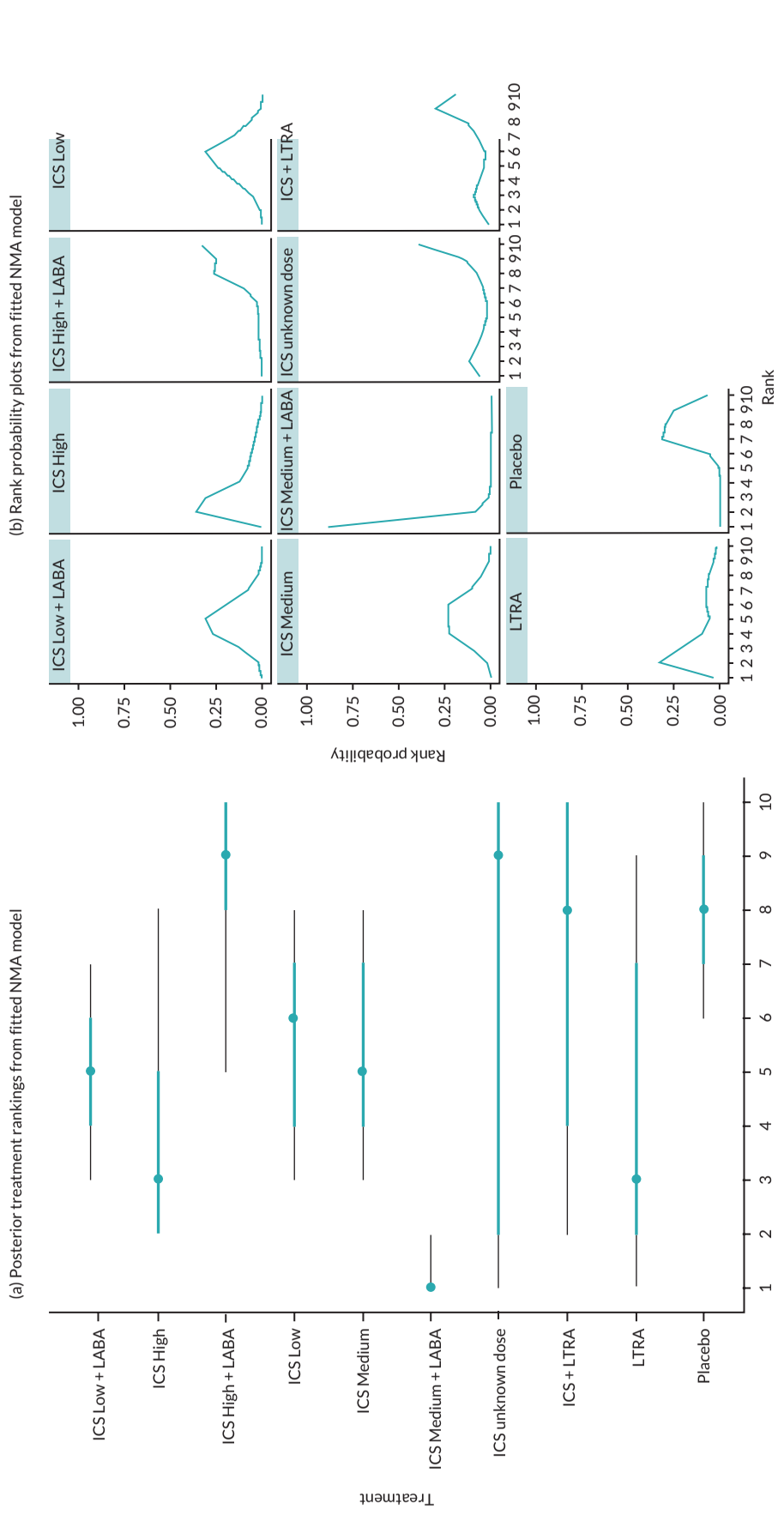

FIGURE 16 Ranks for the FE NMA (b) ICS stratified when combined with LABA for FEV_1. (a) Posterior treatment rankings from fitted NMA model. (b) Rank probability plots from fitted NMA model. Note: Rank median (point), IQR (bold line), 95% interval (thin line). Lower rank is better.

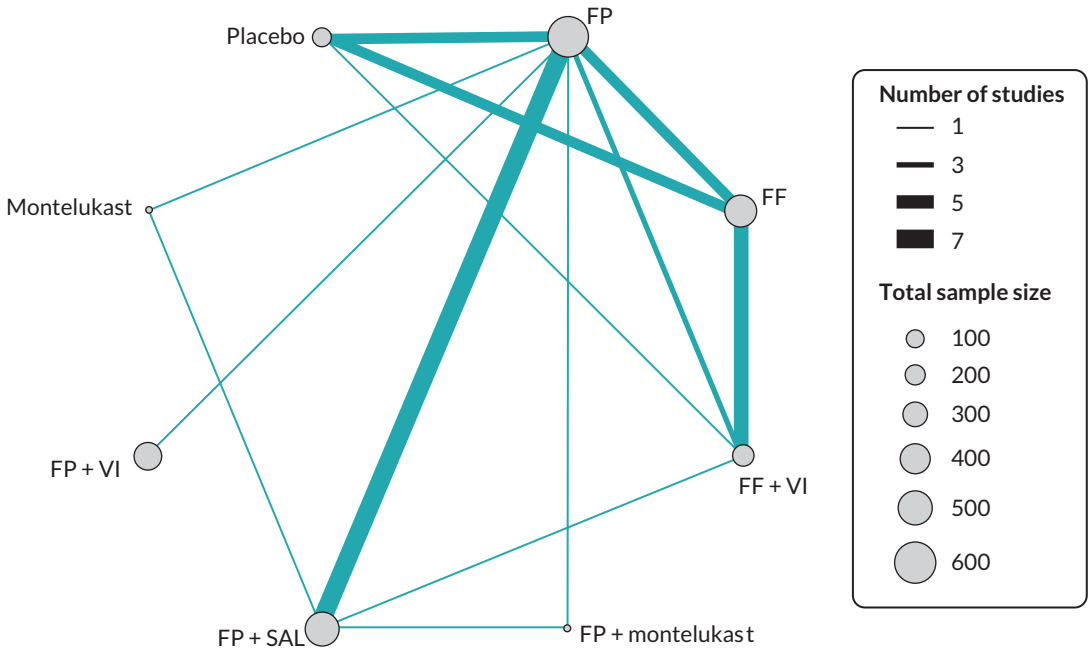

FIGURE 17 Network diagram (IPD only) for FEV_1 (c) individual compounds.

by a change in score of approximately 0.5 on a 7-point scale.[168,169] There were insufficient data to undertake a reliable NMA, and we focus interpretation on the direct pairwise comparison of treatment classes (*Table 30*; *Figure 19*). The latter suggests an improvement in QoL, as measured by PAQLQ, for ICS Medium when compared to ICS + LABA in two studies [MD 95% CrI, −0.91 (−1.53 to −0.29), FE MA] and an improvement in QoL, as measured by AQLQ, for ICS + LABA when compared to placebo in one study [−0.81 (−1.39 to −0.27)]; however, note that in both cases, the upper limit of the 95% CrI includes values that would not be considered clinically important. For all other pairwise comparisons, the 95% CrI includes the value of zero, and there is insufficient evidence to conclude any further differences in QoL among the pairs of treatment classes for which we had sufficient data available. We note the data available for these analyses are limited.

Mortality

There were no deaths recorded in any of the included trials.

Hospital admissions

Data for hospital admissions due to an asthma attack were only recorded in five trials for which IPD were available; AgD could not be extracted from any further trial reports. The data were too limited to perform any synthesis, and only summary data are presented (*Table 31*), showing a low hospitalisation rate due to an asthma attack, ranging from 0.5% to 2.7% of patients.

Adverse events

There was considerable heterogeneity in the recording and coding of AEs data across studies. We were able to summarise the numerical results (see *Appendix 8*, *Figures 21–29*) and conducted frequentist pairwise MA (where more than one study had recorded the same AE) using IPD and AgD for the AEs of infections/infestations; neurological disorders; oral candidiasis; pneumonia; cardiac disorders; clinically significant ECG changes (favourable and unfavourable); HR (mean change at the last visit vs. baseline). There is insufficient evidence to conclude that any of

TABLE 29 Bayesian FE NMA (IPD only) for FEV_1 (c) individual compounds

	TRT 2							
TRT 1	**FF**	**FF + VI**	**FP**	**FP + montelukast**	**FP + SAL**	**FP + VI**	**Montelukast**	**Placebo**
FF	○	−0.05 (−0.22; 0.12)	0.07 (−0.05; 0.19)	0.31 (−0.49; 1.16)	0.05 (−0.09; 0.20)	0.05 (−0.11; 0.21)	−0.08 (−0.57; 0.41)	**0.18 (0.05; 0.30)**
FF + VI	0.05 (−0.12; 0.22)	○	0.12 (−0.08; 0.32)	0.37 (−0.44; 1.23)	0.10 (−0.11; 0.32)	0.10 (−0.12; 0.33)	−0.02 (−0.54; 0.49)	**0.23 (0.03; 0.43)**
FP	−0.07 (−0.19; 0.05)	−0.12 (−0.19; 0.08)	○	0.25 (−0.55; 1.08)	−0.02 (−0.09; 0.06)	−0.02 (−0.12; 0.09)	−0.14 (−0.62; 0.33)	0.11 (−0.04; 0.26)
FP + montelukast	−0.31 (−1.16; 0.49)	−0.37 (−1.23; 0.44)	−0.25 (−1.08; 0.55)	○	−0.26 (−1.10; 0.53)	−0.26 (−1.10; 0.53)	−0.39 (−1.36; 0.55)	−0.14 (−0.99; 0.66)
FP + SAL	−0.05 (−0.20; 0.09)	−0.10 (−0.32; 0.11)	0.02 (−0.06; 0.09)	0.26 (−0.53; 1.10)	○	0.00 (−0.13; 0.13)	−0.13 (−0.61; 0.35)	0.12 (−0.05; 0.29)
FP + VI	−0.05 (−0.21; 0.11)	−0.10 (−0.33; 0.12)	0.02 (−0.09; 0.12)	0.26 (−0.53; 1.10)	0.00 (−0.13; 0.13)	○	−0.13 (−0.62; 0.36)	0.12 (−0.06; 0.31)
Montelukast	0.08 (−0.41; 0.57)	0.02 (−0.49; 0.54)	0.14 (−0.33; 0.62)	0.39 (−0.55; 1.36)	0.13 (−0.35; 0.61)	0.13 (−0.36; 0.62)	○	0.25 (−0.25; 0.75)
Placebo	**−0.18 (−0.30; −0.05)**	**−0.23 (−0.43; −0.03)**	−0.11 (−0.26; 0.04)	0.14 (−0.66; 0.99)	−0.12 (−0.29; 0.05)	−0.12 (−0.31; 0.06)	−0.25 (−0.75; 0.25)	○

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
MD (95% CrI) (17 studies, 1984 participants). Reference treatment: FP – DIC: 1087.7; residual deviance: 1943.1 (on 1984 data points).
MD > 0 favours TRT 1; MD < 0 favours TRT 2. Results with CrI that excludes the MD value of zero are highlighted in bold.

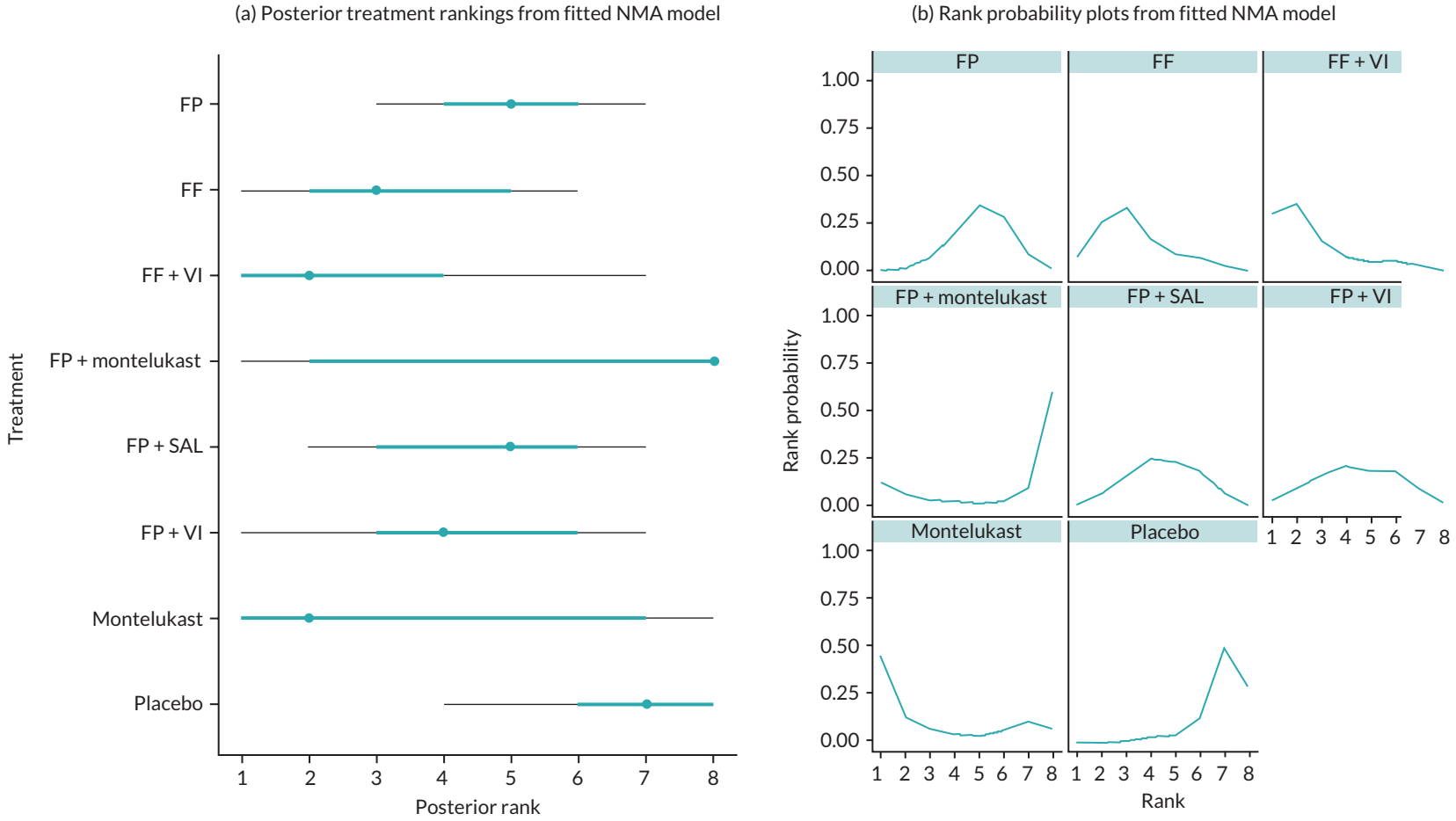

FIGURE 18 Ranks for the FE NMA (individual compounds) for FEV_1. (a) Posterior treatment rankings from fitted NMA model. (b) Rank probability plots from fitted NMA model. Note: Rank median (point), IQR (bold line), 95% interval (thin line). Lower rank is better.

TABLE 30 Direct pairwise comparisons of treatment classes (IPD and AgD) for QoL outcome

Direct comparison TRT 1 vs. TRT 2	Data[a]	Author (year) (participants on each treatment)	Studies (*N*)	Participants (*N*)	QoL Tool	Total score at the last visit (average score) TRT 1 vs. TRT 2 Mean (SD)	Bayesian MA			
							Fixed-effect model MD (95% CrI)	DIC	REs model MD (95% CrI)	DIC
ICS + LABA vs. ICS Low	IPD AgD	Lenney (2013)[4] (15 vs. 10)[b] Murray (2011)[60] (86 vs. 87)[b] Pearlman (2009)[64] (91 vs. 79)[b] Wechsler (2019)[72] (51 vs. 22)	4	243 vs. 198	PAQLQ	5.4 (1.6) vs. 6.3 (0.9) 5.9 (0.8) vs. 5.9 (0.8) 5.8 (0.9) vs. 5.8 (0.9) 6.2 (0.9) vs. 5.7 (1.2)	0.01 (−0.17; 0.19)	431.1	0.06 (−0.53; 0.68)	433.1
ICS + LABA vs. ICS Medium	IPD	Lemanske (2010)[3] (8 vs. 6)[b] Thomas (2014)[69] (11 vs. 11)[b]	2	19 vs. 17	PAQLQ	5.8 (1.0) vs. 5.3 (1.4) 5.4 (1.1) vs. 6.4 (0.6)	**−0.91 (−1.53; −0.29)**	37.6	−0.89 (−2.27; 0.50)	38.3
ICS + LTRA vs. ICS Medium	IPD	Lemanske (2010)[3] (13 vs. 6) Thomas (2014)[69] (11 vs. 11)	2	24 vs. 17	PAQLQ	6.2 (1.1) vs. 6.6 (0.3) 6.1 (0.9) vs. 6.4 (0.6)	−0.35 (−0.85; 0.18)	42.5	−0.35 (−1.68; 0.95)	43.2
ICS + LTRA vs. ICS + LABA	IPD AgD	Lemanske (2010)[3] (13 vs. 8) Lenney (2013)[4] (12 vs. 15)[b] Thomas (2014)[69] (11 vs. 11)[b]	3	36 vs. 34	PAQLQ	6.2 (1.1) vs. 5.8 (1.0) 6.3 (0.9) vs. 5.4 (1.6) 6.1 (0.9) vs. 5.4 (1.1)	0.59 (−0.11; 1.30)	46.7	0.60 (−0.56; 1.76)	47.6
ICS Low vs. ICS High	IPD	Wechsler (2019)[72] (22 vs. 22)	1	22 vs. 22	PAQLQ	5.7 (1.2) vs. 6.3 (0.9)	Bayesian linear regression model (Stan): −0.61 (−1.23; 0.03)			
ICS + LABA vs. ICS High	IPD	Wechsler (2019)[72] (51 vs. 22)	1	51 vs. 22	PAQLQ	6.2 (0.9) vs. 6.3 (0.9)	Bayesian linear regression model (Stan): −0.13 (−0.58; 0.32)			
ICS Low vs. ICS + LTRA	AgD	Lenney (2013)[4] (10 vs. 12)[b]	1	10 vs. 12	PAQLQ	6.3 (0.9) vs. 6.3 (0.9)	Bayesian linear regression model (Stan): not estimable[d]			
ICS + LABA vs. ICS Low	IPD	Bernstein (2015)[48] (24 vs. 16) Bleecker (2014)[50] (13 vs. 14)	2	37 vs. 30	AQLQ	5.5 (1.1) vs. 5.4 (1.1) 6.3 (0.7) vs. 5.9 (0.6)	0.31 (−0.15; 0.75)	14.4	0.27 (−1.10; 1.62)	16
ICS + LABA vs. ICS High	IPD	O'Byrne (2014)[61] (3 vs. 5)[c] Wechsler (2019)[72] (21 vs. 10)	2	24 vs. 15	AQLQ	6.1 (0.3) vs. 5.6 (1.5) 6.1 (0.8) vs. 6.5 (0.5)	−0.17 (−0.50; 0.17)	113.3	−0.03 (−1.57; 1.72)	114.2
placebo vs. ICS Low	IPD	Bleecker (2014)[50] (21 vs. 14) Lötvall (2014)[57] (14 vs. 15)	2	35 vs. 29	AQLQ	5.5 (0.9) vs. 5.9 (0.6) 5.9 (0.7) vs. 6.2 (0.6)	−0.32 (−0.66; 0.03)	59.7	−0.29 (−1.45; 1.03)	60.4
ICS Medium vs. ICS Low	IPD	Lötvall (2014)[57] (10 vs. 15)	1	10 vs. 15	AQLQ	5.6 (1.3) vs. 6.2 (0.6)	Bayesian linear regression model (Stan): −0.55 (−1.33; 0.23)			
placebo vs. ICS Medium	IPD	Lötvall (2014)[57] (14 vs. 10)	1	14 vs. 10	AQLQ	5.9 (0.7) vs. 5.6 (1.3)	Bayesian linear regression model (Stan): 0.31 (−0.50; 1.16)			
placebo vs. ICS + LABA	IPD	Bleecker (2014)[50] (21 vs. 13)	1	21 vs. 13	AQLQ	5.5 (0.9) vs. 6.3 (0.7)	Bayesian linear regression model (Stan): **−0.81 (−1.39; −0.27)**			

N/A, not available; TRT, treatment.
a All data available were used (IPD and AgD where possible).
b ICS Low + LABA.
c ICS High + LABA.
d Same mean and SD in both arms (constant).

Note
MD > 0 favours TRT 1; MD < 0 favours TRT 2.

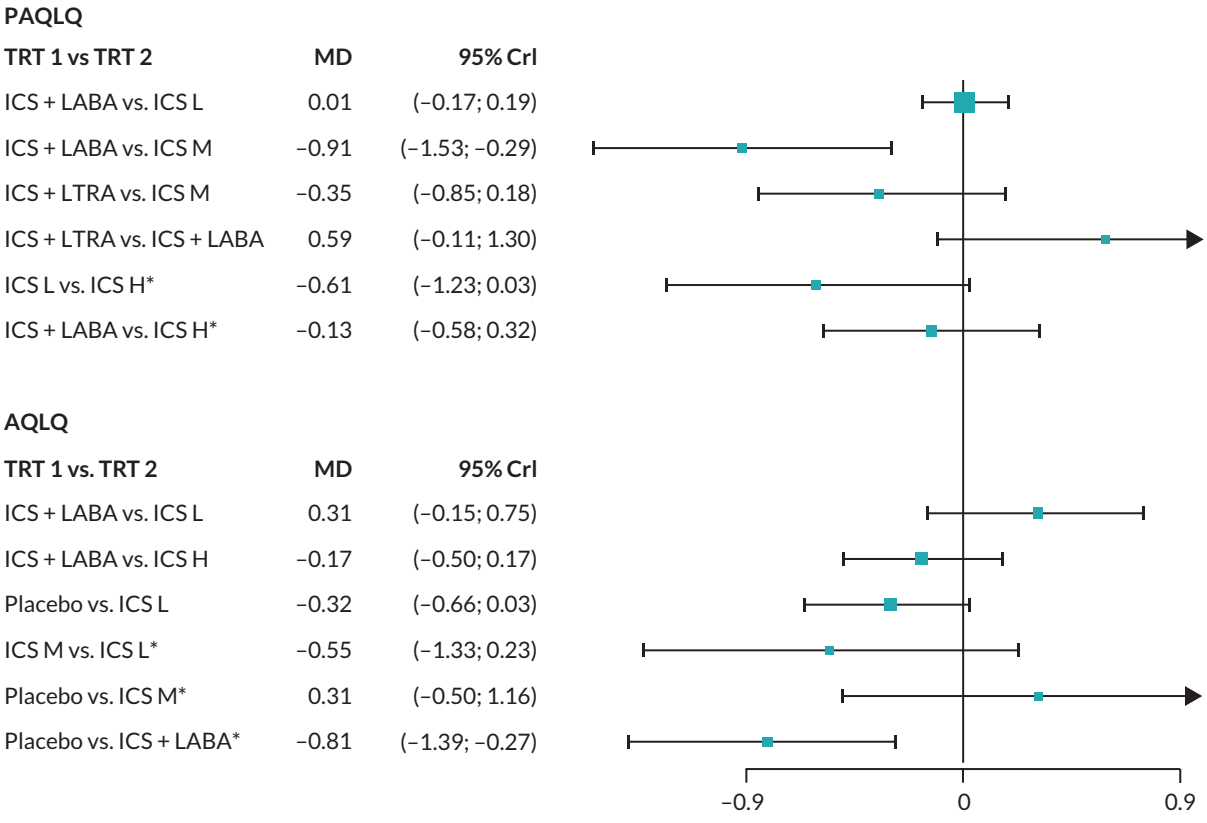

FIGURE 19 Forest plot of MD (95% CrI) for QoL outcome (direct pairwise comparison of treatment classes). L, low dose; M, medium dose; H, high dose. Notes: MD > 0 favours TRT 1; MD < 0 favours TRT 2. All results are from Bayesian FE MA except for those with the star (*), which are from Bayesian linear regression models (Stan) based on one study.

TABLE 31 Hospital admissions

Author (year)	Data	Treatment class	Compounds	Number of patients	Was the patient hospitalised due to an asthma attack? *N* (%)
Bateman (2014)[47]	IPD	ICS Low	FF	102	0
		ICS + LABA	FF + VI	111	3 (2.7%)
de Blic (2009)[52]	IPD	ICS Medium	FP	153	0
		ICS + LABA	FP + SAL	150	1 (0.7%)
Stempel (2016)[68]	IPD	ICS Medium	FP	813	4 (0.5%)
		ICS + LABA	FP + SAL	818	5 (0.6%)
Stempel (2016)[67]	IPD	ICS High	FP	40	0
		ICS Low	FP	15	0
		ICS Medium	FP	50	0
		ICS + LABA	FP + SAL	117	2 (1.7%)
Wechsler (2019)[72]	IPD	ICS High	FP	45	1 (2.2%)
		ICS Low	FP	33	0
		ICS + LABA	FP + SAL	93	1 (1.1%)

these AEs differs markedly between the treatment classes that could be compared, other than slightly fewer patients reported neurological disorders (graded as mild or moderate) on ICS + LABA [1 patient (4.3%) on fluticasone + SAL] compared to ICS + LTRA [seven patients (33.3%) on fluticasone + montelukast] with estimated OR 0.09 (95% CI 0.01 to 0.82; one study), and a greater number of patients reported neurological disorders for ICS Medium compared to placebo with estimated OR 4.8 (95% CI 1.12 to 20.60; three studies). For all other analyses, there is considerable uncertainty with 95% CIs that include values of OR/MD that could be clinically important, and we cannot rule out the possibility of important differences in AEs between treatments.

Chapter 7 Investigating treatment by covariate interactions (effect modifiers) and the transitivity assumption

In this chapter, we report results from Bayesian NMA models that include treatment by covariate interactions for the outcomes *exacerbation*, *asthma control* and FEV_1. The aim of the chapter is to explore whether participant characteristics (i.e. covariates) modify the treatment effects such that different treatment recommendations are made for participants with different clinical and demographic characteristics. Furthermore, evidence of an interaction could invalidate the underlying assumption of transitivity for NMA (see *Chapters 5* and *6*) if there is substantial variation in the covariate distribution across comparisons. For each outcome, the following covariates were studied in turn: *age* (years); *sex* (females vs. males); *ethnicity* (not Hispanic or Latino vs. Hispanic or Latino); *eczema* (present vs. absent); *eosinophilia* (eosinophilic vs. non-eosinophilic); and *baseline severity* (mild, moderate, severe). For each model, the Gelman-Rubin R hat statistic indicated convergence.

Exacerbation

Data were available from 39 studies with 8136 participants for the outcome *exacerbation*, including IPD for 5349 participants from 26 studies and AgD for 2787 participants from 13 studies.

Age

When a model was fitted to the IPD and AgD, the tail ESS was too low, which reflects poor sampling efficiency, and can cause the estimated variances to be unreliable. The issue could not be rectified by increasing the number of iterations [Vehtari (2021)];[170] therefore, the results presented are based on a model that used IPD alone.

The network included 24 IPD studies (4929 participants). Six treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LABA and placebo. *Appendix 9*, *Figure 31* displays the age distribution of participants within each trial, and *Appendix 9*, *Table 59* shows that the average age of participants within studies varies from approximately 3 to 16 years with no substantial differences across comparisons, although data are limited. FE and REs models including interactions were similar in terms of model fit and complexity; the DIC was 2085.1 for the FE model and 2085.5 for the REs model (see *Appendix 9*, *Table 60*); therefore, the FE model was most appropriate. However, the DIC from the FE model that did not include interactions was markedly lower again (DIC = 2080), suggesting that the FE model without interactions was preferred overall. Additionally, no treatment by *age* interactions were apparent based on the CrIs of the estimated regression coefficients for the interactions, which indicated that the ORs for each treatment versus ICS Low did not differ according to the age of participants (see *Appendix 9*, *Table 61*).

Sex

When a model was fitted to the IPD and AgD, the same issue regarding low tail ESS arose; therefore, the results presented are based on a model that used IPD alone. The network included all 26 IPD studies (5349 participants). Six treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 32*). The percentage of female participants within studies varied from 20% to 69% (see *Appendix 9*, *Table 59*). FE and REs models with interactions were similar in terms of model fit and complexity (DIC = 2251.5 and 2253.1, respectively); therefore, the FE model was favoured (see *Appendix 9*, *Table 60*). The DIC from the FE model without interactions was lower (DIC = 2245.7) than the FE model with interactions; therefore, the model without interactions was the most favourable overall. There was no treatment by *sex* interactions based on the CrIs of the estimated regression coefficients; therefore, the log ORs for each treatment versus ICS + LABA were not remarkably different for males and females (see *Appendix 9*, *Table 61*).

Ethnicity

Overall, 27 studies including 5645 participants contributed to the network: 26 IPD studies (5349 participants) and 1 AgD study (296 participants). Six treatments were allocated in trials: ICS High, ICS Medium, ICS Low, LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 33*). The percentage of Hispanic and Latino participants within studies ranged from 0 to 72% (see *Appendix 9*, *Table 59*). FE and REs models including interactions were comparable in terms of model fit and complexity (see *Appendix 9*, *Table 60*; DIC = 2245.0 and 2246.9, respectively); therefore, the FE model was preferred. The DIC from the FE model without interactions (DIC = 2246.1) was fairly similar to that from the same model with interactions and, therefore, the FE model without interactions appeared to be superior overall. However, the 95% CrIs of the interaction regression coefficients exclude zero for ICS Medium versus ICS Low [−1.25, 95% CrI (−2.47 to −0.18)], ICS + LABA versus ICS Low [−1.09, 95% CrI (−2.27 to −0.06)] and placebo versus ICS Low [−2.70, 95% CrI (−5.19 to −0.24)] (see *Appendix 9*, *Table 61*), suggesting there may be differences in the log OR for 'not Hispanic or Latino' participants compared to the log OR for 'Hispanic or Latino' participants. However, examination of the full range of OR (95% CrI) from the model with interactions (*Table 32*) shows there is good overlap of the 95% CrIs for different treatment comparisons, and results do not appear to be qualitatively different to the overall NMA (*Table 16*).

TABLE 32 Odds ratios (95% CrI) from FE NMR including treatment by ethnicity interactions for the outcome exacerbation

Hispanic or Latino (*N* = 1457)						
	TRT 2					
TRT 1	**ICS Low *N* = 418**	**ICS Medium *N* = 258**	**ICS High *N* = 18**	**ICS + LABA *N* = 698**	**LTRA *N* = 3**	**Placebo *N* = 62**
ICS Low	○	0.43 (0.13; 1.21)	1.12 (0.11; 27.11)	0.54 (0.17; 1.43)	*Not estimable*	**0.04 (0.01; 0.28)**
ICS Medium	2.34 (0.83; 7.54)	○	2.61 (0.32; 56.83)	1.26 (0.75; 2.12)	*Not estimable*	**0.10 (0.01; 0.62)**
ICS High	0.90 (0.04; 9.30)	0.38 (0.02; 3.13)	○	0.48 (0.02; 3.86)	*Not estimable*	**0.04 (0.00; 0.61)**
ICS + LABA	1.86 (0.70; 5.75)	0.79 (0.47; 1.34)	2.08 (0.26; 45.15)	○	*Not estimable*	**0.08 (0.01; 0.49)**
LTRA	*Not estimable*	*Not estimable*	*Not estimable*	*Not estimable*	○	*Not estimable*
Placebo	**24.53 (3.56; 192.48)**	**10.49 (1.62; 74.44)**	**27.39 (1.65; 906.87)**	**13.20 (2.03; 93.69)**	*Not estimable*	○
Not Hispanic or Latino (*N* = 4188)						
	TRT 2					
TRT 1	**ICS Low *N* = 941**	**ICS Medium *N* = 1014**	**ICS High *N* = 226**	**ICS + LABA *N* = 1824**	**LTRA *N* = 27**	**Placebo *N* = 156**
ICS Low	○	1.49 (0.80; 2.72)	1.93 (0.95; 3.97)	1.60 (0.94; 2.69)	0.26 (0.05; 1.09)	0.61 (0.27; 1.42)
ICS Medium	0.67 (0.37; 1.25)	○	1.30 (0.69; 2.51)	1.07 (0.75; 1.52)	**0.17 (0.03; 0.83)**	0.41 (0.15; 1.13)
ICS High	0.52 (0.25; 1.05)	0.77 (0.40; 1.45)	○	0.83 (0.47; 1.42)	**0.13 (0.02; 0.67)**	**0.31 (0.11; 0.91)**
ICS + LABA	0.63 (0.37; 1.06)	0.93 (0.66; 1.34)	1.21 (0.70; 2.12)	○	**0.16 (0.03; 0.75)**	0.38 (0.15; 1.00)
LTRA	3.90 (0.91; 20.09)	**5.81 (1.21; 33.45)**	**7.54 (1.49; 44.70)**	**6.23 (1.34; 35.16)**	○	2.36 (0.45; 15.03)

continued

TABLE 32 Odds ratios (95% CrI) from FE NMR including treatment by ethnicity interactions for the outcome exacerbation (*continued*)

Not Hispanic or Latino (*N* = 4188)						
	TRT 2					
TRT 1	ICS Low *N* = 941	ICS Medium *N* = 1014	ICS High *N* = 226	ICS + LABA *N* = 1824	LTRA *N* = 27	Placebo *N* = 156
Placebo	1.65 (0.70; 3.67)	2.46 (0.89; 6.62)	**3.19 (1.09; 9.12)**	2.64 (1.00; 6.69)	0.42 (0.07; 2.20)	○

N, number of patients.

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
OR > 1 favours TRT 2 (the probability of having exacerbation was modelled). Results with CrIs that exclude the OR value of one are highlighted in bold.

Eczema

The network included eight studies (2469 participants), seven of which were IPD studies (2437 participants). Six treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 34*). The percentage of participants with eczema within studies ranged from 15% to 100% (see *Appendix 9*, *Table 59*). FE and REs models with interactions were similar in terms of model fit and complexity (DIC = 1330.6 and 1331.9, respectively); therefore, the FE model was preferred (see *Appendix 9*, *Table 60*). The DIC from the FE model that did not include interactions was noticeably lower (DIC = 1324.7.0) than the same model with interactions, suggesting that the model without interactions was the best. The CrIs of the regression coefficients also indicated that there were no treatment by *eczema* interactions; therefore, the log ORs for each treatment versus ICS Medium did not differ based on whether participants suffered from eczema or not (see *Appendix 9*, *Table 61*).

Eosinophilia

The network involved 13 IPD studies (1898 participants). Six treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 35*). The percentage of participants with eosinophilia within studies varied from 22 to 71% (see *Appendix 9*, *Table 59*). When interactions were included in the model, the FE model appeared most appropriate with respect to model fit and complexity (DIC = 622.1 for the FE model and DIC = 619.7 for the REs model) (see *Appendix 9*, *Table 60*). The DIC from the FE model that did not include interactions (DIC = 616.1) was markedly lower than the same model with interactions; this suggests that the model without interactions was superior overall. The CrIs for the regression coefficients also indicated that there were no treatment by *eosinophilia* interactions; therefore, the log ORs for each treatment versus ICS Low did not differ based on eosinophilia (see *Appendix 9*, *Table 61*).

Baseline severity

The network included 21 IPD studies (2916 participants). Five treatments were allocated in trials: ICS High, ICS Medium, ICS Low, ICS + LABA and placebo (see *Appendix 9*, *Figure 36*). The percentage of participants with mild, moderate and severe disease at baseline within studies ranged from 0% to 100%, 0 to 80% and 0% to 34%, respectively (see *Appendix 9*, *Table 59*). Model fit results in *Appendix 9*, *Table 60* show that FE and REs models including interactions were comparable in terms of model fit and complexity (DIC = 765.7 and 765.9, respectively); therefore, the FE model was most favourable. Yet, the DIC from the FE model without interactions (DIC = 763.8) was similar to that of the FE model with interactions, so the FE model without interactions was preferred overall. In contrast, the 95% CrI of the interaction regression coefficients excludes zero for ICS Medium versus ICS Low [2.11 (0.32, 3.89)] (see *Appendix 9*, *Table 61*), indicating that the difference in the log OR may differ for participants following a one-category increase in severity (i.e. mild to moderate or moderate to severe). However, the number of participants and events is small for some combinations of treatments and covariate. Furthermore, examination of the full range of OR (95% CrI) from the model with interactions (*Table 33*) shows there is a good overlap of the CrIs across levels of the covariate for different treatment comparisons. These results are also generally qualitatively similar to the overall NMA without interactions (*Table 16*) except for ICS Medium versus ICS Low in participants with severe asthma at baseline [25.79 (1.48, 378.61)

TABLE 33 Odds ratios from FE NMA, including treatment by baseline severity interactions for the outcome exacerbation

Mild (*N* = 1716, 60 events)					
	TRT 2				
TRT 1	**ICS Low** *N* = 544 *NE* = 14	**ICS Medium** *N* = 236 *NE* = 1	**ICS High** *N* = 98 *NE* = 18	**ICS + LABA** *N* = 788 *NE* = 25	**Placebo** *N* = 50 *NE* = 2
ICS Low	○	2.64 (0.41; 20.29)	2.05 (0.75; 5.64)	1.39 (0.65; 3.00)	0.12 (0.01; 1.16)
ICS Medium	0.38 (0.05; 2.46)	○	0.78 (0.10; 5.05)	0.53 (0.08; 3.10)	**0.05 (0.00; 0.76)**
ICS High	0.49 (0.18; 1.34)	1.28 (0.20; 10.28)	○	0.68 (0.31; 1.46)	**0.06 (0.01; 0.64)**
ICS + LABA	0.72 (0.33; 1.54)	1.88 (0.32; 13.07)	1.46 (0.68; 3.19)	○	**0.09 (0.01; 0.88)**
Placebo	8.08 (0.86; 85.63)	**21.33 (1.31; 411.58)**	**16.61 (1.57; 194.42)**	**11.36 (1.14; 121.51)**	○
Moderate (*N* = 1007, 40 events)					
	TRT 2				
TRT 1	**ICS Low** *N* = 416 *NE* = 7	**ICS Medium** *N* = 73 *NE* = 4	**ICS High** *N* = 60 *NE* = 9	**ICS + LABA** *N* = 392 *NE* = 17	**Placebo** *N* = 66 *NE* = 3
ICS Low	○	0.32 (0.06; 1.62)	1.00 (0.32; 3.13)	0.85 (0.36; 1.93)	**0.06 (0.01; 0.48)**
ICS Medium	3.13 (0.62; 15.96)	○	3.16 (0.57; 16.78)	2.69 (0.61; 11.47)	0.20 (0.02; 2.01)
ICS High	1.00 (0.32; 3.16)	0.32 (0.06; 1.75)	○	0.85 (0.35; 2.10)	**0.06 (0.01; 0.58)**
ICS + LABA	1.17 (0.52; 2.75)	0.37 (0.09; 1.65)	1.17 (0.48; 2.86)	○	**0.08 (0.01; 0.59)**
Placebo	**15.49 (2.08; 148.41)**	4.90 (0.50; 60.95)	**15.49 (1.73; 165.67)**	**13.20 (1.68; 129.02)**	○
Severe (*N* = 193, 5 events)					
	TRT 2				
TRT 1	**ICS Low** *N* = 49 *NE* = 1	**ICS Medium** *N* = 6 *NE* = 0	**ICS High** *N* = 5 *NE* = 2	**ICS + LABA** *N* = 130 *NE* = 2	**Placebo** *N* = 3 *NE* = 0
ICS Low	○	**0.04 (0.00; 0.68)**	0.49 (0.06; 3.53)	0.52 (0.10; 2.44)	0.03 (0.00; 1.32)
ICS Medium	**25.79 (1.48; 387.61)**	○	12.68 (0.65; 204.38)	13.60 (0.89; 152.93)	0.89 (0.02; 43.82)
ICS High	2.03 (0.28; 15.49)	0.08 (0.00; 1.54)	○	1.06 (0.20; 5.64)	0.07 (0.00; 2.77)
ICS + LABA	1.92 (0.41; 10.49)	0.07 (0.01; 1.13)	0.94 (0.18; 4.95)	○	0.07 (0.00; 2.27)
Placebo	29.37 (0.76; 992.27)	1.13 (0.02; 56.26)	14.44 (0.36; 492.75)	15.33 (0.44; 432.68)	○

N, number of patients; *NE*, number of exacerbations.

Note
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2). OR > 1 favours TRT 2 (the probability of having exacerbation was modelled). Results with CrIs that exclude the OR value of 1 are highlighted in bold.

favouring ICS Low], albeit the direct evidence is sparse (one event out of 49 patients ICS Low; 0 events out of six patients ICS Medium).

Asthma control

Data were available from 15 IPD studies with 2998 participants for the outcome *asthma control*.

Age

The network included all 15 IPD studies (2998 participants). Seven treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 37*). *Appendix 9*, *Figure 38* displays the age distribution of participants within each trial, and *Appendix 9*, *Table 62* shows that the average age of participants within studies varied from approximately 7–16 years. When interactions were included in the model, the FE and REs models differed in terms of model fit and complexity; the DIC was 2833.9 for the FE model and 2827.5 for the REs model (see *Appendix 9*, *Table 63*); therefore, the REs model was most appropriate. The DIC from the REs model without interactions (DIC = 2824.8) was similar to that of the same model but with interactions; therefore, the REs model without interactions was the preferred choice overall. Additionally, no treatment by *age* interactions existed based on the CrIs of the regression coefficients, indicating that the log ORs for each treatment versus ICS + LABA did not differ according to the age of participants (see *Appendix 9*, *Table 64*).

Sex

The network included all 15 IPD studies (2998 participants). Seven treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 37*). The percentage of female participants within studies ranged from 20% to 45% (see *Appendix 9*, *Table 62*). FE and REs models with interactions were similar in terms of model fit and complexity (DIC = 2827.2 and 2826.1, respectively, *Appendix 9*, *Table 63*), which advocates use of the FE model. However, the DIC for the FE model without interactions (DIC = 2823.2) was comparable to that of the same model with interactions, such that the FE model without interactions was the best model overall. In agreement with the model fit statistics, there were no treatment by *sex* interactions based on the CrIs of the regression coefficients; therefore, the log ORs for each treatment versus ICS + LABA were not remarkedly different for males and females (see *Appendix 9*, *Table 64*).

Ethnicity

The network included all 15 IPD studies (2998 participants). Seven treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 37*). The percentage of participants of Hispanic or Latino ethnicity within studies varied between 0% and 71% (see *Appendix 9*, *Table 62*). FE and REs models with interactions were similar in terms of model fit and complexity (DIC = 2834.1 and 2833.1, respectively), favouring the FE model (see *Appendix 9*, *Table 63*). The DIC from the FE model without interactions was lower still (DIC = 2825.3), which suggests it was the superior model overall.

There was also no treatment by *ethnicity* interactions based on the CrIs of the regression coefficients; therefore, the log ORs for each treatment versus ICS + LABA were similar for participants of any ethnicity (see *Appendix 9*, *Table 64*).

Eczema

The network included 6 IPD studies (1968 participants). Six treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LABA and ICS + LTRA (see *Appendix 9*, *Figure 39*). The percentage of participants with eczema within studies ranged from 21 to 70% (see *Appendix 9*, *Table 62*).

When including interactions, the FE model appeared to be most appropriate because FE and REs models were similar in terms of model fit and complexity (DIC = 1627.6 and 1626.2, respectively, *Appendix 9*, *Table 63*). The DIC from the FE model without interactions was noticeably lower still (DIC = 1619.5), and as such this model is preferred overall. There were also no treatment by *eczema* interactions based on the CrIs of the regression coefficients; therefore, the log ORs for each treatment versus ICS + LABA did not differ based on whether participants suffered from eczema or not (see *Appendix 9*, *Table 64*).

Eosinophilia

The network involved 12 IPD studies (1192 participants). Seven treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 40*). The percentage of participants with eosinophilia within studies ranged from 18% to 71% (see *Appendix 9*, *Table 62*). FE and REs models including interactions were similar regarding model fit and complexity (DIC = 1355.0 and 1355.1, respectively, *Appendix 9*, *Table 63*). The DIC from the FE model without interaction was lower again (DIC = 1345.7), so this model was the best overall. There were also no apparent treatment by *eosinophilia* interactions based on the CrIs of the regression coefficients; therefore, the ORs for each treatment versus ICS + LABA did not differ based on *eosinophilia* (see *Appendix 9*, *Table 64*).

Baseline severity

The network included 13 IPD studies (1074 participants). Seven treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 41*). The percentage of participants with mild, moderate and severe disease at baseline within studies ranged from 0% to 100%, 0 to 80% and 0 to 33%, respectively (see *Appendix 9*, *Table 62*). Model fit results in *Appendix 9*, *Table 63* show that FE and REs models with interactions appear to be similar in terms of model fit and complexity (DIC = 1212.7 and 1208.7, respectively); therefore, the FE model was favoured. However, the DIC from the FE model without interactions (DIC = 1207.6) was comparable with that from the same model with interactions; therefore, the model without interactions was the preferred overall. No treatment by *severity* interactions were apparent based on the CrIs of the regression coefficients; therefore, the ORs for each treatment versus ICS + LABA did not differ according to the baseline asthma severity (see *Appendix 9*, *Table 64*).

Forced expiratory volume in 1 second

Data were available from 22 studies with 2486 participants for the outcome FEV_1 including IPD for 2171 participants from 20 trials and AgD for 315 participants from two studies.

Age

The network included 18 IPD studies (1657 participants) and one AgD study (29 participants). Eight treatments were compared: ICS High, ICS Medium, ICS Low, ICS at an unknown dose, LTRA, ICS + LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 42*). The age of participants varied within trials (see *Appendix 9*, *Figure 43*). The average age of participants within studies varied from approximately 8–16 years (see *Appendix 9*, *Table 65*). Including interactions, FE and REs models differed regarding model fit and complexity; the DIC was −714.3 for the FE model and −681.6 for the REs model (see *Appendix 9*, *Table 66*), which advocates the use of the FE model. The FE model without interactions (DIC = −579.2) was not preferred when compared with the same model with interactions. The regression coefficient for the treatment by *age* interaction represents the difference in the MD per 1-year increase in age. In conflict with the model fit statistics, based on the 95% CrIs of the regression coefficients, there was no evidence of treatment by *age* interactions (see *Appendix 9*, *Table 67*).

Sex

The network consisted of 20 studies (1937 participants) including 19 IPD studies (1908 participants) and one AgD study (29 participants). Eight treatments were compared: ICS High, ICS Medium, ICS Low, ICS at an unknown dose, LTRA, ICS + LTRA, ICS + LABA and placebo. The percentage of female participants within studies ranged from 13 to 71% (see *Appendix 9*, *Table 65*). FE and REs models including interactions differed regarding model fit and complexity; the DIC was 761.5 for the FE model and 746.2 for the REs model (see *Appendix 9*, *Table 66*), favouring the REs model. The DIC (DIC = 670.6) suggests that the REs model without interactions is preferred over the same model including interactions. The regression coefficient for the treatment by *sex* interaction represents the difference in the MD for females compared to the MD for males. Based on the 95% CrIs of the interaction regression coefficients, there is a suggestion of an interaction for LTRA versus ICS + LABA [0.68 (0.21 to 1.14) *Appendix 9*, *Table 67*], which results in non-overlap of CrIs around the MD comparing ICS Low to LTRA [0.00 (−0.24 to 0.25) males vs. 0.68 (0.27 to 1.10) females (*Table 34*)] and some further differences between males and females, albeit with overlapping CrI for most comparisons against LTRA. However, with only LTRA data for 14 participants (representing 0.7% of the total number of participants

TABLE 34 Mean differences (95% CrI) from REs NMR including treatment by sex interactions for the outcome FEV_1

Females (*N* = 701)								
	TRT 2							
TRT 1	**ICS Low** ***N* = 195**	**ICS Medium** ***N* = 111**	**ICS High** ***N* = 45**	**ICS + LABA** ***N* = 290**	**ICS unknown dose** ***N* = 2**	**ICS + LTRA** ***N* = 6**	**LTRA** ***N* = 3**	**Placebo** ***N* = 49**
ICS Low	○	−0.01 (−0.11; 0.11)	−0.03 (−0.20; 0.13)	−0.02 (−0.09; 0.06)	0.23 (−7.91; 8.50)	0.24 (−0.03; 0.53)	**−0.68 (−1.10; −0.27)**	0.09 (−0.04; 0.24)
ICS Medium	0.01 (−0.11; 0.11)	○	−0.02 (−0.21; 0.14)	−0.01 (−0.10; 0.07)	0.24 (−7.87; 8.53)	0.25 (−0.02; 0.52)	**−0.67 (−1.10; −0.24)**	0.10 (−0.05; 0.26)
ICS High	0.03 (−0.13; 0.20)	0.02 (−0.14; 0.21)	○	0.02 (−0.14; 0.18)	0.26 (−7.85; 8.57)	0.28 (−0.03; 0.59)	**−0.65 (−1.10; −0.21)**	0.12 (−0.09; 0.35)
ICS + LABA	0.02 (−0.06; 0.09)	0.01 (−0.07; 0.10)	−0.02 (−0.18; 0.14)	○	0.25 (−7.87; 8.55)	0.26 (−0.02; 0.52)	**−0.66 (−1.09; −0.24)**	0.11 (−0.03; 0.26)
ICS unknown dose	−0.23 (−8.50; 7.91)	−0.24 (−8.53; 7.87)	−0.26 (−8.57; 7.85)	−0.25 (−8.55; 7.87)	○	0.01 (−8.22; 8.13)	−0.91 (−9.09; 7.35)	−0.14 (−8.40; 7.99)
ICS + LTRA	−0.24 (−0.53; 0.03)	−0.25 (−0.52; 0.02)	−0.28 (−0.59; 0.03)	−0.26 (−0.52; 0.02)	−0.01 (−8.13; 8.22)	○	**−0.92 (−1.41; −0.43)**	−0.15 (−0.45; 0.16)
LTRA	**0.68 (0.27; 1.10)**	**0.67 (0.24; 1.10)**	**0.65 (0.21; 1.10)**	**0.66 (0.24; 1.09)**	0.91 (−7.35; 9.09)	**0.92 (0.43; 1.41)**	○	**0.77 (0.33; 1.22)**
Placebo	−0.09 (−0.24; 0.04)	−0.10 (−0.26; 0.05)	−0.12 (−0.35; 0.09)	−0.11 (−0.26; 0.03)	0.14 (−7.99; 8.40)	0.15 (−0.16;0.45)	**−0.77 (−1.22; −0.33)**	○
Males (*N* = 1237)								
	TRT 2							
TRT 1	**ICS Low** ***N* = 311**	**ICS Medium** ***N* = 213**	**ICS High** ***N* = 102**	**ICS + LABA** ***N* = 499**	**ICS unknown dose** ***N* = 13**	**ICS + LTRA** ***N* = 23**	**LTRA** ***N* = 11**	**Placebo** ***N* = 65**
ICS Low	○	0.01 (−0.08; 0.12)	−0.05 (−0.19; 0.10)	−0.02 (−0.09; 0.06)	0.35 (−1.19; 1.94)	0.16 (0.00; 0.32)	0.00 (−0.25; 0.24)	**0.13 (0.02; 0.27)**
ICS Medium	−0.01 (−0.12; 0.08)	○	−0.06 (−0.22; 0.08)	−0.03 (−0.11; 0.04)	0.33 (−1.21; 1.93)	0.14 (−0.01; 0.29)	−0.01 (−0.28; 0.24)	0.12 (−0.02; 0.27)
ICS High	0.05 (−0.10; 0.19)	0.06 (−0.08; 0.22)	○	0.03 (−0.10; 0.17)	0.39 (−1.16; 1.98)	**0.20 (0.01; 0.41)**	0.05 (−0.23; 0.33)	**0.18 (0.01; 0.37)**
ICS + LABA	0.02 (−0.06; 0.09)	0.03 (−0.04; 0.11)	−0.03 (−0.17; 0.10)	○	0.36 (−1.17; 1.96)	**0.17 (0.03; 0.32)**	0.02 (−0.24; 0.26)	**0.15 (0.03; 0.29)**

TABLE 34 Mean differences (95% CrI) from REs NMR including treatment by sex interactions for the outcome FEV_1 (*continued*)

Males (*N* = 1237)								
	TRT 2							
TRT 1	**ICS Low** *N* = 311	**ICS Medium** *N* = 213	**ICS High** *N* = 102	**ICS + LABA** *N* = 499	**ICS unknown dose** *N* = 13	**ICS + LTRA** *N* = 23	**LTRA** *N* = 11	**Placebo** *N* = 65
ICS unknown dose	−0.35 (−1.94; 1.19)	−0.33 (−1.93; 1.21)	−0.39 (−1.98; 1.16)	−0.36 (−1.96; 1.17)	○	−0.19 (−1.79; 1.33)	−0.35 (−1.96; 1.20)	−0.21 (−1.81; 1.31)
ICS + LTRA	−0.16 (−0.32; 0.00)	−0.14 (−0.29; 0.01)	**−0.20 (−0.41; −0.01)**	**−0.17 (−0.32; −0.03)**	0.19 (−1.33; 1.79)	○	−0.15 (−0.45; 0.13)	−0.02 (−0.20; 0.17)
LTRA	0.00 (−0.24; 0.25)	0.01 (−0.24; 0.28)	−0.05 (−0.33; 0.23)	−0.02 (−0.26; 0.24)	0.35 (−1.20; 1.96)	0.15 (−0.13; 0.45)	○	0.13 (−0.14; 0.41)
Placebo	**−0.13 (−0.27; −0.02)**	−0.12 (−0.27; 0.02)	**−0.18 (−0.37; −0.01)**	**−0.15 (−0.29; −0.03)**	0.21 (−1.31; 1.81)	0.02 (−0.17; 0.20)	−0.13 (−0.41; 0.14)	○

N, number of patients.

Note
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2). MD > 0 favours TRT 1. Results with CrIs that exclude zero are highlighted in bold.

within the NMA) from a single trial [Sorkness (2007)][66] and lack of clear biological rationale for this apparent difference, this result is potentially spurious, and we refrain from concluding there is evidence of an interaction.

Ethnicity

The network included 19 IPD studies (1908 participants). Seven treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 45*). The percentage of participants of Hispanic or Latino ethnicity within studies ranged from 0% to 70% (see *Appendix 9*, *Table 65*). FE and REs models with interactions differed regarding the DIC (861.7 for the FE model and 835.3 for the REs model), advocating the REs model (see *Appendix 9*, *Table 66*). The DIC (DIC = 659.8) suggests that the REs model without interactions is better than the same model but with interactions. The regression coefficient for the treatment by *ethnicity* interaction represents the difference in the MD for not Hispanic or Latino participants compared to the MD for Hispanic or Latino participants. Based on the 95% CrIs of the regression coefficients, there were no interactions (see *Appendix 9*, *Table 67*).

Eczema

The network included five IPD studies (455 participants). Seven treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 46*). The percentage of participants with eczema within studies ranged from 23% to 100% (see *Appendix 9*, *Table 65*).

With interactions, FE and REs models were similar in terms of model fit and complexity (DIC = 646.7 and 645.1, respectively), so the FE model was most appropriate (see *Appendix 9*, *Table 66*). The DIC indicates that the FE model without interactions (DIC = 640.9) is preferred over the same model but with interactions. There was no evidence of treatment by *eczema* interactions based on the CrIs of the regression coefficients; therefore, the MDs for each treatment versus ICS Medium did not differ based on whether participants suffered from eczema or not (see *Appendix 9*, *Table 67*).

Eosinophilia

The network involved 11 IPD studies (1024 participants). Seven treatments were compared: ICS High, ICS Medium, ICS Low, LTRA, ICS + LTRA, ICS + LABA and placebo (see *Appendix 9*, *Figure 47*). The percentage of participants with eosinophilia within studies ranged from 22 to 67% (see *Appendix 9*, *Table 65*). FE and REs models with interactions differed regarding model fit and complexity; the DIC was 1124.8 for the FE model and 1136.3 for the REs model, supporting the use of the FE model (see *Appendix 9*, *Table 66*). Furthermore, the DIC suggests that the FE model (DIC = 118.3) without interactions is preferred over the same model but with interactions. Although one of the treatment by *eosinophilia* interaction regression coefficients suggests an interaction as the 95% CrI excludes zero [ICS + LABA vs. ICS Low: 0.11 (0.03 to 0.19); *Appendix 9*, *Table 67*], there is a good overlap of CrIs for each between treatment MD comparing participants with eosinophilia and those without eosinophilia (*Table 35*).

Summary of interaction analyses

We compared the DIC between NMR models with and without interaction terms and found no overall evidence of interactions in any of the models. However, for some models, there were non-zero interaction regression coefficients, which are described further below. The lack of consistent robust statistical evidence and clinical rationale to support these suggested effects, along with issues of small numbers of patients in some analyses, suggests that these results should be viewed very cautiously; they are potentially spurious and should not be overinterpreted. Further research would be needed to explore these effects in more detail, and we note that recommendations regarding the treatment and care of patients would not differ according to any of the studied covariates.

Exacerbation

A treatment by *ethnicity* interaction was found for ICS Medium versus ICS Low, ICS + LABA versus ICS Low and placebo versus ICS Low. However, based on the results (OR, 95% CrI) produced, the same treatment recommendations would be made for ICS Medium versus ICS Low and ICS + LABA versus ICS Low for participants of any *ethnicity*. For placebo versus ICS Low, different results (OR, 95% CrI) were obtained for Hispanic or Latino participants and not Hispanic or Latino participants, but this appeared to be caused by lack of data. A treatment by *baseline severity* interaction was

TABLE 35 Mean difference (95% CrI) from FE NMA including treatment by eosinophilia interactions for the outcome FEV_1

Eosinophilic (*N* = 419)							
	TRT 2						
TRT 1	ICS Low *N* = 178	ICS Medium *N* = 11	ICS High *N* = 21	ICS + LABA *N* = 161	ICS + LTRA *N* = 7	LTRA *N* = 10	Placebo *N* = 31
ICS Low	○	0.02 (−0.19; 0.23)	−0.08 (−0.33; 0.17)	−0.07 (−0.14; 0.00)	**0.18 (0.02; 0.34)**	−0.19 (−0.50; 0.13)	0.10 (−0.03; 0.23)
ICS Medium	−0.02 (−0.23; 0.19)	○	−0.10 (−0.40; 0.20)	−0.08 (−0.29; 0.12)	0.16 (−0.06; 0.39)	−0.20 (−0.58; 0.17)	0.09 (−0.15; 0.33)
ICS High	0.08 (−0.17; 0.33)	0.10 (−0.20; 0.40)	○	0.01 (−0.24; 0.27)	0.26 (−0.02; 0.55)	−0.11 (−0.50; 0.30)	0.19 (−0.09; 0.45)
ICS + LABA	0.07 (0.00; 0.14)	0.08 (−0.12; 0.29)	−0.01 (−0.27; 0.24)	○	**0.25 (0.09; 0.40)**	−0.12 (−0.44; 0.20)	**0.17 (0.03; 0.31)**
ICS + LTRA	**−0.18 (−0.34; −0.02)**	−0.16 (−0.39; 0.06)	−0.26 (−0.55; 0.02)	**−0.25 (−0.40; −0.09)**	○	**−0.37 (−0.72; −0.02)**	−0.07 (−0.27; 0.12)
LTRA	0.19 (−0.13; 0.50)	0.20 (−0.17; 0.58)	0.11 (−0.30; 0.50)	0.12 (−0.20; 0.44)	**0.37 (0.02; 0.72)**	○	0.29 (−0.05; 0.63)
Placebo	−0.10 (−0.23; 0.03)	−0.09 (−0.33; 0.15)	−0.19 (−0.45; 0.09)	**−0.17 (−0.31; −0.03)**	0.07 (−0.12; 0.27)	−0.29 (−0.63; 0.05)	○
Non-eosinophilic (*N* = 605)							
	TRT 2						
TRT 1	ICS Low *N* = 270	ICS Medium *N* = 18	ICS High *N* = 15	ICS + LABA *N* = 215	ICS + LTRA *N* = 7	LTRA *N* = 4	Placebo *N* = 76
ICS Low	○	−0.06 (−0.25; 0.12)	−0.22 (−0.52; 0.09)	0.04 (−0.02; 0.10)	0.13 (−0.03; 0.29)	0.07 (−0.43; 0.57)	0.08 (−0.01; 0.16)
ICS Medium	0.06 (−0.12; 0.25)	○	−0.16 (−0.49; 0.18)	0.10 (−0.08; 0.29)	0.19 (0.00; 0.39)	0.13 (−0.39; 0.65)	0.14 (−0.06; 0.34)
ICS High	0.22 (−0.99; 0.52)	0.16 (−0.18; 0.49)	○	0.26 (−0.05; 0.56)	**0.35 (0.02; 0.67)**	0.29 (−0.29; 0.87)	0.29 (−0.02; 0.60)
ICS + LABA	−0.04 (−0.10; 0.02)	−0.10 (−0.29; 0.08)	−0.26 (−0.56; 0.05)	○	0.09 (−0.07; 0.24)	0.03 (−0.46; 0.52)	0.04 (−0.06; 0.14)
ICS + LTRA	−0.13 (−0.29; 0.03)	−0.19 (−0.39; 0.00)	**−0.35 (−0.67; −0.02)**	−0.09 (−0.24; 0.07)	○	−0.06 (−0.57; 0.45)	−0.05 (−0.23; 0.12)

continued

TABLE 35 Mean difference (95% CrI) from FE NMA including treatment by eosinophilia interactions for the outcome FEV_1 (*continued*)

Non-eosinophilic (*N* = 605)							
	TRT 2						
TRT 1	**ICS Low** ***N* = 270**	**ICS Medium** ***N* = 18**	**ICS High** ***N* = 15**	**ICS + LABA** ***N* = 215**	**ICS + LTRA** ***N* = 7**	**LTRA** ***N* = 4**	**Placebo** ***N* = 76**
LTRA	−0.07 (−0.57; 0.43)	−0.13 (−0.65; 0.39)	−0.29 (−0.87; 0.29)	−0.03 (−0.52; 0.46)	0.06 (−0.45; 0.57)	○	0.01 (−0.49; 0.50)
Placebo	−0.08 (−0.16; 0.01)	−0.14 (−0.34; 0.06)	−0.29 (−0.60; 0.02)	−0.04 (−0.14; 0.06)	0.05 (−0.12; 0.23)	−0.01 (−0.50; 0.49)	○

N, number of patients.

Notes
The table compares the effect estimate for an intervention in the row with an intervention in a column (TRT 1 vs. TRT 2).
MD > 0 favours TRT 1. Results with CrIs that exclude zero are highlighted in bold.

found for ICS Medium versus ICS Low. No difference was found between ICS Medium and ICS Low for participants with mild or moderate asthma, but a difference was found for severe asthma; however, this appears to be caused by the lack of patients with severe asthma. There was no evidence of treatment by *age* interactions, treatment by *sex* interactions, treatment by *eczema* interactions or treatment by *eosinophilia* interactions. Based on these findings, the recommendations regarding the treatment and care of participants would not differ according to any of the studied covariates.

Asthma control

There was no evidence of treatment by covariate interactions for *age*, *sex*, *ethnicity*, *eczema*, *eosinophilia* or *baseline severity*. Of note, there were less data available for the analysis of this outcome than for other outcomes.

Forced expiratory volume in 1 second

We found a suggestion of treatment by *sex* interaction for LTRA versus ICS + LABA. For LTRA versus ICS + LABA, the MD indicated no difference between treatments for males, but a difference was found, favouring LTRA, for females. However, this was based on only three females on LTRA. A treatment by *eosinophilia* interaction for ICS + LABA versus ICS Low was detected. For ICS + LABA versus ICS Low, the MD favoured ICS + LABA for participants with *eosinophilia*, but no difference was found for participants with no *eosinophilia*. There was no evidence of treatment by *age* interactions, treatment by *eczema* interactions, or treatment by *ethnicity* interactions.

Transitivity assumption in network meta-analysis

In a NMA, the underlying assumption of transitivity means that any of the comparative effects of two treatments in the network would be similar regardless of whether those treatments were included in any of the individual studies. Qualitatively, we concluded that any patient randomised in one study within each of the NMAs (see *Chapters 5* and *6*) could have been theoretically randomised to any of the other treatments included in any of the other studies within that network. Furthermore, the assumption of transitivity may be implausible if a covariate modifies a relative treatment effect (i.e. interaction), and the distribution of that covariate varies across treatment comparisons included in the NMA. Our detailed analysis of effect modifiers in this chapter does not provide convincing evidence of an effect modifier along with important variation in covariate distribution across comparisons (see *Appendix 9*, *Tables 59*, *62* and *65*). The suggestion of a possible interaction between sex and effects against LTRA for the FEV_1 outcome appears to be driven by the inclusion of a small trial with only 14 participants on LTRA [Sorkness (2007)].[66] The potential impact this could have on transitivity for the full NMA was explored further with three post hoc sensitivity analyses [one for each corresponding NMA (a),(b),(c) in *Chapter 6*] excluding the Sorkness (2007) study. We found that all comparative effects of treatments and 95% CrIs were very similar to the full NMA (apart from those with LTRA, which could no longer be estimated). Therefore, although somewhat restricted by data availability, our limited assessment suggests that, on average, there are unlikely to be important concerns regarding the transitivity assumption in the NMA presented in *Chapters 5* and *6*.

Chapter 8 Results: cost-effectiveness

Resource use and cost analyses

In the base-case analysis, and over the 52 weeks of the model time horizon, simulated patients resided mainly in the controlled asthma state, ranging from 80.5% of the time for LTRA to 92.0% with ICS Medium + LABA (*Table 36*). These were consistent with the findings of the NMA of the clinical evidence, as too is the modelled higher proportion of LTRA patients transitioning to the uncontrolled and exacerbation health states, compared to ICS High and ICS Medium + LABA.

Accordingly, the majority of costs accrued within the controlled asthma state with the exception of LTRA where the majority of costs were associated with the asthma exacerbation state, as presented in *Table 37*. Differences between treatments in total costs are mainly due to (i) the efficacy of the treatment, affecting the frequency of exacerbation, and (ii) differences in the price of inhalers; costs relating to the use of health services, and other items of resource use were comparable across treatments. Overall, LTRA was associated with the highest cost (£670), and ICS Low the lowest (£284).

Quality-adjusted life-years

ICS Medium + LABA provided most benefit with 0.9512 QALYs, and LTRA the least with 0.9366 QALYs. QALYs accrued mainly within the controlled asthma state, reflecting the time patients resided in this health state over the course of the model. *Table 38* presents the distribution of QALYs over the 12-month period, by health state and treatment.

TABLE 36 Percentage of time within each health state, by intervention group

	Asthma control	Asthma uncontrolled	Asthma exacerbation	Death
ICS Medium	91.66	7.45	0.87	4.0×10^{-5}
ICS Low	91.37	7.66	0.95	5.0×10^{-5}
ICS Medium + LABA	91.95	7.28	0.76	3.0×10^{-5}
ICS High	91.00	8.28	0.72	3.0×10^{-5}
ICS + LTRA	90.82	7.82	1.36	9.0×10^{-5}
LTRA	80.48	15.61	3.90	7.0×10^{-4}

TABLE 37 Costs by health state and intervention group

	Asthma control (£)	Asthma uncontrolled (£)	Asthma exacerbation (£)	Total cost (£)
ICS Medium	215	28	134	377
ICS Low	119	21	145	284
ICS Medium + LABA	346	38	117	501
ICS High	432	51	113	596
ICS + LTRA	232	31	207	470
LTRA	47	31	593	670

TABLE 38 Total QALYs, and disaggregated by health state and treatment

	Asthma control	Asthma uncontrolled	Asthma exacerbation	Total QALYs
ICS Medium + LABA	0.8828	0.0627	0.0058	0.9512
ICS Medium	0.8800	0.0641	0.0067	0.9508
ICS Low	0.8772	0.0660	0.0072	0.9504
ICS High	0.8735	0.0712	0.0055	0.9503
ICS + LTRA	0.8718	0.0673	0.0103	0.9495
LTRA	0.7726	0.1343	0.0297	0.9366

Incremental analysis – base case

Analysed incrementally, ICS Low was the cost-effective option, associated with a cost of £284 and 0.9504 QALYs (*Table 39*); ICS Medium was £93 more expensive and yielded 0.0004 additional QALYs compared to ICS Low, with a corresponding ICER of £232,500 per QALY gained. ICS Medium + LABA was modelled to cost £501 and provide 0.9512 QALYs, resulting in an incremental cost of £124 for an additional 0.0004 QALYs when compared to ICS Medium, and a corresponding ICER of £310,000 per QALY gained. These treatments were deemed not cost-effective as their ICERs exceeded the NICE threshold of £20,000 per QALY. ICS High, ICS + LTRA and LTRA were dominated by alternatives which were less costly and associated with more QALYs.

Sensitivity analysis

The results of the one-way sensitivity analyses applied to utilities associated with the uncontrolled asthma and exacerbation health states are presented in *Table 40*. No impact on the rank-ordering of treatments by cost-effectiveness was observed. Within the range of ± 0.05, ICS Medium + LABA had an ICER of £434,000 per QALY gained compared to ICS Low, with the other treatments being dominated strongly or extendedly. Varying utility values for the controlled, uncontrolled and exacerbation states, and within their upper and lower 95% CI ranges, had an inconsequential effect on the ICERs.

A sensitivity analysis of the impact of varying the transition probabilities associated with 'asthma exacerbation' and 'asthma controlled' by ± 50% concurrently for all treatments resulted in ICS Medium becoming cost-effective at £15,102 per QALY gained (*Table 41*).

When the costs of branded inhalers were reduced individually by 50%, potentially reflecting a generic alternative, the most notable change was observed with a price reduction in ICS Medium + LABA. Although the ICER reduced

TABLE 39 Results of the deterministic, base-case analysis

Treatment	Total cost (£)	Total QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY gained)
ICS Medium + LABA	501	0.9512	124	0.0004	310,000
ICS Medium	377	0.9508	93	0.0004	232,500
ICS Low	284	0.9504	–	–	–
ICS High	596	0.9503	–	–	Dominated
ICS + LTRA	470	0.9495	–	–	Dominated
LTRA	670	0.9366	–	–	Dominated

TABLE 40 One-way sensitivity analyses for health state utility

Sensitivity analysis Treatment	Total cost (£)	Total QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY gained)
Utility for uncontrolled asthma increased by 0.05					
ICS Medium + LABA	501	0.9548	217	0.0005	434,000
ICS Low	284	0.9543	–	–	–
ICS Medium	377	0.9545	–	–	Extendedly dominated
ICS High	596	0.9544	–	–	Dominated
ICS + LTRA	470	0.9534	–	–	Dominated
LTRA	670	0.9544	–	–	Dominated
Utility for uncontrolled asthma decreased by 0.05					
ICS Medium + LABA	501	0.9476	124	0.0005	248,000
ICS Medium	377	0.9471	93	0.0005	186,000
ICS Low	284	0.9466	–	–	–
ICS High	596	0.9461	–	–	Dominated
ICS + LTRA	470	0.9455	–	–	Dominated
LTRA	670	0.9288	–	–	Dominated
Utility for asthma exacerbation state increased by 0.05					
ICS Medium + LABA	501	0.9516	124	0.0004	310,000
ICS Medium	377	0.9512	93	0.0003	310,000
ICS Low	284	0.9509	–	–	–
ICS High	596	0.9506	–	–	Dominated
ICS + LTRA	470	0.9501	–	–	Dominated
LTRA	670	0.9385	–	–	Dominated
Utility for asthma exacerbation state decreased by 0.05					
ICS Medium + LABA	501	0.9508	124	0.0005	248,000
ICS Medium	377	0.9503	93	0.0004	232,500
ICS Low	284	0.9499	–	–	–
ICS High	596	0.9499	–	–	Dominated
ICS + LTRA	470	0.9488	–	–	Dominated
LTRA	670	0.9346	–	–	Dominated
Utilities taking the values of the lower bound 95% CIs					
ICS Medium + LABA	501	0.9388	124	0.0004	310,000
ICS Medium	377	0.9384	93	0.0004	232,500
ICS Low	284	0.9380	–	–	–
ICS High	596	0.9379	–	–	Dominated
ICS + LTRA	470	0.9371	–	–	Dominated
LTRA	670	0.9242	–	–	Dominated

TABLE 40 One-way sensitivity analyses for health state utility (*continued*)

Sensitivity analysis Treatment	Total cost (£)	Total QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY gained)
Utilities taking the values of the upper bound 95% CIs					
ICS Medium + LABA	501	0.9636	124	0.0004	310,000
ICS Medium	377	0.9632	93	0.0004	232,500
ICS Low	284	0.9628	–	–	–
ICS High	596	0.9627	–	–	Dominated
ICS + LTRA	470	0.9619	–	–	Dominated
LTRA	670	0.9490	–	–	Dominated

TABLE 41 Impact of increasing the probability of exacerbation

Sensitivity analysis Treatment	Total cost (£)	Total QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY gained)
Change in the probability of exacerbation by 50%					
ICS Medium + LABA	576	0.9430	112	0.0007	160,000
ICS Medium	464	0.9423	74	0.0050	15,102
ICS Low	390	0.9374	–	–	–
ICS High	671	0.9414	–	–	Dominated
ICS + LTRA	598	0.9401	–	–	Dominated
LTRA	1045	0.9190	–	–	Dominated

considerably, it remained non-cost-effective. None of the other treatment options became cost-effective with ICS High, ICS + LTRA and LTRA being consistently dominated (*Table 42*).

Analysis of structural uncertainty

Across all the analyses that considered structural uncertainty, none of the treatment options were cost-effective (*Table 43*). When different strengths of ICS were combined with LABA, ICS Medium + LABA was associated with an additional cost of £113 and 0.0005 more QALYs than ICS Medium alone. ICS High (alone and + LABA), ICS Low + LABA, ICS + LTRA, and LTRA monotherapy were all dominated.

TABLE 42 One-way sensitivity analysis for unit costs

Sensitivity analysis Treatment	Total cost/(£)	Total QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY gained)
Cost of ICS High decreased by 50%					
ICS Medium + LABA	501	0.9512	124	0.0004	310,000
ICS Medium	377	0.9508	93	0.0004	232,500
ICS Low	284	0.9504	–	–	–

continued

TABLE 42 One-way sensitivity analysis for unit costs (*continued*)

Sensitivity analysis Treatment	Total cost/(£)	Total QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY gained)
ICS High	379	0.9503	–	–	Dominated
ICS + LTRA	470	0.9495	–	–	Dominated
LTRA	670	0.9366	–	–	Dominated
Cost of ICS Medium decreased by 50%					
ICS Medium + LABA	501	0.9512	220	0.0004	550,000
ICS Medium	281	0.9508	–	–	–
ICS Low	284	0.9504	–	–	Dominated
ICS High	596	0.9503	–	–	Dominated
ICS + LTRA	470	0.9495	–	–	Dominated
LTRA	670	0.9366	–	–	Dominated
Cost of ICS Medium + LABA decreased by 50%					
ICS Medium + LABA	333	0.9512	49	0.0008	61,250
ICS Low	284	0.9504	–	–	–
ICS Medium	377	0.9508	–	–	Extendedly dominated
ICS High	596	0.9503	–	–	Dominated
ICS + LTRA	470	0.9495	–	–	Dominated
ICS LTRA	670	0.9366	–	–	Dominated
Cost of ICS Low decreased by 50%					
ICS Medium + LABA	501	0.9512	261	0.0008	326,250
ICS Low	240	0.9504	–	–	–
ICS Medium	377	0.9508	–	–	Extendedly dominated
ICS High	596	0.9503	–	–	Dominated
ICS + LTRA	470	0.9495	–	–	Dominated
LTRA	670	0.9366	–	–	Dominated
Cost of ICS Low + LABA decreased by 50%					
ICS Medium + LABA	468	0.9516	113	0.0005	226,000
ICS Medium	355	0.9511	71	0.0007	
ICS Low	284	0.9504	–	–	–
ICS Low + LABA	377	0.9511	–	–	Dominated
ICS High + LABA	545	0.9510	–	–	Dominated
ICS High	603	0.9502	–	–	Dominated
ICS + LTRA	455	0.9497	–	–	Dominated
LTRA	670	0.9367	–	–	Dominated

TABLE 43 Results of the analysis of structural uncertainty

Sensitivity analysis Treatment	Total cost (£)	Total QALY	Incremental cost (£)	Incremental QALY	ICER (£/QALY gained)
ICS Low as referent – REs NMA					
ICS M + LABA	499	0.9514	118	0.0004	295,000
ICS Medium	381	0.9510	97	0.0006	161,667
ICS Low	284	0.9504	–	–	–
High	595	0.9505	–	–	Dominated
ICS + LTRA	477	0.9495	–	–	Dominated
LTRA	692	0.9363	–	–	Dominated
ICS Medium as referent – FE NMA					
ICS Medium	389	0.9504	88	0.0004	220,000
ICS Low	301	0.9500	–	–	–
ICS Medium + LABA	527	0.9504	–	–	Extendedly dominated
ICS High	619	0.9499	–	–	Dominated
ICS + LTRA	509	0.9484	–	–	Dominated
LTRA	680	0.9379	–	–	Dominated
ICS Medium as reference – REs NMA					
ICS Medium	389	0.9504	87	0.0007	124,286
ICS Low	302	0.9497	–	–	–
ICS Medium + LABA	526	0.9500	–	–	Dominated
ICS High	619	0.9494	–	–	Dominated
ICS + LTRA	514	0.9479	–	–	Dominated
LTRA	703	0.9361	–	–	Dominated
Separation of ICS when combined with LABA					
ICS Medium + LABA	468	0.9516	113	0.0005	226,000
ICS Medium	355	0.9511	–	–	–
ICS Low + LABA	377	0.9511	–	–	Dominated
ICS High + LABA	545	0.9510	–	–	Dominated
ICS Low	284	0.9504	–	–	Dominated
ICS High	603	0.9502	–	–	Dominated
ICS + LTRA	455	0.9497	–	–	Dominated
LTRA	670	0.9367	–	–	Dominated

ICERs were comparable to the base-case analysis where the transition probability matrix was based on RRs derived from the Bayesian REs NMA. ICS Medium alone and in combination with LABA were generally associated with higher QALYs, while ICS Low appears consistently as a baseline comparator due to being the least costly.

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analyses were consistent with the deterministic analyses (*Table 44*). The treatment with the highest probability of being cost-effective was ICS Low, at 0.45 for a threshold of £20,000 per QALY, and 0.44 at £30,000 per QALY. ICS Medium + LABA and ICS Medium alone had probabilities of 0.07 and 0.20, respectively, of being cost-effective at the £20,000 per QALY threshold.

The cost-effectiveness acceptability curve indicates that ICS Low is the optimal strategy in terms of cost-effectiveness (*Figure 20*).

Value of information analysis

The overall EVPI per person affected by the decision was estimated at £566 per person. This is equivalent to 0.0283 QALYs per person in decision uncertainty when valuing uncertainty on the QALY scale.

Assuming an annual number of children affected by the decision of 5996 the overall EVPI per year is £3,394,000 for England. Cumulatively over 10 years, the overall expected value of removing decision uncertainty for England would be over £33,940,000 in total. Research or data collection exercises costing more than this amount would not be considered a cost-effective use of resources.

TABLE 44 Results of the probabilistic sensitivity analysis

Treatment	Total cost (£) (95% central range)	Total QALY (95% central range)	Probability of cost-effectiveness at £20,000 per QALY	Probability of cost-effectiveness at £30,000 per QALY
ICS Low	281 (63 to 974)	0.9505 (0.5800 to 0.9991)	0.45	0.44
ICS Medium	381 (114 to 1108)	0.9509 (0.5791 to 0.9992)	0.20	0.21
ICS + LTRA	476 (127 to 1519)	0.9491 (0.5796 to 0.9990)	0.11	0.12
LTRA	678 (40 to 3864)	0.9333 (0.6073 to 0.9980)	0.10	0.07
ICS Medium + LABA	498 (175 to 1223)	0.9513 (0.5794 to 0.9993)	0.07	0.09
ICS High	812 (158 to 2913)	0.8656 (0.3449 to 0.9978)	0.07	0.07

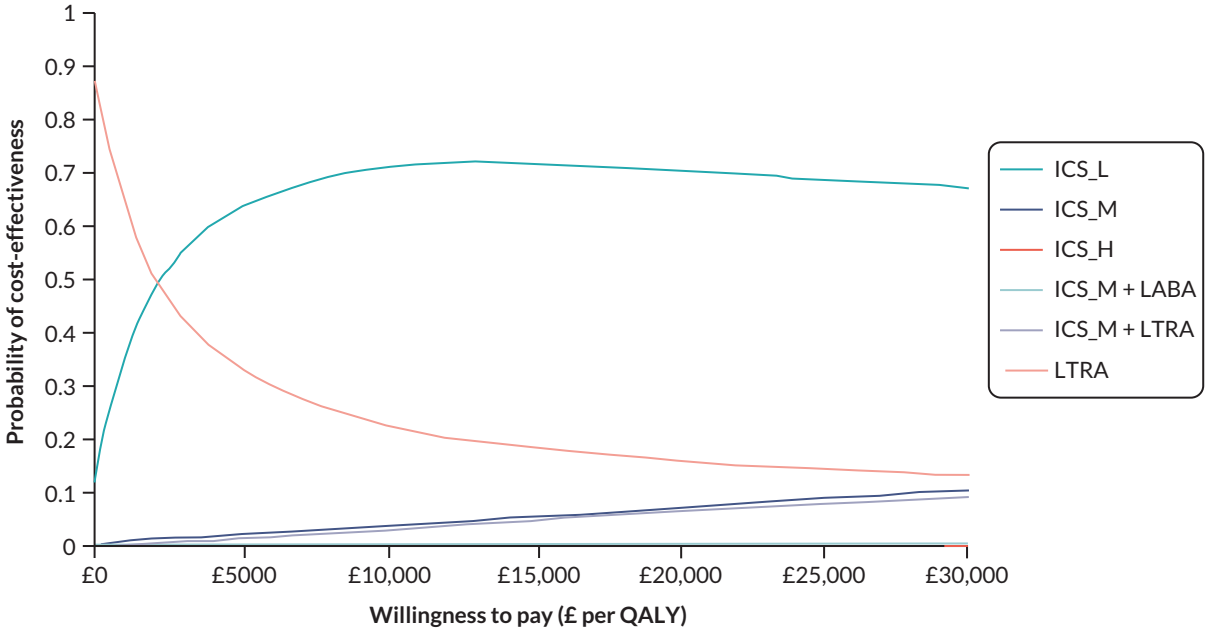

FIGURE 20 Cost-effectiveness acceptability curve.

Chapter 9 Patient and public involvement

When planning our application, we were keen to identify whether this review would be of use to children with asthma and their parents. We sought the views of two parents and one adolescent. A mother of a wheezy young child told us it *'Seems such a shame that the information is out there but is incomplete or hasn't been pulled together or compared before'*, and a mother of an 8-year-old girl with asthma said of the NMA, *'I can't believe that isn't done already. I assumed that's how you knew which treatment to use'*. A 14-year-old girl with asthma felt that one important uncertainty from her experience was the choice of ICS/LABA combination. From the planning stage through to writing the review report, we have involved a PPI representative (OF) as a research team member.

When planning the review methods, we selected our outcomes based on a core outcome set, which had been previously developed and led by one of the reviewers (IS), and where the views of children with asthma, their parents, and healthcare professionals about which outcomes were most important in clinical practice,[171] were fundamental.

We included a PPI perspective to EINSTEIN to gain the perspectives of parents of children with asthma, and children themselves, on our results and suggested interpretation. To achieve this, we held a virtual meeting with two families (two mothers and their teenage sons) to discuss what we had found and ask their opinions on the results. This was attended by three members of the EINSTEIN team (CTS, OF and IS). The meeting was not recorded; however, IS took notes. They offered useful insights into our findings and experiences of the review, and how we might best disseminate findings to patients, and we considered their comments in our conclusions.

We asked them their view on either adding LABA and increasing the dose of ICS or just making one change in the context of a child with poorly controlled asthma on ICS Low. This was an important question since different clinical guidelines suggest either adding LABA or increased ICS dose. The parents and children told us that making both changes simultaneously would be fine from their perspective, and that one of the frustrations they encountered in their patient journey was delays in seeing improvement. This provided reassurance to us that parents and children would find it acceptable for a recommendation to be made for increasing to ICS Medium and adding a LABA should be strongly considered the next step for children who are uncontrolled when taking ICS Low.

They told us that the finding of little clinical benefit from LTRA at this stage was important for families to know, particularly in the context of current concerns about side effects.[172] These side effects are now an important topic among parents of children with asthma, and the views of the parents we spoke to would support our conclusion that LTRA should not be used at this stage of asthma management in children aged 6–17.

We discussed how there were no clear signals that the medications considered had any consistent side effects. This was an important gap in the evidence for these parents. They felt that the side effects of using OCS during acute exacerbation were very difficult for children and parents. This was useful for us to know, as we were unsure of the parental response to the concept that at this stage of asthma management, ICS should be increased from a low-dose to a medium-dose strategy.

We explained that there was no evidence that treatment effects would vary between groups of children based on their characteristics. The parents and children told us that this was not a huge concern to them. They suggested that having a 'generic' approach to stepping up treatment at this stage would be easier for parents and healthcare professionals. They did feel that at later stages of asthma management having a more personalised approach may be useful and felt this would be a gap in the current evidence that would be worth exploring.

They shared our frustration that the evidence in children under 5 years of age still precludes meaningful conclusions and recommendations.

When discussing the data collection, parents were frustrated that we were not fully supported in ascertaining as much IPD as might be made available to us. They said that *'whenever there were studies, parents put their children in because they wanted to help*', and that it was 'disheartening' that we were unable to use those data in our review. They described

how in general asthma is such a negative thing on their lives, that being able to help other children through research would have been seen by these families as a very positive thing – and that those children would be disappointed that their efforts could not be used in a review such as ours. They described how this led to decisions being made in a disjointed way '*it is not reflective of a unified service*'. The children summed up by saying *'it's my data'*, which reflects the strong feelings of people who are included in clinical trials that they would like the maximum benefit from their involvement in clinical research.

Chapter 10 Equality, diversity and inclusion

We attempted to obtain as detailed IPD as possible, so that we could understand differential effects of treatments based on different groups. In most studies, there was a slight predominance of male participants. Across the studies, the representation of ethnic groups (and the detail to which this was reported) was variable. We have highlighted that further research would help identify variations between treatments based on characteristics, such as age and gender, but this reflects a gap in the current evidence.

Our research team was well represented by both men (3) and women (7), of different ethnicities, and included members at different levels of seniority. The more junior members were supported and mentored in the systematic review process, which was necessary given the complexity of the review. The PPI representation came from two cities (Liverpool and Edinburgh); we had planned a more geographically diverse approach to PPI but were somewhat hindered by the COVID-19 pandemic.

Chapter 11 Discussion

Summary of the main clinical results

The purpose of this IPD NMA, supplemented with AgD, was to synthesise all available published and unpublished evidence from RCTs to establish the clinical effectiveness of pharmacological treatments in children and adolescents with uncontrolled asthma on ICS and help to make evidence-informed treatment choices.

Of treatment options currently recommended for a child with uncontrolled asthma despite ICS treatment, using medium-dose ICS in combination with LABA was associated with the greatest reduced risk for exacerbation and associated increase in FEV_1. There is insufficient evidence to suggest adding LTRA to ICS as the next step in preventing exacerbation or improving asthma control if the child is already taking ICS, and LTRA on its own should be avoided (as per guidelines for treatment of children aged over 5 years).

The results of the NMA suggest that the approach most likely to reduce the risk of exacerbation is to use medium-dose ICS in combination with LABA. Compared with placebo, we found that medium-dose and high-dose ICS, and using ICS in combination with LABA, were all associated with a reduction in the risk of exacerbation. Neither adding LTRA nor theophylline to ICS reduces the risk of exacerbation compared with placebo (limited data). Using ICS in combination with LABA is more likely than LTRA to achieve better overall asthma control. There is insufficient evidence with the available data to recommend a specific compound combination of ICS + LABA over another.

Individually, using ICS at low or medium doses, either on their own or in combination with LABA, is better than placebo with regard to FEV_1. Of these, the approach most likely to work with regard to this outcome is to use medium-dose ICS in combination with LABA. The available data do not suggest that LTRA or ICS High (alone or in combination with LABA) improve FEV_1. There is insufficient evidence with the available data to recommend a specific compound combination of ICS + LABA over another to improve FEV_1.

Availability of data reduced our ability to examine the impact of treatments on QoL. Acknowledging that data were available from only two studies of 36 participants, ICS at medium doses was associated with improved QoL than ICS + LABA with regard to QoL, and ICS + LABA was better than placebo. The difference was greater than the minimum clinically important difference but was not seen for the corresponding comparison of asthma control (QoL and asthma control are strongly correlated), so we advise a very cautious interpretation of this result.

Across the studies, there were no deaths, and relatively few hospitalisation admissions due to asthma, so we were unable to formulate conclusions around mortality or hospitalisations.

There is currently uncertainty around short-term and long-term side effects of the treatments included in this review. On the basis of what we have found, it is not possible to confidently say that one treatment is any more or less likely to cause side effects than another, and the wide CIs around safety mean that it is not possible to rule out clinically important risks of treatments.

Although patients undoubtedly respond to treatments differently, we did not find consistent, robust evidence that any single treatment option would be more effective in improving asthma outcomes according to *age*, *sex*, *ethnicity*, *eczema*, *asthma severity* and *eosinophilia*, with the data available to us, and we cannot make patient-specific treatment recommendations based on these data.

Health economics

The economic analysis indicated that ICS Medium alone and in combination with LABA were the most effective treatment options based on a model structure and parameterisation that assumed generalisability to the population of

interest. However, neither were cost-effective, with ICERs far exceeding the willingness-to-pay threshold operating in the UK. ICS High, and ICS + LTRA and LTRA monotherapy were dominated by alternatives which were less costly and associated with more QALYs. These results were mostly stable to sensitivity analyses that considered structural and parameter uncertainty. However, when the probability of exacerbation increased for all treatments concomitantly, ICS Medium yielded the best improvement in health-related QoL becoming the cost-effective choice at the £20,000 per QALY threshold, suggesting that the value of ICS Medium is more pronounced in patients experiencing more frequent asthma exacerbations. When the treatment cost was reduced, the ranking of treatment cost-effectiveness remained largely unchanged. The most significant improvement in cost-effectiveness was observed when the cost of ICS Medium + LABA was reduced by 50%; however the resulting ICER was still not cost-effective. When the RRs of the NMA related to ICS Medium were considered, and ICS Medium was serving as the reference treatment, ICS Medium (alone and + LABA) yielded the highest QALY, however ICS Medium alone was associated to the lowest costs among the two. Subgroup analysis would be recommended in further research to assess patient heterogeneity.

The economic analysis indicated that the unit cost of treatments and the rates of exacerbation were key determinants of cost-effectiveness – most notably for ICS Medium which became cost-effective with a change of probability of exacerbation. This is because greater cost savings may be achieved through the avoidance of hospital admissions and ED visits, when patients are at higher risk of exacerbation.

Consistent with the clinical analysis, LTRA was the least preferred treatment associated with the highest cost and least QALYs compared to alternative treatments. QALY differences between treatments reflected the time patients resided in each of the health states, and this was comparable for all treatments. The rank ordering of treatments based on total QALYs was consistent with the ordering derived from the ORs for asthma control or exacerbation, which were obtained from the FE NMA. In other words, treatments that demonstrated higher effectiveness in terms of asthma control or the prevention of exacerbations also yielded higher total QALYs. This implies that the treatments that were more successful in managing asthma symptoms and reducing exacerbations also resulted in better overall QoL for patients, as reflected by the higher total QALYs.

The cost-effectiveness analysis assumed that health states and comparator transition probabilities derived from a previous economic model applied to the EINSTEIN study population. While the trials that informed the core model were of children prescribed continuous dosing of ICS, patients might have been adequately managed with ICS Low plus a bronchodilator (e.g. GINA step 2). Indeed, a sensitivity analysis in which the risk of exacerbation was increased resulted in ICS Medium becoming cost-effective.

Comparison against other network meta-analyses

Two other groups have used NMA to address the same uncertainty as EINSTEIN. Van der Mark *et al.* (2012) were unable to synthesise results due to variation in the measurement and reporting of outcomes and concluded that ranking of effectiveness was not possible at that time. In 2015, an NMA by Zhao *et al.* suggested that combining ICS (dose not specified) and LABA treatments were most effective in preventing exacerbation, and that there was little difference between continuing low-dose ICS, increasing the ICS dose to the medium-dose or high-dose range, or combining ICS with LTRA. Our approach, of using IPD where available, enabled us to analyse the data more robustly, identify more relevant dose-specific differences between treatments that were not evident in this review, conduct cost-effectiveness analyses and explore the potential for treatment effect modification.

Gaps in the evidence

Our understanding of how to manage asthma in children whose symptoms are not controlled on ICS Low remains incomplete. Areas in which further evidence is needed include the following:

- Best practice in young children, for example, are ICS and LTRA monotherapy equally efficient in under 5-year-olds? Are LABAs safe and effective combination in under 4-year-olds?

- An understanding of whether some ICS molecules are superior to others for asthma outcomes, in isolation and combination with different LABA molecules.
- Increase understanding of the long-term side effects of treatments.
- A better understanding of how treatment choices can be personalised by phenotype, endotype or genotype.
- How to achieve optimal adherence and inhalation technique for inhaler preventer treatment.

One important question at the moment is the regime of ICS + LABA that people with asthma should use. In the studies in our review, the main method has been to use 'fixed dose' steroids, but there is now a shift in some guidelines to use 'symptom-driven' ICS, that enables a more flexible dosing regimen depending on a person's asthma control at a given time. This approach has been used with some inhaler preparations, in an approach called 'MART' (using one inhaler containing ICS + LABA as maintenance and reliever therapy). Currently, in children, it is unclear whether using ICS in a more flexible way may improve asthma and reduce exacerbation. One NIHR study (ASYMPTOMATIC) is addressing this question in children with mild asthma, but no studies are evaluating whether ICS + LABA in children with uncontrolled asthma should be given as a fixed-dose or MART regime.

Future reviews should focus also on the wider approach to managing asthma in children, as many aspects of this have been identified as key questions in the James Lind Alliance Asthma[173] prioritisation process. These include better understanding of managing asthma in people with comorbidities, the role of non-medical interventions, such as complementary therapies and breathing exercises, the best way to manage consultations, and the key components of 'self-management'.

Strengths and limitations

To the best of our knowledge, this is the first NMA using IPD and is the most detailed analysis to date of evidence around therapies for childhood asthma after children remain uncontrolled despite ICS. This is the first review to thoroughly explore the potential modifying effect of patient characteristics using IPD and the first review to consider the cost-effectiveness of treatments in a network approach. The NMA enabled us to include direct and indirect evidence comparing different treatments that have not been compared against each other in previous RCTs, leading to a ranking of treatments, which has identified that increasing ICS to medium dose and using LABA in combination with this should strongly be considered the best next step in the management of children that are uncontrolled on ICS.

A strength of our NMA was that we had IPD for 29 studies (from 5494 children), including from two unpublished studies and were able to supplement this with AgD from 19 further studies. A limitation was that we were not able to include data from a further 96 potentially eligible studies, that is 67% of the eligible studies on this question, and this may have potential for bias. We had very limited data for ICS + theophylline and insufficient data to stratify ICS dose when combined with LTRA; therefore, uncertainty remains about these treatments. We were promised 24 (17%) studies from three pharmaceutical companies but despite lengthy negotiation, we failed to reach an agreement on the data-sharing contract. A further 41 (28%) studies declined to provide IPD due to issues around potential patient identification (14 studies), trialists unable to find or share the data (15 studies) or other reasons that could potentially be overcome (12 studies). We would have been able to formulate stronger conclusions had we been able to ascertain IPD from some of the other studies that might otherwise have contributed data to our analyses. This should be revisited as incorporating this additional data may change the conclusions of this review.

The review methodology was robust and conducted according to high standards. As we had IPD, we were able to standardise the outcome definitions and patient inclusion (e.g. identifying those patients that were only on ICS at the screening visit and selecting patients < 18 years old from studies of mixed age groups) to homogenise the data that were included in the NMA and increase the plausibility of the underlying assumption of transitivity. Although restricting our analysis in this way allows a purer analysis, the discarding of data from trials that included adults or patients not currently taking ICS alone means that the comparative effects of treatments are no longer based on the premise of strict randomisation, and we cannot rule out the possibility of bias. The IPD also allowed a robust statistical evaluation of the potential modifying effects of patient-level characteristics that would otherwise have been prone to ecological bias.[174] The quality of evidence from the included trials was generally good, and there were no problems with

a particular domain of bias across a large proportion of included studies. One issue was that there was non-uniformity across studies with regards selection, measurement and reporting of outcomes. This meant, for example, that our analysis of differential effects of treatments on QoL was impaired. Most children had mild asthma, and so the results are less externally generalisable to children with more severe disease, although it is likely that they would require additional therapies beyond this step of treatment regardless of what was started as the next step after ICS.

There are two aspects of childhood asthma management that we were unable to consider in this review:

- During the design and conduct of this review, the role of MART therapy and symptom-driven approaches to using ICS has been investigated in clinical research studies. We have not considered this important topic as part of our review.
- We were unable to formulate firm conclusions about long-term or rare side effects of treatments. RCTs (the only design eligible for our review) are not always the best research methodology to assess drug safety. Future attempts to synthesise evidence around the safety of asthma medications for children should be conducted with that specific question in mind, and include other study designs, such as observational research and postmarketing surveillance.

Chapter 12 Conclusions

Recommendations/implications for practice/policy

The current recommendation for the treatment of children with asthma, who are not well controlled on ICS, is to firstly check adherence, inhaler technique and comorbidities; then, consider a 'step-up' to their treatment by increasing the dose of ICS or adding another treatment. The 2019 GINA guideline[16] recommends the preferred controller for children age 6–11 is 'ICS Medium' or 'ICS Low-LABA', which have similar benefit. However, the EINSTEIN analysis suggests that the preferred first 'step-up' option, when considering 'fixed-dose' steroids, should be to increase the dose of ICS to a 'medium' dose in combination with LABA, as this had the most beneficial effect for exacerbation prevention and improving asthma control and lung function (*Table 45*). ICS Medium + LABA is also associated with the greatest number of QALYs, although low dose is more cost-effective due to the lower price of inhalers. The parents we consulted were supportive of the recommendation of ICS Medium with LABA, preferring to avoid trying alternative 'small step' treatment adjustments, which could potentially put children at an increased risk of exacerbation and hospital admission for a longer period of time.

Recommendations/implications for further research

A further update of the review is needed to incorporate additional IPD and ensure maximum representation of treatments within the NMA and to be able to make reliable recommendations regarding specific formulations. Further primary research is needed to establish whether using 'symptom-driven' ICS, rather than 'fixed-dose' as included in our review, may offer further improvement for children with uncontrolled asthma, and future updates of this review should specifically consider this question. Future research could seek to identify factors of biomarkers, which might identify an individual who will gain the best response from treatment options as LABA versus LTRA versus increased dose ICS. Researchers could undertake RCTs designed to compare 'medium-dose ICS' versus 'low-dose ICS plus LABA' versus 'medium-dose plus LABA' in children on low-dose ICS and uncontrolled symptoms. More 'real-world' research, for example using routinely acquired data, would be welcome to understand the generalisability of RCT data as RCT participants often have more regular clinical contact and many 'unsuitable' participants are excluded (often due to poor adherence).

TABLE 45 Key conclusions from EINSTEIN analyses

Comparison to	Exacerbation *Table 17*	Asthma control *Table 24*	Lung function FEV_1 *Table 28*	QoL *Table 29*	Adverse effects	Health economics	Effect modification
ICS Low	ICS Medium +LABA reduces odds 0.44 (0.19 to 0.90)	No option superior	ICS Medium + LABA increases FEV_1 0.71 (0.35, 1.06) [Also ICS Low + LABA step up to ICS Medium + LABA increases FEV_1 0.68 (0.33, 1.04)]	No option superior	No option superior	Most cost-effective	No clear evidence of effect modification. Further research needed
ICS Medium	No option superior	No option superior	ICS Medium + LABA increases FEV_1 0.69 (0.33, 1.05)[a]	ICS + LABA reduces QoL −0.91 (−1.53 to −0.29)[b]	No option superior	ICER exceeds the threshold	No clear evidence of effect modification. Further research needed
ICS High	No option superior	No option superior	ICS Medium + LABA increases FEV_1 0.54 (0.24, 0.81)[c]	No option superior	No option superior	Dominated	No clear evidence of effect modification. Further research needed

a Unexpected reduction in FEV_1 when ICS Medium + LABA stepped up to ICS High + LABA.
b Not NMA: 2 studies, 36 patients.
c Unexpected fall in FEV_1 from step up from ICS High to ICS High + LABA.

Additional information

Contributions of authors

Sofia Cividini (https://orcid.org/0000-0003-2705-9224) (Research Assistant, Biostatistics) developed the protocol, screened and selected studies for inclusion, contacted authors and pharmaceutical companies and retrieved, extracted, and analysed data, interpreted results and drafted the report.

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Data-sharing statement

All data extracted from publicly available sources can be obtained by contacting the corresponding author.

Ethics statement

The EINSTEIN study was granted an exemption from requiring ethical approval from the University of Liverpool Research Integrity and Ethics Committee as the study uses data that are either publicly available or have been provided as anonymised data.

Information governance statement

There were no personal data involved in the production of this report.

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Appendix 1 Search strategy

Main NMA search strategy example MEDLINE (Ovid) search

1 exp Asthma/
2 asthma.ti,ab.
3 1 or 2
4 exp Infant/
5 infant*.ti,ab.
6 infancy.ti,ab.
7 newborn*.ti,ab.
8 baby*.ti,ab.
9 babies.ti,ab.
10 neonat*.ti,ab.
11 preterm*.ti,ab.
12 prematur*.ti,ab.
13 postmatur*.ti,ab.
14 exp child/
15 child*.ti,ab.
16 schoolchild*.ti,ab.
17 'school age*'.ti,ab.
18 preschool*.ti,ab.
19 kid.ti,ab.
20 kids.ti,ab.
21 toddler*.ti,ab.
22 exp Adolescent/
23 adoles*.ti,ab.
24 teen*.ti,ab.
25 boy*.ti,ab.
26 girl*.ti,ab.
27 exp Minors/
28 minor*.ti,ab.
29 exp Puberty/
30 pubert*.ti,ab.
31 pubescen*.ti,ab.
32 prepubescen*.ti,ab.
33 exp Pediatrics/
34 paediatric*.ti,ab.
35 pediatric*.ti,ab.
36 exp Schools/
37 'nursery school*'.ti,ab.
38 kindergar*.ti,ab.
39 'primary school*'.ti,ab.
40 'secondary school*'.ti,ab.
41 'elementary school*'.ti,ab.
42 'high school*'.ti,ab.
43 highschool*.ti,ab.
44 or/4–43
45 'inhaled corticosteroid*'.mp.
46 ICS.mp.

47 exp Beclomethasone/
48 beclomethasone.mp.
49 'beclomethasone dipropionate'.mp.
50 becotide.mp.
51 clenil.mp.
52 ciclesonide.mp.
53 'clenil modulite'.mp.
54 exp Fluticasone/
55 'fluticasone propionate'.mp.
56 fluticasone.mp.
57 flixotide.mp.
58 exp Budesonide/
59 budesonide.mp.
60 Mometasone Furoate/
61 mometasone.mp.
62 exp Adrenergic beta-Agonists/
63 'long acting beta-2 agonist*'.mp.
64 'long acting beta2 agonist*'.mp.
65 LABA.mp.
66 exp Formoterol Fumarate/
67 formoterol.mp.
68 Oxis.mp.
69 'fluticasone furoate'.mp.
70 exp Salmeterol Xinafoate/
71 salmeterol.mp.
72 serevent.mp.
73 vilanterol.mp.
74 exp Leukotriene Antagonists/
75 'leukotriene receptor antagonist*'.mp.
76 LTRA.mp.
77 zafirlukast.mp.
78 montelukast.mp.
79 exp Theophylline/
80 theophylline.mp.
81 Tiotropium.mp.
82 spiriva.mp.
83 Symbicort.mp.
84 Seretide.mp.
85 flutiform.mp.
86 relvar.mp.
87 or/45–86
88 Clinical Trial.pt.
89 Randomized Controlled Trial.pt.
90 exp Random Allocation/
91 exp Single-Blind Method/
92 exp Double-Blind Method/
93 exp Cross-Over Studies/
94 exp Placebos/
95 RCT.ti,ab.
96 Random*.ti,ab.
97 'Single blind*'.ti,ab.
98 'Double blind*'.ti,ab.
99 'triple blind*'.ti,ab.

100 placebo*.ti,ab.
101 or/88–100
102 3 and 44 and 87 and 101
103 limit 102 to ed = 20140701–20190911
104 limit 103 to english language
105 (case reports or editorial or letter).pt.
106 104 not 105

Treatment effect modifier searches

Search 1: Database: Ovid MEDLINE ALL <1946 to July 02, 2019>

1 exp Asthma/
2 asthma.ti,ab.
3 1 or 2
4 exp Infant/
5 infant*.ti,ab.
6 infancy.ti,ab.
7 newborn*.ti,ab.
8 baby*.ti,ab.
9 babies.ti,ab.
10 neonat*.ti,ab.
11 preterm*.ti,ab.
12 prematur*.ti,ab.
13 postmatur*.ti,ab.
14 exp child/
15 child*.ti,ab.
16 schoolchild*.ti,ab.
17 'school age*'.ti,ab.
18 preschool*.ti,ab.
19 kid.ti,ab.
20 kids.ti,ab.
21 toddler*.ti,ab.
22 exp Adolescent/
23 adolescen*.ti,ab.
24 teen*.ti,ab.
25 boy*.ti,ab.
26 girl*.ti,ab.
27 exp Minors/
28 minor*.ti,ab.
29 exp Puberty/
30 pubert*.ti,ab.
31 pubescen*.ti,ab.
32 prepubescen*.ti,ab.
33 exp Pediatrics/
34 paediatric*.ti,ab.
35 pediatric*.ti,ab.
36 exp Schools/
37 'nursery school*'.ti,ab.
38 kindergar*.ti,ab.
39 'primary school*'.ti,ab.
40 'secondary school*'.ti,ab.

41 'elementary school*'.ti,ab.
42 'high school*'.ti,ab.
43 highschool*.ti,ab.
44 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 3 and 44
46 'inhaled corticosteroid*'.ti,ab,kw.
47 exp Beclomethasone/
48 'beclomethasone dipropionate'.ti,ab,kw.
49 ciclesonide.ti,ab,kw.
50 exp Fluticasone/
51 'fluticasone propionate'.ti,ab,kw.
52 exp Budesonide/
53 budesonide.ti,ab,kw.
54 Mometasone Furoate/
55 mometasone.ti,ab,kw.
56 exp Adrenal Cortex Hormones/ or exp Adrenergic beta-Agonists/
57 'long acting beta-2 agonist*'.ti,ab,kw.
58 'long acting beta2 agonist*'.ti,ab,kw.
59 exp Formoterol Fumarate/
60 formoterol.ti,ab,kw.
61 exp Salmeterol Xinafoate/
62 salmeterol.ti,ab,kw.
63 vilanterol.ti,ab,kw.
64 exp Leukotriene Antagonists/
65 'leukotriene receptor antagonist*'.ti,ab,kw.
66 zafirlukast.ti,ab,kw.
67 montelukast.ti,ab,kw.
68 exp Theophylline/
69 theophylline.ti,ab,kw.
70 Tiotropium.ti,ab,kw.
71 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70
72 45 and 71
73 modifi*.ti,ab,kw.
74 72 and 73
75 ((age or gender or ethnicity or eczema or asthma severity) adj3 (outcome* or effect* or modif* or success* or response or differen*)).mp.
76 72 and 75
77 ((age or gender or ethnic* or racial or eczema or asthma severity) and (effect* or differen* or modif* or success* or response or outcome*)).ti.
78 72 and 77
79 74 or 76 or 78
80 limit 79 to english language

Search 2: Database: Ovid MEDLINE ALL <1946 to July 02, 2019>

1 exp Asthma/
2 asthma.ti,ab.
3 1 or 2
4 exp Infant/
5 infant*.ti,ab.
6 infancy.ti,ab.

7 newborn*.ti,ab.
8 baby*.ti,ab.
9 babies.ti,ab.
10 neonat*.ti,ab.
11 preterm*.ti,ab.
12 prematur*.ti,ab.
13 postmatur*.ti,ab.
14 exp child/
15 child*.ti,ab.
16 schoolchild*.ti,ab.
17 'school age*'.ti,ab.
18 preschool*.ti,ab.
19 kid.ti,ab.
20 kids.ti,ab.
21 toddler*.ti,ab.
22 exp Adolescent/
23 adolescen*.ti,ab.
24 teen*.ti,ab.
25 boy*.ti,ab.
26 girl*.ti,ab.
27 exp Minors/
28 minor*.ti,ab.
29 exp Puberty/
30 pubert*.ti,ab.
31 pubescen*.ti,ab.
32 prepubescen*.ti,ab.
33 exp Pediatrics/
34 paediatric*.ti,ab.
35 pediatric*.ti,ab.
36 exp Schools/
37 'nursery school*'.ti,ab.
38 kindergar*.ti,ab.
39 'primary school*'.ti,ab.
40 'secondary school*'.ti,ab.
41 'elementary school*'.ti,ab.
42 'high school*'.ti,ab.
43 highschool*.ti,ab.
44 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 3 and 44
46 'inhaled corticosteroid*'.ti,ab,kw.
47 exp Beclomethasone/
48 'beclomethasone dipropionate'.ti,ab,kw.
49 ciclesonide.ti,ab,kw.
50 exp Fluticasone/
51 'fluticasone propionate'.ti,ab,kw.
52 exp Budesonide/
53 budesonide.ti,ab,kw.
54 Mometasone Furoate/
55 mometasone.ti,ab,kw.
56 exp Adrenal Cortex Hormones/ or exp Adrenergic beta-Agonists/
57 'long acting beta-2 agonist*'.ti,ab,kw.
58 'long acting beta2 agonist*'.ti,ab,kw.

59 exp Formoterol Fumarate/
60 formoterol.ti,ab,kw.
61 exp Salmeterol Xinafoate/
62 salmeterol.ti,ab,kw.
63 vilanterol.ti,ab,kw.
64 exp Leukotriene Antagonists/
65 'leukotriene receptor antagonist*'.ti,ab,kw.
66 zafirlukast.ti,ab,kw.
67 montelukast.ti,ab,kw.
68 exp Theophylline/
69 theophylline.ti,ab,kw.
70 Tiotropium.ti,ab,kw.
71 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70
72 45 and 71
73 limit 72 to English language and randomized controlled trials.pt

Appendix 2 Data-checking

Note: supply any additional information (e.g. detailed responses to questions) in the note sections

Checks of the supplied data and accompanying documents

Documentation list

Has all documentation been supplied with the data sets?	**Yes □/No □**
Are the protocol(s) available?	**Yes □/No □**
Are the CRFs available?	**Yes □/No □**
Are the documents with variables' coding and labels available?	**Yes □/No □**
Is the SAP available?	**Yes □/No □**
Are any references for papers related to this study available?	**Yes □/No □**
Notes:	

List all files received relating to this study below, with a description of their type (e.g. paper, data set)	
Name	*Type*

List any references (if any) for papers related to this study below

Usability of provided files

Do the data set files and any additional documentation open?	**Yes □/No □**
Is reformatting of the data sets required to allow them to be read into R?	**Yes □/No □**
Are all supplied documents, data labels, text variable, etc. written clearly in English?	**Yes □/No □**
Are there any ambiguous terms to be clarified with the study authors?	**Yes □/No □**
Notes:	

Data sets

Have single or multiple data sets been supplied?	**Single □/Multiple □**
If multiple data sets have been supplied, do all data sets contain a common patient ID?	**Yes □/No □**
Are all patients present in all data sets?	**Yes □/No □**
Did the data provider complete the provided data availability form specifying what data could be provided?	**Yes □/No □** **Not sent □**
If yes, have data been supplied for all variables specified as available in the data availability form, or have reasons for the absence of data been given?	**Yes □/No □** **Skip if No/Not sent □**
Have sufficient data been provided for the study to contribute to the analysis?	**Yes □/No □**
Are variables' labels with full and clear descriptions provided?	**Yes □/No □**

Does each column of each data set have a name and label of the included variables?	**Yes □/No □**
Are clear labels provided for coded or categorical variables?	**Yes □/No □**
Have the study authors provided original or de-identified (anonymised) data?	**Original□/ De-identified □**
If the data has been de-identified, are sufficient details provided of the de-identification? For example, whether actual or offset dates are provided, do empty cells correspond to missing or redacted values?	**Yes □/No □/Skip if original □**

Notes:

Actions:

Contact with the data providers will be necessary if:

Files provided do not open.
Data are not provided in a useable format.
Essential accompanying documentation is missing or insufficient.
May be beneficial to obtain the protocol? **Yes □/No □/Already provided □**
Important data stated to be available is missing.
Data are not clearly labelled or supplied.
If data and provided documentation satisfy these initial checks (either immediately or after contact with the data providers), data can be loaded into the SAS programming software, and further data-checks undertaken.

General checks on data content

ID variables

Has a unique ID been provided for each participant in the data set?	**Yes □/No □**
Is this the original randomisation number or a new number produced for de-identification purposes?	**Original □/ New □**
In the case that a new de-identified ID number has been used, have the study authors provided details regarding the way of the generation of this number? If not, it is not possible to perform checks on the ID variable.	**Yes □/No □/ Skip if original □**
If the original randomisation number, or a de-identified number that considers the original sequence, is used:	
Are there any missing numbers in the sequence, which may indicate excluded patients?	**Yes □/No □ Unclear □**
Does the randomisation sequence look random? Is it possible to identify any trends in participants being randomised to any treatment? Are baseline characteristics balanced across allocations?	**Yes □/No □ Unclear □ See notes □**

Notes:

Missing values/errors in data

Is it clear how missing values are identified in the supplied data sets?	**Yes □/No □**
What characters identify missing values in the supplied data sets? *Specify the details in the notes below.*	**NA □/• □/" " □/"" □/others □**
For each variable, perform exploratory analysis (range for continuous variables, frequencies in each category for categorical variables), and list information concerning the following questions in the notes section below:	
Are there any extreme values (e.g. age of 100) or impossible values (age of −1)?	**Yes □/No □**
How many data are missing for each variable?	

Will missing data for a given variable affect calculation of outcomes (e.g. missing 'Variable's name?')	**Yes □/No □/ Unclear □**

Notes:
1. Comment on the encoding of missing data.
*2. **Name of the data set** with the following comments:*
Impossible or extreme value.
Level of missing data for each variable (n and percentage).
Comment on the possibility that missing data for a given variable affect calculation of outcomes.

Comparison to publications

Compared to any publications linked to the data (journal articles, entries on ClinicalTrials.gov, etc.) or other related documents (protocols, clinical study reports):	
Is there the same number of patients included both in the publications/other documents and in the provided data sets?	**Yes □/No □**
Does all the information stated in the publications/other documents correspond to that supplied with the data? For example:	
Inclusion and exclusion criteria.	**Yes □/No □/Unclear □**
Enrolment/randomisation dates/other specified dates.	**Yes □/No □/Unclear □**
Demographics and participant characteristics.	**Yes □/No □/Unclear □**
Number of participants contributing to each outcome (e.g. exclusions).	**Yes □/No □/Unclear □**
Number of participants randomised to each treatment.	**Yes □/No □/Unclear □**
Is it possible to recreate the relevant results within the publication (where possible), given the data provided?	**Yes □/No □/Unclear □**
If not, is it possible to determine a reason for the discrepancy? For example, numerical differences between published results and IPD, unclear analysis methods in the publications.	**Yes □/No □/Unclear □**

Notes:
– Comments on points 1–8:
Inclusion and exclusion criteria:
Enrolment/randomisation/other dates
Demographics and participant characteristics:
– Selected tables from published papers have been replicated below.
***Paper**: author, journal, year of publication*
Data description present in the paper:
Table X/Comments on the obtained results
Table Y/Comments on the obtained results

Actions

If IDs do not seem to follow a random sequence, inquire with data providers regarding the randomisation methods used. The data not properly randomised may not be able to be used.

If large levels of missing data exist, particularly for the variables needed to code outcomes, contact the data providers to establish the reason for the missingness.

The data cannot be included in the analysis of the outcome if the data providers cannot explain the reasons for the missingness or cannot provide the data required for the outcome.

Contact the data provider for clarification regarding numerical inconsistencies between published results and results got after recarrying out the analyses by using the provided data, or when published results cannot be recreated because of unclear methodology in the publications or other documents.

Write a list of 'general' inconsistencies (e.g. large numerical inconsistencies or inconsistencies that may influence the calculation of outcome priorities) for the attention of the data provider. Combine this list with any queries or inconsistencies arising from specific checks of the data content and the initial coding of the analysis data set (data-checks and coding are described in the following sections).

Actions to be taken:

Request clarification of the following variables, as the data sets do not match the published reports:

To list

General numerical inconsistencies:

To list

Once these cleaning and checking procedures have been completed, and any questions arising from the procedures have been answered, the data can be coded in preparation for inclusion in the analysis data set. For the description of the required variable names, and details of units, scales and categorical levels, see *Appendix 3*.

Appendix 3 Variable dictionary

Variable name	Type	Label	Code
STUDY'S FEATURES			
STUDY_ID	Num	New study identifier	
ORIG_STUDY_ID	Char	Original study identifier	Alphanumeric code
AUTHOR	Char	First author (year of publication)	
PHARMA_CO	Char	Pharmaceutical company's name providing data	
SUBJID	Num	Original subject identifier	
STUDY_DESIGN	Char/ categorical	Type of experimental design	Parallel groups Crossover
BLIND	Char/ categorical	Blinding	Open-label Single-blind Double-blind Complete-blind
BASELINE FEATURES OF PATIENTS			
***Note 1**: The randomisation visit was considered as baseline unless there were no data. In that case, we used data from the screening visit by accounting for that. However, most of the demographic data were only collected at the screening visit in almost all studies, unlike clinical data. For the latter, the measurement was also often repeated at the randomisation visit. A note concerning the data collection visit for every variable and RCT was also taken in a separate file.*			
DEMOGRAPHICS			
AGE	Num/ continuous	Age at baseline visit (years)	
SEX	Char/ categorical	Sex	F = female M = male
ETHNICITY	Char/ categorical	Ethnicity	Hispanic or Latino Not Hispanic or Latino
RACE	Char/ categorical	Race background	• White (white/Caucasian/European Heritage; Arabic/North African heritage) • African American/African heritage • Asian (Central/South Asian heritage; East Asian heritage; Japanese heritage; South-East Asian heritage) • American Indian or Alaskan Native • Hawaiian or Pacific Islander Native • Mixed race
CLINICAL DATA			
ECZEMA	Num/ categorical	Eczema disease status	0 = no 1 = yes
EOSIN_PTC	Num/ continuous	Percentage of eosinophils (%) at baseline	
EOSIN_CELLS	Num/ continuous	Cells/µl at baseline *Notes: best reference*	
eNO	Num/ continuous	eNO in ppb at baseline	

Variable name	Type	Label	Code
AP_BLOOD_PTC	Char/ categorical	AP assessed on the blood percentage of eosinophils (%) at baseline	eosinophilic ▷ PTC ≥ 5% non-eosinophilic ▷ PTC < 5% undefined ▷ not tested
AP_BLOOD	Char/ categorical	AP assessed on the blood count of eosinophils (cells/µl) at baseline	eosinophilic ▷ cells/µl ≥ 370 non-eosinophilic ▷ cells/µl < 370 undefined ▷ not tested
AP_eNO	Char/ categorical	AP assessed through eNO (ppb) at baseline	eosinophilic ▷ eNO ≥ 30 non-eosinophilic ▷ eNO < 30 undefined ▷ not tested
Eosinophilia	Char/ categorical	Based on AP_BLOOD with AP_BLOOD_PTC and AP_eNO integration if there is no data for AP_BLOOD	eosinophilic non-eosinophilic undefined (considered as missing)
BL_FEV_1PDPC	Num/ continuous	Percent predicted normal FEV_1 (%) at baseline	
BL_SEVERITY	Char/ categorical	Baseline asthma severity measured through percent predicted normal FEV_1 (%)	mild ▷ PCPDFEV$_1$ > 80% moderate ▷ PCPDFEV$_1$ = 60–80% severe ▷ PCPDFEV$_1$ < 60%
PRE_TRT	Char/ categorical	Pharmacological treatment (ICS alone) used at the screening visit (active principles of interest)	BDP = beclomethasone dipropionate FP = fluticasone propionate FF = fluticasone furoate CIC = ciclesonide BUD = budesonide MF = mometasone furoate
PRE_TRT_CLASS	Char/ categorical	Pharmacological class of treatment used before entry *Notes: any ICS above cited, any dose*	ICS = any inhaled corticosteroids
PRE_TRT_DOSE	Num/ continuous	Overall daily pre-study dose (i.e. before entering the study, at the screening visit)	Expressed in mcg (ICS alone)
PRE_TRT_DOSE2	Char/ categorical	Overall daily pre-study dose (i.e. before entering the study, at the screening visit) *Notes:* Categorisation *based on the values reported in the GINA Table by drug and age class*	Low Medium High Unknown (missing)
BL_FEV_1	Num/ continuous	Baseline FEV_1 (in l/1s)	
BASELINE_ CLINICS	Char/ categorical	Visit at which baseline clinical data were collected	R = randomisation visit S = screening visit M = mixed
POPULATION'S FEATURES			
ITT	Char/ categorical	Intention-to-treat (ITT) population	Yes ▷ only ITT population is considered
PP	Char/ categorical	Per-protocol (PP) population	No = the patient is not in PP Yes = the patient is in PP
VISITS' DATES			
VISIT DESCRIPTION	It is not a variable included in the database, but a description of the visit management	Description of the type of visit. The number of intermediate visits is different from study to study *Notes: there can be visits after the end of the treatment (follow-up visit)*	screening visit* randomisation visit (baseline)* *i* = intermediate visits (with *i* = 3, 4, 5, … , *n* = last visit at the end of the study) **See Note 1*
SCREEN_DATE	Date	Date of screening visit	
RAND_DATE	Date	Date of randomisation visit	

Variable name	Type	Label	Code
VISITi_DATE	Date	Dates of all other visits *Notes: we have as many variables as the number of intermediate visits (i = 3, 4, 5, … , n).*	*i* = intermediate visits (see above) *n* = last visit at the end of the study
DAYSi Example: DAYS_SCREEN DAYS_RAND DAYS_VISITi	Num/ continuous	These variables represent the number of days last from the randomisation visit or the screening visit (if not possible otherwise) to a particular event/outcome/visit *Notes: This group of variables were defined better along the extraction way. We had a certain number of these variables for the studies that did not provide dates. We managed the number of days to an event/outcome/visit in the analysis phase integrating these data with those derived from the difference of dates supplied by the other studies*	In the CARE Network trials, for instance, all dates were converted in days from the first visit
LENGTH_FU	Num/ continuous	It represents the follow-up length from the randomisation visit to the last useful treatment visit that the patient attended *Notes: also useful for the economic model*	
STUDY TREATMENTS			
TRT	Char/ categorical	Pharmacological treatments used in the RCTs (active principles of interest) *Notes: The list on the right is only indicative of concerning combined drugs*	placebo BDP = beclomethasone dipropionate FP = fluticasone propionate FF = fluticasone furoate CIC = ciclesonide BUD = budesonide MF = mometasone furoate FORM = formoterol SAL = salmeterol VI = vilanterol zafirlukast montelukast theophylline FP + SAL FF + VI
TRT_ORIGINAL	Char/ categorical	Pharmacological treatments used in the RCTs (active principles of interest)	Original categorisation
TRT_CLASS	Char/ categorical	Pharmacological classes of treatments used in the RCTs *Notes: Any ICS, LABA, LTRA, others, and their combination*	ICS = any inhaled corticosteroids LABA = any long-acting β_2-agonist LTRA = any leukotriene receptor antagonist Theophylline ICS + LABA (any combination) ICS + LTRA (any combination) CIC placebo
TRT_DOSE	Char/ categorical	The overall daily dose of the study treatment reported in each RCT	Expressed in mcg
TRT_DOSE2	Char/ categorical	The overall daily dose of the study treatment reported in each RCT based on the ICS dose only, even when combined with something else *Notes: Categorisation based on the values reported in the GINA Table by drug and age class*	Low Medium High
TRT_UNITS	Char/ categorical	Measuring units	mcg mg

Variable name	Type	Label	Code
DEVICE	Char/ categorical	Type of device used	Metered dose inhaler (MDI) MDI with spacer pressurised MDI (pMDI) Diskus Dry powder inhaler (DPI) Combination inhaler (more actives) Other types No indication
ADHERENCE	Num/ categorical OR Num/ continuous	Adherence to the protocol (based on the PP population)	PP/ITT (%)
COMPL	Num/ continuous	Compliance (adherence to the treatment)	GSK used the formula reported in the notes to calculate overall compliance. This formula could be somehow used to standardise the compliance in the other RTCs
OUTCOMES			
FIRST PRIMARY OUTCOME (exacerbation)			
EXACERB_ORD	Num/ordinal	Has the patient experienced exacerbation?	In order of severity: 0 = no 1 = yes, with oral steroids 2 = yes, with unscheduled ED* or GP** 3 = yes, with hospitalisation 4 = yes, but unknown condition **Emergency department* ***General practitioner*
EXACERB_BIN	Num (binary)	Has the patient experienced exacerbation?	0 = no 1 = yes
EXACERB_COUNT	Num (count)	Total number of exacerbations occurred during the follow-up	
DATE_F_EXACERB	Num (date)	Date of the first exacerbation	
EXACERB_ FROM_AE	Num (binary)	It accounts for exacerbation derived from AE data set when there is nothing else	0 = no 1 = yes
EXACERB_SURV	Num/ categorical	First exacerbation	0 = censored (non-event) 1 = exacerbation (event)
TIME_SURV	Time-to-event	Days from randomisation to the first exacerbation	
SECOND PRIMARY OUTCOME (asthma control)			
AC_TEST	Char/ categorical	Type of validated test used to measure asthma control	ACT 4–11 ACT 12+ ACQ Other None
AC_TEST_SCORE	Num/ continuous	Overall mean score from all tests (carried out in all visits) *Notes: stationary variable (single value)*	
AC_TEST_SCORE_ INTi	Num/ continuous	Overall mean score recorded at every predefined visit (intermediate scores) *Notes: longitudinal variables – we will have as many variables as visits. From this set of values, it should be also possible to establish a clinically relevant time point*	

Variable name	Type	Label	Code
ASTHMA_CTRL	Num/binary	Asthma control measured by a validated test (e.g. ACT, ACQ, other) *Notes: categorised based on AC_TEST_SCORE (overall mean value from all tests carried out)*	**ACT (4–11 years):** 0 = poor control (≤ 19) 1 = total/good control (20–27) **ACT (over 12 years):** 0 = poor control (≤ 19) 1 = total/good control (20–25) **ACQ** 0 = poor control (> 1) 1 = total/good control (≤ 1) **Other** 0 = poor control (to establish) 1 = good/total control (to establish) *Notes: between the two tests above, chose ACT as the best choice if both are present.*
ASTHMA_CTRL_INTi2	Num/binary	Asthma control measured by a validated test (e.g. ACT, ACQ, other) *Notes: variables categorised based on* AC_TEST_SCORE_INTi *(overall value collected at every scheduled visit). We will have as many variables as visits*	**ACT (4–11 years):** 0 = poor control (≤ 19) 1 = total/good control (20–27) **ACT (over 12 years):** 0 = poor control (≤ 19) 1 = total/good control (20–25) **ACQ** 0 = poor control (> 1) 1 = total/good control (≤ 1) **Other** 0 = poor control (to establish) 1 = good/total control (to establish) *Notes: between the two tests above, chose ACT as the best choice if both are present.*
SECONDARY OUTCOMES			
SYMPTOMS	Char/ categorical	Every type of symptoms (cough, wheezing, etc.)	Yes No
SYM_SCORE	Char/ categorical	Intensity of the symptoms	None Mild Moderate Severe
QoL_Tool	Char/ categorical	Type of tool used to record patients' QoL.	
QoL	Num/ continuous	QoL	Standardised score (to be defined)
Mortality	Num/ categorical	Mortality due to asthma	0 = alive 1 = deceased
FEV_1_VISITi	Num/ continuous	FEV_1 (in L/1s) – values recorded at visits after the randomisation visit (i = 3, 4, 5, … ,n) *Notes: We will have as many variables as visits*	
AEs CONSIDERED	It is not a variable included in the database, but a description of the AE to be considered	Type of AE (definition ideally based on the MedDRA system organ class text)	Cardiac disorders: Heart rate change from baseline Any ECG changes Neuropsychiatric disorders Sleep Behavioural difficulty Infestations/Infections: Pneumonia Oral candidiasis Cataract/glaucoma Diabetes Growth

Variable name	Type	Label	Code
AE_{-type}	Num/ categorical	Has the patient experienced the AE?	0 = no 1 = yes
AE_ECG	Num/ categorical	Has the patient experienced ECG changes?	0 = no 1 = yes (favourable) 2 = yes (unfavourable) 3 = unable to compare
AE_HRchange	Num/ continuous	Heart rate change from BL to the last scheduled visit	
Withdrawals_AE	Num/ categorical	Withdrawals due to an AE	0 = no 1 = yes
Hosp_Admis	Char/ categorical	Hospital admissions due to asthma. Has the patient be hospitalised?	N = no Y = yes U = unknown NA = not applicable ND = not done

Appendix 4 Characteristics of included studies

TABLE 46 Characteristics of the included studies with IPD

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
Bateman (2014)[47]	USA, Argentina, Australia, Germany, Japan, Mexico, Philippines, Poland, Romania, Russian Federation, Ukraine	*N* = 213 mean age (SD) = 14.1 (1.7) Females – *N* (%) = 82 (38) Not Hispanic or Latino – *N* (%) = 141 (66) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 75 (38) BL-severity (mild) – *N* (%) = 104 (49)	Patients ≥ 12 years of age with persistent asthma using ICS alone (the doses in look low, medium and high) or ICS + LABA	Subjects must be using an approved dose of an ICS (as per specific prescribing information) for at least 12 weeks preceding Visit 1 and at a stable dose for at least 4 weeks preceding Visit 1. In addition, subjects may be using a combination products with an ICS (as per specific prescribing information) or an ICS plus a LABA for at least 12 weeks preceding Visit 1 and at a stable dose for at least 4 weeks preceding Visit 1	Parallel groups double-blind	FF/VI 100/25 mcg OD (DPI) FF 100 mcg OD (DPI)	≥ 24–78 Mean days (SD):[d] 378.7 (43.1)
Bernstein (2015)[48]	USA, Russia, Argentina, Ukraine, Romania, Chile, Germany, Poland, Mexico, the Netherlands, Sweden	*N* = 42 mean age (SD) = 14.6 (1.8) Females – *N* (%) = 15 (36) Not Hispanic or Latino – *N* (%) = 23 (55) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 18 (44) BL-severity (mild) – *N* (%) = 0 (0)	Patients ≥ 12 years of age with moderate to severe, persistent asthma using ICS or ICS/LABA.	Subjects are eligible if they have received ICS for at least 12 weeks prior to Visit 1 and their treatment during the 4 weeks immediately prior to Visit 1	Parallel groups double-blind	FF/VI 200/25 mcg OD (DPI) FF/VI 100/25 mcg OD (DPI) FF 100 mcg OD (DPI)	12 Mean days (SD):[d] 87.2 (13.8)
Bleecker (2012)[49]	USA, Canada, Estonia, Germany, Greece, Korea, Mexico, Philippines, Poland, Romania, Russian Federation, Slovakia, South Africa	*N* = 69 mean age (SD) = 14.1 (1.6) Females – *N* (%) = 28 (41) Not Hispanic or Latino – *N* (%) = 60 (87) Eczema – *N* (%) = 42 (61) Eosinophilia – *N* (%) = 35 (52) BL-severity (mild) – *N* (%) = 29 (42)	Patients ≥ 12 years of age with persistent asthma and symptomatic on ICS	Subjects must have been using an ICS for at least 8 weeks prior to visit 1 and maintained on a stable dose of ICSs for 4 weeks prior to visit 1	Parallel groups double-blind	FP 250 mcg BID (Diskus/ Accuhaler) FF 100 mcg OD (DPI) FF 200 mcg OD (DPI) FF 300 mcg OD (DPI) FF 400 mcg OD (DPI) placebo	8 Mean days (SD):[d] 52.2 (20.2)

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
Bleecker (2014)[50]	USA, Germany, Japan, Poland, Romania, Ukraine	*N* = 61 mean age (SD) = 14.4 (1.6) Females – *N* (%) = 24 (39) Not Hispanic or Latino – *N* (%) = 44 (72) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 14 (23) BL-severity (mild) – *N* (%) = 17 (28)	Patients with persistent asthma aged 12 years and older (child, adult, older adult)	All patients must be using an ICS with or without LABA for at least 12 weeks before visit 1	parallel groups double-blind	FF/VI 100/25 OD (DPI) FF 100 OD (DPI) placebo	12 mean days (SD):[d] 86.6 (25.3)
Carroll (2010)[51]	UK	*N* = 39 mean age (SD) = 10.6 (2.8) Females – *N* (%) = 15 (38) Not Hispanic or Latino – *N* (%) = 39 (100) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 30 (81)	Age 7–18 years (effective range: 7–15). Asthmatic children on 400 mcg/day BDP equivalent	This study contains 37 participants under 18, although the inclusion criteria allowed the inclusion until 18. All participants were using ICS alone at entry. We included all participants from the dataset provided (39 subjects of whom two withdrew at week 4). One of these was withdrawn because of an asthma exacerbation considered as an AE, and the other patient does not have contributing data	Parallel groups double-blind	Fluticasone 100 mcg BD SAL/fluticasone 50/100 mcg BD	8 Mean days (SD):[d] 56.0 (0.0)
de Blic (2009)[52]	Belgium, Denmark, France, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Russian Federation, Spain, Sweden	*N* = 303 mean age (SD) = 8.0 (2.0) Females – *N* (%) = 108 (36) Not Hispanic or Latino – *N* (%) = 292 (96) Eczema – *N* (%) = 265 (88) Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 243 (80)	Patients are asthmatic children aged 4 to 11 years not controlled by ICS alone at medium dose	Patients were receiving beclomethasone HFA or BUD or fluticasone at least 3 months prior to Visit 1	Parallel groups double-blind	FP/SAL 100/50 mcg BID FP 200 mcg BID	12 Mean days (SD):[d] 85.0 (7.7)

continued

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
Fitzpatrick (2016)[53]	USA	*N* = 60[b] mean age (SD) = 3.0 (1.0) Females – *N* (%) = 23 (38) Not Hispanic or Latino – *N* (%) = 52 (87) Eczema – *N* (%) = 34 (57) Eosinophilia – *N* (%) = 14 (27) BL-severity (mild) – *N* (%) = NA	Pre-school children 12–59 months of age who meet criteria for treatment with long-term, step 2 asthma controller therapy	(1) ICS- and LTRA-naïve children treated only with intermittent SABA who require step-up therapy. (2) Children on current step 2 therapy who are treated with daily ICS, daily LTRA, or intermittent ICS or LTRA. Thus, the inclusion criteria for this study differ somewhat according to prior ICS and LTRA exposure	Crossover double-blind	FP HFA – 186 mcg/day montelukast – 4 mg as-needed ICS (FP HFA – 88 mcg) + SABA	P1: 16 P2: 16 P3: 16 Mean days (SD):[d] 109.9 (17.3)
Gappa (2009)[54]	Germany	*N* = 262 mean age (SD) = NA Females – *N* (%) = 81 (31) Not Hispanic or Latino – *N* (%) = 262 (100) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 192 (76)	Patients are children and adolescents 4 to 16 years of age with documented history of persisting seasonal or perennial bronchial asthma	Patients must have been pre-treated with an ICS at a dosage of 200–400 µg BDP equivalents/day during the last 4 weeks	Parallel groups double-blind	FP/SAL 100/50 mcg BID (Diskus) FP 200 mcg BID (Diskus)	8 Mean days (SD):[d] 56.7 (3.9)

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
Lemanske (2010)[2]	USA	*N* = 31 mean age (SD) = 10.6 (3.7) Females – *N* (%) = 8 (26) Not Hispanic or Latino – *N* (%) = 17 (55) Eczema – *N* (%) = 7 (23) Eosinophilia – *N* (%) = 14 (45) BL-severity (mild) – *N* (%) = 27 (87)	Patients aged 6 to 17 with a lack of acceptable asthma control during run-in period	Children enrolled into BADGER can be characterised as falling into one of three groups: • Step-neutral – currently receiving an ICS dose = 200 ug/day fluticasone equivalent • Step-up – naïve to controller therapy or receiving an ICS dose < 200 ug/day fluticasone equivalent or non-ICS controller therapy (e.g. montelukast, theophylline or cromolyn), and needing step-up therapy • Step-down – currently receiving controller therapy considered by the NAEPP guidelines to be a step above 1 × ICS (e.g. 2 × ICS or combination therapy of 1 × ICS + LABA, montelukast, theophylline or cromolyn)	Crossover double-blind	2 × ICS: DPI 250 mcg fluticasone + DPI 250 mcg fluticasone + placebo 1 × ICS + LTRA: DPI 100 mcg fluticasone + DPI 100 mcg fluticasone + montelukast 1 x ICS + LABA: DPI 100 mcg fluticasone/50 mcg SAL + DPI 100 mcg fluticasone/50 mcg SAL + placebo	P1: 16 P2: 16 P3: 16 Mean days (SD):[d] 106.4 (17.4)
Li (2010)[55]	USA, Australia, Canada, Chile, Costa Rica, Germany, Latvia, Lithuania, Mexico, Peru, Poland, Russian Federation, Spain	*N* = 350 mean age (SD) = 7.6 (2.1) Females – *N* (%) = 137 (39) Not Hispanic or Latino – *N* (%) = 207 (59) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 191 (56) BL-severity (mild) – *N* (%) = 195 (71)	Patients are children aged 4 to 11 years with asthma requiring pharmacotherapy for at least 2 months. Patients were using ICS at a consistent dose (low-medium doses) and SABA	ICS doses: beclomethasone (CFC): 84–100 to 336–400 beclomethasone (HFA): 84–100 to 160–200 FP (powder): 100 to 200 FP (CFC or HFA): 88–100 to 176–200 BUD (powder): 200 to 400 BUD repulse: 500	Parallel groups double-blind	FP/SAL 100/50 mcg BID (HFA) FP 100 mcg BID (HFA)	12 Mean days (SD):[d] 80.5 (19.3)

continued

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
[e]Lötvall (2014)[56]	USA, Germany, Peru, Poland, Ukraine	*N* = 20 mean age (SD) = 14.3 (1.9) Females – *N* (%) = 8 (40) Not Hispanic or Latino – *N* (%) = 6 (30) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 5 (25)	Patients ≥ 12 years of age with persistent asthma using a low, medium, or high dose of ICS at visit 1.	All subjects must be using an ICS for at least 12 weeks prior to Visit 1. Subjects must be taking a stable dose of ICS (e.g. FP 200–1000 mcg twice daily or equivalent) for at least 4 weeks prior to Visit 1. Subjects will be stratified at randomisation according to whether they are on low-, medium- or high-dose ICS at Visit 1	Parallel groups double-blind	VI 25 mcg OD (DPI) SAL 50 mcg BID (DPI) placebo All patients were additionally using their baseline ICS dose	12 Mean days (SD):[d] 91.0 (18.0)
[e]Lötvall (2014)[56]		*N* = 26 mean age (SD) = 14.1 (1.6) Females – *N* (%) = 15 (58) Not Hispanic or Latino – *N* (%) = 13 (50) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 4 (16)					12 Mean days (SD):[d] 95.3 (8.1)
Lötvall (2014)[57]	USA, Belgium, Germany, Poland, Romania	*N* = 46 mean age (SD) = 13.9 (1.7) Females – *N* (%) = 20 (43) Not Hispanic or Latino – *N* (%) = 44 (96) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 14 (31) BL-severity (mild) – *N* (%) = 16 (36)	Patients ≥ 12 years of age with persistent asthma taking a stable dose of ICS	All subjects must be taking a stable dose of ICS for at least 4 weeks prior to Visit 1	Parallel groups double-blind	FF 100 mcg OD (DPI) FP 250 mcg BID (Diskus/ Accuhaler) placebo	24

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
							Mean days (SD):[d] 163.4 (31.9)
Martin (2020)[58]	USA, Canada	*N* = 11 mean age (SD) = 13.7 (2.1) Females – *N* (%) = 4 (36) Not Hispanic or Latino – *N* (%) = 11 (100) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 11 (100)	Patients aged 12 to 50 years taking low or moderate dose ICS for 12 weeks before Visit 1	Patients with intermittent asthma, seasonal asthma, or exercise-induced bronchoconstriction only were NOT eligible	Crossover double-blind	FF/VI 100/25 mcg QD via Ellipta + Placebo BD via Diskus FP 250 mcg BD via Diskus + Placebo QD via Ellipta	P1: 2 washout: 2 P2: 2
							Mean days (SD):[d] 14.4 (1.0)
Murray (2010)[59]	New Zealand, UK	*N* = 13 mean age (SD) = 7.7 (2.1) Females – *N* (%) = 9 (69) Not Hispanic or Latino – *N* (%) = 13 (100) Eczema – *N* (%) = 13 (100) Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Patients aged 4 to 11 years with asthma diagnosed by physicians	Receiving a total daily dose of 200–800 mcg/day BDP or equivalent for at least 4 weeks prior to the start of the run-in period, and in physicians' opinion be sufficiently stable to receive FP 200 mcg/day during the 2-week run-in period	parallel groups double-blind	FP 100 mcg bd BID + FP 100 mcg BID (ACTIVE/ACTIVE) FP/SAL 100/50 mcg BID + placebo (ACTIVE/PLACEBO)	6
							Mean days (SD):[d] 42.5 (0.9)

continued

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
Murray (2011)[60]	USA	*N* = 230 mean age (SD) = 11.5 (3.4) Females – *N* (%) = 99 (43) Not Hispanic or Latino – *N* (%) = 202 (88) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 157 (68)	Patients are children aged 4 to 17 years with persistent asthma on ICS alone (low-medium doses) and SABA	Each subject must have been treated for their asthma with one of the following ICSs at the specified daily dosing range for at least 4 weeks prior to Visit 1 and with no other inhaled long acting bronchodilators for at least 2 weeks prior to Screening. Beclomethasone: 84–336 (4–11 years); 168–504 (12–17 years) FP: 88–220 (4–11 years); 88264 (12–17 years) BUD: 200–400 (4–11 years); 200–600 (12–17 years) Not of interest: QVAR, triamcinolone, flunisolide	parallel groups double-blind	FP/SAL 100/50 mcg BID (Diskus) FP 100 mcg BID (Diskus)	4 Mean days (SD):[d] 28.1 (3.6)
O'Byrne (2014)[61]	USA, Germany, Japan, Poland, Romania, Russian Federation	*N* = 10 mean age (SD) = 15.8 (1.4) Females – *N* (%) = 2 (20) Not Hispanic or Latino – *N* (%) = 10 (100) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 2 (22) BL-severity (mild) – *N* (%) = 1 (10)	Patients ≥ 12 years of age with persistent asthma using ICS alone (FP 500 mcg twice daily or equivalent) or ICS + LABA.	All patients must be using an ICS with or without LABA for at least 12 weeks before Visit 1	Parallel groups double-blind	FF/VI 200/25 mcg OD (DPI) FF 200 mcg OD (DPI) FP 500 mcg BID (Diskus/Accuhaler) placebo	24 Mean days (SD):[d] 174.4 (4.8)

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
Oliver (2016)[62]	USA, Argentina, Chile, Georgia, Germany, Japan, Mexico, Peru, Philippines, Poland, Puerto Rico, Slovakia, South Africa, Ukraine	*N* = 456 mean age (SD) = 7.9 (1.8) Females – *N* (%) = 180 (39) Not Hispanic or Latino – *N* (%) = 129 (28) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 175 (41) BL-severity (mild) – *N* (%) = 173 (45)	Patients aged 5–11 with a history of symptoms consistent with asthma diagnosis for at least 6 months prior to Visit 1. Asthma on a background of ICS therapy	Subjects with persistent uncontrolled asthma must have been receiving stable asthma therapy for at least 4 weeks prior to screening: SABA + ICS (total daily dose FP 250 mcg or equivalent)	Parallel groups double-blind	placebo OD + FP 100 BID VI 6.25 mcg OD + FP 100 BID VI 12.5 mcg OD + FP 100 BID VI 25 mcg OD + FP 100 BID	5 Mean days (SD):[d] 32.8 (7.2)
Oliver (2016)[63]	USA, Bulgaria, Georgia, Germany, Japan, Latvia, Mexico, Peru, Philippines, Poland, Puerto Rico, Russian Federation, South Africa, Sweden, Ukraine	*N* = 318 mean age (SD) = 8.1 (1.9) Females – *N* (%) = 119 (37) Not Hispanic or Latino – *N* (%) = 165 (52) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 96 (34) BL-severity (mild) – *N* (%) = 150 (47)	Patients aged 5–11 with a history of symptoms consistent with asthma diagnosis for at least 6 months prior to Visit 1	Subjects with persistent uncontrolled asthma must been receiving stable asthma therapy for at least 4 weeks prior to screening: SABA alone, SABA + leukotriene, or SABA + low-dose ICS	Parallel groups double-blind	Placebo FP 100 mcg Diskus FF 25 mcg NDPI FF 50 mcg NDPI FF 100 mcg NDPI	13 Mean days (SD):[d] 75.4 (27.3)

continued

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
Pearlman (2009)[64]	USA	*N* = 248 mean age (SD) = 11.1 (3.4) Females – *N* (%) = 99 (40) Not Hispanic or Latino – *N* (%) = 228 (92) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 167 (67)	Patients are children aged 4 to 17 years with persistent asthma using ICS (low-medium doses) and SABA	Each subject must have been treated for their asthma with ICSs at the specified daily dosing range for at least 4 weeks prior to Visit 1 and with no other inhaled long-acting bronchodilators for at least 2 weeks prior to screening. Beclomethasone: 84–336 (4–11 years); 168–504 (12–17 years) FP: 88–220 (4–11 years); 88–264 (12–17 years) BUD: 200–400 (4–11 years); 200–600 (12–17 years) Not of interest: QVAR, triamcinolone, flunisolide	Parallel groups double-blind	FP/SAL 100/50 mcg BID (Diskus) FP 100 mcg BID (Diskus)	4 Mean days (SD):[d] 27.9 (4.3)
Scott (2005)[65]	USA, Canada	*N* = 199 mean age (SD) = 8.0 (2.2) Females – *N* (%) = 73 (37) Not Hispanic or Latino – *N* (%) = 181 (91) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 99 (51) BL-severity (mild) – *N* (%) = 70 (43)	Patients are children aged 4 to 11 years with asthma requiring maintenance treatment (ICS or medication other than ICS or SABA alone)	Concurrent antiasthma therapy. GROUP 1 > ICSs: subjects must have been using ICSs for at least 3 months prior to Visit 1; and at least 1 month before Visit 1, must have been on a consistent daily dose of one of the reported table (doses are low-medium). GROUP 2 > Maintenance asthma medication other than ICSs: subjects are eligible if treated with a maintenance asthma medication other than ICS (e.g. SAL , cromolyn or nedocromil, or montelukast) on a regular basis for at least 4 weeks prior to Visit 1 OR Short acting beta2 agonists: subjects are eligible if treated with SABA alone for relief of respiratory for at least 4 weeks prior to Visit 1 and should not have received an ICS or maintenance asthma medication other than ICSs for at least 4 weeks prior to Visit 1	Parallel groups double-blind	FP/SAL 100/50 mcg BID (Diskus) FP mcg BID (Diskus)	12

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
							Mean days (SD):[d] 79.0 (17.7)
Sorkness (2007)[66]	USA	*N* = 49 mean age (SD) = 9.3 (2.2) Females – *N* (%) = 15 (31) Not Hispanic or Latino – *N* (%) = 36 (73) Eczema – *N* (%) = 30 (61) Eosinophilia – *N* (%) = 29 (63) BL-severity (mild) – *N* (%) = 42 (86)	Children ages 6–14 years with mild-moderate persistent asthma defined by symptom criteria and positive methacholine challenge	Only the naïve group could not use ICS at entry	Parallel groups double-blind	FP (100 mcg BID – Diskus) fluticasone/SAL (100 mcg/50 mcg qd – Diskus) + SAL (50 mcg qd – Diskus) montelukast (5 mg qd)	48
							Mean days (SD):[d] 331.6 (32.2)
Stempel (2016)[67]	USA, Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Croatia, Czechia, Germany, Hungary, Italy, Korea, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Taiwan, Thailand, Ukraine, UK	*N* = 1631 mean age (SD) = 7.4 (2.2) Females – *N* (%) = 647 (40) Not Hispanic or Latino – *N* (%) = 1164 (71) Eczema – *N* (%) = 334 (20) Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Patients are children aged 4 to 11 years with persistent asthma	The allowed pre-treatment consisted of ICS alone (different doses) or ICS with other medicines (LABA, LTRA, theophylline) or SABA, LABA, LTRA, theophylline alone	Parallel groups double-blind	FP – SAL combination 100/50 FP – SAL combination 250/50 FP 100 FP 250	26

continued

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
							Mean days (SD):[d] 168.1 (45.8)
Stempel (2016)[68]	USA, Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Croatia, Czechia, Denmark, Germany, Hungary, Indonesia, Italy, Korea, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Taiwan, Ukraine, UK	*N* = 222 mean age (SD) = 14.2 (1.6) Females – *N* (%) = 104 (47) Not Hispanic or Latino – *N* (%) = 156 (70) Eczema – *N* (%) = 33 (15) Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Patients are adolescents (12–17) and adults (18+) with persistent asthma	Patients were stratified based on the entry medicine (ICS alone or ICS + LABA, ICS + LTRA, ICS + theophylline) and ACQ score	Parallel groups double-blind	FP 100 mcg FP + SAL 100/50 mcg FP 250 mcg FP + SAL 250/50 mcg FP 500 mcg FP + SAL 500/50 mcg	26
							Mean days (SD):[d] 161.8 (51.0)
Thomas (2014)[69]	Singapore	*N* = 33 mean age (SD) = 11.1 (3.1) Females – *N* (%) = 12 (36) Not Hispanic or Latino – *N* (%) = 33 (100) Eczema – *N* (%) = 16 (48) Eosinophilia – *N* (%) = 6 (18) BL-severity (mild) – *N* (%) = 17 (52)	Children and adolescents aged 6–18 years with uncontrolled or partially controlled asthma on 400 mcg BDP.	Children with uncontrolled or partially controlled asthma, on low-medium dose [400 mg BDP (Beclomethasone dipropionate) equivalent] ICS monotherapy	Parallel groups open-label	ICS: 200 mcg of fluticasone twice daily ICS + LABA: 100 mcg of fluticasone plus 50 mg of SAL (Seretide 50/100 Accuhaler, GlaxoSmithKline) twice daily ICS + LTRA: 100 mcg of fluticasone twice daily plus montelukast (Singulair, MSD) 5 mg (for children 15 years) or 10 mg (for > 15 years)	8

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
							Mean days (SD):[d] 60.0 (0.0)
Vaessen-Verberne (2010)[70]	The Netherlands	*N* = 158 mean age (SD) = NA Females – *N* (%) = 67 (42) Not Hispanic or Latino – *N* (%) = 158 (100) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Children aged 6–16 years with symptomatic asthma	Subjects who have received BDP, BUD up to 100–200 mcg bd or FP at a dose of up to 125 mcg bd for at least 4 weeks before the start of the run-in period	Parallel groups double-blind	FP/SAL 100/50 mcg BID FP 200 mcg BID	10
							Mean days (SD):[d] NA
Verberne (1998)[71]	The Netherlands	*N* = 177 mean age (SD) = 11.2 (2.7) Females – *N* (%) = 58 (33) Not Hispanic or Latino – *N* (%) = 177 (100) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 119 (67)	Children aged 6 to 16 years with moderate asthma	A history of stable asthma for at least 1 month without exacerbations or respiratory tract infections; (6) used ICSs between 200 and 800 mcg daily for at least 3 months before the start of the study. From discussion: During the 6-week run-in period they were treated with 200 mg beclomethasone twice daily, which is considered a moderate dose in the treatment of childhood asthma (14). Despite this treatment all children were symptomatic and had reversible airway obstruction and airway hyperresponsiveness	Parallel groups double-blind	Beclomethasone + SAL (BDP400 + SAL100 mcg) beclomethasone (BDP800) placebo + beclomethasone (BDP400)	54

continued

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
							Mean days (SD):[d] 362.8 (61.5)
Wechsler (2019)[72]	USA	*N* = 172 mean age (SD) = 9.2 (2.9) Females – *N* (%) = 77 (45) Not Hispanic or Latino – *N* (%) = 172 (100) Eczema – *N* (%) = 98 (70) Eosinophilia – *N* (%) = 63 (37) BL-severity (mild) – *N* (%) = 28 (100)	Patients aged 5 or older with at least one black grandparent	To enter the run-in, participants must be either: (A) inadequately controlled on low-, medium- or high-dose ICS monotherapy, or low- or medium-dose ICS/LABA, or (B) well controlled on low-, medium- or high-dose ICS monotherapy, or low-, medium- or high-dose ICS/LABA (see Study Visits, Screen A, at −10 weeks)	crossover double-blind	**5–11 years** 2 × ICS = fluticasone 100 mcg (Diskus) BID 2 × ICS/LABA = 100/50 mcg (Advair Diskus – FP + SAL) BID 5 × ICS = fluticasone 250 mcg (Diskus) BID 5 × ICS/LABA = 250/50 mcg (Advair Diskus – FP + SAL) BID **12–17 years** 2.5 × ICS = fluticasone 250 mcg (Diskus) BID 1 × ICS/LABA = 100/50 mcg (Advair Diskus – FP + SAL) BID 5 × ICS = fluticasone 500 mcg (Diskus) BID 2.5 × ICS/LABA = 250/50 mcg (Advair Diskus – FP + SAL) BID	P1: 14 P2: 14 P3: 14 P4: 14 Mean days (SD):[d] 91.4 (27.1)
Woodcock (2013)[73]	USA, Argentina, Chile, Korea, the Netherlands, Philippines	*N* = 32 mean age (SD) = 13.8 (1.6) Females – *N* (%) = 9 (28) Not Hispanic or Latino – *N* (%) = 19 (59) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 17 (65) BL-severity (mild) – *N* (%) = 8 (25)	Patients ≥ 12 years of age with persistent asthma using ICS	Subjects must have been using an ICS for at least 12 weeks prior to Visit 1 and be maintained on a medium dose (e.g. FP 250 mcg twice daily) for at least 4 weeks prior to Visit 1	Parallel groups double-blind	FF/VI 100/25 mcg OD (DPI) FP/SAL 250/50 mcg BID (Diskus/Accuhaler) placebo	24

TABLE 46 Characteristics of the included studies with IPD (*continued*)

Author (year)	Countries	Subjects included,[a] demographics, and clinical features	Patients' characteristics	Protocol inclusion criteria	Study type blinding	Treatment arms	Follow-up (weeks)
							Mean days (SD):[d] 164.5 (29.9)
Woodcock (2014)[74]	USA, Argentina, Chile, France, Mexico, Russian Federation	*N* = 13 mean age (SD) = 14.7 (1.4) Females – *N* (%) = 5 (38) Not Hispanic or Latino – *N* (%) = 10 (77) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 5 (71) BL-severity (mild) – *N* (%) = 5 (42)	Patients ≥ 12 years of age with persistent asthma with a stable dose, and regimen of ICS	All subjects must be on stable dose, and regimen of ICS for at least 4 weeks prior to Visit 1	Parallel groups double-blind	FF 100 mcg OD (DPI) FF 200 mcg OD (DPI)	24
							Mean days (SD):[d] 174.5 (14.9)

CFC, chlorofluorocarbon propellant; BD/BID, twice a day; BL-severity, baseline asthma severity; OD/QD, once a day; HFA, hydrofluoroalkane propellant; NA, not available; NAEPP, National Asthma Education and Prevention Program.
a < 18 and on ICS alone at randomisation or at screening visit if not available.
b As-needed group was not considered.
c No publication; only two no longer working links of congress abstracts.
d Follow-up of included participants.
e Split into two substudies because of randomisation bias due to the treatment dose categorisation based on age class with GINA.

TABLE 47 Characteristics of the included studies with AgD

Study	Countries	Patients included, demographics, clinical features	Patient characteristics	Study type blinding	Follow-up (weeks)	Interventions (participants)
Akpinarli (1999)[75]	Turkey	*N* = 32 Mean age (SD) = 10.3 (13.1) Females – *N* (%) = 17 (53) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = 21 (65.6) Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: 15 M and 17 F Mean age: 10.25 – SE age: 2.31 (SD = 13.07) Eczema: ICS + LABA = 11; ICS + placebo = 10 Asthma severity (FEV_1% predicted): ICS + LABA = 79; ICS + placebo = 80	Parallel groups double-blind	6	ICS + FORM (16) ICS + placebo (16) ICS: 400–800 mcg day (no medicine specified)
Berger (2006)[76]	USA	*N* = 296 Mean age (SD) = 8.6 (1.8) Females – *N* (%) = 109 (37) Not Hispanic or Latino – *N* (%) = 228 (77) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: 100 mcg: F = 41; M = 57; 200 mcg: F = 32; M = 67; placebo: F = 36; M = 63 Mean age: 100 mcg = 9.0 (SD = 1.8); 200 mcg = 8.7 (SD = 1.8); Placebo = 8.2 (SD = 1.9) Ethnicity: 100 mcg: white = 56; black = 16; Hispanic = 22; Asian = 1; Native American = 1; other = 2 200 mcg: white = 63; black = 11; Hispanic = 22; Asian = 1; Native American = 2; other = 0 placebo: white = 60; black = 12; Hispanic = 24; Asian = 0; Native American = 0; other = 3 Asthma severity (FEV_1% predicted): 100 mcg = 79.2; 200 mcg = 79.7; placebo = 77.3 BL_FEV_1 (mean): 100 mcg = 1.60; 200 mcg = 1.57; placebo = 1.45 Baseline ICS use includes a small percentage of triamcinolone and flunisolide.	Parallel groups double-blind	12	MF DPI 100 mcg (98) MF DPI 200 mcg (99) Placebo (99)

TABLE 47 Characteristics of the included studies with AgD (*continued*)

Study	Countries	Patients included, demographics, clinical features	Patient characteristics	Study type blinding	Follow-up (weeks)	Interventions (participants)
Bisgaard (2006)[77]	Argentina, Brazil, Bulgaria, Canada, China, France, Great Britain, Hungary, Indonesia, Israel, Italy, Malaysia, Mexico, Norway, Philippines, Poland, Romania, Singapore, South Africa, Sweden, Taiwan, Turkey	*N* = 341 Mean age (SD) = 8 (NA) Females – *N* (%) = 104 (30) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: BUD M = 70, F = 36; BUD/FORM M = 85, F = 35; SMART M = 85, F = 33 Mean age: BUD = 8; BUD/FORM = 8; SMART = 8 (no SD) Race: BUD white = 90, other = 16; BUD/FORM white = 101, other = 16; SMART white = 100, other = 18 Asthma severity (FEV_1% predicted): BUD = 76; BUD/FORM = 76; SMART = 76 Exacerbation: BUD = 28; BUD/FORM = 44; SMART = 17 BL_FEV_1(L): BUD = 1.6; BUD/FORM = 1.5; SMART = 1.6 FEV_1(L): BUD = 1.76; BUD/FORM = 1.70; SMART = 1.86	Parallel groups double-blind	52	BUD 320 mcg qd (fixed dose) (106) BUD/FORM 80/4.5 mcg qd (fixed dose) (117) BUD/FORM 80/4.5 mcg qd maintenance + as needed (SMART) (118)
[a]Buchvald (2003)[78]	Denmark	*N* = 23 Mean age (SD) = 12 (NA) Females – *N* (%) = 11 (48) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = 7 (30) Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: M = 12; F = 11 Mean age: 12 (no SD) eczema: 7 Mean asthma severity: 101 Mean FEV_1(L): BUD + placebo = 2.48; BUD + LTRA = 2.57; BUD + SAL = 2.63 (*N* = 22) Mean BL_FEV_1(L): 2.54 (*N* = 22) Exacerbation: 0 Crossover study without the possibility to use the data from the first period only	Crossover double-blind	P1 = NA P2 = NA P3 = NA No Washout	BUD 400 mcg die + SAL 50 mcg BID (23) BUD 400 mcg die + montelukast 5 mg OD (23) BUD 400 mcg die + placebo (23)
[b]Everden (2004)[79]	UK, Republic of Ireland	*N* = 155 Mean age (SD) = 11.8 (2.9) Females – *N* (%) = 67 (43) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: ICS + FORM M = 50, F = 29; ICS + SAL M = 38, F = 38 Mean age: ICS + FORM = 11.7 (SD = 3.0); ICS + SAL = 11.8 (SD = 2.8) Exacerbation (mean episodes): ICS + FORM = 8; ICS + SAL = 12 Asthma aggravation (AEs): ICS + FORM = 8; ICS + SAL = 10	Parallel groups open-label	12	ICS + FORM (79) ICS + SAL (76) The ICS dose is unknown

continued

TABLE 47 Characteristics of the included studies with AgD (*continued*)

Study	Countries	Patients included, demographics, clinical features	Patient characteristics	Study type blinding	Follow-up (weeks)	Interventions (participants)
Heuck (2000)[80]	Denmark	*N* = 24 Mean age (SD) = 9.5 (NA) Females – *N* (%) = 10 (42) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Mean age: 9.5 (3 patients more) (no SD) Sex: M = 14; F = 13 (3 patients more) Exacerbation: BUD + placebo = 2; BUD + FORM = 0	Crossover double-blind	P1 = 6 P2 = 6	BUD + FORM 200/24 mcg die DPI (14) BUD DPI (400 mcg) + placebo die (10)
Jat (2006)[81]	India	*N* = 63 Mean age (SD) = 9.8 (2.6) Females – *N* (%) = 18 (29) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: ICS + LTRA M = 21, F = 9; ICS M = 24, F = 9 Mean age: ICS + LTRA = 10.13 (SD = 2.67); ICS = 9.39 (SD = 2.46) Asthma severity (FEV_1% predicted): ICS + LABA = 64.17; ICS = 63.36 Exacerbation: ICS + LTRA = 10; ICS = 3 (first exacerbation)	Parallel groups blinded	12	A: BUD (200 mcg) + montelukast (5 mg) die (30) B: BUD (400 mcg) die (33)
Kondo (2006)[82]	Japan	*N* = 75 Mean age (SD) = 9.1 (2.3) Females – *N* (%) = 31 (41) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = 46 (61) BL-severity (mild) – *N* (%) = 42 (56)	Sex: montelukast M = 21, F = 18; theophylline M = 23, F = 13 Mean age: montelukast = 9.4 (SD = 2.4); theophylline = 8.8 (SD = 2.2) Asthma severity: montelukast – mild = 24, moderate = 12, severe = 3 theophylline – mild = 18, moderate = 16, severe = 2 Phenotype: montelukast – non-eosinophilic = 12, eosinophilic = 27 theophylline – non-eosinophilic = 17, eosinophilic = 19 Exacerbation: montelukast = 1; theophylline = 1 (status asthmaticus and asthma aggravation) Data available for the PP population only (75 of 79 ITT) – randomised: 84	Parallel groups open-label	4	ICS (CFC-BDP: 100–400 mcg or FP: 100–200 mcg) + montelukast 5 mg die (39) ICS (CFC-BDP: 100–400 mcg or FP: 100–200 mcg) + theophylline 10–16 mg/kg/day or 200–400 mg/day (36)

TABLE 47 Characteristics of the included studies with AgD (*continued*)

Study	Countries	Patients included, demographics, clinical features	Patient characteristics	Study type blinding	Follow-up (weeks)	Interventions (participants)
Lenney (2013)[4]	UK	*N* = 63 Mean age (SD) = 10 (21) Females – *N* (%) = 23 (37) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: ICS – M = 17, F = 2; ICS + LABA – M = 13, F = 10; ICS + LTRA – M = 10, F = 11 Mean age: ICS = 10.37 (SD = 19); ICS + LABA = 10.46 (SD = 23); ICS + LTRA = 10.33 (SD = 21) Asthma severity (FEV_1% predicted): ICS = 88.29; ICS + LABA = 79.79; ICS + LTRA = 86.47 BL_FEV_1(L): ICS = 1.98; ICS + LABA = 1.83; ICS + LTRA = 1.82 Exacerbation (any): ICS = 4/19; ICS + LABA = 7/23; ICS + LTRA = 3/21 (Tot: 14/63) Exacerbation (OC): ICS = 4/18; ICS + LABA = 3/17; ICS + LTRA = 3/19 (Tot: 10/54) (24 weeks)	Parallel groups double-blind	48	FP 200 mcg die (19) FP 200 mcg + SAL 100 mcg die (23) FP 200 mcg + montelukast 5 mg die (21)
Malone (2005)[83]	USA, Canada	*N* = 203 Mean age (SD) = 8.1 (NA) Females – *N* (%) = 73 (36) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: FP – M = 59, F = 41; FP + SAL – M = 68, F = 32; Mean age: FP = 8.1; FP + SAL = 8.0 (no SD) Race: FP – white = 72, black = 16, other = 12; FP + SAL – white = 67, black = 23, other = 10; Asthma severity (FEV_1% predicted): FP ≥ 80%; FP + SAL > 80% Exacerbation: FP = 8; FP + SAL = 3	Parallel groups double-blind	12	FP 200 mcg die (102) FP + SAL 200/100 mcg die (101)
Morice (2008)[84]	UK	*N* = 622 Mean age (SD) = 8 (NA) Females – *N* (%) = 212 (34) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: BUD – M = 137, F = 70; BUD + FORM DPI – M = 141, F = 71; BUD + FORM pMDI – M = 132, F = 71 Mean age: BUD = 9; BUD + FORM DPI = 8; BUD + FORM pMDI = 8 (no SD) Asthma severity (FEV_1% predicted): BUD = 87; BUD + FORM DPI = 89; BUD + FORM pMDI = 89 The mean change of FEV_1(L) is in a graph. Exacerbation: BUD = 13, BUD + FORM DPI = 7, BUD + FORM pMDI = 7 (asthma aggravated)	Parallel groups double-blind	12	BUD pMDI 400 mcg die (207) BUD + FORM DPI 320/18 mcg die (212) BUD + FORM pMDI 320/18 mcg die (203)

continued

TABLE 47 Characteristics of the included studies with AgD (*continued*)

Study	Countries	Patients included, demographics, clinical features	Patient characteristics	Study type blinding	Follow-up (weeks)	Interventions (participants)
Russell (1995)[85]	UK	*N* = 206 Mean age (SD) = 10.2 (2.7) Females – *N* (%) = 82 (40) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: ICS + LABA – M = 59, F = 40; ICS – M = 65, F = 42 Mean age: ICS + LABA = 10.2 (SD = 2.7); ICS = 10.3 (SD = 2.7) Exacerbation (asthma-related AEs): ICS + LABA = 10; ICS = 13	Parallel groups double-blind	12	ICS (beclomethasone or BUD) + SAL 50 mcg BID (99) ICS (beclomethasone or BUD) + placebo (107) ICS dose from 400 to 2400 mcg die; the average dose was 750 mcg
Shapiro (2001)[86]	USA	*N* = 274 Mean age (SD) = 12.1 (2.8) Females – *N* (%) = 96 (35) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: BUD 200 – M = 55, F = 35; BUD 400 – M = 66, F = 27; placebo – M = 57, F = 34 Mean age: BUD 200 = 12.1 (SD = 2.8); BUD 400 = 12.1 (SD = 2.8); placebo = 12.1 (SD = 2.8) Race: BUD 200 – Caucasian = 75; African American = 10; Asian = 4; other = 1 BUD 400 – Caucasian = 85; African American = 6; Asian = 0; other = 2 Placebo – Caucasian = 83; African American = 6; Asian = 2; other = 0 BL_FEV_1(L): BUD 200 = 2.1; BUD 400 = 2.1; placebo = 2.1 Exacerbation (aggravated asthma): BUD 200 = 9; BUD 400 = 8; placebo = 10 Some patients used triamcinolone (*N* = 107) and flunisolide (*N* = 23) at entry	Parallel groups double-blind	12	BUD 200 mcg die Turbuhaler (90) BUD 400 mcg die Turbuhaler (93) Placebo (91)

TABLE 47 Characteristics of the included studies with AgD (*continued*)

Study	Countries	Patients included, demographics, clinical features	Patient characteristics	Study type blinding	Follow-up (weeks)	Interventions (participants)
[a]Simons (2001)[87]	Argentina, Australia, Austria, Brazil, Canada, France, Germany, Greece, Norway, Portugal, Sweden, the Netherlands, Russia, Turkey	*N* = 279 Mean age (SD) = 10.4 (2.2) Females – *N* (%) = 92 (33) Not Hispanic or Latino – *N* (%) = 17 (6) Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Mean age: 10.4 (SD = 2.2) Sex: F = 92; M = 187 Ethnicity: 83% were white, 10% were Asian, 6% were Hispanic, and 1% were members of other ethnic groups Exacerbation (asthma worsening – AEs): BUD = 35/270; BUD + LTRA = 32/277 Some patients used triamcinolone and flunisolide at entry. First period data not available	Crossover double-blind	P1: 4 P2: 4 P3: 4 No washout	BUD 400 mcg die (270) BUD 400 mcg die + montelukast 5 mg OD (277)
Strauch (2003)[88]	Germany	*N* = 25 Mean age (SD) = 10 (NA) Females – *N* (%) = 9 (36) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: 16 M; 9 F Age (IPD): table 1 (no indication of the treatment group) asthma severity (FEV_1% predicted): table 1 (IPD) (no indication of the treatment group); table 2 (median) overall QoL (median, 95% CI) (PAQLQ; cores are expressed as the mean score per item): placebo – 7.0 (5.0 –7.0); montelukast – 7.0 (6.0 –7.0)	Parallel groups double-blind	4	ICS (400–800 mcg BUD die) + montelukast 5 mg ICS (400–800 mcg BUD die) + placebo
Tal (2002)[89]	Czech Republic, Belgium, Hungary, Israel, South Africa, Spain, UK	*N* = 286 Mean age (SD) = 11 (NA) Females – *N* (%) = 109 (38) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: ICS + LABA – M = 90, F = 58; ICS – M = 87, F = 51 Mean age: ICS + LABA = 11; ICS = 11 (no SD) Asthma severity: ICS + LABA = 74; ICS = 76 mean FEV_1(L): ICS + LABA = 2.01; ICS = 1.91 (no SD) Exacerbation (asthma aggravated): ICS + LABA = 8; ICS = 4;	Parallel groups double-blind	12	BUD/FORM 320/18 mcg die (148) BUD 400 mcg die (138)

continued

TABLE 47 Characteristics of the included studies with AgD (*continued*)

Study	Countries	Patients included, demographics, clinical features	Patient characteristics	Study type blinding	Follow-up (weeks)	Interventions (participants)
[b]Vermeulen (2007)[90]	Hungary, Poland, Serbia/ Montenegro, South Africa, Spain	*N* = 403 Mean age (SD) = NA Females – *N* (%) = 131 (33) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: CIC – M = 192, F = 80; ICS – M = 80, F = 51 Age: no mean, only the median Asthma severity: CIC = 73.2; ICS = 73.1 BL FEV_1 (ml): CIC = 2310 (2.31 L) (*N* = 270); ICS = 2310 (2.31 L) (N = 130) FEV_1 (ml): CIC = 2815 (2.82 L) (*N* = 270); ICS = 2846 (2.85 L) (*N* = 130) Exacerbation: CIC = 7; ICS = 2	Parallel groups double-blind	12	CIC (320 mcg OD) (272) BUD (800 mcg OD) (31) Randomisation 2 (CIC) : 1 (BUD)
Visitsunthorn (2011)[91]	Thailand	*N* = 29 Mean age (SD) = 9 (1) Females – *N* (%) = 6 (21) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = 29 (100) Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = 25 (86)	Sex: ICS + placebo – M = 13, F = 2; ICS + LTRA – M = 10, F = 4 Age: ICS + placebo = 9.1 (SD = 1.1); ICS + LTRA = 8.9 (SD = 0.9) Eczema: all patients Asthma severity: ICS + placebo – mild = 14, moderate = 1; ICS + LTRA – mild = 11, moderate = 3 Phenotype: ICS + placebo = 566.34 (eosinophilic); ICS + LTRA = 706.87 (cells) (eosinophilic) FEV_1(L): ICS + placebo = 1.38; ICS + LTRA = 1.43 BL FEV_1(L): ICS + placebo = 1.42; ICS + LTRA = 1.31	Crossover double-blind	P1: 6 Washout: 2 P2: 6	ICS + placebo (ICS unknown dose) (15) ICS + montelukast (14)
Zimmerman (2004)[92]	Canada	*N* = 302 Mean age (SD) = 8.7 (NA) Females – *N* (%) = 114 (38) Not Hispanic or Latino – *N* (%) = NA Eczema – *N* (%) = NA Eosinophilia – *N* (%) = NA BL-severity (mild) – *N* (%) = NA	Sex: ICS → M = 65, F = 36; ICS + LABA 4.5 mcg → M = 65, F = 41; ICS + LABA 9 mcg → M = 58, F = 37 Mean age: ICS = 9; ICS + LABA 4.5 mcg = 8; ICS + LABA 9 mcg = 9 (no SD) Asthma severity: ICS = 77.2; ICS + LABA 4.5 mcg = 78.3; ICS + LABA 9 mcg = 77.5 BL FEV_1(L): ICS = 1.49; ICS + LABA 4.5 mcg = 1.53; ICS + LABA 9 mcg = 1.50 FEV_1(L): ICS = 1.61; ICS + LABA 4.5 mcg = 1.71; ICS + LABA 9 mcg = 1.68 Exacerbation: ICS = 11; ICS + LABA 4.5 mcg = 5; ICS + LABA 9 mcg = 6	Parallel groups double-blind	12	ICS + placebo (101) ICS + FORM 4.5 mcg BID (106) ICS + FORM 9 mcg BID (95) ICS dose is unknown

CFC, chlorofluorocarbon propellant.
a Trial could not be included in analyses as AgD for the first period were not presented in the publication.
b Trial could not be included in analyses as no comparison could be made when treatment groups considered at the treatment class level.

Appendix 5 Eligible studies without individual participant data or aggregate data

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Abbas (2016)[93]	–	Abbas A, Maheshwari MP, Siddiqui ZA, Maheshwari RR. Role of long acting beta2 agonist salmeterol, in management of mild to moderate asthmatic patients. *Pakistan Journal of Medical and Health Sciences* 2016;**10**:1112–5	Population of both adults and adolescents	Parallel groups	50 (15–65)	Not possible to establish	SAL 50 mcg and FP 250 mcg twice daily (24) BDP 500 mcg twice daily (23)	Symptoms
Amar (2017)[94]	MERCK	Amar NJ, Shekar T, Varnell TA, Mehta A, Philip G. Mometasone furoate (MF) improves lung function in pediatric asthma: a double-blind, randomized controlled dose-ranging trial of MF metered-dose inhaler. *Pediatr Pulmonol* 2017;52(3):310–8. https://doi.org/10.1002/ppul.23563. Epub October 14 2016. Erratum in: *Pediatr Pulmonol*. 2019;**54**(5):655–6.	ICS or ICS + LABA at screening	Parallel groups	578 (5–11)	578	MF-MDI 50 mcg BID (120) MF-MDI 100 mcg BID (113) MF-MDI 200 mcg BID (108) MF-DPI 100 mcg QD PM (125) Placebo (112)	FEV_1 QoL AEs
Arama (2016)[95§]	–	Arama M, Gorelco T, Kuleshina T. Antileukotriens in management of paediatric asthma: the hormone reducing force. *Eur J Resp Med* 2016;**48**:PA1249. https://doi.org/10.1183/13993003.congress-2016.PA1249	Congress abstract with no data	Parallel groups	40 (5–15)	40	ICS + montelukast (NA) ICS + placebo (NA)	Symptoms FEV_1 (spirometry)
Arsovski (2016)[96§]	–	Arsovski Z, Dokic D, Kjaeva B, Goseva Z, Pejkovska S, Arbutina S, Janeva E. Different therapeutic response to inhaled fluticasone propionate in smokers and non-smokers with asthma. *Allergy* 2016;**71**:365–6.	Congress abstract with no data	Parallel groups	38 (NA)	Not possible to establish	FP 250 mcg BID in smokers and non-smokers	Asthma control FEV_1
Bensch (2002)[97]	Novartis	Bensch G, Berger WE, Blokhin BM, Socolovsky AL, Thomson MH, Till MD, *et al*; International Study Group on Foradil Evaluation in Pediatric Asthma. One-year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. *Ann Allergy Asthma Immunol* 2002;**89**(2):180–90.	Not only ICS alone at screening	Parallel groups	518 (5–12)	518	FORM 12 mcg BID (171) FORM 24 mcg BID (171) Placebo (176)	FEV_1 AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents[a]	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Berger (2010)[98]	AstraZeneca	Berger WE, Leflein JG, Geller DE, Parasuraman B, Miller CJ, O'Brien CD, O'Dowd L. The safety and clinical benefit of budesonide/formoterol pressurized metered-dose inhaler versus budesonide alone in children. *Allergy Asthma Proc* 2010;**31**(1):26–39. https://doi.org/10.2500/aap.2010.31.3301	LABA too at screening	Parallel groups	187 (6–11)	187	BUD/FORM pMDI 320/9 mcg BID (124) BUD DPI 400 µg BID (63)	FEV_1 AEs QoL Symptoms
Berger (2014)[99]	MERCK	Berger WE, Bensch GW, Weinstein SF, Skoner DP, Prenner BM, Shekar T, *et al.* Bronchodilation with mometasone furoate/formoterol fumarate administered by metered-dose inhaler with and without a spacer in children with persistent asthma. *Pediatr Pulmonol* 2014;**49**(5):441–50. https://doi.org/10.1002/ppul.22850. Epub September 9 2013.	ICS or ICS + LABA at screening	Crossover	92 (5–11)	92	MF/FORM without spacer 100/10 mcg (23) MF/FORM with spacer 100/10 mcg (23) FORM-DPI 10 mcg (23) Placebo (23) All patients used MF DPI 100 mcg once daily (QD) in the evening (PM) throughout the whole study, including the treatment periods	
Bernstein (2011)[100]	MERCK	Bernstein DI, Hébert J, Cheema A, Murphy KR, Chérrez-Ojeda I, Matiz-Bueno CE, *et al.* Efficacy and onset of action of mometasone furoate/formoterol and fluticasone propionate/salmeterol combination treatment in subjects with persistent asthma. *Allergy Asthma Clin Immunol* 2011;**7**:21. https://doi.org/10.1186/1710-1492-7-21	Population of both adults and children/adolescents ICS or ICS + LABA at screening	Parallel groups	722 (12–82)	Not possible to establish	FP/SAL DPI 250/50 mcg BID (351) MF/FORM MDI 200/10 mcg BID (371)	Exacerbation Asthma control QoL Symptoms FEV_1 AEs
Bernstein (2017)[101]	TEVA	Bernstein DI, Gillespie M, Song S, Steinfeld J. Safety, efficacy, and dose response of fluticasone propionate delivered via the novel MDPI in patients with severe asthma: a randomized, controlled, dose-ranging study. *Asthma* 2017;**54**(6):559–69. https://doi.org/10.1080/02770903.2016.1242137	Population of both adults and children/adolescents ICS or ICS + LABA at screening	Parallel groups	640 (12–65+)	9	FP MDPI 50 mcg (107) FP MDPI 100 mcg BID (107) FP MDPI 200 mcg BID (106) FP MDPI 400 mcg BID (107) FP DPI 250 mcg BID (107) Placebo MDPI (106)	FEV_1 AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Bernstein (2019)[102§]	Unknown	Bernstein DI. Efficacy comparison of mometasone furoate/formoterol versus fluticasone propionate/salmeterol combination therapies in subjects with persistent asthma: noninferiority and onset-of-action findings. *Breast (Edinburgh, Scotland)* 2019;**44**:S62.	Not found	Parallel groups	—	—	MF/FORM (NA) FP/SAL (NA)	—
Bose (1987)[103]	—	Bose B, Cater JI, Clark RA. A once daily theophylline preparation in prevention of nocturnal symptoms in childhood asthma. *Eur J Pediatr* 1987;**146**(5):524–7.	Other medicine used at screening	Crossover	20 (5–16)	20	Theophylline (OD) (20) Placebo (20)	Symptoms AEs
Botan (2019)[104]	—	Botan V, Miranda M, Couto S, Rocha E, Imaculada Muniz-Junqueira M. Influence of *Montelukast on the State of Eosinophil Activation in Asthmatic Children. Breast (Edinburgh, Scotland)* 2019;**44**:S64.	Different outcomes in the publication; the author confirmed to have the outcomes of interest, but after the first consensus, she no longer replied	Parallel groups	83 (2–18)	83	Montelukast (NA) Placebo (NA) Healthy control (NA)	None of interest
Byrnes (2000)[105§]	GSK	Byrnes C, Shrewsbury S, Barnes PJ, Bush A. Salmeterol in paediatric asthma. *Thorax* 2000;**55**(9):780–4.	Control group: salbutamol it is not clear if ICS treatment was maintained after the run-in	Crossover	45 (5–16)	45	SAL 50 µg bd (45) SAL 100 µg bd (45) Salbutamol 200 µg qds (45)	FEV_1 AEs
D'Alonzo (1994)[106]	GSK	D'Alonzo GE, Nathan RA, Henochowicz S, Morris RJ, Ratner P, Rennard SI. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. *JAMA*. 1994;**271**(18):1412–6.	Population of both adults and children/adolescents only 20% used ICS at screening	Parallel groups	322 (NA)	Not possible to establish	ICS + SAL 42 mcg BID (106) ICS + albuterol 180 mcg 4x/day (108) ICS + placebo (108)	Exacerbation FEV_1 AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
D'Urzo (2005)[107]	MERCK	D'Urzo A, Karpel JP, Busse WW, Boulet LP, Monahan ME, Lutsky B, Staudinger H. Efficacy and safety of mometasone furoate administered once-daily in the evening in patients with persistent asthma dependent on inhaled corticosteroids. *Curr Med Res Opin* 2005;**21**(8):1281–9.	Population of both adults and children/ adolescents	Parallel groups	400 (12–78)	Not possible to establish	MF-DPI 200 µg qd PM (78) MF-DPI 400 µg qd PM as one inhalation (from a DPI delivering 400 µg/inhalation) (80) MF-DPI 400 µg qd PM as two inhalations (from a DPI delivering 200 µg/inhalation) (78) MF-DPI 200 µg bid (81) Placebo (83)	FEV_1 Symptoms QoL AEs
Emeryk (2016)[108]	Mundipharma	Emeryk A, Klink R, McIver T, Dalvi P. A 12-week open-label, randomized, controlled trial and 24-week extension to assess the efficacy and safety of fluticasone propionate/formoterol in children with asthma. *Ther Adv Resp Dis* 2016;**10**(4):324–37.	ICS or LABA at screening	Parallel groups	211 (4–12)	211 (180 eligible)	FP/FORM 100/10 mcg BID (106) FP/SAL 100/50 mcg BID (105)	FEV_1 AEs
EudraCT number: 2014-005047-40[§]	Sanofi	No publication	No publication population of both adults and children/ adolescents	Crossover	122 (12–64)	12	SAL /FP 12.5/250 mcg via DPI PulmoJet (122) SAL /FP 50/250 mcg via DPI PulmoJet (122) SAL /FP 50/250 mcg Seretide Diskus (122)	FEV_1 AEs
EudraCT number: 2017-004424-29-NL (PUFFIN)[§]	—	No publication	Still recruiting	–	–	–	–	–

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Farzan (2017)[109]	–	Farzan S, Khan S, Elera C, Tsang J, Akerman M, DeVoti J. Effectiveness of montelukast in overweight and obese atopic asthmatics. *Ann Allergy Asthma Immunol* 2017;**119**:189–93.	Population of both adults and children/ adolescents not possible to use ACT as a binary variable	Parallel groups	26 (NA)	23	ICS + montelukast (overweight/obese) ICS + placebo (overweight/obese) ICS + montelukast (normal weight) ICS + placebo (normal weight)	Asthma control
Fitzgerald (2003)[110§]	AstraZeneca	FitzGerald JM, Sears MR, Boulet L-P, Becker AB, *et al.* Adjustable maintenance dosing with budesonide/formoterol reduces asthma exacerbation compared with traditional fixed dosing: a five-month multicentre Canadian study. *Can Respir J* 2003;**10**(8):427–34.	Population of both adults and children/ adolescents ICS or ICS + LABA at screening	Parallel groups	995 (12–96)	Not possible to establish	BUD/FORM (adjustable maintenance) (499) BUD/FORM (fixed maintenance) (496)	Exacerbation hospitalisation and health economic parameters AEs
Gelfand (2006)[111]	COVIS PHARMA	Gelfand EW, Georgitis JW, Noonan M, Ruff ME. Once-daily ciclesonide in children: efficacy and safety in asthma. *J Pediatr* 2006;**148**(3):377–83.	ICS or leukotriene or cromones at screening	Parallel groups	1031 (4–11)	1031	CIC 40 mcg OD (252) CIC 80 mcg OD (259) CIC 160 mcg OD (253) Placebo mcg OD (254)	FEV_1 (not in L/1s) QoL Symptoms AEs
Gustafsson (1993)[112]	–	Gustafsson P, Tsanakas J, Gold M, Primhak R, Radford M, Gillies E. Comparison of the efficacy and safety of inhaled fluticasone propionate 200 micrograms/day with inhaled beclomethasone dipropionate 400 micrograms/ day in mild and moderate asthma. *Arch Dis Child* 1993;**69**(2):206–11.	Children/adolescent until 19 Other medicines at screening	Parallel groups	398 (4–19)	Not possible to establish	FP 200 mcg OD (197) Beclometasone dipropionate 400 mcg OD (201)	Exacerbation FEV_1 Symptoms AEs
Hampel (2017)[113]	TEVA	Hampel FC Jr, Carr W, Gillespie M, Small CJ. Evaluation of beclomethasone dipropionate (80 and 160 micrograms/day) delivered via a breath-actuated inhaler for persistent asthma. *Allergy Asthma Proc* 2017;**38**(6):419–30. https://doi.org/10.2500/aap.2017.38.4089. Epub September 8 2017.	Population of both adults and children/ adolescents ICS and non-ICS therapy at screening	Parallel groups	273 (12–65+)	30	Beclometasone dipropionate BAI 80 mcg OD (90) Beclometasone dipropionate BAI 160 mcg OD (92) Placebo BAI (91)	FEV_1 QoL Symptoms AEs
Ikeda (2015)[114§]	Kyorin pharmaceutical Co	Ikeda K. Comparison of efficacy onset and clinical benefit between formoterol/fluticasone and salmeterol/fluticasone in unstable chronic asthma: an open-label, randomized study. *Am J Respir Crit Care Med* 2015;**191**:A4238.	Abstract with no age range ICS or ICS + LABA at screening	Parallel groups	21 (NA)	Not possible to establish	FORM/fluticasone combination 636 mcg/day (11) SAL /fluticasone combination 620 mcg/day (10)	Pulmonary function Asthma control (ACQ) Symptoms

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Ilowite (2004)[115]	MERCK	Ilowite J, Webb R, Friedman B, Kerwin E, Bird SR, Hustad CM, Edelman JM. Addition of montelukast or salmeterol to fluticasone for protection against asthma attacks: a randomized, double-blind, multicenter study. *Ann Allergy Asthma Immunol* 2004;**92**(6):641–8.	Population of both adults and children/ adolescents	Parallel groups	1473 (14–73)	Not possible to establish	fluticasone 220 mcg + montelukast 10 mg OD (743) fluticasone 220 mcg + SAL 84 mcg OD (730)	Exacerbation (asthma attack) Symptoms AEs
Jamaati (2015)[116]	COVIS PHARMA	Jamaati H, Malekmohammad M, Fahimi F, Najafi A, Hashemian SM. Efficacy of low-dose ciclesonide and fluticasone propionate for mild to moderate persistent asthma. *Tanaffos* 2015;**14**(1):1–9.	Population of both adults and children/ adolescents	Parallel groups	230 (15–65)	Not possible to establish	CIC 80 mcg OD (115) FP 100 mcg BID (115)	FEV_1 QoL Asthma control AEs
Jehan (2014)[117]	—	Jehan N, Rehman MU, Zarkoon MH. To determine the efficacy of inhaled corticosteroids compared to montelukast in reducing exacerbation in uncontrolled asthma in children 6 months to 5 years. *Pak J Med Health Sci* 2014;**8**(3):662–6.	Recruitment at the emergency room and no indication of previous treatment patients were given ICS and tab Montelukast by lottery method to remove the bias	Parallel groups	2400 (6 months to 5 years)	2400	ICS 200 mcg die (1200) montelukast 4 or 5 mg die (1200)	Exacerbation
Kerwin (2017)[118]	TEVA	Kerwin EM, Yiu G, Hickey L, Small CJ. Analysis of the relationship between handheld and clinic-based spirometry measurements in a randomized, double-blind, placebo-controlled study of beclomethasone dipropionate via breath-actuated inhaler for persistent asthma. *Am J Respir Crit Care Med* 2017;**195**:A3205.	Population of both adults and children/ adolescents only abstract	Parallel groups	425 (12–NA)	Not possible to establish	BDP (BAI) 40 mcg/ inhalation × 4 inhalations twice daily (BID) (320 mcg/ day) BDP (BAI) 80 mcg/ inhalation × 4 inhalations twice daily (BID) (640 mcg/ day) BDP (MDI) 40 mcg/ inhalation × 4 inhalations BID (320 mcg/day) Placebo BAI Placebo MDI	FEV_1

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Knorr (1998)[119]	MERCK	Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, Becker A. Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. Pediatric Montelukast Study Group. *JAMA* 1998;**279**(15):1181–6. https://doi.org/10.1001/jama.279.15.1181.	Only 20–24% of patients used ICS at screening	Parallel groups	336 (6–15)	72	Montelukast 5 mg OD (201) Placebo (135)	FEV_1 AEs
Knorr (2001)[120]	MERCK	Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;**108**(3):E48. https://doi.org/10.1542/peds.108.3.e48.	Up to 50% of patients used inhaled or nebulised corticosteroids or cromolyn at screening and during the study	Parallel groups	689 (2–6)	56	Montelukast 4 mg (461) Placebo (228)	Asthma control Symptoms QoL AEs
Kunoe (2016)[121§]	—	Kunoe A, Agertoft L, Chawes BL, Bonnelykke K, Bisgaard H, Pedersen S. Early intervention with high-dose inhaled corticosteroids for preschool wheezing does not improve lung function at school age. *Allergy Eu J Allergy Clin Immunol* 2016;**71**(Suppl 102):365.	Poster – no information on the pre-study treatment (perhaps, naive) *'a trial to investigate if use of high-dose inhaled corticosteroids for pre-school wheezing improves lung function at 6 years of age'*	Parallel groups	220 (6–35 months)	220	FP 1000 mcg/day pMDI (112) Placebo (108)	FEV_1
Langton Hewer (1995)[122]	—	Langton Hewer S, Hobbs J, French D, Lenney W. Pilgrim's progress: the effect of salmeterol in older children with chronic severe asthma. *Respir Med* 1995;**89**(6):435–40.	34.8% of patients used OC and other medicine besides ICS at screening	Parallel groups	24 (12–17)	23	ICS (range 50–1000 mcg BID) + SAL 100 mcg BID (11) ICS (range 50–1000 mcg BID) + placebo (12)	Exacerbation FEV_1 Symptoms AEs
Lin (2015)[123] (IPD supplied)	GSK	Lin J, Kang J, Lee SH, Wang C, Zhou X, Crawford J, *et al.* Fluticasone furoate/vilanterol 200/25 mcg in Asian asthma patients: a randomized trial. *Respir Med* 2015;**109**(1):44–53. https://doi.org/10.1016/j.rmed.2014.10.012. Epub October 31 2016.	Population of both adults and children/adolescents all eligible participants were using ICS + LABA at screening	Parallel groups	309 (13–79)	0	FF/VI 200/25 mcg OD (155) FP 500 mcg BID (154)	ACT Exacerbation FEV_1 Symptoms QoL AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents[a]	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Lin (2016)[124] (IPD supplied)	GSK	Lin J, Tang H, Chen P, Wang H, Kim MK, Crawford J, *et al.* Efficacy and safety evaluation of once-daily fluticasone furoate/vilanterol in Asian patients with asthma uncontrolled on a low- to mid-strength inhaled corticosteroid or low-dose inhaled corticosteroid/long-acting beta2-agonist. *Allergy Asthma Proc* 2016;**37**(4):302–10. https://doi.org/10.2500/aap.2016.37.3968	Population of both adults and children/adolescents only one participant was using ICS alone at screening	Parallel groups	307 (14–79)	1	FF/VI 100/25 mcg OD (153) Placebo (154)	ACT Exacerbation FEV_1 Symptoms QoL AEs
Mallol (2016)[125]	COVIS PHARMA	Mallol J, Aguirrea V, Gallardoa A, Corteza E, Sáncheza C, Riquelmea C, *et al.* Effect of once-daily generic ciclesonide on eNO in atopic children with persistent asthma. *Allergolo immunopathol* 2016;**44**(2):106–12.	1. Not possible to use ACT as a binary variable; 2. not possible to classify ICS dose based on age for the secondary analysis	Parallel groups	60 (7–15)	60	CIC 80 mcg OD (27) CIC 160 mcg OD (29)	ACT AEs
Mansfield (2017)[126]	TEVA	Mansfield L, Yiu G, Sakov A, Liu S, Caracta C. A 6-month safety and efficacy study of fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers in persistent asthma. *Allergy Asthma Proc* 2017;**38**(4):264–76. https://doi.org/10.2500/aap.2017.38.4061. Epub May 24 2017.	Population of both adults and children/adolescents ICS or ICS + LABA at screening	Parallel groups	674 (12–65+)	73	FP MDPI 100 mcg BID (127) FP HFA 220 mcg BID (42) FP MDPI 200 mcg BID (126) FP HFA 440 mcg BID (41) FP/SAL MDPI 100/12.5 mcg BID (120) FP/SAL DPI 250/50 mcg BID (41) FP/SAL MDPI 200/12.5 mcg BID (133) FP/SAL DPI 500/50 mcg BID (44)	FEV_1 AEs
Maspero (2010)[127]	MERCK	Maspero JF, Nolte H, Chérrez-Ojeda I. P04139 Study Group. Long-term safety of mometasone furoate/formoterol combination for treatment of patients with persistent asthma. *J Asthma* 2010;**47**(10):1106–15. https://doi.org/10.3109/02770903.2010.514634. Epub November 1 2010. Erratum in: *J Asthma* 2011;**48**(1):114.	Population of both adults and children/adolescents ICS or ICS + LABA at screening	Parallel groups	404 (NA)	Not possible to establish	MF/FORM 200/10 mcg (141) FP/SAL 250/50 mcg (68) MF/FORM 400/10 mcg (130) FP/SAL 500/50 mcg (65)	AEs FEV_1 Symptoms

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
McIver (2011)[128]	Mundipharma	McIver T, Emeryk A, Klink R, Schwab B. Fluticasone propionate/formoterol fumarate (FLUT/FORM) combination therapy has comparable efficacy to fluticasone propionate/salmeterol xinafoate (FLUT/SAL) in paediatric patients with asthma. *Eur Resp J* 2011;**38**(Suppl. 55).	Likely conference abstract – no information on pre-treatment at screening	Parallel groups	211 (4–12)	211	FP/FORM 100/10 µg BID (102) FP/SAL 100/50 µg BID (99)	FEV_1
Meltzer (2012)[129]	MERCK	Meltzer EO, Kuna P, Nolte H, Nayak AS, Laforce C; P04073 Study Investigators. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. *Eur Respir J* 2012;**39**(2):279–89. https://doi.org/10.1183/09031936.00020310	Population of both adults and children/adolescents ICS or ICS + LABA at screening	Parallel groups	746	Not possible to establish	FORM 10 mcg MDI BID (188) MF 100 mcg MDI BID (188) MF/FORM 100/10 mcg MDI BID (182) Placebo (188)	Exacerbation (asthma deterioration) ACQ FEV_1 QoL AEs
Meltzer (2019)[130]	—	Meltzer. Efficacy and safety of combined mometasone furoate/formoterol 100/10 µG twice daily in subjects with asthma inadequately controlled on low-dose inhaled corticosteroids. *Breast (Edinburgh, Scotland)* 2019;**44**:S63–64.	Paper not found	–	–	–	–	–
Miller (2016)[131§]	TEVA	Miller DS, Yiu G, Hellriegel ET, Steinfeld J. Dose-ranging study of salmeterol using a novel fluticasone propionate/salmeterol multidose dry powder inhaler in patients with persistent asthma. *Allergy Asthma Proc* 2016;**37**:291–301. https://doi.org/10.2500/aap.2016.37.3963	Population of both adults and children/adolescents	Crossover	72 (12–65+)	3	FP/SAL MDPI 100/6.25 mcg (one dose per treatment) FP/SAL MDPI 100/12.5 mcg (one dose per treatment) FP/SAL MDPI 100/25 mcg (one dose per treatment) FP/SAL MDPI 100/50 mcg (one dose per treatment) FP MDPI 100 mcg (one dose per treatment) FP/SAL DPI 100/50 mcg (one dose per treatment)	FEV_1 AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents[a]	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Murphy (2015)[132]	AstraZeneca	Murphy KR, Dhand R, Trudo F, Uryniak T, Aggarwal A, Eckerwall G. Therapeutic equivalence of budesonide/formoterol delivered via breath-actuated inhaler vs. pMDI. *Resp Med* 2015;**109**:170–9. http://doi.org/10.1016/j.rmed.2014.12.009	Population of both adults and children/adolescents *'Two patients receiving ICS/LABA combination therapy before study screening were not switched to monocomponent ICS before run-in but were subsequently included in the study'.*	Parallel groups	214 (12–75+)	21	BUD/FM BAI 320/9 mcg BID (71) BUD/FM pMDI 320/9 mcg BID (71) BUD pMDI 320 mcg BID (72)	FEV_1 AEs
Nathan (2010)[133]	MERCK	Nathan RA, Nolte H, Pearlman DS; P04334 Study Investigators. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 µg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. *Allergy Asthma Proc* 2010;31(4):**269**–79. https://doi.org/10.2500/aap.2010.31.3364. Epub July 30 2010.	Population of both adults and children/adolescents ICS or ICS + LABA at screening	Parallel groups	781 (NA)	Not possible to establish	MF/FORM 200/10 µg BID (191) MF 200 µg BID (192) Formotero 10 µg BID (202) Placebo (196)	Exacerbation (asthma deterioration) ACQ FEV_1 QoL AEs
NCT00392288 or EFC6695	COVIS PHARMA	No publication	No publication ICS or montelukast at screening	Parallel groups	501 (4–12)	501	CIC MDI 40 µg BID (166) CIC MDI 80 µg BID (172) Placebo (163)	FEV_1 Symptoms
NCT00419952 or D5896C00022	AstraZeneca	No publication	No publication population of both adults and children/adolescents	Parallel groups	742 (NA)	Not possible to establish	BUD + FORM pMDI 160/4.5 µg × 2 actuations (twice daily) BID (377) BUD HFA pMDI 160 µg × 2 actuations (twice daily) BID (365)	Exacerbation Symptoms FEV_1 AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents[a]	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
NCT00442117 or P04880	MERCK	No publication	No publication population of both adults and children/ adolescents	Parallel groups	180 (NA)	Not possible to establish	MF DPI 200 mcg, two puffs once daily PM (total of 400 mcg/day) (85) BUD DPI DPI 200 mcg, two puffs twice daily (total of 800 mcg/day) (87)	FEV_1
NCT00442559	MERCK	No publication	No publication Unknown pre-treatment	Parallel groups	191 (2–14)	191	Montelukast 4/5 mg tablet (oral chewable), OD (100) ICS solution, 1–4 puffs daily (91)	Symptoms
NCT00651768	AstraZeneca	No publication	No publication population of both adults and children/ adolescents	Parallel groups	570 (NA)	Not possible to establish	BUD/FORM Symbicort pMDI 2 X 160/4.5 mcg and BUD HFA pMDI 4 X 160 mcg	Exacerbation Lung function AEs
NCT01845025[b]	Novartis	No publication	No publication population of both adults and children/ adolescents *'Use of ICS, LABA, ICS + LABA, LTRAs, leukotriene modifiers, anticholinergics, or theophylline must be discontinued prior to the first dose of investigational treatment'.*	parallel groups	820 (NA)	Not possible to establish	FORM 12 mcg + FP 100 mcg/FP 250 mcg/FP 500 mcg (411) Placebo + FP 100 mcg/FP 250 mcg/FP 500 mcg (409)	Exacerbation ACQ Symptoms Hospitalisation Mortality AEs Unplanned healthcare utilisation

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
NCT02298205[b]	Washington University School of Medicine	No publication	No publication ICS or LTRA or ICS + LABA at screening	Parallel groups	206 (6–17)	206	Provider-based adjustment: The provider will adjust the dose of beclomethasone based on the participant's asthma control at their encounter with them Asthma controller medication (beclomethasone) adjustment strategy: The participant will adjust the dose of beclomethasone based on symptoms	Asthma control Exacerbation FEV_1 QoL
NCT02495168	TEVA	No publication	No publication population of both adults and children/adolescents	Parallel groups	1714 (12–75)	Not possible to establish	Generic BUD/FORM – 2 inhalations BID (80/4.5 mcg) pMDI (501) Symbicort BUD/FORM – 2 inhalations BID (80/4.5 mcg) pMDI (514) Placebo (126)	FEV_1
NCT02577497	University of Virginia	No publication	No publication ICS and/or an antileukotriene at screening	Crossover	31 (6–17)	31	Beclomethasone (31) Fluticasone (31)	None of interest
NCT02649478	HIKMA	No publication	No publication population of both adults and children/adolescents ICS with or without LABA, LTRA, theophylline	Parallel groups	1430	Not possible to establish	Fluticasone/SAL 100/50 mcg (NA) Advair Diskus 100/50 mcg (NA) Placebo (NA)	FEV_1 AEs
NCT02680561 (§)	TEVA	No publication	No publication	Crossover	20 (4–11)	20	FP MDPI (20) FP/SAL MDPI (20) FP/SAL (20)	AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents[a]	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
NCT02758873	University of Sussex	No publication	No publication ICS with/without second line controller (i.e. LABA/LTRA) at screening	Parallel groups	241 (12–18)	Not possible to establish	Salmeterol (NA) Montelukast (NA) Standard care (NA)	ACQ QoL
NCT03096327	PharmEvo Pvt Ltd	No publication	No publication population of both adults and children/adolescents	Parallel groups	180 (NA)	Not possible to establish	Montelukast 4–10 mg (NA) Placebo (NA)	QoL AEs
NCT03248128 or 107116A	GSK	No publication	Recruiting	Parallel groups	870 (5–17)	870	FF/VI 50 or 100/25 mcg DPI (NA) FF 50 or 100 mcg DPI (NA)	Exacerbation ACQ FEV_1 Symptoms AEs
NCT03387241	Mundipharma	No publication	No publication/no plan to share IPD population of both adults and children/adolescents	Parallel groups	330 (12–75)	Not possible to establish	Fluticasone/FORM Fluticasone/SAL	FEV_1 Asthma control (ACQ) Exacerbation
NCT03535870	HIKMA	No publication	No publication/no plan to share IPD population of both adults and children/adolescents ICS with or without LABA/LTM at screening	parallel groups	1556 (12–65)	Not possible to establish	FP/SAL 100/50 mcg DPI Advair Diskus, 100/50 mcg DPI Placebo	FEV_1
NCT03676413[b]	Respirent Pharmaceuticals	No publication	No publication/no plan to share IPD population of both adults and children/adolescents ICS and LABA at screening	Parallel groups	451 (NA)	Not possible to establish	FP/SAL 100/50 mcg DPI BID ADVAIR DISKUS® 100/50 mcg DPI BID Placebo	FEV_1 AEs
NCT03756883	TEVA	No publication	No publication/no plan to share IPD population of both adults and children/adolescents	Parallel groups	999 (12–75)	Not possible to establish	FP/SAL DPI 100/50 mcg (485) ADVAIR DISKUS® 100/50 (FP and SAL) DPI (413) Placebo (101)	FEV_1

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
NCT03847896	Bond Avillion 2 Development LP	No publication	No publication no plan to share IPD population of both adults and children/adolescents ICS + SABA or SABA alone at screening	Parallel groups	1001 (NA)	Not possible to establish	BUD/albuterol sulphate metered-dose inhaler 80/180 mcg (NA) BUD/albuterol sulphate metered-dose inhaler 160/180 mcg (NA) BUD metered-dose inhaler 160 mcg (NA) albuterol sulphate metered-dose inhaler 180 mcg (NA) Placebo (NA)	FEV_1 ACQ
Nielsen (2000)[134]	AstraZeneca	Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;**162**:1500–6.	ICS or other medicines (SABA as needed, LABA, sodio cromoglycate – four patients, 11%) at entry	Parallel groups	38 (2–5)	34	BUD (19) Placebo (19)	Symptoms
Pearlman (2011)[135]	SkyePharma AG	Pearlman DS, La-Force C, Kaiser K. Fluticasone propionate/formoterol fumarate combination therapy has superior efficacy to both fluticasone and formoterol alone. *Eur Resp J* 2011;**38**(Suppl. 55).	Population of both adults and children/adolescents congress abstract, the author is retired	Parallel groups	357 (NA)	Not possible to establish	Fluticasone/FORM 100/10 mcg BID (in a single inhaler) (NA) Fluticasone 100 mcg BID (NA) FORM 10 mcg BID (NA)	FEV_1
Pearlman (2017)[136]	AstraZeneca	Pearlman DS, Eckerwall G, McLaren J, Lamarca R, Puu M, Gilbert I, *et al.* Efficacy and safety of budesonide/formoterol pMDI vs. budesonide pMDI in asthmatic children (6–<12 years). *Ann Allergy Asthma Immunol* 2017;**118**(4):489–99.e1	ICS or ICS + LABA at screening	Parallel groups	279 (6–11)	137	BUD/FORM pMDI 160/9 mcg BID (92) BUD/FORM pMDI 160/4.5 mcg BID (95) BUD pMDI 160 mcg BID (92)	Exacerbation FEV_1 Symptoms QoL AEs
Pearlman (2019)[137]	—	Pearlman D, Nathan R, Meltzer E, Nolte H, Weinstein S. Effect of Mometasone Furoate/Formoterol Combination Therapy on Nocturnal Awakenings in Subjects With Persistent Asthma. *Breast (Edinburgh, Scotland)* 2019;**44**:S63-2019.	Author retired and paper not found	–	–	–	–	–

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Peden (1998)[138]	GSK	Peden DB, Berger WE, Noonan MJ, Thomas MR, Hendricks VL, Hamedani AG, *et al.* Inhaled fluticasone propionate delivered by means of two different multidose powder inhalers is effective and safe in a large pediatric population with persistent asthma. *J Allergy Clin Immunol* 1998;**102**(1):32–8.	ICS or cromolyn or LABA alone at screening	Parallel groups	437 (4–11)	437	FP 50 mcg BID Diskus (90) FP 100 mcg BID Diskus (87) FP 50 mcg BID Diskhaler (91) FP 100 mcg BID Diskhaler (83) placebo (86)	FEV_1 Symptoms AEs
Pedersen (2009)[139]	COVIS PHARMA	Pedersen S, Engelstätter R, Weber HJ, Hirsch S, Barkai L, Emeryk A, *et al.* Efficacy and safety of ciclesonide once daily and fluticasone propionate twice daily in children with asthma. *Pulm Pharmacol Ther* 2009;**22**(3):214–20. https://doi.org/10.1016/j.pupt.2008.12.013. Epub December 27 2008.	ICS and non-ICS at screening	Parallel groups	744 (6–11)	366	CIC 80 mcg OD (252) CIC 160 mcg OD (242) FP 88 mcg BID (250)	FEV_1 Symptoms QoL AEs
Pedersen (2017)[140]	COVIS PHARMA	Pedersen SE, Prasad N, Goehring UM, Andersson H, Postma DS. Control of moderate-to-severe asthma with randomized ciclesonide doses of 160, 320 and 640 µg/day. *J Asthma Allergy* 2017;**10**:35–46.	Population of both adults and children/ adolescents	Parallel groups	367 (12–70)	Not possible to establish	CIC 160 mcg/day (120) CIC 320 mcg /day (122) CIC 640 mcg/day (125)	FEV_1 ACQ AEs
Pertseva (2012)[141]	—	Efficacy and safety of fluticasone/formoterol compared to fluticasone alone in patients with asthma. *Eur Resp J* 2012;**40**(Suppl. 56).	Congress abstract population of both adults and children/ adolescents	Parallel groups	438 (NA)	Not possible to establish	FP/FORM 250/10 mcg BID pMDI (146) Fluticasone 250/10 mcg BID (146) SkyePharma pMDI Fluticasone 250/10 mcg BID (146) GSK pMDI	FEV_1
Peters (2016)[142]	AstraZeneca	Peters SP, Bleecker ER, Canonica GW, Park YB, Ramirez R, Hollis S, *et al.* Serious asthma events with budesonide + formoterol vs. budesonide alone. *New Eng J Med* 2016;**375**(9):850–60.	Population of both adults and children/ adolescents ICS or ICS + LABA at screening	Parallel groups	11693 (12–65+)	1268	BUD–FORM 80/4.5 mcg BID (1645) BUD 80 mcg BID (1646) BUD–FORM 160/4.5 mcg BID (4201) BUD 160 mcg BID (4201)	Exacerbation ACQ AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Petnak (2016)[143§]	–	Petnak T, Pornsuriysak P, Boonsarngsuk V, Amornputtisathaporn N, Kawamatawong T. Effect of inhaled mometasone/formoterol vs. inhaled fluticasone/salmeterol on peripheral airway function in asthma patients: a randomized open label trial. *Chest* 2016;**150**(4):16A-2016.	No age range (likely naive)	Parallel groups	50	Not possible to establish	Mometasone/FORM (25) Fluticasone/SAL (25)	None of interest
Philip (2011)[144]	MERCK	Philip G, Villarán C, Shah SR, Vandormael K, Smugar SS, Reiss TF. The efficacy and tolerability of inhaled montelukast + inhaled mometasone compared with mometasone alone in patients with chronic asthma. *J Asthma* 2011;**48**(5):495–502. https://doi.org/10.3109/02770903.2011.573042. Epub May 5 2011.	Population of both adults and children/adolescents not only ICS alone at screening (ICS + LABA and montelukast: 35%)	Crossover	134 (15–74)	Not possible to establish	Montelukast 1 mg + mometasone 220 µg (delivered by separate DPIs) OD (66 - first period) Placebo + mometasone 220 µg OD (68 - first period)	Exacerbation Asthma control FEV_1 AEs
Phipatanakul (2003)[145]	MERCK	Phipatanakul W, Greene C, Downes SJ, Cronin B, Eller TJ, Schneider LC, Irani AM. Montelukast improves asthma control in asthmatic children maintained on inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2003;**91**(1):49–54.	No useful data in the article	Two-period parallel groups	36 (6–14)	36	ICS + montelukast (run-in dose/5 mg) (19) ICS + placebo (run-in dose) (17)	None of interest
Płoszczuk (2018)[146]	Mundipharma	Płoszczuk A, Bosheva M, Spooner K, McIver T, Dissanayake S. Efficacy and safety of fluticasone propionate/formoterol fumarate in pediatric asthma patients: a randomized controlled trial. *Ther Adv Respir Dis* 2018;**12**:1–15. https://doi.org/10.1177/1753466618777924	ICS (uncontrolled asthma) or ICS + LABA (controlled asthma) at screening	Parallel groups	512 (5–12)	379	FP/FORM pMDI 100/10 mcg BID (169) FP pMDI 100 mcg BID (173) Fluticasone/SAL pMDI 100/50 mcg BID (170)	Exacerbation FEV_1 QoL Asthma control AEs
Pohunek (2006)[147]	AstraZeneca	Pohunek P, Kuna P, Jorup C, De Boeck K. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. *Pediatr Allergy Immunol* 2006;**17**:458–65.	ICS (any brand) or ICS + LABA or LABA at screening	Parallel groups	630 (4–11)	630	BUD/FORM (Symbicort) 80/4.5 mcg, two inhalations BID (216) BUD (Pulmicort) 100 mcg, two inhalations BID (213) BUD, 100 mcg, two inhalations BID (Pulmicort) + FORM 4.5 mcg, two inhalations BID (Oxis) (201)	FEV_1 QoL AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Pohunek (2014)[148]	Chiesi Farmaceutici	Pohunek P, Scuri M, Reznichenko Y, Varoli G, Mokia-Serbina S, Baronio R, *et al.* Bronchodilating effects of extrafine beclometasone dipropionate and formoterol fumarate via pressurized metered dose inhaler in asthmatic children. Pediatr Pulmonol2014;**49**(Suppl. 37):S55.	Abstract	Crossover	56 (5–12)	56	BDP/FF 100/12 mcg (CHF1535) BDP pMDI 100 mcg + FF 12 mcg pMDI	FEV_1 AEs
Rani (2016)[149]	—	Rani S, Rawal M, Kumar S, Lamba S. To compare efficacy and safety of fixed drug combination of salmeterol/fluticasone and budesonide/formoterol on the lung functions in childhood patients with moderate persistent asthma. *Indian J Public Health Res Dev* 2016;**7**(4):203–7.	Abstract (no data or enough information)	Parallel groups	68 (NA)	68	SAL/fluticasone (NA) BUD/FORM (NA)	FEV_1
Raphael (2018)[150]	TEVA	Raphael G, Yiu G, Sakov A, Liu S, Caracta C. Randomized, double-blind trial evaluating the efficacy and safety of fluticasone propionate and fluticasone propionate/salmeterol delivered via multidose dry powder inhalers in patients with persistent asthma aged 12 years and older. *J Asthma*. 2018;**55**(6):640–50. https://doi.org/10.1080/02770903.2017.1350971	Population of both adults and children/adolescents ICS or ICS + LABA at screening	Parallel groups	625 (12–65+)	86	FP 50 mcg DPI BID (125) FP 100 mcg DPI BID (125) FP/SAL 50/12.5 DPI BID (125) FP/SAL 100/12.5 DPI BID (125) Placebo (125)	Exacerbation FEV_1 QoL AEs
Saeed (2018)[151]	—	Saeed R, Mustafa K, Saqib NU. Comparison of montelukast with fluticasone for control of Asthma in children. *Med Forum Mon* 2018;**29**(3):25–8.	Unknown if patients used ICS at screening	Parallel groups	780 (4–10)	780	Montelukast 5–10 mg OD (390) Fluticasone 100 mcg BID (390)	FEV_1
Shapiro (1998)[152]	AstraZeneca	Shapiro GG, Bronsky EA, LaForce CF, Mendelson L, Pearlman D, Schwartz RH, Szefler SJ. Dose-related efficacy of budesonide administered via a dry powder inhaler in the treatment of children with moderate to severe persistent asthma. *J Pediatr* 1998;**132**(6):976–82.	6–18 years not only ICS on entry triamcinolone is not on our list	Parallel groups	404 (6–18)	Not possible to establish	BUD 100 mcg DPI BID (102) BUD 200 mcg DPI BID (100) BUD 400 mcg DPI BID (99) Placebo (103)	FEV_1 Symptoms AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents[a]	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Shatalina (2017)[153]	—	Shatalina S, Geppe N, Denisova A, Denisova V, Kolosova N. Intermittent therapy with budesonide/formoterol in children with moderate asthma. *Eur Resp J* 2017;**50**(Suppl. 61).	Congress abstract 6–18 years	Parallel groups	95 (6–18)	Not possible to establish	Group 1: BUD/FORM in a fixed dose twice a day Group 2: BUD/FORM once a day and in exacerbation of asthma patient increased BUD/FORM to 4 inhalations/day for 7–14 days (intermittent therapy) Group 3: ICS (100–200 µg BUD/day)	FEV_1 Asthma Symptoms
Sher (2017)[154]	TEVA	Sher LD, Yiu G, Sakov A, Liu S, Caracta CF. Fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers compared with placebo for persistent asthma. *Allergy Asthma Proc* 2017;**38**(5):343–53. https://doi.org/10.2500/aap.2017.38.4069	Population of both adults and children/adolescents ICS or ICS + LABA at entry	Parallel groups	728 (12–65+)	45	FP 100 mcg MDPI BID (146) FP 200 mcg MDPI BID (146) FP/SAL 100/12.5 mcg MDPI BID (145) FP/SAL 200/12.5 mcg MDPI BID (146) Placebo (145)	FEV_1 QoL AEs
Skoner (2008)[155]	COVIS PHARMA	Skoner DP, Maspero J, Banerji D; Ciclesonide Pediatric Growth Study Group. Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. *Pediatrics* 2008;**121**(1):e1–14. https://doi.org/10.1542/peds.2006-2206. Epub December 10 2007.	ICS or LTRA or SABA at screening	Parallel groups	661 (5.5–9.1)	661	CIC 40 mcg QD (221) CIC 160 mcg QD (219) Placebo (221)	FEV_1 AEs (growth)

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Steinfeld (2015)[156§]	TEVA	Steinfeld J, Yiu G, Miller SD. Dose-ranging study to evaluate the efficacy and safety of four doses of fluticasone propionate/salmeterol multidose dry powder inhaler (FS MDPI) compared with fluticasone propionate (FP) MDPI and FS DPI in subjects with persistent asthma. *J Allergy Clin Immunol*. 2015;**135**(2 Suppl. 1):AB6 2015.	Conference abstract population of both adults and children/ adolescents single dose	Crossover	72 (NA)	Not possible to establish	Fluticasone/SAL MDPI 100/6.25 mcg Fluticasone/SAL MDPI 100/12.5 mcg Fluticasone/SAL MDPI 100/25 mcg Fluticasone/SAL MDPI 100/50 mcg FP MDPI 100 mcg Fluticasone/SAL DPI 100/50 mcg	FEV_1
Strunk (2008)[157] (IPD)	CARE Network	Strunk RC, Bacharier LB, Phillips BR, Szefler SJ, Zeiger RS, Chinchilli VM, *et al.*; CARE Network. Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderate-to-severe childhood asthma study. *J Allergy Clin Immunol* 2008;**122**(6):1138–44. e4. https://doi.org/10.1016/j.jaci.2008.09.028. Epub October 25 2008.	Not enough eligible patients ICS alone (uncontrolled) or ICS + LABA or other (controlled)	Parallel groups	55 (6–17)	1	Placebo and BUD (400 mcg as minimum) + SAL (50 mcg) BID (19) Montelukast (5 or 10 mg) OD and BUD (400 mcg as minimum) + SAL (50 mcg) BID (19)	Asthma control AEs
Suessmuth (2003)[158]	—	Suessmuth S, Freihorst J, Gappa M. Low-dose theophylline in childhood asthma: a placebo-controlled, double-blind study. *Pediatr Allergy Immunol* 2003;**14**(5):394–400.	Adolescents aged 18	Parallel groups	36 (6–18)	36	ICS + theophylline 10 mg/kg bodyweight ICS + placebo	Symptoms Lung function
van Adelsberg (2005)[159]	MERCK	van Adelsberg J, Moy J, Wei LX, Tozzi CA, Knorr B, Reiss TF. Safety, tolerability, and exploratory efficacy of montelukast in 6- to 24-month-old patients with asthma. *Curr Med Res Opin* 2005;**21**(6):971–9.	50% used ICS; other medicine or no medicine used at screening and concomitant use of those during the study	Parallel groups	256 (6–24 months)	128	ICS (87/175) + montelukast 4 mg (175) ICS (41/81) + placebo (81)	Exacerbation (asthma attack) Hospitalisation AEs
Vandewalker (2017)[160]	TEVA	Vandewalker M, Hickey L, Small CJ. Efficacy and safety of beclomethasone dipropionate breath-actuated or metered-dose inhaler in pediatric patients with asthma. *Allergy Asthma Proc* 2017;**38**(5):354–64.	ICS or NCS at entry	Parallel groups	628 (4–11)	445	BDP BAI 80 mcg die (126) BDP BAI 160 mcg die (125) BDP MDI 80 mcg die (125) BDP MDI 160 mcg die (125) Placebo (127)	FEV_1 Exacerbation Symptoms Asthma control AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents*	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Venugopal (2019)[161§]	–	Venugopal S, Mohan G, Cherungonath A. Effect of addition of single dose of oral montelukast to standard therapy in acute moderate asthma in children 5 to 12 years of age: a randomised double-blind placebo controlled trial. *Chest* **156**(4):A1603.	Abstract – no information on previous treatments single dose of montelukast to standard therapy in exacerbation	Parallel groups	43 (5–12)	43	Standard therapy + single tablet of montelukast (5 mg) (29) Standard therapy + single tablet of placebo (14)	None of interest
Verini (2007)[162]	–	Verini M, Peroni D, Piacentini G, Nicodemo A, Rossi N, Bodini A, *et al.* Comparison of add-on therapy to inhaled fluticasone propionate in children with asthma: residual volume and eNO as outcome measures. *Allergy Asthma Proc* 2007;**28**(6):691–4.	No data for the first period	Crossover	12 (6–13)	12	FP 100 mcg BID + montelukast 5 mg OD (12) FP 100 mcg BID + SAL 50 mcg BID (12)	Exacerbation (none) AEs (none)
von Berg (1998)[163]	GSK	von Berg A, de Blic J, la Rosa M, Kaad PH, Moorat A. A comparison of regular salmeterol vs. 'as required' salbutamol therapy in asthmatic children. *Respir Med* 1998 Feb;**92**(2):292–9.	Only 50% of patients used ICS at entry patients were allowed to use ICS, cromoglycate, nedocromyl, or ketotifen during the study	Parallel groups	426 (5–15)	223	ICS (122/220) + SAL 50 mcg BID Diskhaler (220) ICS (101/206) + placebo (206)	Exacerbation FEV_1 Symptoms AEs
Weinstein (1998)[164]	GSK	Weinstein SF, Pearlman DS, Bronsky EA, Byrne A, Arledge T, Liddle R, Stahl E. Efficacy of salmeterol xinafoate powder in children with chronic persistent asthma. *Ann Allergy Asthma Immunol* 1998;**81**(1):51–8.	Other medicine used at screening patients were allowed to use ICS, cromolyn, nedocromil or immunotherapy during the study	Parallel groups	207 (4–11)	118	ICS (no patient number) + SAL 50 mcg BID (102) ICS (no patient number) + placebo (105)	FEV_1 AEs
Weinstein (2010)[165]	MERCK	Weinstein SF, Corren J, Murphy K, Nolte H, White M; P04431 Study Investigators. Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/10 µg and 400/10 µg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids. *Allergy Asthma Proc* 2010;**31**(4):280–9. https://doi.org/10.2500/aap.2010.31.3381. Epub August 3 2010.	Population of both adults and children/adolescents ICS or ICS + LABA at entry	Parallel groups	728 (NA)	Not possible to establish	MF/FORM 200/10 mcg BID (233) MF/FORM 400/10 mcg BID (255) MF 400 mcg BID (240)	FEV_1 Exacerbation ACQ QoL AEs

First author (year)	Sponsor	Study reference	Reasons for not extracting AgD	Study	Total randomised participants (age range)	Total randomised children/adolescents[a]	Treatments (number of participants reported)	Outcome(s) reported in the publication (does not imply adequate AgD)
Weiss (2010)[166]	MERCK	Weiss KB, Gern JE, Johnston NW, Sears MR, Jones CA, Jia G, *et al.* The Back to School asthma study: the effect of montelukast on asthma burden when initiated prophylactically at the start of the school year. *Ann Allergy Asthma Immunol* 2010;**105**(2):174–81. https://doi.org/10.1016/j.anai.2010.04.018. Epub July 1 2010.	Only 50% of patients used ICS	Parallel groups	1162 (6–14)	597	ICS (314) + montelukast 5 mg (580) ICS (283) + placebo (582)	Worsening Asthma AEs
Zangrilli (2001)[167]	AstraZeneca	Zangrilli J, Mansfield LE, Uryniak T, O'Brien CD. Efficacy of budesonide/formoterol pressurized metered-dose inhaler versus budesonide pressurized metered-dose inhaler alone in Hispanic adults and adolescents with asthma: a randomized, controlled trial. *Ann Allergy Asthma Immunol* 2011;**107**(3):258–65.e2. https://doi.org/10.1016/j.anai.2011.05.024. Epub July 14 2011.	Population of both adults and children/adolescents	Parallel groups	250 (NA)	Not possible to establish	BUD/FORM pMDI 160/4.5 µg × 2 inhalations (320/9 µg) twice daily (127) BUD pMDI 160 µg × 2 inhalations (320 µg) twice daily (123)	Exacerbation FEV_1 Symptoms AEs

HFA, hydrofluoroalkane propellant.
a Not all reported participants can be eligible for inclusion because it is not possible to establish if all inclusion criteria are met (e.g., pre-study treatment with ICS alone).
b Study that may be not eligible after further assessment.

Appendix 6 Full results from fixed-effect and random effects Bayesian network meta-analysis

TABLE 48 Model comparison assessments from NMA models

Outcome	Analysis	Model	Number of trials (number of participants)	Number of data points	Residual deviance	Effective number of parameters (Pd)	DIC	Between trial SD
Exacerbation	a	FE consistency	39 (8136)	5377	2254.1	42.1	2296.3	–
		RE consistency	39 (8136)	5377	2246.9	50	2296.9	0.31 (0.02, 0.81)
	b	FE consistency	40 (8168)	5410	2252.1	44.3	2296.4	–
		RE consistency	40 (8168)	5410	2234.8	55.8	2290.6	0.50 (0.09, 0.98)
Asthma control	a	FE consistency	15 (2998)	2998	2801.3	21.3	2822.5	–
		RE consistency	15 (2998)	2998	2796.2	26.4	2822.6	0.38 (0.02, 0.99)
	b	FE consistency	16 (3027)	3027	2839.7	24.4	2864.1	–
		RE consistency	16 (3027)	3027	2827.2	32.7	2859.9	0.62 (0.08, 1.33)
	c	FE consistency	15 (3014)	3014	2818.9	22.1	2841.1	–
		RE consistency	15 (3014)	3014	2808.4	28.5	2836.9	0.66 (0.11, 1.53)
FEV_1	a	FE consistency	22 (2485)	2175	2129.1	−324.9	1804.2	–
		RE consistency	22 (2485)	2175	2129.2	−360.8	1768.4	0.03 (0.00, 0.15)
	b	FE consistency	23 (2518)	2207	2157.3	−2267.9	−110.6	–
		RE consistency	23 (2518)	2207	2155.4	−2262.4	−107	0.09 (0.00, 0.35)
	c	FE consistency	17 (1984)	1984	1943.1	−855.4	1087.7	–
		RE consistency	17 (1984)	1984	1943.4	−837.6	1105.9	0.04 (0.00, 0.17)

TABLE 49 Parameter estimates (log ORs or MDs) from NMA models (analysis a)

	Exacerbation		Asthma control		FEV_1	
Model	**FE consistency**	**RE consistency**	**FE consistency**	**RE consistency**	**FE consistency**	**RE consistency**
ICS + LABA vs. ICS High	0.11 (−0.34, 0.57)	0.12 (−0.47, 0.74)	0.47 (−0.07, 1.00)	0.48 (−0.30, 1.26)	−0.13 (−0.32, 0.07)	−0.13 (−0.35, 0.08)
ICS Low vs. ICS High	0.36 (−0.18, 0.90)	0.37 (−0.32, 1.08)	0.31 (−0.27, 0.89)	0.20 (−0.67, 0.98)	−0.15 (−0.36, 0.05)	−0.15 (−0.37, 0.07)
ICS Medium vs. ICS High	0.26 (−0.25, 0.76)	0.29 (−0.38, 1.04)	0.42 (−0.17, 0.99)	0.47 (−0.41, 1.46)	−0.15 (−0.36, 0.07)	−0.15 (−0.38, 0.09)
ICS unknown vs. ICS High	–	–	–	–	−0.42 (−1.67, 0.83)	−0.45 (−1.76, 0.83)
ICS + LTRA vs. ICS High	0.65 (−0.37, 1.64)	0.68 (−0.53, 1.90)	0.52 (−1.29, 2.38)	0.54 (−1.46, 2.65)	−0.37 (−1.21, 0.45)	−0.39 (−1.26, 0.43)
ICS + theophylline vs. ICS High	0.66 (−2.98, 4.29)	0.76 (−3.22, 4.62)	–	–	–	–
LTRA vs. ICS High	**1.61 (0.08, 3.35)**	1.64 (−0.10, 3.64)	−1.15 (−2.89, 0.48)	−1.27 (−3.28, 0.65)	0.00 (−0.53, 0.51)	0.00 (−0.54, 0.53)
Placebo vs. ICS High	**1.21 (0.54, 1.88)**	**1.24 (0.36, 2.21)**	−0.04 (−0.86, 0.78)	−0.13 (−1.31, 0.98)	**−0.31 (−0.54, −0.07)**	**−0.31 (−0.57, −0.05)**
ICS + LABA vs. ICS Low	−0.24 (−0.58, 0.10)	−0.25 (−0.66, 0.18)	0.16 (−0.16, 0.48)	0.27 (−0.20, 0.86)	0.03 (−0.05, 0.10)	0.02 (−0.08, 0.11)
ICS High vs. ICS Low	−0.36 (−0.90, 0.18)	−0.37 (−1.08, 0.32)	−0.31 (−0.89, 0.27)	−0.20 (−0.98, 0.67)	0.15 (−0.05, 0.36)	0.15 (−0.07, 0.37)
ICS Medium vs. ICS Low	−0.10 (−0.49, 0.29)	−0.08 (−0.60, 0.49)	0.11 (−0.31, 0.52)	0.26 (−0.41, 1.16)	0.00 (−0.11, 0.12)	0.00 (−0.14, 0.14)
ICS unknown vs. ICS Low	–	–	–	–	−0.27 (−1.51, 0.97)	−0.29 (−1.60, 0.97)
ICS + LTRA vs. ICS Low	0.30 (−0.64, 1.21)	0.31 (−0.80, 1.38)	0.21 (−1.56, 2.00)	0.33 (−1.58, 2.41)	−0.22 (−1.04, 0.57)	−0.23 (−1.09, 0.58)
ICS + theophylline vs. ICS Low	0.31 (−3.32, 3.90)	0.38 (−3.52, 4.23)	–	–	–	–
LTRA vs. ICS Low	1.25 (−0.16, 2.91)	1.27 (−0.35, 3.11)	−1.46 (−3.09, 0.07)	−1.46 (−3.30, 0.30)	0.15 (−0.34, 0.62)	0.15 (−0.35, 0.63)
Placebo vs. ICS Low	**0.85 (0.42, 1.29)**	**0.87 (0.25, 1.57)**	−0.35 (−0.94, 0.26)	−0.34 (−1.16, 0.53)	**−0.16 (−0.27, −0.04)**	**−0.16 (−0.30, −0.01)**
ICS + LABA vs. ICS Medium	−0.14 (−0.39, 0.10)	−0.17 (−0.61, 0.22)	0.06 (−0.22, 0.33)	0.01 (−0.71, 0.61)	0.02 (−0.07, 0.11)	0.02 (−0.10, 0.13)
ICS High vs. ICS Medium	−0.26 (−0.76, 0.25)	−0.29 (−1.04, 0.38)	−0.42 (−0.99, 0.17)	−0.47 (−1.46, 0.41)	0.15 (−0.07, 0.36)	0.15 (−0.09, 0.38)
ICS Low vs. ICS Medium	0.1 (−0.29, 0.49)	0.08 (−0.49, 0.60)	−0.11 (−0.52, 0.31)	−0.26 (−1.16, 0.41)	0.00 (−0.12, 0.11)	0.00 (−0.14, 0.14)
ICS unknown vs. ICS Medium	–	–	–	–	−0.27 (−1.51, 0.97)	−0.29 (−1.59, 0.96)
ICS + LTRA vs. ICS Medium	0.39 (−0.50, 1.28)	0.39 (−0.70, 1.43)	0.10 (−1.63, 1.89)	0.04 (−1.85, 2.03)	−0.22 (−1.05, 0.57)	−0.24 (−1.08, 0.57)
ICS + theophylline vs. ICS Medium	0.4 (−3.20, 4.00)	0.46 (−3.46, 4.34)	–	–	–	–
LTRA vs. ICS Medium	1.35 (−0.11, 3.06)	1.35 (−0.36, 3.24)	−1.56 (−3.23, 0.00)	−1.74 (−3.75, 0.12)	0.14 (−0.35, 0.63)	0.15 (−0.36, 0.65)
Placebo vs. ICS Medium	**0.95 (0.41, 1.50)**	**0.95 (0.18, 1.72)**	−0.46 (−1.14, 0.23)	−0.60 (−1.74, 0.36)	−0.16 (−0.32, 0.00)	−0.16 (−0.35, 0.04)
ICS + LABA vs. ICS unknown	–	–	–	–	0.29 (−0.94, 1.53)	0.31 (−0.95, 1.61)

continued

TABLE 49 Parameter estimates (log ORs or MDs) from NMA models (analysis a) (*continued*)

	Exacerbation		Asthma control		FEV_1	
Model	**FE consistency**	**RE consistency**	**FE consistency**	**RE consistency**	**FE consistency**	**RE consistency**
ICS High vs. ICS unknown	–	–	–	–	0.42 (−0.83, 1.67)	0.45 (−0.83, 1.76)
ICS Low vs. ICS unknown	–	–	–	–	0.27 (−0.97, 1.51)	0.29 (−0.97, 1.60)
ICS Medium vs. ICS unknown	–	–	–	–	0.27 (−0.97, 1.51)	0.29 (−0.96, 1.59)
ICS + LTRA vs. ICS unknown	–	–	–	–	0.04 (−0.91, 1.00)	0.05 (−0.91, 1.02)
LTRA vs. ICS unknown	–	–	–	–	0.42 (−0.91, 1.75)	0.44 (−0.91, 1.81)
Placebo vs. ICS unknown	–	–	–	–	0.11 (−1.14, 1.36)	0.14 (−1.13, 1.44)
ICS + LABA vs. ICS + LTRA	−0.54 (−1.42, 0.37)	−0.56 (−1.61, 0.53)	−0.04 (−1.83, 1.68)	−0.05 (−2.04, 1.82)	0.24 (−0.54, 1.07)	0.25 (−0.55, 1.10)
ICS High vs. ICS + LTRA	−0.65 (−1.64, 0.37)	−0.68 (−1.90, 0.53)	−0.52 (−2.38, 1.29)	−0.54 (−2.65, 1.46)	0.37 (−0.45, 1.21)	0.39 (−0.43, 1.26)
ICS Low vs. ICS + LTRA	−0.30 (−1.21, 0.64)	−0.31 (−1.38, 0.80)	−0.21 (−2.00, 1.56)	−0.33 (−2.41, 1.58)	0.22 (−0.57, 1.04)	0.23 (−0.58, 1.09)
ICS Medium vs. ICS + LTRA	−0.39 (−1.28, 0.50)	−0.39 (−1.43, 0.70)	−0.10 (−1.89, 1.63)	−0.04 (−2.03, 1.85)	0.22 (−0.57, 1.05)	0.24 (−0.57, 1.08)
ICS unknown vs. ICS + LTRA	–	–	–	–	−0.04 (−1.00, 0.91)	−0.05 (−1.02, 0.91)
ICS + theophylline vs. ICS + LTRA	0.01 (−3.47, 3.51)	0.08 (−3.65, 3.79)	–	–	–	–
LTRA vs. ICS + LTRA	0.96 (−0.73, 2.82)	0.98 (−1.00, 3.12)	−1.68 (−4.11, 0.66)	−1.80 (−4.52, 0.75)	0.36 (−0.56, 1.32)	0.38 (−0.56, 1.37)
Placebo vs. ICS + LTRA	0.56 (−0.43, 1.57)	0.57 (−0.63, 1.86)	−0.56 (−2.43, 1.28)	−0.67 (−2.87, 1.39)	0.06 (−0.74, 0.89)	0.08 (−0.73, 0.94)
ICS + LABA vs. ICS + theophylline	−0.55 (−4.16, 3.08)	−0.64 (−4.49, 3.31)	–	–	–	–
ICS High vs. ICS + Theophylline	−0.66 (−4.29, 2.98)	−0.76 (−4.62, 3.22)	–	–	–	–
ICS Low vs. ICS + theophylline	−0.31 (−3.9, 3.32)	−0.38 (−4.23, 3.52)	–	–	–	–
ICS Medium vs. ICS + theophylline	−0.40 (−4.00, 3.20)	−0.46 (−4.34, 3.46)	–	–	–	–
ICS + LTRA vs. ICS + theophylline	−0.01 (−3.51, 3.47)	−0.08 (−3.79, 3.65)	–	–	–	–
LTRA vs. ICS + theophylline	0.96 (−2.93, 4.89)	0.92 (−3.26, 5.19)	––	–	–	–
Placebo vs. ICS + theophylline	0.54 (−3.08, 4.19)	0.50 (−3.39, 4.43)	–	–	–	–
ICS + LABA vs. LTRA	**−1.49 (−3.19, −0.05)**	−1.52 (−3.40, 0.13)	1.62 (0.08, 3.28)	1.74 (−0.05, 3.63)	−0.12 (−0.60, 0.36)	−0.12 (−0.61, 0.36)
ICS High vs. LTRA	**−1.61 (−3.35, −0.08)**	−1.64 (−3.64, 0.10)	1.15 (−0.48, 2.89)	1.27 (−0.65, 3.28)	0.00 (−0.51, 0.53)	0.00 (−0.53, 0.54)
ICS Low vs. LTRA	−1.25 (−2.91, 0.16)	−1.27 (−3.11, 0.35)	1.46 (−0.07, 3.09)	1.46 (−0.30, 3.30)	−0.15 (−0.62, 0.34)	−0.15 (−0.63, 0.35)
ICS Medium vs. LTRA	−1.35 (−3.06, 0.11)	−1.35 (−3.24, 0.36)	**1.56 (0.00, 3.23)**	1.74 (−0.12, 3.75)	−0.14 (−0.63, 0.35)	−0.15 (−0.65, 0.36)

TABLE 49 Parameter estimates (log ORs or MDs) from NMA models (analysis a) (*continued*)

	Exacerbation		Asthma control		FEV_1	
Model	**FE consistency**	**RE consistency**	**FE consistency**	**RE consistency**	**FE consistency**	**RE consistency**
ICS Unknown vs. LTRA	–	–	–	–	−0.42 (−1.75, 0.91)	−0.44 (−1.81, 0.91)
ICS + LTRA vs. LTRA	−0.96 (−2.82, 0.73)	−0.98 (−3.12, 1.00)	1.68 (−0.66, 4.11)	1.80 (−0.75, 4.52)	−0.36 (−1.32, 0.56)	−0.38 (−1.37, 0.56)
ICS + theophylline vs. LTRA	−0.96 (−4.89, 2.93)	−0.92 (−5.19, 3.26)	–	–	–	–
Placebo vs. LTRA	−0.40 (−2.12, 1.10)	−0.40 (−2.34, 1.38)	1.11 (−0.52, 2.86)	1.13 (−0.80, 3.16)	−0.30 (−0.79, 0.20)	−0.30 (−0.81, 0.21)
ICS + LABA vs. placebo	**−1.1 (−1.62, −0.58)**	**−1.12 (−1.89, −0.42)**	0.51 (−0.13, 1.17)	0.61 (−0.28, 1.57)	**0.18 (0.05, 0.32)**	**0.18 (0.00, 0.34)**
ICS High vs. placebo	**−1.21 (−1.88, −0.54)**	**−1.24 (−2.21, −0.36)**	0.04 (−0.78, 0.86)	0.13 (−0.98, 1.31)	**0.31 (0.07, 0.54)**	**0.31 (0.05, 0.57)**
ICS Low vs. placebo	**−0.85 (−1.29, −0.42)**	**−0.87 (−1.57, −0.25)**	0.35 (−0.26, 0.94)	0.34 (−0.53, 1.16)	**0.16 (0.04, 0.27)**	**0.16 (0.01, 0.30)**
ICS Medium vs. placebo	**−0.95 (−1.5, −0.41)**	**−0.95 (−1.72, −0.18)**	0.46 (−0.23, 1.14)	0.60 (−0.36, 1.74)	**0.16 (0.00, 0.32)**	0.16 (−0.04, 0.35)
ICS Unknown vs. placebo	–	–	–	–	−0.11 (−1.36, 1.14)	−0.14 (−1.44, 1.13)
ICS + LTRA vs. placebo	−0.56 (−1.57, 0.43)	−0.57 (−1.86, 0.63)	0.56 (−1.28, 2.43)	0.67 (−1.39, 2.87)	−0.06 (−0.89, 0.74)	−0.08 (−0.94, 0.73)
ICS + Theophylline vs. placebo	−0.54 (−4.19, 3.08)	−0.50 (−4.43, 3.39)	–	–	–	–
LTRA vs. placebo	0.40 (−1.10, 2.12)	0.40 (−1.38, 2.34)	−1.11 (−2.86, 0.52)	−1.13 (−3.16, 0.80)	0.30 (−0.20, 0.79)	0.30 (−0.21, 0.81)

Note
Posterior mean (95% CrI). Bold indicates that zero is excluded from the CrI. Log OR presented for exacerbation and asthma control; MD presented for FEV_1.

TABLE 50 Parameter estimates from NMA models (analysis b)

	Exacerbation		Asthma control		FEV_1	
	FE consistency	RE consistency	FE consistency	RE consistency	FE consistency	RE consistency
ICS Low vs. ICS High	0.31 (−0.38, 0.97)	0.30 (−0.61, 1.22)	0.28 (−0.36, 0.90)	0.24 (−0.80, 1.26)	−0.16 (−0.46, 0.15)	−0.16 (−0.50, 0.19)
ICS High + LABA vs. ICS High	0.24 (−0.27, 0.75)	0.24 (−0.54, 1.03)	0.67 (−0.03, 1.39)	0.72 (−0.35, 1.91)	**−0.45 (−0.64, −0.25)**	−0.42 (−0.71, 0.01)
ICS Low + LABA vs. ICS High	0.08 (−0.58, 0.72)	0.12 (−0.78, 1.04)	0.43 (−0.20, 1.05)	0.63 (−0.35, 1.78)	−0.14 (−0.43, 0.17)	−0.16 (−0.52, 0.18)
ICS Medium vs. ICS High	0.00 (−0.66, 0.65)	0.05 (−0.89, 1.00)	0.35 (−0.31, 1.00)	0.42 (−0.72, 1.68)	−0.14 (−0.45, 0.16)	−0.13 (−0.50, 0.24)
ICS Medium + LABA vs. ICS High	−0.30 (−0.97, 0.33)	−0.52 (−1.53, 0.38)	0.39 (−0.26, 1.04)	0.22 (−1.02, 1.29)	**0.55 (0.24, 0.81)**	**0.50 (0.06, 0.82)**
ICS Unknown dose vs. ICS High	–	–	–	–	−0.43 (−1.72, 0.83)	−0.46 (−1.84, 0.89)
ICS + LTRA vs. ICS High	0.50 (−0.57, 1.60)	0.53 (−0.93, 1.97)	0.47 (−1.32, 2.36)	0.61 (−1.63, 3.01)	−0.39 (−1.25, 0.46)	−0.42 (−1.33, 0.49)
ICS + theophylline vs. ICS High	0.52 (−3.28, 4.06)	0.60 (−3.48, 4.70)	–	–	–	–
LTRA vs. ICS High	1.57 (0.01, 3.33)	1.58 (−0.42, 3.76)	−1.17 (−2.90, 0.49)	−1.20 (−3.48, 1.04)	−0.02 (−0.58, 0.55)	−0.02 (−0.66, 0.63)
Placebo vs. ICS High	1.13 (0.34, 1.92)	1.16 (0.02, 2.37)	−0.07 (−0.91, 0.77)	−0.09 (−1.52, 1.36)	−0.32 (−0.63, 0.01)	−0.32 (−0.70, 0.07)
ICS Low vs. ICS High + LABA	0.06 (−0.64, 0.76)	0.05 (−0.88, 1.02)	−0.39 (−1.08, 0.27)	−0.49 (−1.57, 0.48)	0.29 (−0.05, 0.64)	0.25 (−0.20, 0.65)
ICS High vs. ICS High + LABA	−0.24 (−0.75, 0.27)	−0.24 (−1.03, 0.54)	−0.67 (−1.39, 0.03)	−0.72 (−1.91, 0.35)	**0.45 (0.25, 0.64)**	0.42 (−0.01, 0.71)
ICS Low + LABA vs. vs. ICS High + LABA	−0.17 (−0.85, 0.51)	−0.13 (−1.04, 0.82)	−0.24 (−0.93, 0.41)	−0.10 (−1.08, 0.94)	0.31 (−0.03, 0.66)	0.25 (−0.24, 0.64)
ICS Medium vs. ICS High + LABA	−0.24 (−0.93, 0.43)	−0.19 (−1.11, 0.78)	−0.33 (−1.05, 0.36)	−0.31 (−1.50, 0.89)	0.30 (−0.04, 0.66)	0.28 (−0.19, 0.68)
ICS Medium + LABA vs. ICS High + LABA	−0.55 (−1.24, 0.12)	−0.76 (−1.77, 0.16)	−0.29 (−1.01, 0.40)	−0.51 (−1.81, 0.55)	**1.00 (0.67, 1.27)**	**0.92 (0.36, 1.25)**
ICS Unknown dose vs. ICS High + LABA	–	–	–	–	0.01 (−1.27, 1.28)	−0.06 (−1.47, 1.28)
ICS + LTRA vs. ICS High + LABA	0.26 (−0.83, 1.37)	0.28 (−1.18, 1.72)	−0.21 (−2.01, 1.71)	−0.12 (−2.35, 2.25)	0.06 (−0.81, 0.92)	−0.01 (−0.98, 0.91)
ICS + theophylline vs. ICS High + LABA	0.29 (−3.52, 3.82)	0.36 (−3.71, 4.44)	–	–	–	–
LTRA vs. ICS High + LABA	1.32 (−0.25, 3.09)	1.34 (−0.69, 3.53)	−1.84 (−3.58, −0.16)	−1.93 (−4.24, 0.27)	0.43 (−0.15, 1.02)	0.39 (−0.34, 1.05)
Placebo vs. ICS High + LABA	0.88 (0.09, 1.69)	0.91 (−0.23, 2.15)	−0.75 (−1.64, 0.14)	−0.82 (−2.26, 0.56)	0.13 (−0.22, 0.50)	0.10 (−0.40, 0.52)
ICS Low + LABA vs. ICS Low	–	–	0.15 (−0.19, 0.48)	0.38 (−0.22, 1.21)	0.02 (−0.05, 0.10)	0.01 (−0.19, 0.13)
ICS High vs. ICS Low	–	–	−0.28 (−0.90, 0.36)	−0.24 (−1.26, 0.80)	0.16 (−0.15, 0.46)	0.16 (−0.19, 0.50)
ICS High + LABA vs. vs. ICS Low	–	–	0.39 (−0.27, 1.08)	0.49 (−0.48, 1.57)	−0.29 (−0.64, 0.05)	−0.25 (−0.65, 0.20)
ICS Medium vs. ICS Low	–	–	0.06 (−0.55, 0.69)	0.18 (−0.78, 1.25)	0.02 (−0.09, 0.13)	0.03 (−0.19, 0.25)
ICS Medium + LABA vs. ICS Low	–	–	0.11 (−0.51, 0.72)	−0.03 (−1.10, 0.94)	**0.71 (0.35, 1.06)**	**0.65 (0.21, 1.05)**
ICS unknown dose	–	–			−0.27 (−1.52, 0.95)	−0.30 (−1.64, 0.99)

TABLE 50 Parameter estimates from NMA models (analysis b) (*continued*)

	Exacerbation		Asthma control		FEV_1	
	FE consistency	RE consistency	FE consistency	RE consistency	FE consistency	RE consistency
ICS + LTRA vs. ICS Low	–	–	0.19 (−1.55, 2.03)	0.37 (−1.73, 2.64)	−0.23 (−1.04, 0.56)	−0.26 (−1.13, 0.58)
LTRA vs. ICS Low	–	–	−1.45 (−3.07, 0.10)	−1.43 (−3.51, 0.62)	0.15 (−0.33, 0.63)	0.14 (−0.41, 0.69)
Placebo vs. ICS Low	–	–	−0.36 (−0.94, 0.25)	−0.33 (−1.33, 0.72)	**−0.15 (−0.27, −0.04)**	−0.16 (−0.38, 0.07)
ICS Low vs. ICS Low + LABA	0.23 (−0.13, 0.59)	0.18 (−0.32, 0.67)	–	–	–	–
ICS High vs. ICS Low + LABA	−0.08 (−0.72, 0.58)	−0.12 (−1.04, 0.78)	–	–	–	–
ICS High + LABA vs. ICS Low + LABA	0.17 (−0.51, 0.85)	0.13 (−0.82, 1.04)	–	–	–	–
ICS Medium vs. ICS Low + LABA	−0.07 (−0.43, 0.27)	−0.07 (−0.64, 0.51)	–	–	–	–
ICS Medium + LABA vs. ICS Low + LABA	−0.38 (−0.80, 0.03)	−0.63 (−1.46, 0.05)	–	–	–	–
ICS + LTRA vs. ICS Low + LABA	0.43 (−0.50, 1.37)	0.41 (−0.82, 1.59)	–	–	–	–
ICS + theophylline vs. ICS Low + LABA	0.45 (−3.28, 3.96)	0.48 (−3.56, 4.46)	–	–	–	–
LTRA vs. ICS Low + LABA	1.48 (0.06, 3.16)	1.45 (−0.41, 3.47)	–	–	–	–
Placebo vs. ICS Low + LABA	**1.06 (0.52, 1.59)**	**1.04 (0.17, 1.96)**	–	–	–	–
ICS Low vs. ICS Medium	0.30 (−0.13, 0.74)	0.25 (−0.40, 0.89)	−0.06 (−0.69, 0.55)	−0.18 (−1.25, 0.78)	−0.02 (−0.13, 0.09)	−0.03 (−0.25, 0.19)
ICS High vs. ICS Medium	0.00 (−0.65, 0.66)	−0.05 (−1.00, 0.89)	−0.35 (−1.00, 0.31)	−0.42 (−1.68, 0.72)	0.14 (−0.16, 0.45)	0.13 (−0.24, 0.50)
ICS High + LABA vs. ICS Medium	0.24 (−0.43, 0.93)	0.19 (−0.78, 1.11)	0.33 (−0.36, 1.05)	0.31 (−0.89, 1.50)	−0.30 (−0.66, 0.04)	−0.28 (−0.68, 0.19)
ICS Low + LABA vs. ICS Medium	0.07 (−0.27, 0.43)	0.07 (−0.51, 0.64)	0.08 (−0.52, 0.69)	0.21 (−0.75, 1.24)	0.01 (−0.09, 0.10)	−0.02 (−0.25, 0.14)
ICS Medium + LABA vs. ICS Medium	**−0.31 (−0.61, −0.02)**	−0.56 (−1.32, 0.04)	0.04 (−0.24, 0.32)	−0.18 (−1.37, 0.67)	**0.69 (0.33, 1.05)**	**0.62 (0.18, 1.03)**
ICS unknown dose vs. ICS Medium	–	–	–	–	−0.30 (−1.53, 0.93)	−0.33 (−1.67, 0.96)
ICS + LTRA vs. ICS Medium	0.50 (−0.41, 1.43)	0.48 (−0.74, 1.66)	0.12 (−1.60, 1.96)	0.18 (−1.93, 2.42)	−0.25 (−1.05, 0.55)	−0.29 (−1.15, 0.55)
ICS + theophylline vs. ICS Medium	0.52 (−3.21, 4.03)	0.55 (−3.43, 4.56)	–	–	–	–
LTRA vs. ICS Medium	**1.56 (0.12, 3.25)**	1.52 (−0.37, 3.61)	−1.52 (−3.23, 0.14)	−1.61 (−3.94, 0.56)	0.13 (−0.36, 0.63)	0.12 (−0.47, 0.68)
Placebo vs. ICS Medium	**1.13 (0.56, 1.70)**	**1.10 (0.20, 2.05)**	−0.42 (−1.23, 0.41)	−0.50 (−1.87, 0.77)	**−0.17 (−0.33, −0.01)**	−0.18 (−0.47, 0.09)
ICS Low vs. ICS Medium + LABA	**0.61 (0.15, 1.09)**	**0.82 (0.10, 1.65)**	−0.11 (−0.72, 0.51)	0.03 (−0.94, 1.10)	**−0.71 (−1.06, −0.35)**	**−0.65 (−1.05, −0.21)**
ICS High vs. ICS Medium + LABA	0.30 (−0.33, 0.97)	0.52 (−0.38, 1.53)	−0.39 (−1.04, 0.26)	−0.22 (−1.29, 1.02)	**−0.55 (−0.81, −0.24)**	**−0.50 (−0.82, −0.06)**
ICS High + LABA vs. ICS Medium + LABA	0.55 (−0.12, 1.24)	0.76 (−0.16, 1.77)	0.29 (−0.40, 1.01)	0.51 (−0.55, 1.81)	**−1.00 (−1.27, −0.67)**	**−0.92 (−1.25, −0.36)**

continued

TABLE 50 Parameter estimates from NMA models (analysis b) (*continued*)

	Exacerbation		Asthma control		FEV_1	
	FE consistency	RE consistency	FE consistency	RE consistency	FE consistency	RE consistency
ICS Low + LABA vs. ICS Medium + LABA	0.38 (−0.03, 0.80)	0.63 (−0.05, 1.46)	0.04 (−0.56, 0.65)	0.42 (−0.49, 1.60)	**−0.68 (−1.04, −0.33)**	**−0.65 (−1.05, −0.23)**
ICS Medium vs. ICS Medium + LABA	**0.31 (0.02, 0.61)**	0.56 (−0.04, 1.32)	−0.04 (−0.32, 0.24)	0.18 (−0.67, 1.37)	**−0.69 (−1.05, −0.33)**	**−0.62 (−1.03, −0.18)**
ICS unknown dose vs. ICS Medium + LABA	–	–	–	–	−0.99 (−2.27, 0.30)	−0.95 (−2.32, 0.40)
ICS + LTRA vs. ICS Medium + LABA	0.81 (−0.13, 1.78)	1.04 (−0.24, 2.39)	0.08 (−1.65, 1.94)	0.41 (−1.75, 2.80)	**−0.93 (−1.82, −0.07)**	−0.91 (−1.82, 0.02)
ICS + theophylline vs. ICS Medium + LABA	0.83 (−2.93, 4.34)	1.12 (−2.90, 5.20)	–	–	–	–
LTRA vs. ICS Medium + LABA	1.87 (0.40, 3.57)	2.09 (0.18, 4.24)	−1.56 (−3.26, 0.09)	−1.41 (−3.66, 0.90)	−0.56 (−1.15, 0.04)	−0.51 (−1.17, 0.19)
Placebo vs. ICS Medium + LABA	1.44 (0.84, 2.04)	1.67 (0.71, 2.84)	−0.46 (−1.28, 0.37)	−0.31 (−1.64, 1.15)	**−0.86 (−1.24, −0.49)**	**−0.81 (−1.24, −0.32)**
ICS Low + LABA vs. ICS unknown dose	–	–	–	–	0.30 (−0.92, 1.54)	0.30 (−0.99, 1.63)
ICS High vs. ICS unknown dose	–	–	–	–	0.43 (−0.83, 1.72)	0.46 (−0.89, 1.84)
ICS High + LABA vs. ICS unknown dose	–	–	–	–	−0.01 (−1.28, 1.27)	0.06 (−1.28, 1.47)
ICS Low vs. ICS unknown dose	–	–	–	–	0.27 (−0.95, 1.52)	0.30 (−0.99, 1.64)
ICS Medium vs. ICS unknown dose	–	–	–	–	0.30 (−0.93, 1.53)	0.33 (−0.96, 1.67)
ICS Medium + LABA vs. ICS unknown dose	–	–	–	–	0.99 (−0.30, 2.27)	0.95 (−0.40, 2.32)
ICS + LTRA vs. ICS unknown dose	–	–	–	–	0.05 (−0.91, 1.01)	0.05 (−0.95, 1.06)
LTRA vs. ICS unknown dose	–	–	–	–	0.42 (−0.90, 1.75)	0.44 (−0.94, 1.88)
Placebo vs. ICS unknown dose	–	–	–	–	0.12 (−1.11, 1.37)	0.15 (−1.15, 1.50)
ICS Low vs. ICS + LTRA	−0.20 (−1.15, 0.74)	−0.23 (−1.47, 1.01)	−0.19 (−2.03, 1.55)	−0.37 (−2.64, 1.73)	0.23 (−0.56, 1.04)	0.26 (−0.58, 1.13)
ICS High vs. ICS + LTRA	−0.50 (−1.60, 0.57)	−0.53 (−1.97, 0.93)	−0.47 (−2.36, 1.32)	−0.61 (−3.01, 1.63)	0.39 (−0.46, 1.25)	0.42 (−0.49, 1.33)
ICS High + LABA vs. ICS + LTRA	−0.26 (−1.37, 0.83)	−0.28 (−1.72, 1.18)	0.21 (−1.71, 2.01)	0.12 (−2.25, 2.35)	−−0.06 (−0.92, 0.81)	0.01 (−0.91, 0.98)
ICS Low + LABA vs. ICS + LTRA	−0.43 (−1.37, 0.50)	−0.41 (−1.59, 0.82)	−0.03 (−1.90, 1.67)	0.04 (−2.11, 2.10)	0.25 (−0.54, 1.06)	0.26 (−0.57, 1.11)
ICS Medium vs. ICS + LTRA	−0.50 (−1.43, 0.41)	−0.48 (−1.66, 0.74)	−0.12 (−1.96, 1.60)	−0.18 (−2.42, 1.93)	0.25 (−0.55, 1.05)	0.29 (−0.55, 1.15)
ICS + LABA vs. ICS + LTRA	−0.81 (−1.78, 0.13)	−1.04 (−2.39, 0.24)	−0.08 (−1.94, 1.65)	−0.41 (−2.80, 1.75)	**0.93 (0.07, 1.82)**	0.91 (−0.02, 1.82)
ICS unknown dose vs. ICS + LTRA	–	–	–	–	−0.05 (−1.01, 0.91)	−0.05 (−1.06, 0.95)
ICS + theophylline vs. ICS + LTRA	0.02 (−3.67, 3.44)	0.08 (−3.72, 3.87)	–	–	–	–
LTRA vs. ICS + LTRA	1.07 (−0.64, 2.93)	1.04 (−1.11, 3.36)	−1.64 (−4.10, 0.66)	−1.82 (−4.83, 1.11)	0.38 (−0.55, 1.31)	0.39 (−0.60, 1.41)

TABLE 50 Parameter estimates from NMA models (analysis b) (*continued*)

	Exacerbation		Asthma control		FEV_1	
	FE consistency	RE consistency	FE consistency	RE consistency	FE consistency	RE consistency
Placebo vs. ICS + LTRA	0.62 (−0.41, 1.64)	0.64 (−0.76, 2.10)	−0.54 (−2.47, 1.26)	−0.69 (−3.16, 1.58)	0.08 (−0.72, 0.90)	0.10 (−0.75, 1.00)
ICS Low vs. ICS + theophylline	−0.23 (−3.73, 3.54)	−0.30 (−4.31, 3.72)	–	–	–	–
ICS High vs. ICS + theophylline	−0.52 (−4.06, 3.28)	−0.60 (−4.70, 3.48)	–	–	–	–
ICS High + LABA vs. ICS + theophylline	−0.29 (−3.82, 3.52)	−0.36 (−4.44, 3.71)	–	–	–	–
ICS Low + LABA vs. ICS + theophylline	−0.45 (−3.96, 3.28)	−0.48 (−4.46, 3.56)	–	–	–	–
ICS Medium vs. ICS + theophylline	−0.52 (−4.03, 3.21)	−0.55 (−4.56, 3.43)	–	–	–	–
Medium + LABA vs. ICS + theophylline	−0.83 (−4.34, 2.93)	−1.12 (−5.20, 2.90)	–	–	–	–
ICS + theophylline vs. ICS + theophylline	−0.02 (−3.44, 3.67)	−0.08 (−−3.87, 3.72)	–	–	–	–
LTRA vs. ICS + theophylline	1.05 (−2.75, 5.11)	0.97 (−3.39, 5.44)	–	–	–	–
Placebo vs. ICS + theophylline	0.60 (−2.90, 4.38)	0.57 (−3.46, 4.61)	–	–		
ICS Low vs. LTRA	−1.25 (−2.89, 0.14)	−1.26 (−3.21, 0.52)	1.45 (−0.10, 3.07)	1.43 (−0.62, 3.51)	−0.15 (−0.63, 0.33)	−0.14 (−0.69, 0.41)
ICS High vs. LTRA	**−1.57 (−3.33, −0.01)**	−1.58 (−3.76, 0.42)	1.17 (−0.49, 2.90)	1.20 (−1.04, 3.48)	0.02 (−0.55, 0.58)	0.02 (−0.63, 0.66)
ICS High + LABA vs. LTRA	−1.32 (−3.09, 0.25)	−1.34 (−3.53, 0.69)	**1.84 (0.16, 3.58)**	1.93 (−0.27, 4.24)	−0.43 (−1.02, 0.15)	−0.39 (−1.05, 0.34)
ICS Low + LABA vs. LTRA	**−1.48 (−3.16, −0.06)**	−1.45 (−3.47, 0.41)	**1.59 (0.04, 3.24)**	1.83 (−0.20, 4.08)	−0.12 (−0.61, 0.36)	−0.14 (−0.70, 0.40)
ICS Medium vs. LTRA	**−1.56 (−3.25, −0.12)**	−1.52 (−3.61, 0.37)	1.52 (−0.14, 3.23)	1.61 (−0.56, 3.94)	−0.13 (−0.63, 0.36)	−0.12 (−0.68, 0.47)
ICS Medium + LABA vs. LTRA	**−1.87 (−3.57, −0.40)**	−2.09 (−4.24, −0.18)	1.56 (−0.09, 3.26)	1.41 (−0.90, 3.66)	0.56 (−0.04, 1.15)	0.51 (−0.19, 1.17)
ICS unknown dose vs. LTRA	–	–	–	–	−0.42 (−1.75, 0.90)	−0.44 (−1.88, 0.94)
ICS + LTRA vs. LTRA	−1.07 (−2.93, 0.64)	−1.04 (−3.36, 1.11)	1.64 (−0.66, 4.10)	1.82 (−1.11, 4.83)	−0.38 (−1.31, 0.55)	−0.39 (−1.41, 0.60)
ICS + theophylline vs. LTRA	−1.05 (−5.11, 2.75)	−0.97 (−5.44, 3.39)	–	–	–	–
Placebo vs. LTRA	−0.43 (−2.12, 1.03)	−0.41 (−2.50, 1.55)	1.09 (−0.56, 2.81)	1.11 (−1.15, 3.42)	−0.30 (−0.80, 0.19)	−0.30 (−0.87, 0.29)
ICS Low vs. placebo	**−0.83 (−1.26, −0.39)**	−0.86 (−1.69, −0.09)	0.36 (−0.25, 0.94)	0.33 (−0.72, 1.33)	**0.15 (0.04, 0.27)**	0.16 (−0.07, 0.38)
ICS High vs. placebo	**−1.13 (−1.92, −0.34)**	−1.16 (−2.37, −0.02)	0.07 (−0.77, 0.91)	0.09 (−1.36, 1.52)	0.32 (−0.01, 0.63)	0.32 (−0.07, 0.70)
ICS High + LABA vs. placebo	**−0.88 (−1.69, −0.09)**	−0.91 (−2.15, 0.23)	0.75 (−0.14, 1.64)	0.82 (−0.56, 2.26)	−0.13 (−0.50, 0.22)	−0.10 (−0.52, 0.40)
ICS Low + LABA vs. placebo	**−1.06 (−1.59, −0.52)**	**−1.04 (−1.96, −0.17)**	0.51 (−0.15, 1.15)	0.72 (−0.37, 1.96)	**0.18 (0.04, 0.31)**	0.16 (−0.13, 0.39)
ICS Medium vs. placebo	**−1.13 (−1.70, −0.56)**	**−1.10 (−2.05, −0.20)**	0.42 (−0.41, 1.23)	0.50 (−0.77, 1.87)	**0.17 (0.01, 0.33)**	0.18 (−0.09, 0.47)

continued

TABLE 50 Parameter estimates from NMA models (analysis b) (*continued*)

	Exacerbation		Asthma control		FEV_1	
	FE consistency	RE consistency	FE consistency	RE consistency	FE consistency	RE consistency
ICS Medium + LABA vs. placebo	**−1.44 (−2.04, −0.84)**	**−1.67 (−2.84, −0.71)**	0.46 (−0.37, 1.28)	0.31 (−1.15, 1.64)	**0.86 (0.49, 1.24)**	**0.81 (0.32, 1.24)**
ICS + LTRA vs. placebo	−0.62 (−1.64, 0.41)	−0.64 (−2.10, 0.76)	0.54 (−1.26, 2.47)	0.69 (−1.58, 3.16)	−0.08 (−0.90, 0.72)	−0.10 (−1.00, 0.75)
ICS unknown dose vs. placebo	–	–	–	–	−0.12 (−1.37, 1.11)	−0.15 (−1.50, 1.15)
ICS + theophylline vs. placebo	−0.60 (−4.38, 2.90)	−0.57 (−4.61, 3.46)	–	–	–	–
LTRA vs. placebo	0.43 (−1.03, 2.12)	0.41 (−1.55, 2.50)	−1.09 (−2.81, 0.56)	−1.11 (−3.42, 1.15)	0.30 (−0.19, 0.80)	0.30 (−0.29, 0.87)

Note
Posterior mean (95% CrI). Bold indicates that zero is excluded from the CrI. Log OR presented for exacerbation and asthma control; MD presented for FEV_1.

TABLE 51 Parameter estimates from NMA models (analysis c)

	Asthma control		FEV_1	
	FE consistency	RE consistency	FE consistency	RE consistency
FP vs. FF	−0.48 (−1.09, 0.16)	−0.49 (−1.61, 0.64)	−0.07 (−0.19, 0.05)	−0.08 (−0.24, 0.08)
FF + VI vs. FF	0.30 (−0.21, 0.82)	0.64 (−0.23, 1.86)	0.05 (−0.12, 0.22)	0.05 (−0.14, 0.24)
FP + Montelukast vs. FF	−0.32 (−2.15, 1.64)	−0.46 (−2.91, 2.01)	−0.30 (−1.16, 0.49)	−0.34 (−1.17, 0.47)
FP + SAL vs. FF	−0.34 (−0.99, 0.34)	−0.52 (−1.99, 0.70)	−0.05 (−0.20, 0.09)	−0.07 (−0.29, 0.10)
FP + VI vs. FF	−0.50 (−1.31, 0.29)	−0.52 (−2.55, 1.53)	−0.05 (−0.21, 0.11)	−0.06 (−0.30, 0.17)
Montelukast vs. FF	**−1.95 (−3.66, −0.28)**	−2.08 (−4.55, 0.25)	0.08 (−0.41, 0.57)	0.06 (−0.46, 0.58)
Placebo vs. FF	−0.45 (−1.06, 0.20)	−0.43 (−1.52, 0.70)	**−0.18 (−0.30, −0.05)**	**−0.18 (−0.34, −0.02)**
FP vs. FF + VI	**−0.78 (−1.51, −0.04)**	−1.14 (−2.53, 0.03)	−0.12 (−0.32, 0.08)	−0.13 (−0.36, 0.09)
FF vs. FF + VI	−0.30 (−0.82, 0.21)	−0.64 (−1.86, 0.23)	−0.05 (−0.22, 0.12)	−0.05 (−0.24, 0.14)
FP + Montelukast vs. FF + VI	−0.62 (−2.49, 1.36)	−1.11 (−3.78, 1.33)	−0.36 (−1.23, 0.44)	−0.39 (−1.24, 0.43)
FP + SAL vs. FF + VI	−0.64 (−1.40, 0.12)	−1.17 (−2.92, 0.07)	−0.11 (−0.32, 0.11)	−0.13 (−0.40, 0.11)
FP + VI vs. FF + VI	−0.80 (−1.70, 0.08)	−1.15 (−3.46, 0.79)	−0.10 (−0.33, 0.12)	−0.11 (−0.40, 0.17)
Montelukast vs. FF + VI	**−2.25 (−4.00, −0.56)**	**−2.74 (−5.36, −0.42)**	0.03 (−0.49, 0.54)	0.01 (−0.54, 0.56)
Placebo vs. FF + VI	−0.75 (−1.49, 0.00)	−1.07 (−2.58, 0.13)	**−0.23 (−0.43, −0.03)**	**−0.23 (−0.47, 0.00)**
FP vs. FP + Montelukast	−0.16 (−2.00, 1.55)	−0.04 (−2.30, 2.20)	0.24 (−0.55, 1.08)	0.26 (−0.54, 1.07)
FF vs. FP + Montelukast	0.32 (−1.64, 2.15)	0.46 (−2.01, 2.91)	0.30 (−0.49, 1.16)	0.34 (−0.47, 1.17)
FF + VI vs. FP + MONTELUKAST	0.62 (−1.36, 2.49)	1.11 (−1.33, 3.78)	0.36 (−0.44, 1.23)	0.39 (−0.43, 1.24)
FP + SAL vs. FP + Montelukast	−0.02 (−1.86, 1.67)	−0.08 (−2.36, 2.05)	0.25 (−0.53, 1.10)	0.26 (−0.54, 1.08)
FP + VI vs. FP + Montelukast	−0.18 (−2.08, 1.59)	−0.08 (−2.81, 2.76)	0.26 (−0.53, 1.10)	0.28 (−0.54, 1.12)
Montelukast vs. FP + Montelukast	−1.63 (−4.03, 0.69)	−1.65 (−4.69, 1.38)	0.38 (−0.55, 1.36)	0.40 (−0.55, 1.35)
Placebo vs. FP + Montelukast	−0.13 (−2.14, 1.76)	0.03 (−2.54, 2.58)	0.13 (−0.66, 0.99)	0.15 (−0.66, 1.00)
FP vs. FP + SAL	−0.13 (−0.39, 0.12)	0.01 (−0.70, 1.07)	−0.02 (−0.09, 0.06)	0.00 (−0.10, 0.13)
FF vs. FP + SAL	0.34 (−0.34, 0.99)	0.52 (−0.70, 1.99)	0.05 (−0.09, 0.20)	0.07 (−0.10, 0.29)
FF + VI vs. FP + SAL	0.64 (−0.12, 1.40)	1.17 (−0.07, 2.92)	0.11 (−0.11, 0.32)	0.13 (−0.11, 0.40)
FP + MONTELUKAST vs. FP + SAL	0.02 (−1.67, 1.86)	0.08 (−2.05, 2.36)	−0.25 (−1.10, 0.53)	−0.26 (−1.08, 0.54)
FP + VI vs. FP + SAL	−0.16 (−0.74, 0.40)	−0.02 (−1.74, 2.08)	0.00 (−0.13, 0.13)	0.01 (−0.17, 0.25)
Montelukast vs. FP + SAL	**−1.60 (−3.24, −0.08)**	−1.55 (−3.70, 0.67)	0.13 (−0.35, 0.61)	0.14 (−0.37, 0.64)
Placebo vs. FP + SAL	−0.10 (−0.91, 0.69)	0.09 (−1.27, 1.75)	−0.12 (−0.29, 0.05)	−0.11 (−0.30, 0.12)
FP v vs. FP + VI s. FP + VI	0.03 (−0.47, 0.55)	0.02 (−1.67, 1.72)	−0.02 (−0.12, 0.09)	−0.02 (−0.20, 0.16)
FF vs. FP + VI	0.50 (−0.29, 1.31)	0.52 (−1.53, 2.55)	0.05 (−0.11, 0.21)	0.06 (−0.17, 0.30)
FF + VI	0.80 (−0.08, 1.70)	1.15 (−0.79, 3.46)	0.10 (−0.12, 0.33)	0.11 (−0.17, 0.40)
FP + Montelukast vs. FP + VI	0.18 (−1.59, 2.08)	0.08 (−2.76, 2.81)	−0.26 (−1.10, 0.53)	−0.28 (−1.12, 0.54)
FP + SAL vs. FP + VI	0.16 (−0.40, 0.74)	0.02 (−2.08, 1.74)	0.00 (−0.13, 0.13)	−0.01 (−0.25, 0.17)
Montelukast vs. FP + VI	−1.44 (−3.13, 0.18)	−1.56 (−4.32, 1.03)	0.13 (−0.36, 0.62)	0.12 (−0.41, 0.65)

continued

TABLE 51 Parameter estimates from NMA models (analysis c) (*continued*)

	Asthma control		FEV_1	
	FE consistency	RE consistency	FE consistency	RE consistency
Placebo vs. FP + VI	0.06 (−0.86, 0.99)	0.09 (−2.02, 2.23)	−0.13 (−0.31, 0.06)	−0.12 (−0.37, 0.13)
FP vs. Montelukast	1.47 (−0.06, 3.09)	1.59 (−0.49, 3.80)	−0.14 (−0.62, 0.33)	−0.14 (−0.64, 0.37)
FF vs. Montelukast	**1.95 (0.28, 3.66)**	2.08 (−0.25, 4.55)	−0.08 (−0.57, 0.41)	−0.06 (−0.58, 0.46)
FF + VI vs. Montelukast	**2.25 (0.56, 4.00)**	**2.74 (0.42, 5.36)**	−0.03 (−0.54, 0.49)	−0.01 (−0.56, 0.54)
FP + Montelukast vs. Montelukast	1.63 (−0.69, 4.03)	1.65 (−1.38, 4.69)	−0.38 (−1.36, 0.55)	−0.40 (−1.35, 0.55)
FP + SAL vs. Montelukast	**1.60 (0.08, 3.24)**	1.55 (−0.67, 3.70)	−0.13 (−0.61, 0.35)	−0.14 (−0.64, 0.37)
FP + VI vs. Montelukast	1.44 (−0.18, 3.13)	1.56 (−1.03, 4.32)	−0.13 (−0.62, 0.36)	−0.12 (−0.65, 0.41)
Placebo vs. Montelukast	1.51 (−0.22, 3.28)	1.65 (−0.77, 4.25)	−0.25 (−0.75, 0.25)	−0.24 (−0.77, 0.29)
FP vs. placebo	−0.03 (−0.79, 0.74)	−0.07 (−1.37, 1.21)	0.11 (−0.04, 0.26)	0.10 (−0.08, 0.29)
FF vs. placebo	0.45 (−0.20, 1.06)	0.43 (−0.70, 1.52)	**0.18 (0.05, 0.30)**	**0.18 (0.02, 0.34)**
FF + VI vs. placebo	0.75 (0.00, 1.49)	1.07 (−0.13, 2.58)	**0.23 (0.03, 0.43)**	**0.23 (0.00, 0.47)**
FP + Montelukast vs. placebo	0.13 (−1.76, 2.14)	−0.03 (−2.58, 2.54)	−0.13 (−0.99, 0.66)	−0.15 (−1.00, 0.66)
FP + SAL vs. placebo	0.10 (−0.69, 0.91)	−0.09 (−1.75, 1.27)	0.12 (−0.05, 0.29)	0.11 (−0.12, 0.30)
FP + VI vs. placebo	−0.06 (−0.99, 0.86)	−0.09 (−2.23, 2.02)	0.13 (−0.06, 0.31)	0.12 (−0.13, 0.37)
Montelukast vs. placebo	−1.51 (−3.28, 0.22)	−1.65 (−4.25, 0.77)	0.25 (−0.25, 0.75)	0.24 (−0.29, 0.77)

Note
Posterior mean (95% CrI). Bold indicates that zero is excluded from the CrI. Log OR presented for exacerbation and asthma control; MD presented for FEV_1.

Appendix 7 Exploring inconsistency

We explored inconsistency in the NMA models by fitting UME and compared the log OR from the consistency model and UME

TABLE 52 Posterior summaries from FE consistency and inconsistency models for exacerbation (ICS all doses when combined with LABA)

Model parameter		NMA consistency model	NMA inconsistency model (UME)
Log OR	ICS High vs. ICS + LABA	−0.11 (−0.57, 0.34)	−0.08 (−0.53, 0.38)
	ICS Low vs. ICS + LABA	0.24 (−0.10, 0.58)	0.24 (−0.13, 0.60)
	ICS Medium vs. ICS + LABA	0.14 (−0.10, 0.39)	0.17 (−0.08, 0.42)
	ICS + LTRA vs. ICS + LABA	0.54 (−0.37, 1.42)	−0.76 (−2.38, 0.64)
	Placebo vs. ICS + LABA	**1.10 (0.58, 1.62)**	−4.04 (−20.76, 10.09)
	ICS Low vs. ICS High	0.35 (−0.18, 0.90)	**5.73 (0.42, 13.58)**
	ICS Medium vs. ICS High	0.26 (−0.25, 0.76)	−4.86 (−21.28, 7.38)
	Placebo vs. ICS High	**1.21 (0.54, 1.88)**	−4.72 (−21.07, 7.51)
	ICS Medium vs. ICS Low	−0.10 (−0.49, 0.29)	0.26 (−0.68, 1.16)
	LTRA vs. ICS Low	1.28 (−0.16, 2.91)	1.29 (−0.14, 2.95)
	Placebo vs. ICS Low	**0.85 (0.42, 1.29)**	**0.93 (0.48, 1.39)**
	ICS + LTRA vs. ICS Medium	0.39 (−0.50, 1.28)	**1.71 (0.34, 3.28)**
	ICS + theophylline vs. ICS + LTRA	0.00 (−3.47, 3.51)	−0.01 (−3.54, 3.41)
Model fit	Data points	5377	5377
	Residual deviance	2254.1	2245.3
	pD	42.1	44.5
	DIC	2296.3	2289.9

Note
Figures in bold are values where the interval excludes the null value.

TABLE 53 Posterior summaries from REs consistency and inconsistency models for exacerbation (ICS stratified by dose when combined with LABA)

Model parameter		NMA consistency model	NMA inconsistency model (UME)
Log OR	ICS High vs. ICS Low	−0.30 (−1.22, 0.61)	−0.59 (−1.69, 0.47)
	ICS High + LABA vs. ICS Low	−0.06 (−1.02, 0.88)	−0.41 (−1.59, 0.72)
	ICS Low + LABA vs. ICS Low	−0.18 (−0.67, 0.32)	−0.07 (−0.56, 0.42)
	ICS Medium vs. ICS Low	−0.25 (−0.89, 0.40)	−0.35 (−1.44, 0.64)
	ICS Medium + LABA vs. ICS Low	**−0.83 (−1.65, −0.10)**	−0.76 (−1.78, 0.19)
	ICS + LTRA vs. ICS Low	0.22 (−1.01, 1.47)	−0.89 (−2.74, 0.78)
	LTRA vs. ICS Low	1.29 (−0.52, 3.21)	1.30 (−0.47, 3.24)
	Placebo vs. ICS Low	**0.87 (0.09, 1.69)**	**0.84 (0.08, 1.64)**
	ICS High + LABA vs. ICS High	0.24 (−0.54, 1.03)	0.31 (−0.65, 1.23)
	ICS Medium + LABA vs. ICS High	−0.53 (−1.53, 0.38)	**−2.59 (−5.88, −0.35)**
	ICS Medium vs. ICS Low + LABA	−0.07 (−0.64, 0.51)	0.36 (−0.33, 1.18)
	ICS Medium + LABA vs. ICS Low + LABA	−0.65 (−1.46, 0.05)	−37.91 (−209.37, 111.49)
	ICS Medium + LABA vs. ICS Medium	−0.58 (−1.32, 0.04)	−0.35 (−1.25, 0.44)
	ICS + LTRA vs. ICS Medium	0.47 (−0.74, 1.66)	1.75 (−0.02, 3.67)
	ICS + Theophylline vs. ICS + LTRA	0.07 (−3.72, 3.87)	0.07 (−3.75, 3.89)
Model fit	Between trial SD	0.51 (0.09, 0.98)	0.45 (0.04, 0.96)
	Data points	5410	5410
	Residual deviance	2234.8	2233.1
	Effective number of parameters (pD)	55.8	58.4
	DIC	2290.6	2291.5

Note
Figures in bold are values where the interval excludes the null value.

TABLE 54 Posterior summaries from FE consistency and inconsistency models for asthma control (ICS grouped when combined with LABA)

Model parameter		NMA consistency model	NMA inconsistency model (UME)
Log OR	ICS High vs. ICS + LABA	−0.47 (−1.00, 0.07)	−0.50 (−1.04, 0.06)
	ICS Low vs. ICS + LABA	−0.16 (−0.48, 0.16)	−0.12 (−0.46, 0.21)
	ICS Medium vs. ICS + LABA	−0.06 (−0.33, 0.22)	−0.05 (−0.33, 0.23)
	ICS + LTRA vs. ICS + LABA	0.05 (−1.68, 1.83)	0.07 (−1.65, 1.86)
	LTRA vs. ICS + LABA	**−1.64 (−3.28, −0.08)**	**−1.59 (−3.21, −0.03)**
	Placebo vs. ICS + LABA	−0.51 (−1.17, 0.13)	**−1.57 (−2.85, −0.36)**
	ICS Low vs. ICS High	0.31 (−0.27, 0.89)	−0.33 (−2.72, 2.04)
	ICS Medium vs. ICS Low	0.11 (−0.31, 0.52)	0.14 (−1.47, 1.90)
	Placebo vs. ICS Low	−0.35 (−0.94, 0.26)	0.05 (−0.70, 0.83)
Model fit	Data points	2998	2998
	Residual deviance	2801.3	2800.3
	Effective number of parameters (pD)	21.3	24.7
	DIC	2822.5	2825.1

Note
Figures in bold are values where the interval excludes the null value.

TABLE 55 Posterior summaries from FE consistency and inconsistency models for asthma control (ICS stratified when combined with LABA)

Model parameter		NMA consistency model	NMA inconsistency model (UME)
Log OR	ICS High vs. ICS Low + LABA	−0.43 (−1.05, 0.20)	−0.43 (−1.08, 0.22)
	ICS High + LABA vs. ICS Low + LABA	0.25 (−0.41, 0.93)	0.22 (−0.46, 0.91)
	ICS Low vs. ICS Low + LABA	−0.15 (−0.48, 0.19)	−0.10 (−0.44, 0.24)
	ICS Medium vs. ICS Low + LABA	−0.08 (−0.69, 0.52)	0.11 (−0.70, 0.95)
	ICS Medium + LABA vs. ICS Low + LABA	−0.04 (−0.65, 0.56)	−0.14 (−0.87, 0.57)
	ICS + LTRA vs. ICS Low + LABA	0.05 (−1.67, 1.90)	0.11 (−1.65, 1.96)
	LTRA vs. ICS Low + LABA	**−1.61 (−3.24, −0.04)**	−1.57 (−3.19, 0.02)
	Placebo vs. ICS Low + LABA	−0.5 (−1.15, 0.15)	**−1.56 (−2.82, −0.34)**
	ICS High + LABA vs. ICS High	0.68 (−0.03, 1.39)	8.09 (−0.45, 22.38)
	ICS Low vs. ICS High	0.28 (−0.36, 0.90)	−0.32 (−2.71, 1.98)
	ICS Medium vs. ICS Low	0.06 (−0.55, 0.69)	0.14 (−1.46, 1.88)
	ICS Placebo vs. ICS Low	−0.35 (−0.94, 0.25)	0.05 (−0.70, 0.85)
	ICS Medium + LABA vs. ICS Medium	0.04 (−0.24, 0.32)	0.07 (−0.23, 0.38)
Model fit	Data points	3027	3027
	Residual deviance	2839.7	2838.5
	Effective number of parameters (pD)	24.4	28.8
	DIC	2864.1	2867.3

Note
Figures in bold are values where the interval excludes the null value.

TABLE 56 Posterior summaries from REs consistency and inconsistency models for asthma control (individual compounds)

Model parameter		NMA consistency model	NMA inconsistency model (UME)
Log OR	FF vs. FP	0.49 (−0.64, 1.61)	−0.06 (−1.20, 0.95)
	FF + VI vs. FP	1.18 (−0.03, 2.53)	2.18 (−0.64, 5.78)
	FP + Montelukast vs. FP	0.04 (−2.20, 2.30)	0.14 (−1.85, 2.12)
	FP + SAL vs. FP	−0.06 (−1.07, 0.70)	0.13 (−0.65, 0.75)
	FP + VI vs. FP	−0.02 (−1.72, 1.67)	−0.03 (−1.29, 1.22)
	Montelukast vs. FP	−1.61 (−3.80, 0.49)	−1.50 (−3.42, 0.34)
	Placebo vs. FP	0.07 (−1.21, 1.37)	0.07 (−1.12, 1.29)
	FF + VI vs. FF	**0.70 (0.11, 1.53)**	0.11 (−0.75, 1.12)
	Placebo vs. FF	0.30 (−0.21, 0.16)	−1.48 (−3.11, 0.14)
	FP + SAL vs. FF + VI	−0.45 (−1.06, 0.20)	**−3.02 (−6.50, −0.44)**
Model fit	Between trial SD	−0.64 (−1.40, 0.12)	0.45 (0.03, 1.25)
	Data points	3014	3014
	Residual deviance	2808.4	2809.3
	Effective number of parameters (pD)	28.5	29.4
	DIC	2836.9	2838.7

Note
Figures in bold are values where the interval excludes the null value.

TABLE 57 Posterior summaries from REs consistency and inconsistency models for FEV_1 (ICS grouped when combined with LABA)

Model parameter		NMA consistency model	NMA inconsistency model (UME)
Mean difference	ICS High vs. ICS + LABA	0.13 (−0.08, 0.35)	0.04 (−0.25, 0.32)
	ICS Low vs. ICS + LABA	−0.02 (−0.11, 0.08)	−0.01 (−0.11, 0.13)
	ICS Medium vs. ICS + LABA	−0.02 (−0.13, 0.10)	−0.01 (−0.15, 0.14)
	ICS + LTRA vs. ICS + LABA	−0.26 (−1.10, 0.55)	−0.26 (−1.08, 0.56)
	LTRA vs. ICS + LABA	0.13 (−0.36, 0.61)	0.13 (−0.38, 0.63)
	Placebo vs. ICS + LABA	−0.18 (−0.34, 0.00)	−0.23 (−0.68, 0.22)
	ICS Low vs. ICS High	−0.15 (−0.37, 0.07)	−0.42 (−0.86, 0.03)
	ICS Medium vs. ICS High	−0.15 (−0.38, 0.09)	−0.17 (−0.70, 0.37)
	Placebo vs. ICS High	**−0.31 (−0.57, −0.05)**	−0.41 (−1.13, 0.32)
	ICS Medium vs. ICS Low	0.00 (−0.14, 0.14)	−0.13 (−0.63, 0.35)
	Placebo vs. ICS Low	**−0.16 (−0.03, −0.01)**	−0.16 (−0.35, 0.03)
	ICS + LTRA vs. ICS unknown dose	0.05 (−0.91, 1.02)	0.05 (−0.92, 1.02)
Model fit	Between trial SD	0.04 (0.00, 0.15)	0.06 (0.00, 0.21)
	Data points	2175	2175
	Residual deviance	2129.2	2128.3
	Effective number of parameters (pD)	−360.8	−311.2
	DIC	1768.4	1817.1

Note
Figures in bold are values where the interval excludes the null value.

TABLE 58 Posterior summaries from FE consistency and inconsistency models for FEV_1 (ICS stratified when combined with LABA)

Model parameter		NMA consistency model	NMA inconsistency model (UME)
Mean difference	ICS High + LABA vs. ICS Low + LABA	−0.31 (−0.66, 0.03)	0.40 (−0.17, 0.99)
	ICS Low vs. ICS Low LABA	−0.02 (−0.10, 0.05)	−0.02 (−0.09, 0.06)
	ICS Medium vs. ICS Low + LABA	−0.01 (−0.10, 0.09)	−0.01 (−0.11, 0.09)
	ICS Medium + LABA vs. ICS Low + LABA	**0.68 (0.33, 1.04)**	−0.13 (−0.73, 0.48)
	ICS + LTRA vs. ICS Low + LABA	−0.25 (−1.06, 0.54)	−0.26 (−1.05, 0.54)
	LTRA vs. ICS Low + LABA	0.12 (−0.36, 0.61)	0.13 (−0.36, 0.61)
	Placebo vs. ICS Low + LABA	**−0.18 (−0.31, −0.04)**	−0.24 (−0.66, 0.19)
	ICS High + LABA vs. ICS High	**−0.45 (−0.64, −0.25)**	**−0.46 (−0.66, −0.26)**
	ICS Low vs. ICS High	−0.16 (−0.46, 0.15)	−0.41 (−0.84, 0.03)
	ICS Medium vs. ICS High	−0.14 (−0.45, 0.16)	−0.17 (−0.68, 0.34)
	ICS Medium + LABA vs. ICS High	**0.54 (0.24, 0.81)**	**0.74 (0.48, 1.00)**
	Placebo vs. ICS High	−0.32 (−0.63, 0.01)	−0.40 (−1.12, 0.32)
	ICS Medium vs. ICS Low	0.02 (−0.09, 0.13)	−0.13 (−0.59, 0.33)
	Placebo vs. ICS Low	**−0.15 (−0.27, −0.04)**	**−0.15 (−0.28, −0.03)**
	ICS Medium + LABA vs. ICS Medium	**0.69 (0.33, 1.05)**	0.20 (−0.46, 0.85)
	ICS + LTRA vs. ICS unknown dose	0.05 (−0.91, 1.01)	0.05 (−0.90, 0.99)

TABLE 58 Posterior summaries from FE consistency and inconsistency models for FEV_1 (ICS stratified when combined with LABA) (*continued*)

Model parameter		NMA consistency model	NMA inconsistency model (UME)
Model fit	Data points	2207	2207
	Residual deviance	2157.3	2156.9
	Effective number of parameters (pD)	−2267.9	−2255.9
	DIC	−110.6	−98.9

Note
Figures in bold are values where the interval excludes the null value.

Appendix 8 Adverse events forest plots

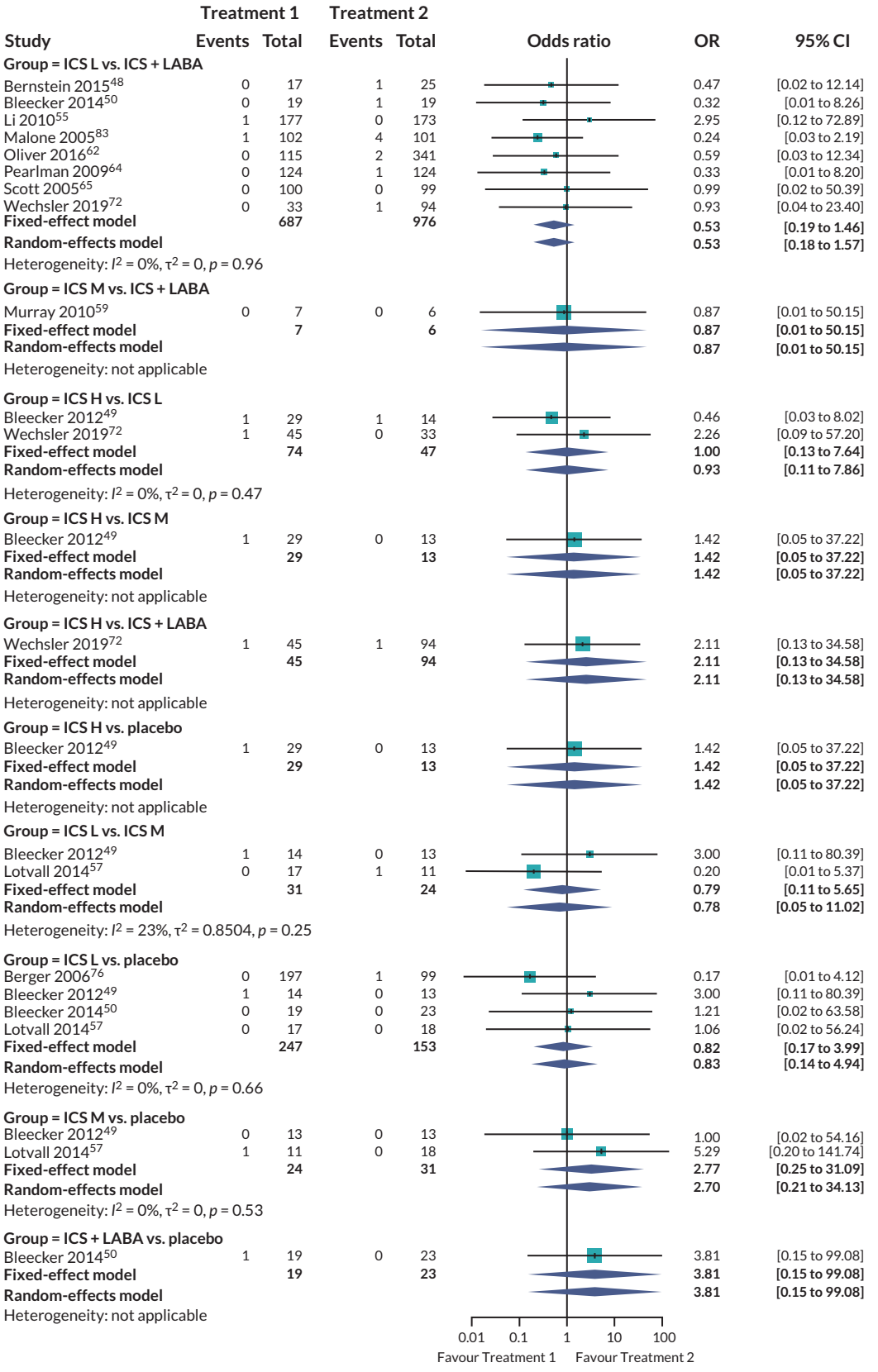

FIGURE 21 Oral candidiasis MA 26-Feb-25 03:25:35 (a) ICS dose grouped. Frequentist meta-analysis (Mantel–Haenszel) based on all available comparisons. All data included (IPD). L, low dose; M, medium dose; H, high dose. Note: OR > 1 favours treatment 2.

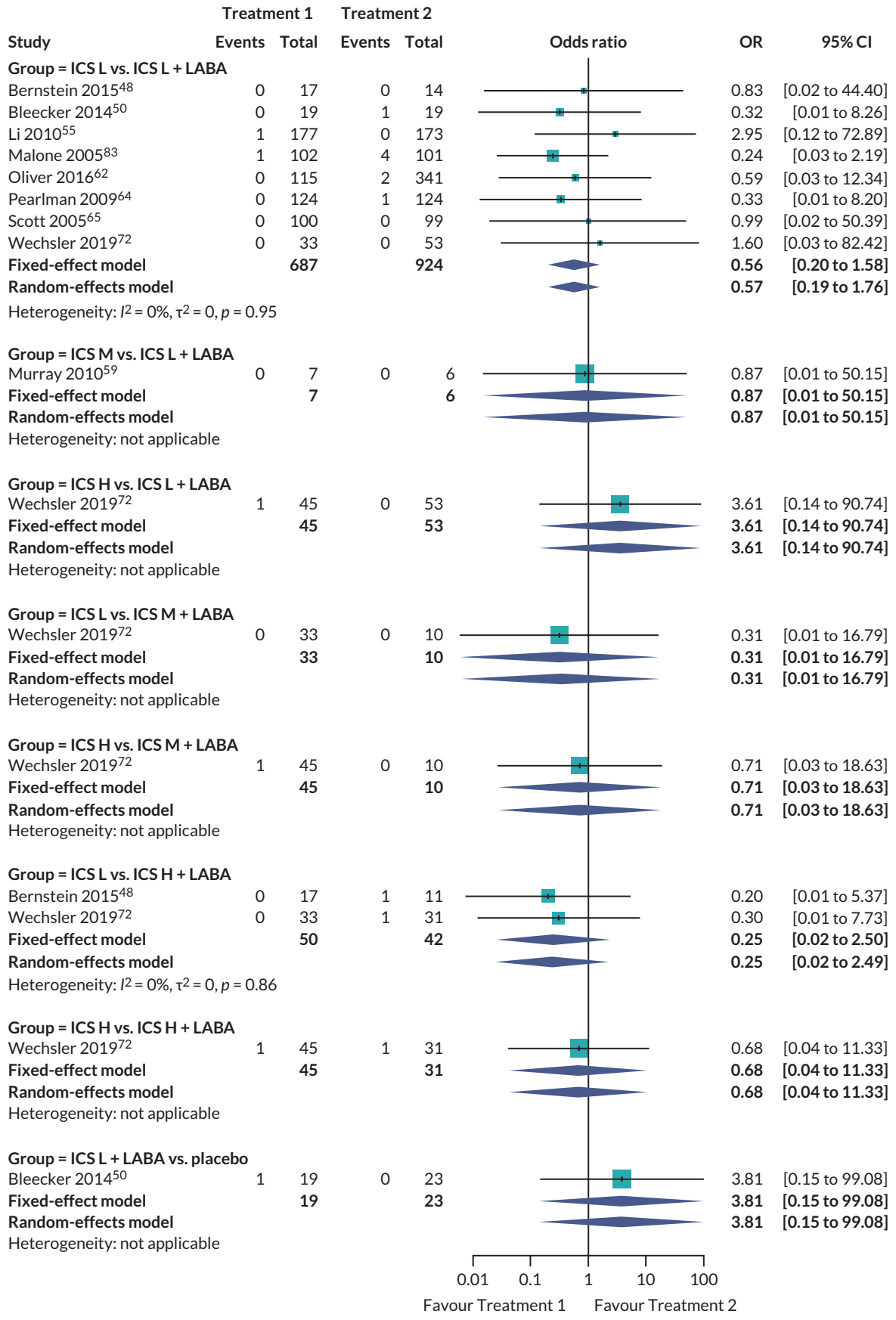

FIGURE 22 Oral candidiasis (b) ICS dose stratified. Frequentist meta-analysis (Mantel–Haenszel) based on all available comparisons. All data included (IPD). L, low dose; M, medium dose; H, high dose. Note: OR > 1 favours treatment 2.

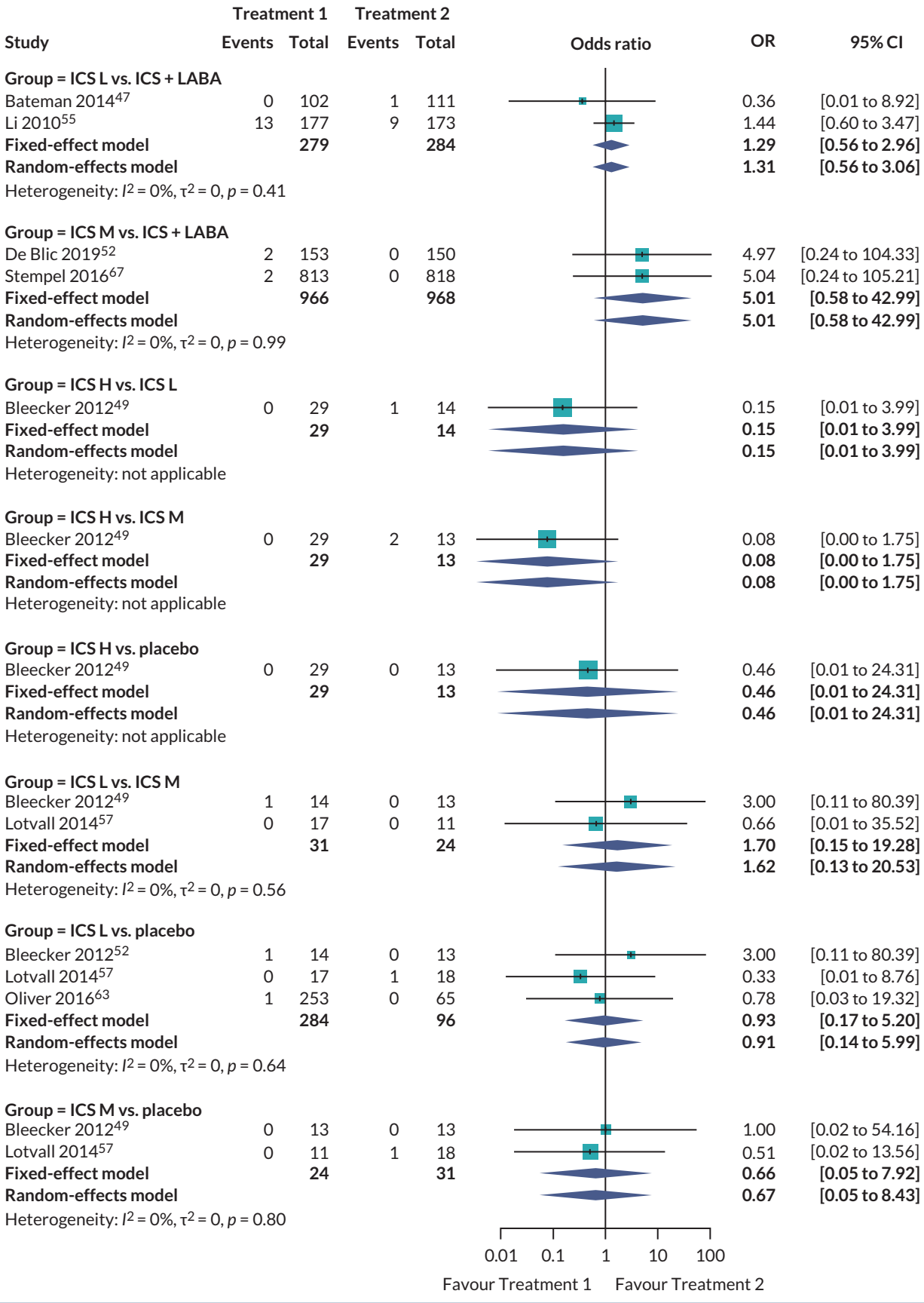

FIGURE 23 Cardiac disorders (a) ICS dose grouped. Frequentist meta-analysis (Mantel–Haenszel) based on all available comparisons. All data included (IPD). L, low dose; M, medium dose; H, high dose. Note: OR > 1 favours treatment 2.

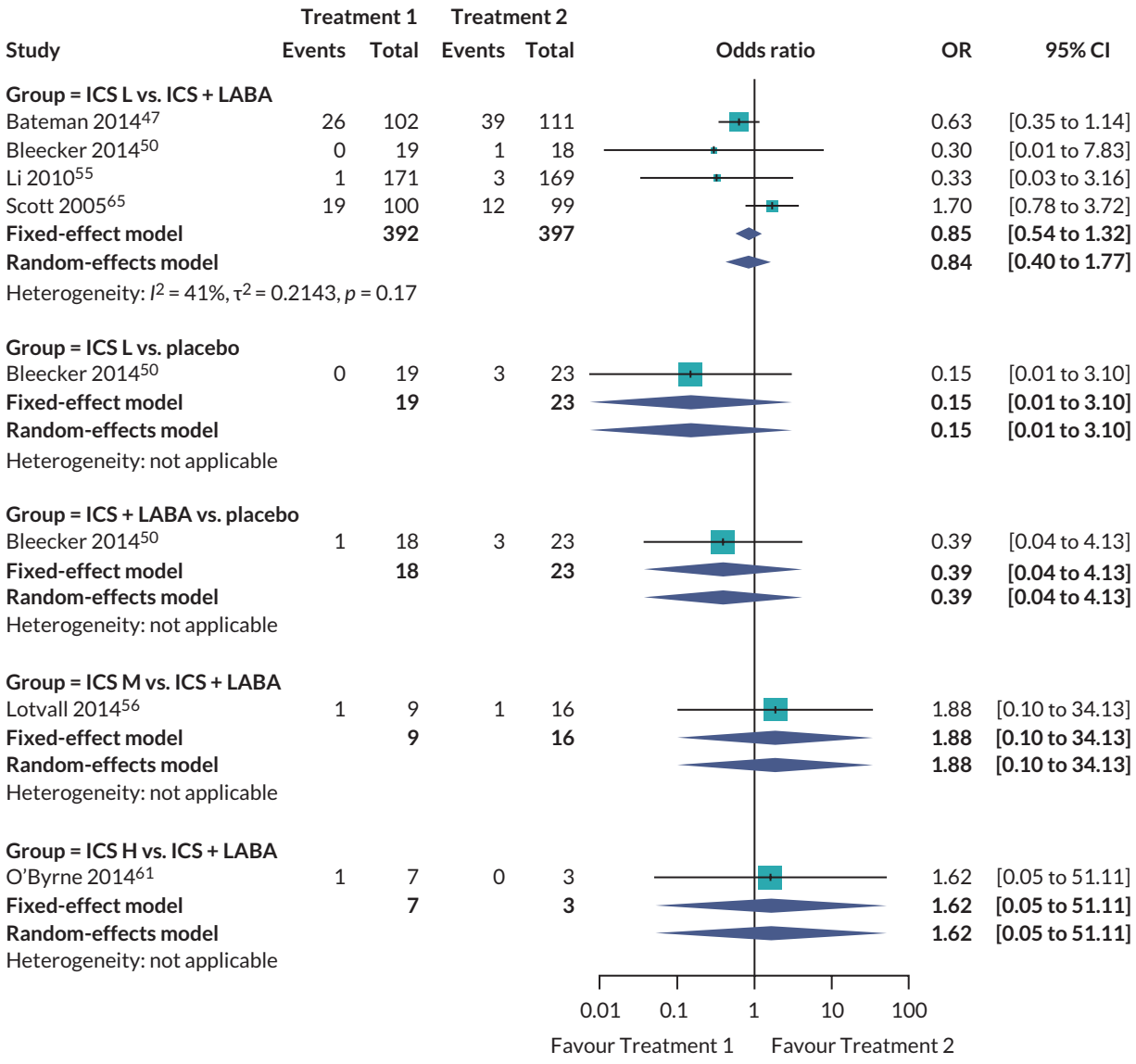

FIGURE 24 Clinically significant ECG favourable changes a) ICS dose stratified. Frequentist meta-analysis (Mantel–Haenszel) based on all available comparisons. All data included (IPD). L, low dose; M, medium dose; H, high dose. Note: OR > 1 favours treatment 2.

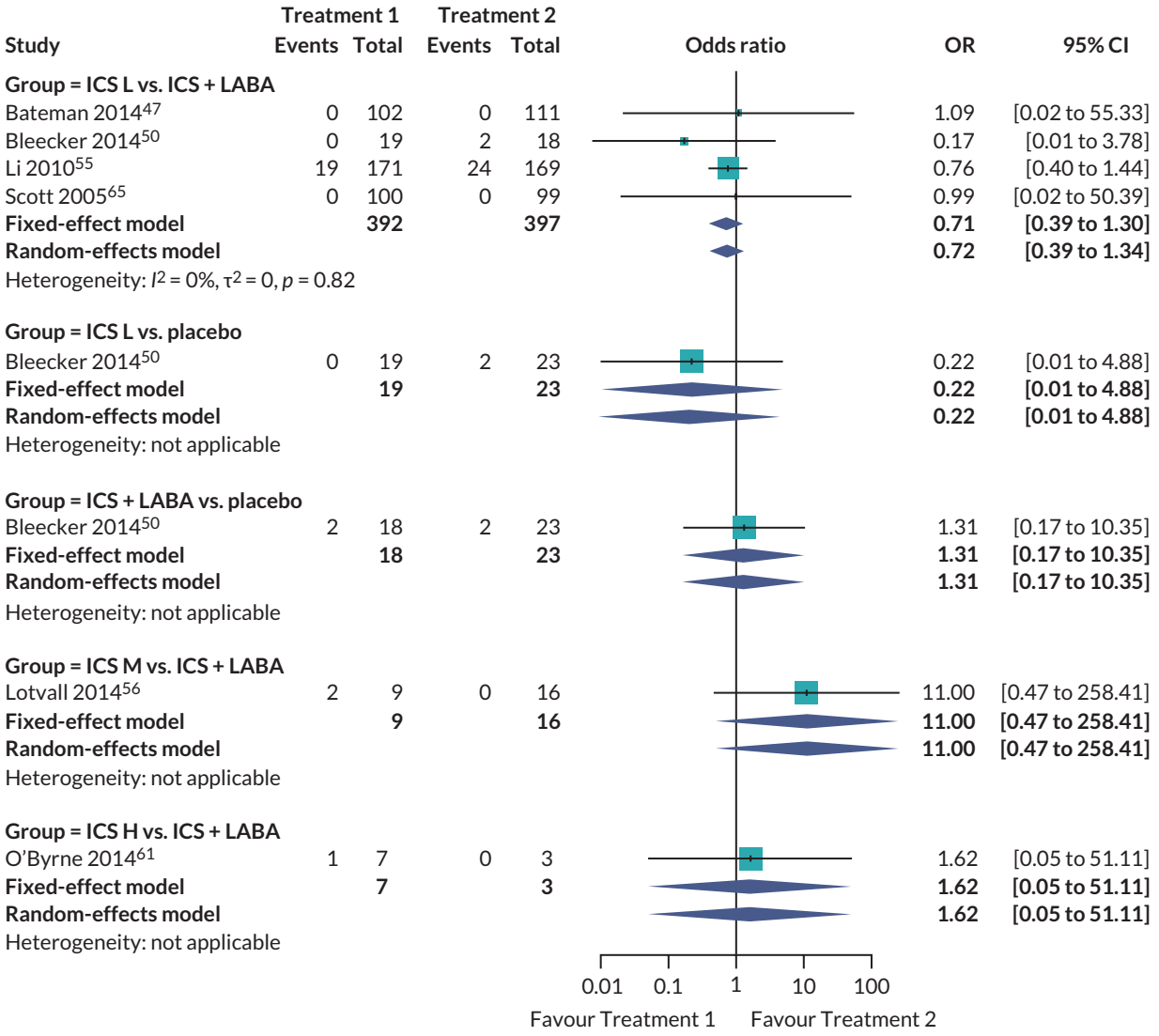

FIGURE 25 Clinically significant ECG unfavourable changes. Frequentist meta-analysis (Mantel–Haenszel) based on all available comparisons. All data included (IPD). L, low dose; M, medium dose; H, high dose. Note: OR > 1 favours treatment 2.

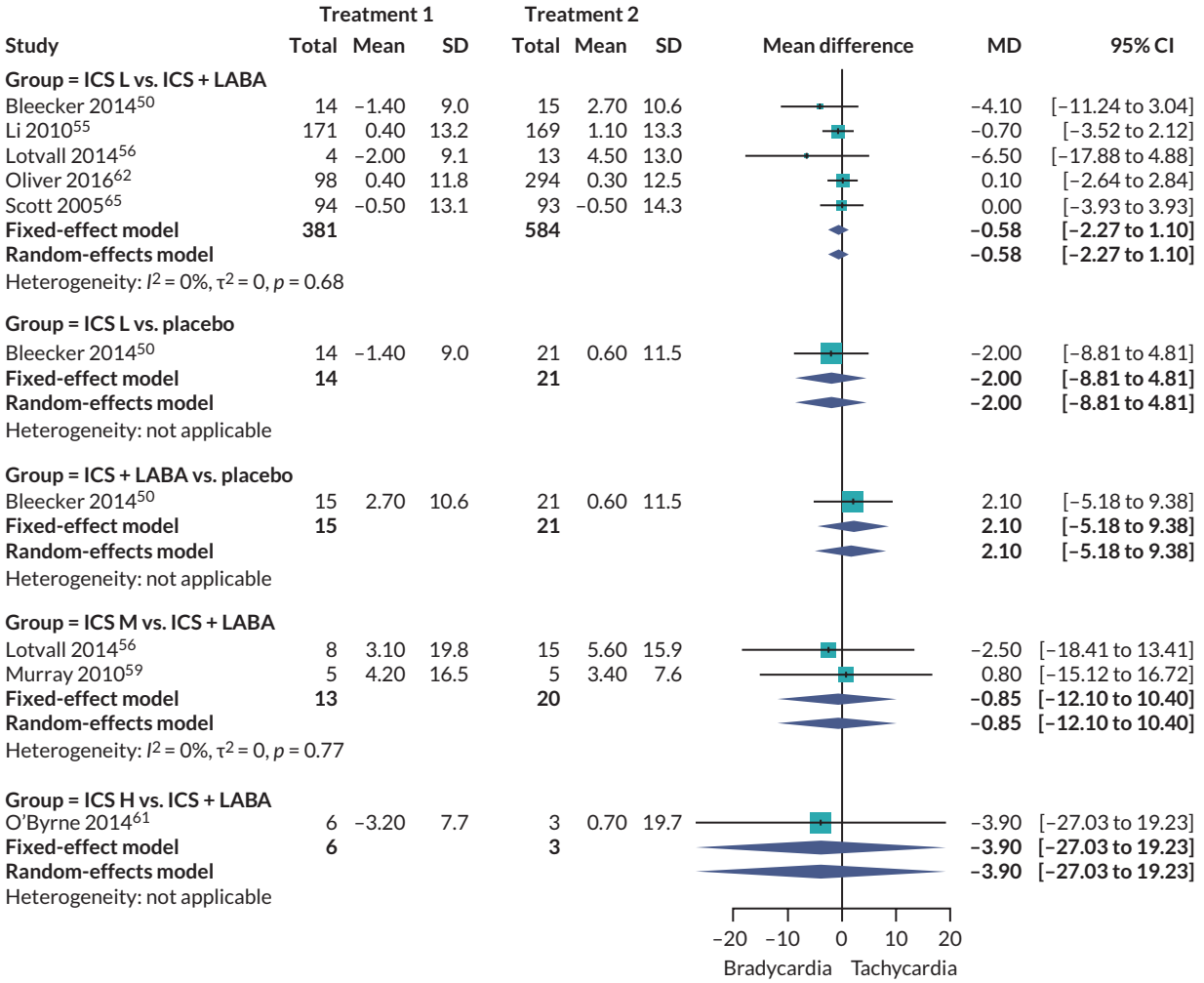

FIGURE 26 Heart rate change (last visit vs. baseline); meta-analysis. Frequentist meta-analysis (IV) based on all available comparisons. All data included (IPD). L, low dose; M, medium dose; H, high dose. Notes: MD > 0: treatment 1 causes an increase of HR compared to treatment 2; MD < 0: treatment 1 causes a decrease of HR compared to treatment 2.

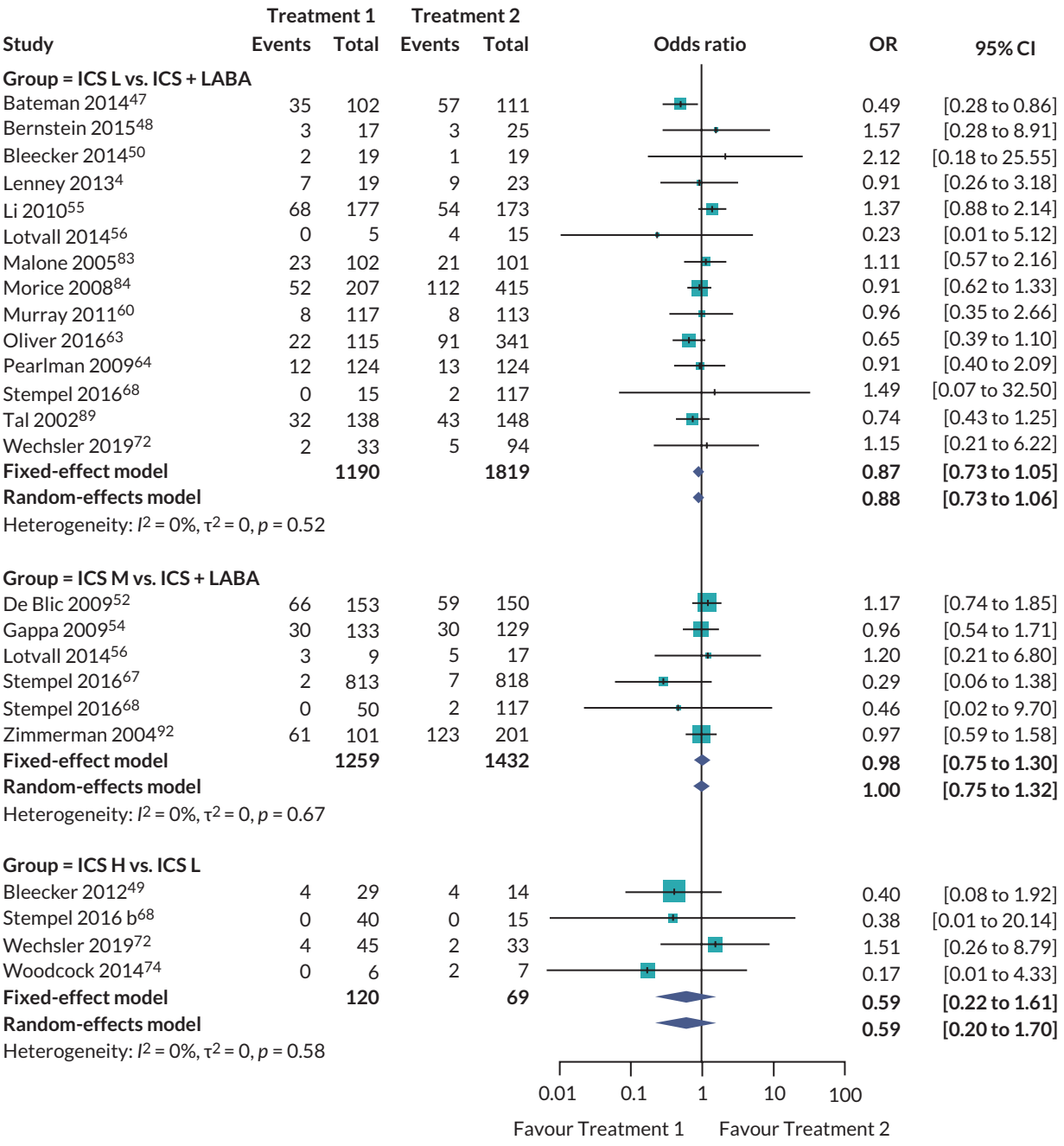

FIGURE 27 Infections and infestations. Frequentist meta-analysis (Mantel–Haenszel) based on all available comparisons. All data included (IPD and AgD where possible). L, low dose; M, medium dose; H, high dose. Note: OR > 1 favours treatment 2.

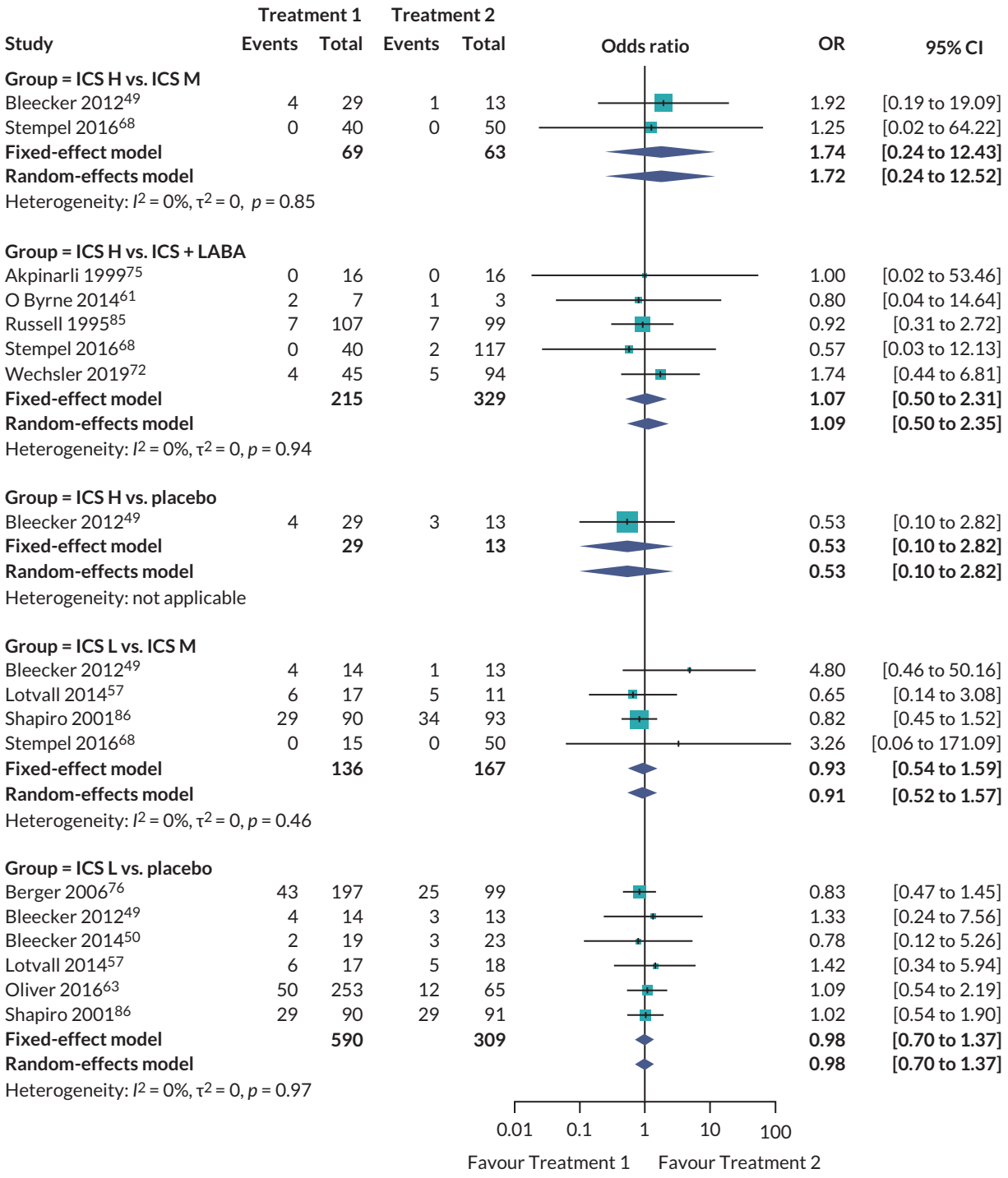

FIGURE 27 Continued

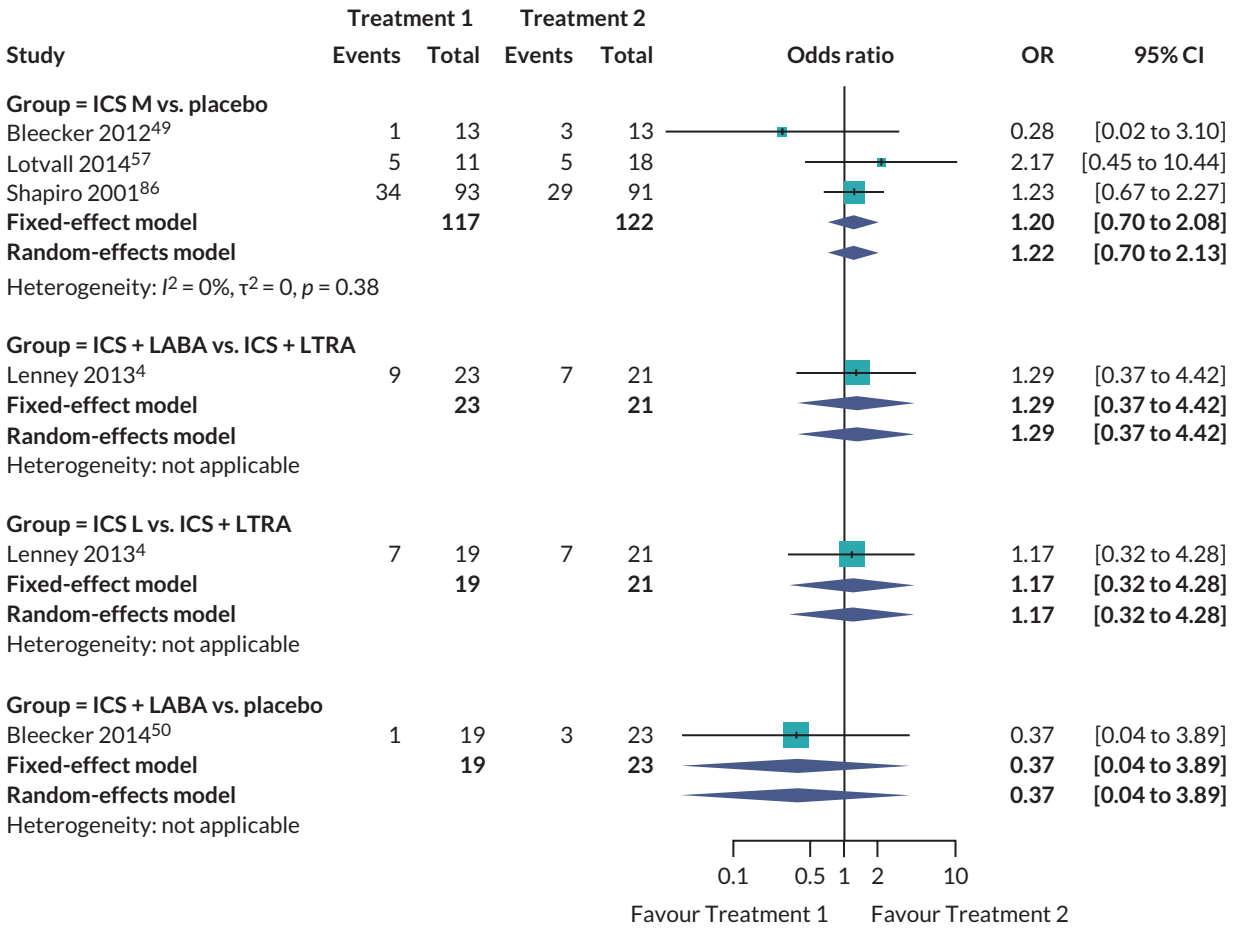

FIGURE 27 Continued

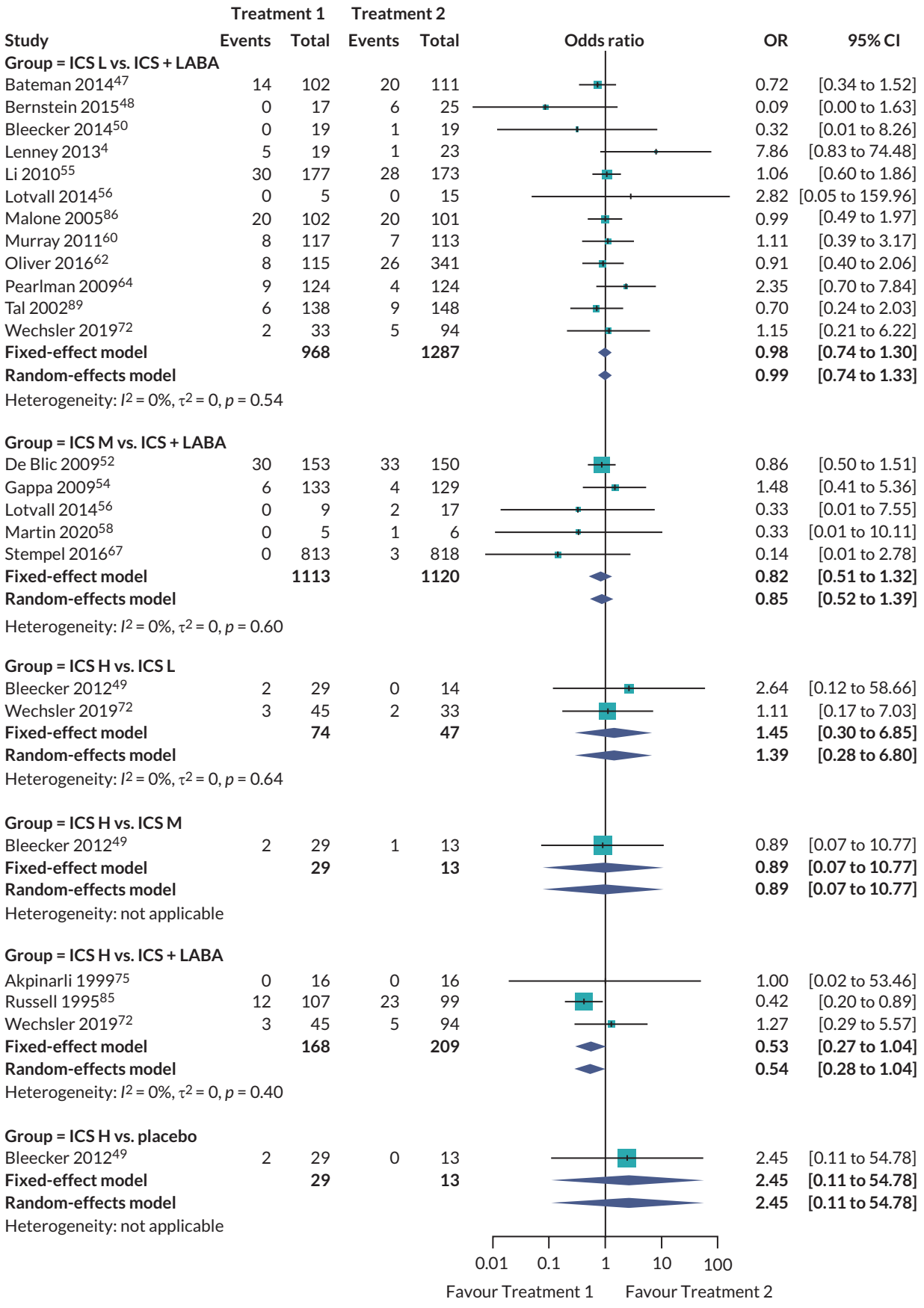

FIGURE 28 Neurological disorders. Frequentist meta-analysis (Mantel–Haenszel) based on all available comparisons. All data included (IPD and AgD where possible). L, low dose; M, medium dose; H, high dose. Note: OR > 1 favours treatment 2.

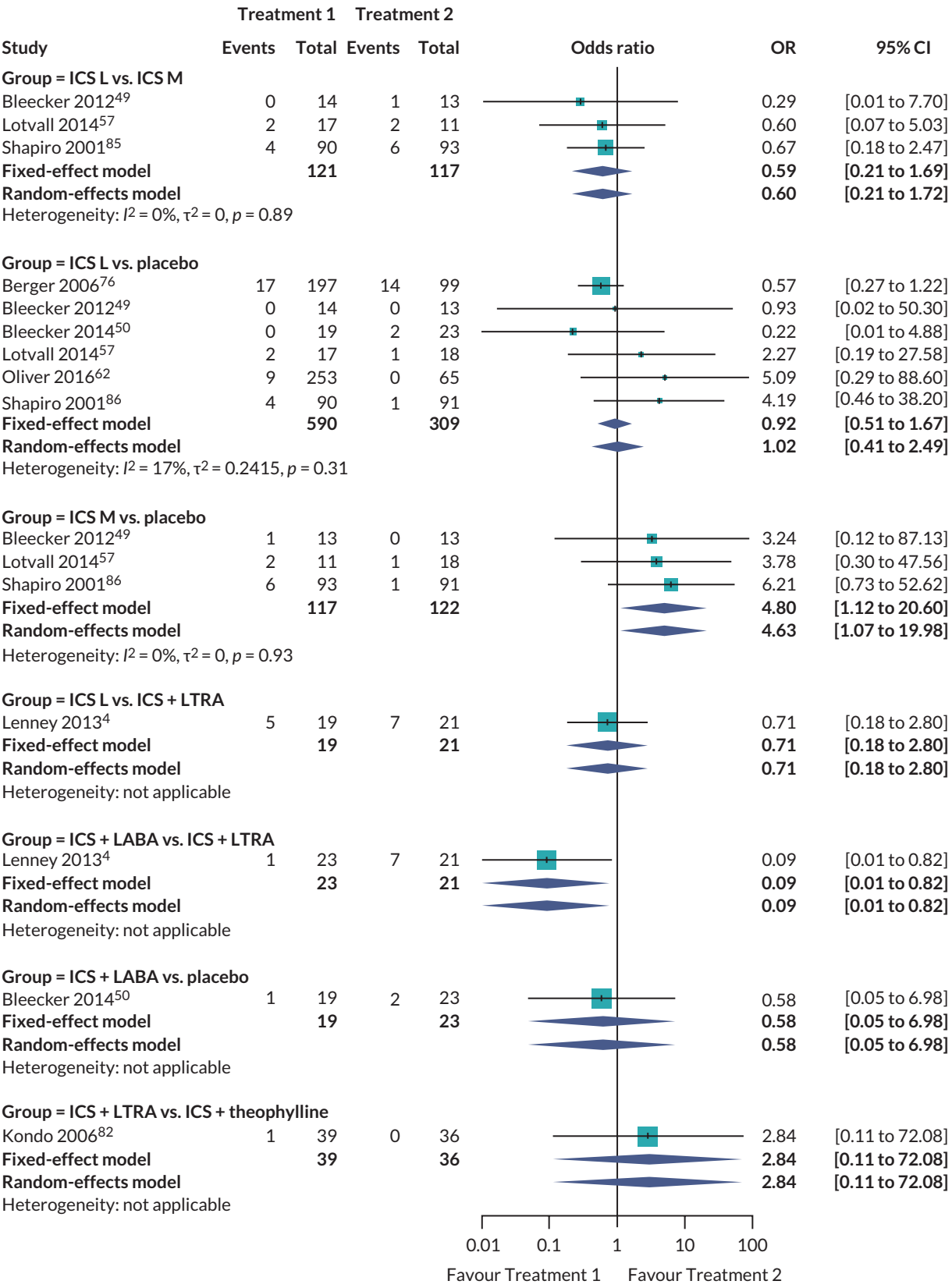

FIGURE 28 Continued

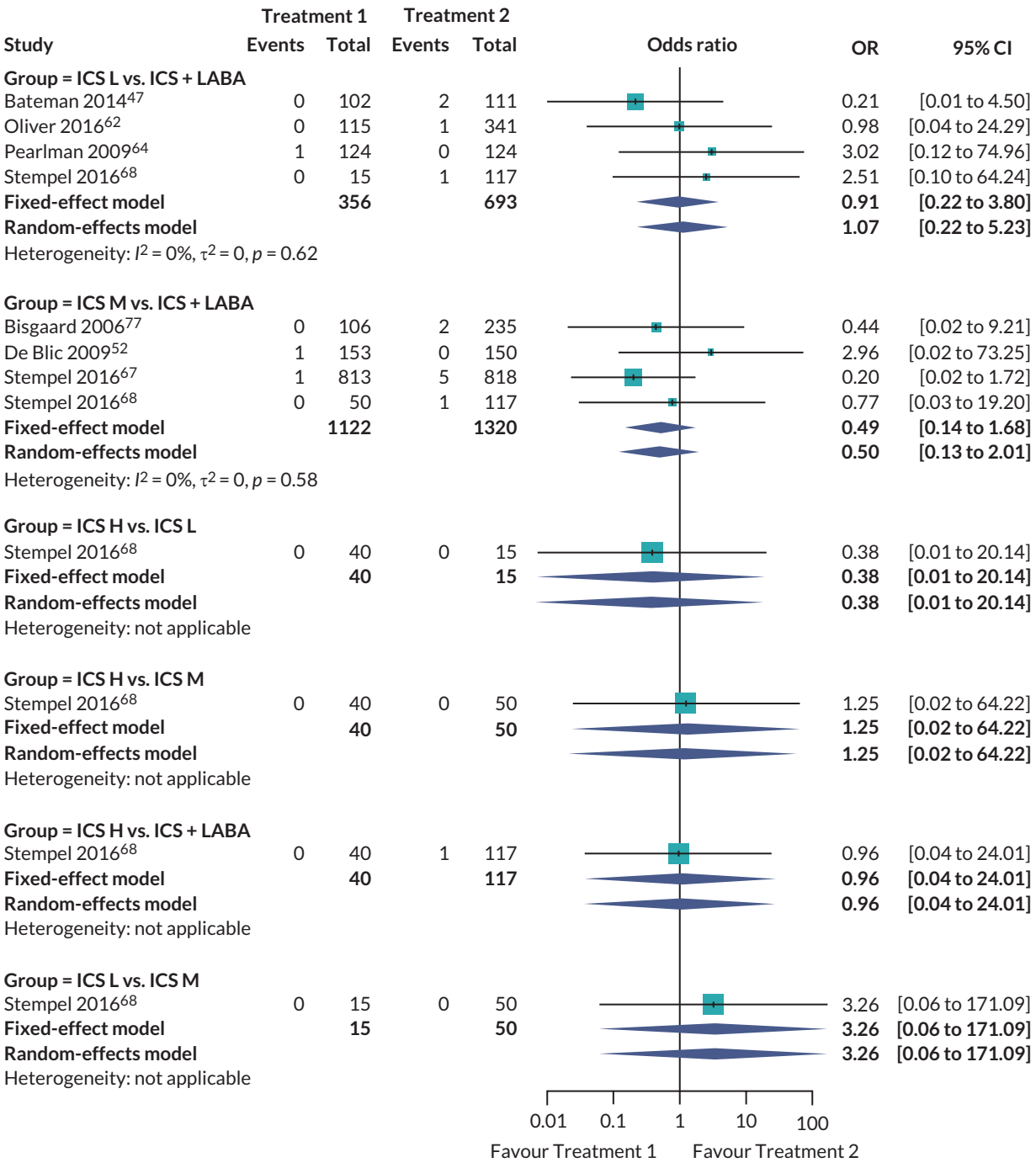

FIGURE 29 Pneumonia. Frequentist meta-analysis (Mantel–Haenszel) based on all available comparisons. All data included (IPD and AgD where possible). L, low dose; M, medium dose; H, high dose. Note: OR > 1 favours treatment 2.

Appendix 9 Network meta-regression

Additional material to supplement Chapter 7

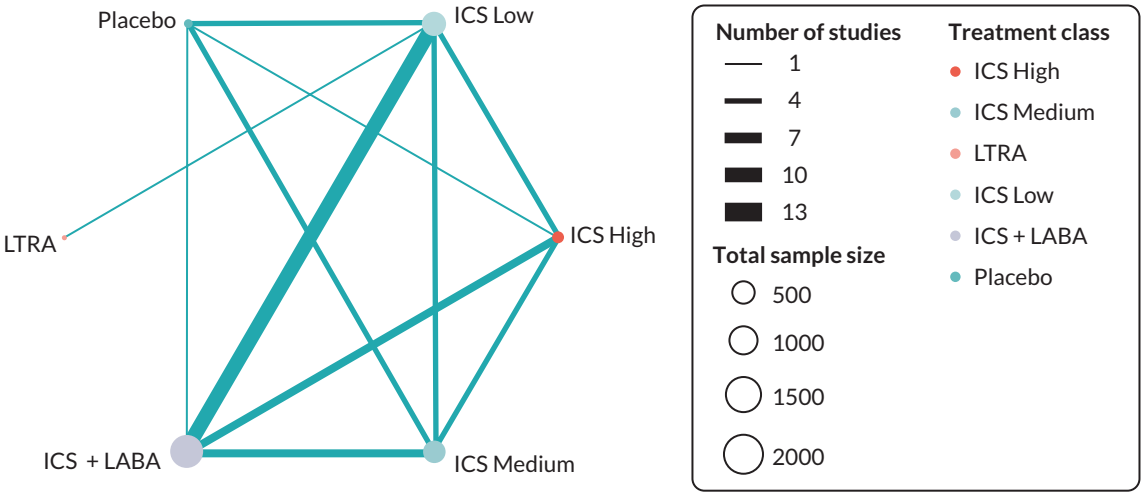

FIGURE 30 Network diagram of studies for the outcome exacerbation and the covariate age.

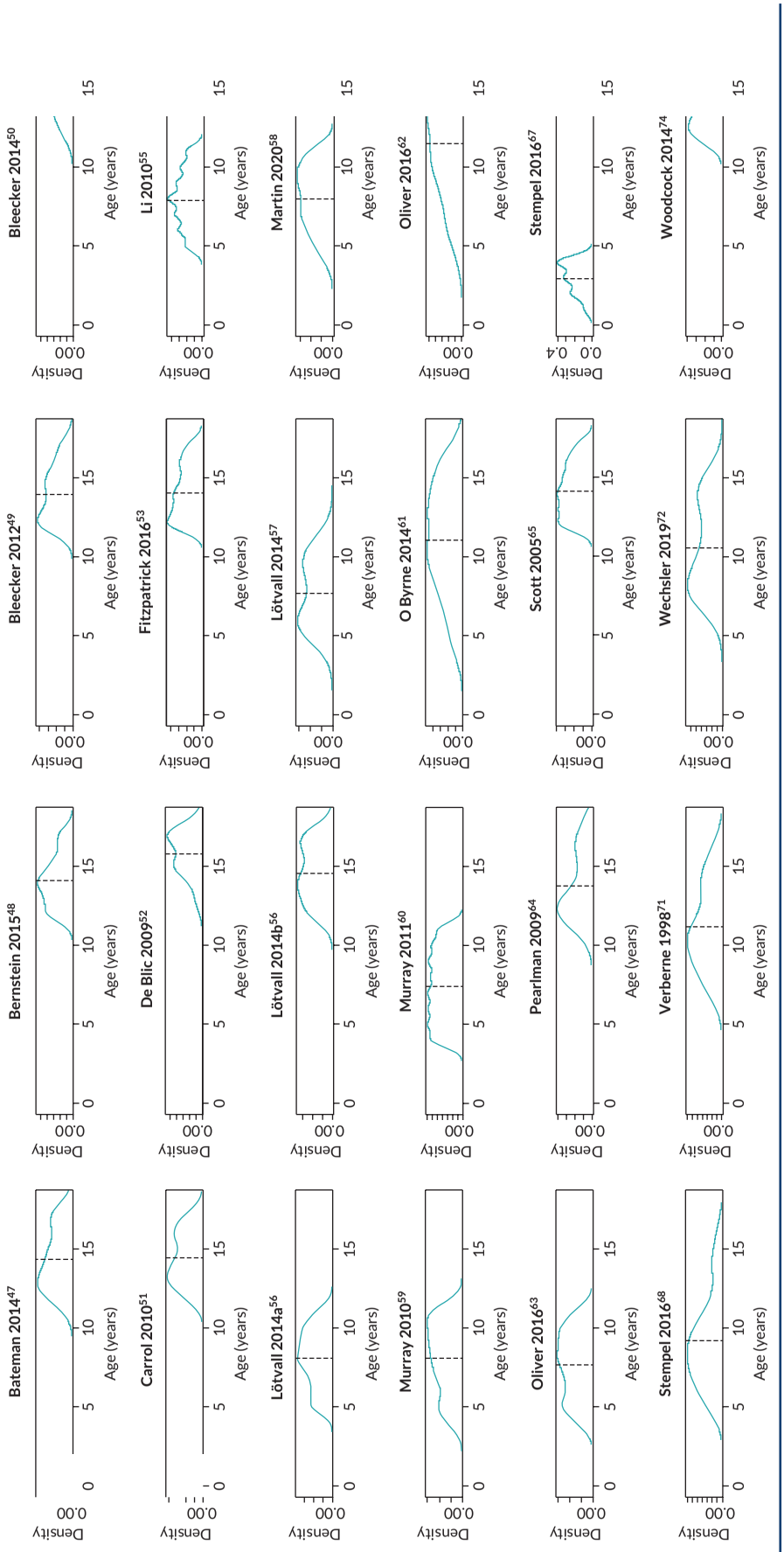

FIGURE 31 Covariate distributions for the continuous covariate age for the outcome exacerbation. Note: Dashed line represents the mean age.

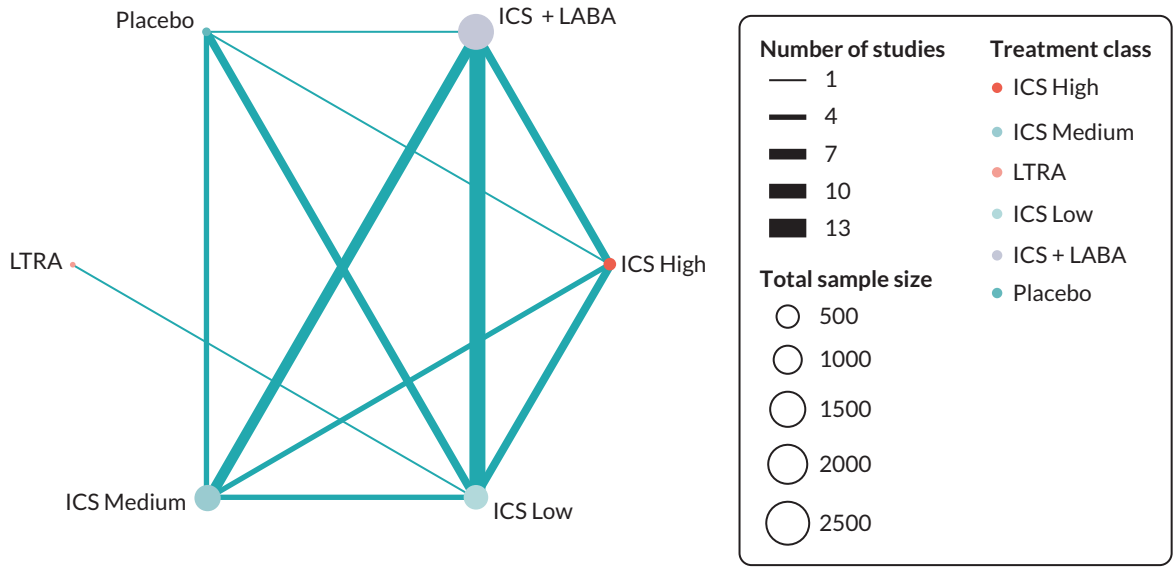

FIGURE 32 Network diagram of studies for the outcome exacerbation and the covariate sex.

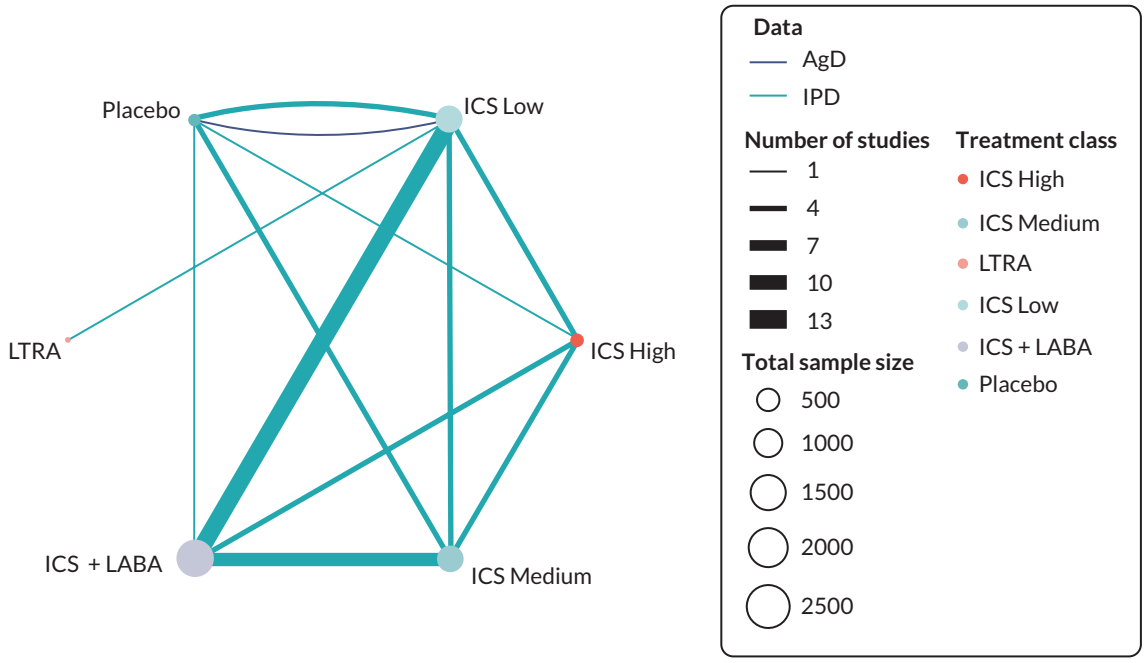

FIGURE 33 Network diagram of studies for the outcome exacerbation and the covariate ethnicity.

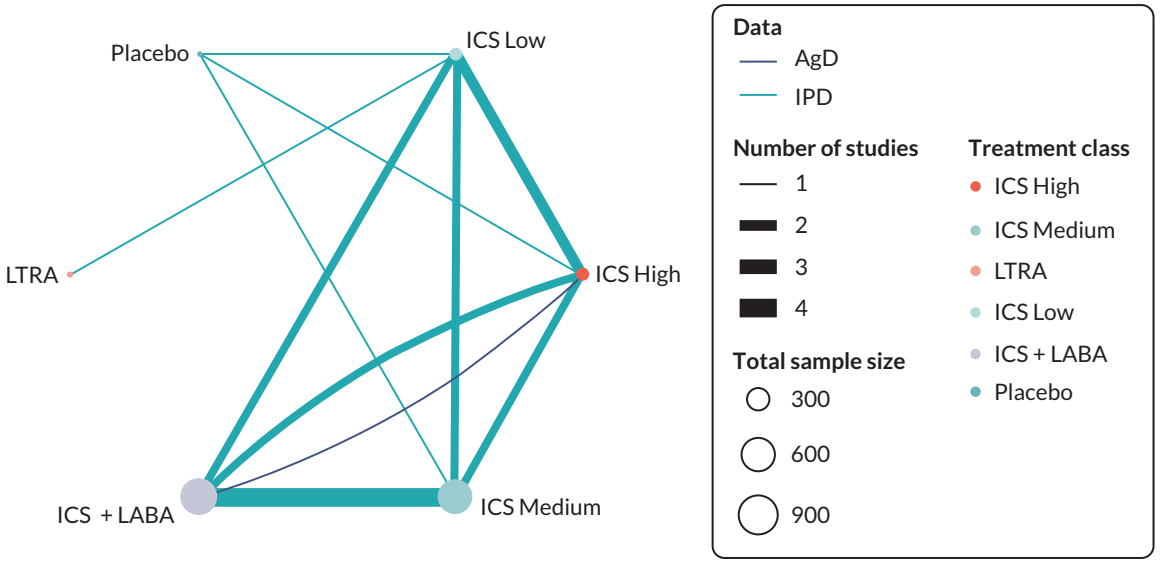

FIGURE 34 Network diagram of studies for the outcome exacerbation and the covariate eczema.

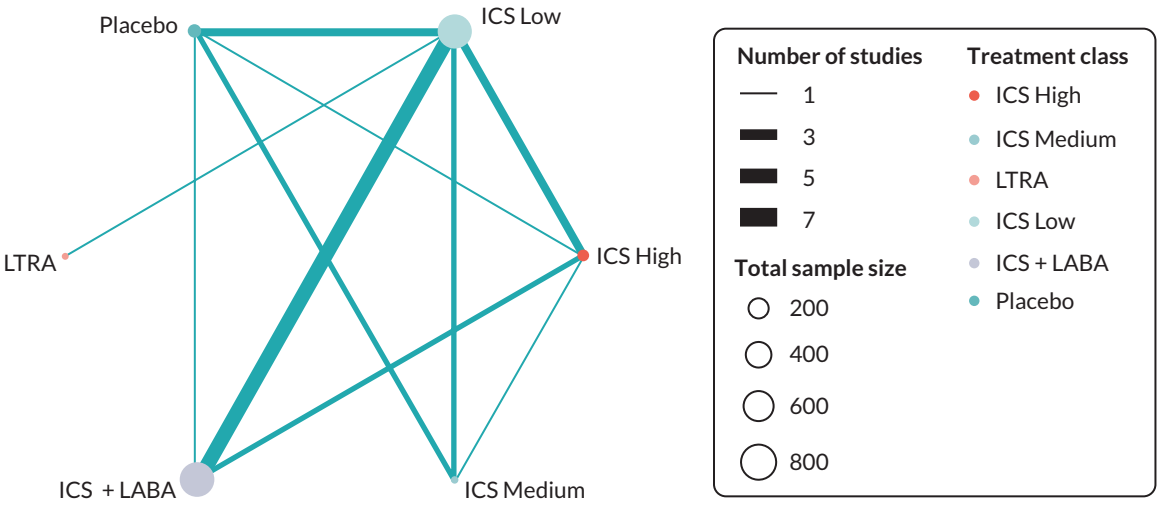

FIGURE 35 Network diagram of studies for the outcome exacerbation and the covariate eosinophilia.

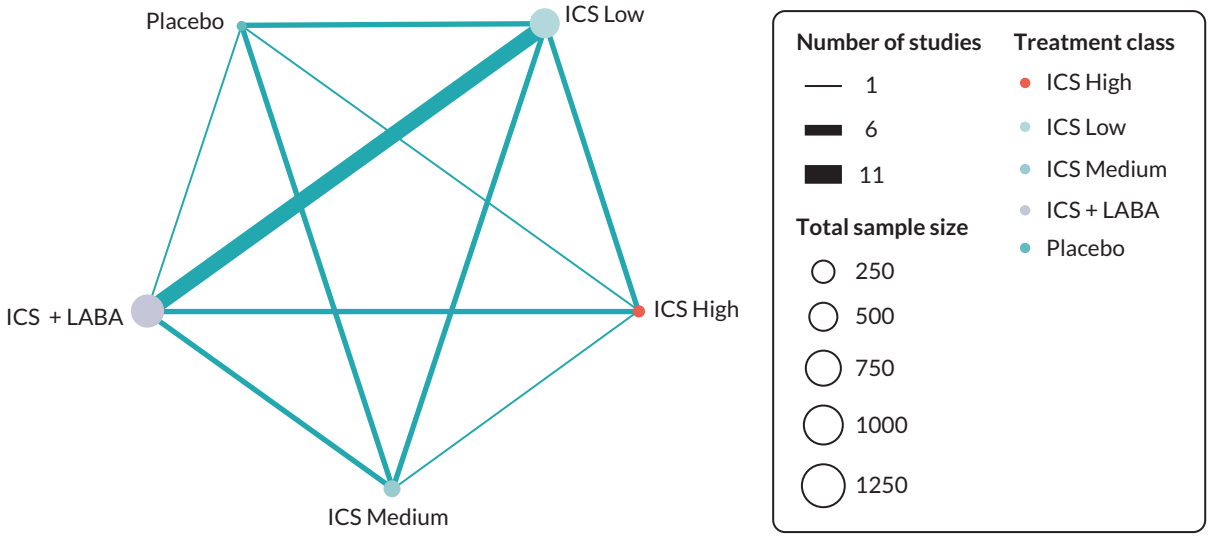

FIGURE 36 Network diagram of studies for the outcome exacerbation and the covariate baseline severity (based on FEV_1).

TABLE 59 Covariate distributions for covariates for the outcome exacerbation

Study	Data type	Comparison	Mean age (years)	Female (%)	Hispanic or Latino ethnicity (%)	Eczema (%)	Eosinophilic *eosinophilia* (%)	% Baseline severity (based on FEV_1)		
								Mild	Moderate	Severe
Bateman (2014)[47]	IPD	1	14.3	38	34	–	38	49	46	5
Bernstein (2015)[48]	IPD	1	14.1	36	45	–	44	0	76	24
Carrol (2010)[51]	IPD	1	14.41	38	0	–	–	81	19	0
Li (2010)[55]	IPD	1	7.94	39	41	–	56	71	28	1
Murray (2011)[60]	IPD	1	7.36	43	12	–	–	68	32	0
Oliver (2016)[62]	IPD	1	11.52	39	72	–	41	45	21	34
Pearlman (2009)[64]	IPD	1	13.73	40	8	–	–	67	33	0
Scott (2005)[65]	IPD	1	14.18	37	9	–	51	43	53	4
de Blic (2009)[52]	IPD	2	15.8	36	4	88	–	80	18	1
Gappa (2009)[54]	IPD	2	–	31	0	–	–	76	20	4
Martin (2020)[58]	IPD	2	8.05	36	0	–	–	100	0	0
Murray (2010)[59]	IPD	2	8.05	69	0	100	–	–	–	–
Stempel (2016)[67]	IPD	2	2.98	40	29	20	–	–	–	–
Vaessen-Verberne (2010)[70]	IPD	2	–	42	0	–	–	–	–	–
O'Byrne (2014)[61]	IPD	3	11.08	20	0	–	22	10	80	10
Verberne (1998)[71]	IPD	3	11.19	33	0	–	–	67	30	3
Akpinarli (1999)[75]	AgD	3	–	–	–	66	–	–	–	–
Oliver (2016)[63]	IPD	4	7.63	37	48	–	34	47	53	0
Berger (2006)[76]	AgD	4	–	–	33	–	–	–	–	–
Woodcock (2014)[74]	IPD	13	14.08	38	23	–	71	42	42	17
Fitzpatrick (2016)[53]	IPD	17	14.08	38	13	57	27	–	–	–
Lötvall (2014)[56]	IPD	1, 2, 12	8.05	40	70	–	–	25	55	20

TABLE 59 Covariate distributions for covariates for the outcome exacerbation (*continued*)

Study	Data type	Comparison	Mean age (years)	Female (%)	Hispanic or Latino ethnicity (%)	Eczema (%)	Eosinophilic *eosinophilia* (%)	% Baseline severity (based on FEV_1)		
								Mild	Moderate	Severe
Lötvall (2014)[56]	IPD	1, 2, 12	14.57	58	50	–	–	16	72	12
Stempel (2016)[68]	IPD	1, 2, 3, 12, 13, 14	9.17	47	30	15	–	–	–	–
Wechsler (2019)[72]	IPD	1, 3, 13	10.56	45	0	70	37	100	0	0
Bleecker (2014)[50]	IPD	1, 4, 7	14.69	39	28	–	23	28	70	2
Lötvall (2014)[57]	IPD	4, 5, 12	7.69	43	4	–	31	36	64	0
Bleecker (2012)[49]	IPD	4, 5, 6, 12, 13, 14	13.93	41	13	61	52	42	51	7

Comparison: 1 = ICS Low vs. ICS + LABA; 2 = ICS Medium vs. ICS + LABA; 3 = ICS High vs. ICS + LABA; 4 = ICS Low vs. placebo; 5 = ICS Medium vs. placebo; 6 = ICS High vs. placebo; 7 = ICS + LABA vs. placebo; 8 = ICS + LABA vs. ICS + LTRA; 9 = ICS Low vs. ICS + LTRA; 10 = ICS Medium vs. ICS + LTRA; 11 = ICS High vs. ICS + LTRA; 12 = ICS Low vs. ICS Medium; 13 = ICS Low vs. ICS High; 14 = ICS Medium vs. ICS High; 15 = ICS + theophylline vs. ICS + LTRA; 16 = ICS + LABA vs. LTRA; 17 = ICS Low vs. LTRA; 18 = ICS Low + LABA vs. ICS Medium + LABA.

TABLE 60 Model comparison assessments from NMA models including interactions for the outcome exacerbation

Interaction	Model	Number of trials (no. of participants)	Number of data points	Residual deviance	Effective number of parameters (Pd)	Deviance information criterion (DIC)	Between trial SD
Treatment by *age*	Fixed-effect without interactions	24 (4929)	4929	2052.7	27.4	2080.0	–
	Fixed-effect with interactions	24 (4929)	4929	2052.0	33.1	2085.1	–
	Random-effects with interactions	24 (4929)	4929	2049.1	36.4	2085.5	0.47 (0.02, 1.37)
Treatment by *sex*	Fixed-effect without interactions	26 (5349)	5349	2216.2	29.5	2245.7	–
	Fixed-effect with interactions	26 (5349)	5349	2216.7	34.7	2251.5	–
	Random-effects with interactions	26 (5349)	5349	2215.1	38.0	2253.1	0.34 (0.01, 1.01)
Treatment by *ethnicity*	Fixed-effect without interactions	27 (5645)	5351	2215.8	30.3	2246.1	–
	Fixed-effect with interactions	27 (5645)	5351	2210.3	34.8	2245.0	–
	Random-effects with interactions	27 (5645)	5351	2209.7	37.3	2246.9	0.22 (0.01, 0.85)
Treatment by *eczema*	Fixed-effect without interactions	8 (2469)	2439	1312.4	12.3	1324.7	–
	Fixed-effect with interactions	8 (2469)	2439	1313.9	16.7	1330.6	–
	Random-effects with interactions	8 (2469)	2439	1313.4	18.5	1331.9	0.69 (0.02, 2.44)
Treatment by *eosinophilia*	Fixed-effect without interactions	13 (1898)	1898	600.3	15.9	616.1	–
	Fixed-effect with interactions	13 (1898)	1898	601.8	20.3	622.1	–
	Random-effects with interactions	13 (1898)	1898	596.0	23.6	619.7	1.04 (0.09, 3.17)

TABLE 60 Model comparison assessments from NMA models including interactions for the outcome exacerbation (*continued*)

Interaction	Model	Number of trials (no. of participants)	Number of data points	Residual deviance	Effective number of parameters (Pd)	Deviance information criterion (DIC)	Between trial SD
Treatment by *baseline severity (based on FEV$_1$)*	Fixed-effect without interactions	21 (2916)	2916	741.7	22.1	763.8	–
	Fixed-effect with interactions	21 (2916)	2916	740.2	25.4	765.7	–
	Random-effects with interactions	21 (2916)	2916	736.0	29.8	765.9	0.87 (0.04, 3.07)

TABLE 61 Parameter estimates from NMA models including interactions for the outcome exacerbation

		Fixed-effect with interactions		Random-effects with interactions	
Interaction	**Comparison**	**Log OR at the mean covariate value (95% CrI)**	**Regression coefficient treatment by covariate interaction (95% CrI)**	**Log OR at the mean covariate value (95% CrI)**	**Regression coefficient treatment by covariate interaction (95% CrI)**
Treatment by *age*	ICS High vs. ICS Low	−0.33 (−1.05 to 0.39)	0.02 (−0.16 to 0.19)	−0.31 (−1.33 to 0.74)	0.00 (−0.19 to 0.19)
	ICS Medium vs. ICS Low	−0.19 (−0.81 to 0.42)	0.11 (−0.04 to 0.26)	−0.29 (−1.35 to 0.66)	0.11 (−0.04 to 0.27)
	ICS + LABA vs. ICS Low	−0.28 (−0.78 to 0.22)	0.09 (−0.04 to 0.21)	−0.23 (−0.86 to 0.47)	0.07 (−0.08 to 0.21)
	LTRA vs. ICS Low	−2.74 (−9.05 to 2.74)	−0.65 (−1.60 to 0.19)	−2.83 (−9.25 to 2.89)	−0.66 (−1.60 to 0.19)
	placebo vs. ICS Low	**2.41 (0.65 to 4.44)**	0.20 (−0.23 to 0.67)	**2.28 (0.18 to 4.52)**	0.21 (−0.22 to 0.69)
Treatment by *sex*	ICS High vs. ICS + LABA	−0.23 (−0.78 to 0.30)	0.27 (−0.56 to 1.11)	−0.26 (−1.03 to 0.47)	0.28 (−0.56 to 1.12)
	ICS Low vs. ICS + LABA	0.24 (−0.26 to 0.72)	−0.02 (−0.80 to 0.75)	0.22 (−0.40 to 0.80)	−0.03 (−0.80 to 0.76)
	ICS Medium vs. ICS + LABA	0.12 (−0.18 to 0.42)	−0.28 (−0.85 to 0.28)	0.13 (−0.45 to 0.73)	−0.28 (−0.84 to 0.27)
	LTRA vs. ICS + LABA	1.53 (−0.03 to 3.27)	0.94 (−0.84 to 2.76)	1.51 (−0.34 to 3.44)	0.95 (−0.84 to 2.80)
	placebo vs. ICS + LABA	**2.33 (0.35 to 4.49)**	−1.80 (−5.21 to 0.56)	**2.28 (0.18 to 4.56)**	−1.78 (−5.06 to 0.55)
Treatment by *ethnicity*	ICS High vs. ICS Low	−0.52 (−1.51 to 0.32)	−0.55 (−2.97 to 2.65)	−0.54 (−1.66 to 0.41)	−0.50 (−2.97 to 2.91)
	ICS Medium vs. ICS Low	−0.08 (−0.66 to 0.52)	**−1.25 (−2.47 to −0.18)**	−0.06 (−0.77 to 0.70)	**−1.21 (−2.40 to −0.11)**
	ICS + LABA vs. ICS Low	−0.19 (−0.70 to 0.32)	**−1.09 (−2.27 to −0.06)**	−0.18 (−0.75 to 0.39)	−1.03 (−2.20 to 0.04)
	LTRA vs. ICS Low	Not estimable	Not estimable	Not estimable	Not estimable
	Placebo vs. ICS Low	**1.19 (0.59 to 1.80)**	**−2.70 (−5.19 to −0.24)**	**1.24 (0.43 to 2.15)**	**−2.61 (−5.14 to −0.06)**
Treatment by *eczema*	ICS High vs. ICS Medium	−0.01 (−1.34 to 1.52)	−1.89 (−4.40 to 0.43)	0.00 (−1.88 to 2.02)	−1.88 (−4.46 to 0.45)
	ICS Low vs. ICS Medium	0.07 (−1.14 to 1.52)	−1.04 (−3.06 to 0.63)	0.05 (−1.94 to 2.21)	−0.99 (−3.06 to 0.71)
	ICS + LABA vs. ICS Medium	−0.04 (−1.20 to 1.37)	−1.29 (−3.30 to 0.37)	0.01 (−1.74 to 1.97)	−1.22 (−3.29 to 0.48)
	ICS + LTRA vs. ICS Medium	Not estimable	Not estimable	Not estimable	Not estimable
	LTRA vs. ICS Medium	1.49 (−0.40 to 3.48)	−0.67 (−3.34 to 2.05)	1.46 (−1.18 to 4.18)	−0.63 (−3.39 to 2.13)
	Placebo vs. ICS Medium	Not estimable	Not estimable	Not estimable	Not estimable

TABLE 61 Parameter estimates from NMA models including interactions for the outcome exacerbation (*continued*)

Interaction	Comparison	Fixed-effect with interactions		Random-effects with interactions	
		Log OR at the mean covariate value (95% CrI)	Regression coefficient treatment by covariate interaction (95% CrI)	Log OR at the mean covariate value (95% CrI)	Regression coefficient treatment by covariate interaction (95% CrI)
Treatment by *eosinophilia*	ICS High vs. ICS Low	−1.20 (−2.72 to 0.02)	−1.38 (−4.73 to 1.18)	−1.67 (−4.91 to 0.57)	−1.38 (−4.66 to 1.11)
	ICS Medium vs. ICS Low	Not estimable	Not estimable	Not estimable	Not estimable
	ICS + LABA vs. ICS Low	−0.40 (−0.98 to 0.16)	−0.28 (−1.31 to 0.75)	−0.44 (−1.94 to 0.98)	−0.25 (−1.31 to 0.79)
	LTRA vs. ICS Low	1.12 (−0.45 to 2.86)	0.18 (−2.19 to 2.39)	1.09 (−2.36 to 4.37)	0.19 (−2.22 to 2.41)
	Placebo vs. ICS Low	**2.15 (0.29 to 4.26)**	1.32 (−0.79 to 3.61)	1.88 (−0.97 to 4.76)	1.37 (−0.78 to 3.69)
Treatment by *Baseline severity (based on FEV_1)*	ICS High vs. ICS Low	−0.38 (−1.31 to 0.55)	0.71 (−0.39 to 1.85)	−1.24 (−5.13 to 0.71)	0.65 (−0.47 to 1.80)
	ICS Medium vs. ICS Low	0.04 (−1.57 to 1.61)	**2.11 (0.32 to 3.89)**	−0.31 (−3.02 to 1.81)	**2.01 (0.16 to 3.89)**
	ICS + LABA vs. ICS Low	−0.10 (−0.74 to 0.55)	0.49 (−0.43 to 1.47)	−0.32 (−1.79 to 0.79)	0.39 (−0.59 to 1.40)
	Placebo vs. ICS Low	**2.40 (0.60 to 4.54)**	0.64 (−1.45 to 2.78)	2.22 (−0.48 to 4.98)	0.61 (−1.44 to 2.73)

Note
Posterior mean (95% CrI). Bold indicates that zero is excluded from the CrI. Regression coefficient: change in the log OR per unit increase in the covariate value.

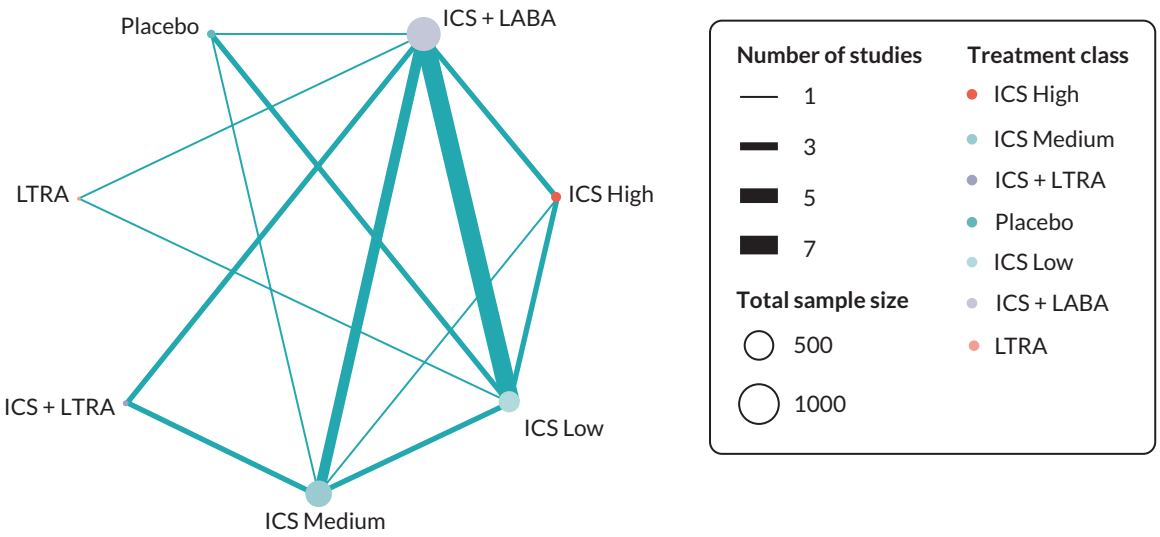

FIGURE 37 Network diagram of studies for the outcome asthma control and the covariate age, sex and ethnicity.

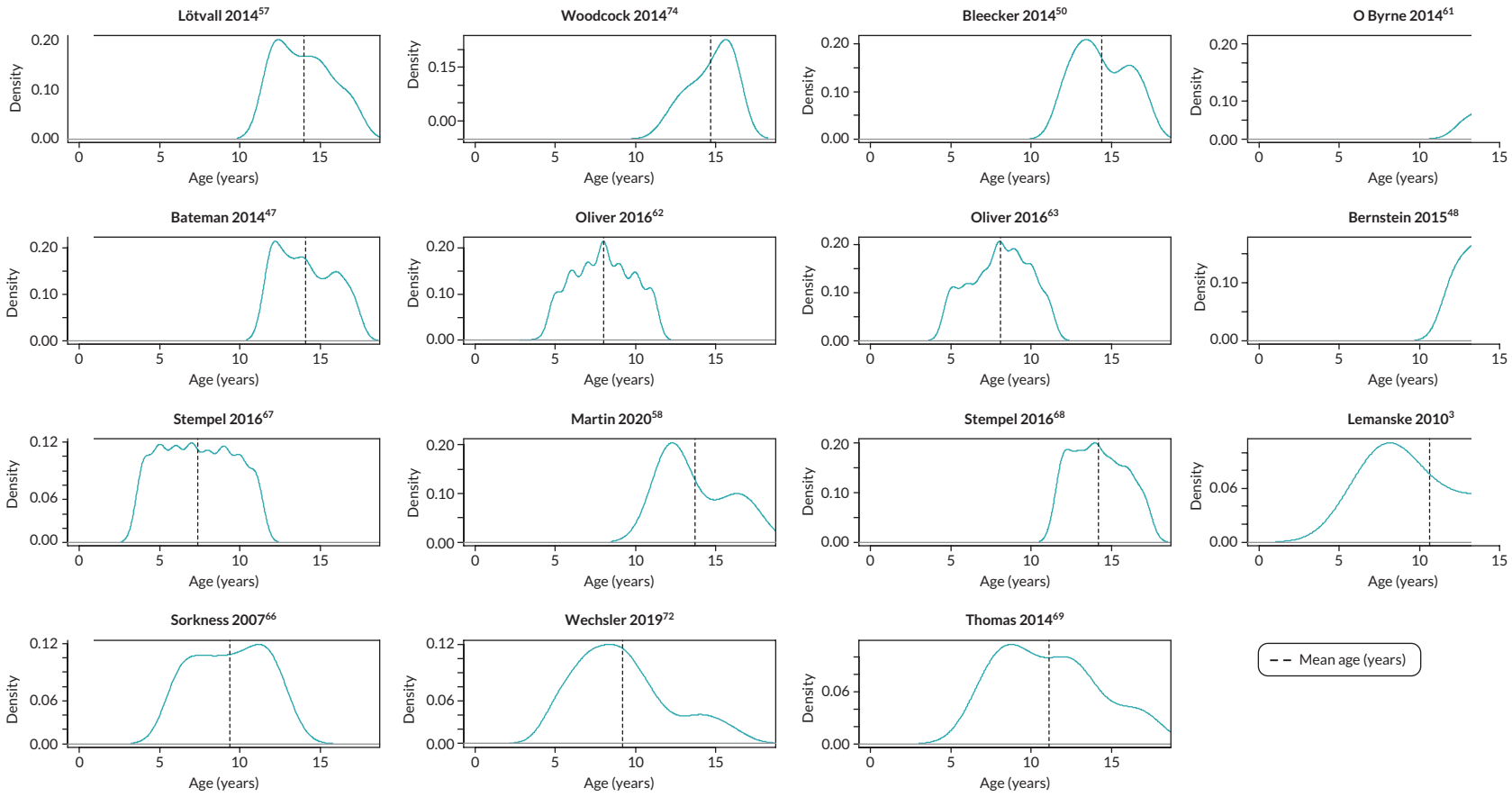

FIGURE 38 Covariate distributions for the continuous covariate age for the outcome asthma control.

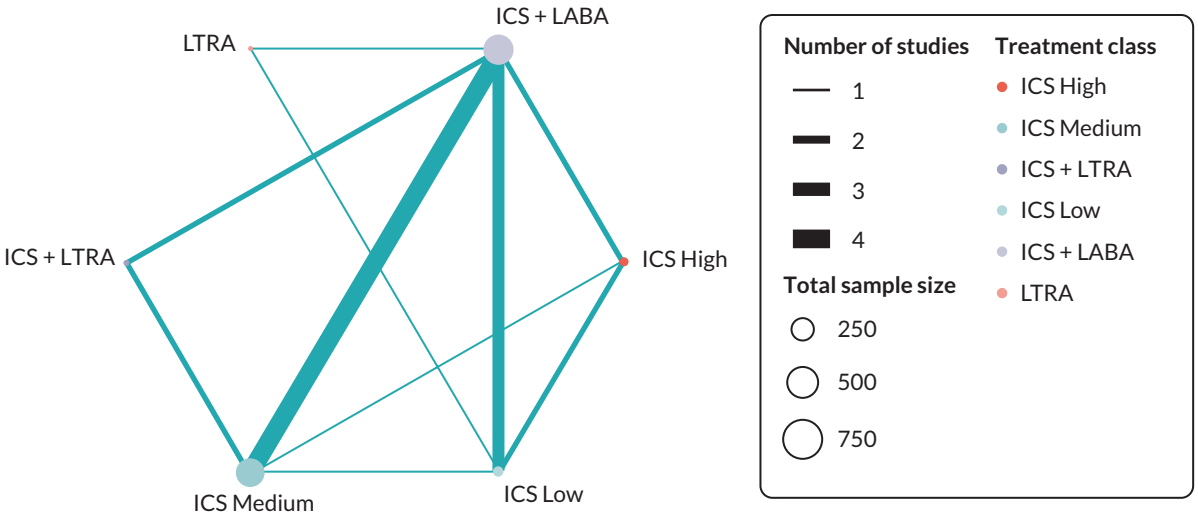

FIGURE 39 Network diagram of studies for the outcome asthma control and the covariate eczema.

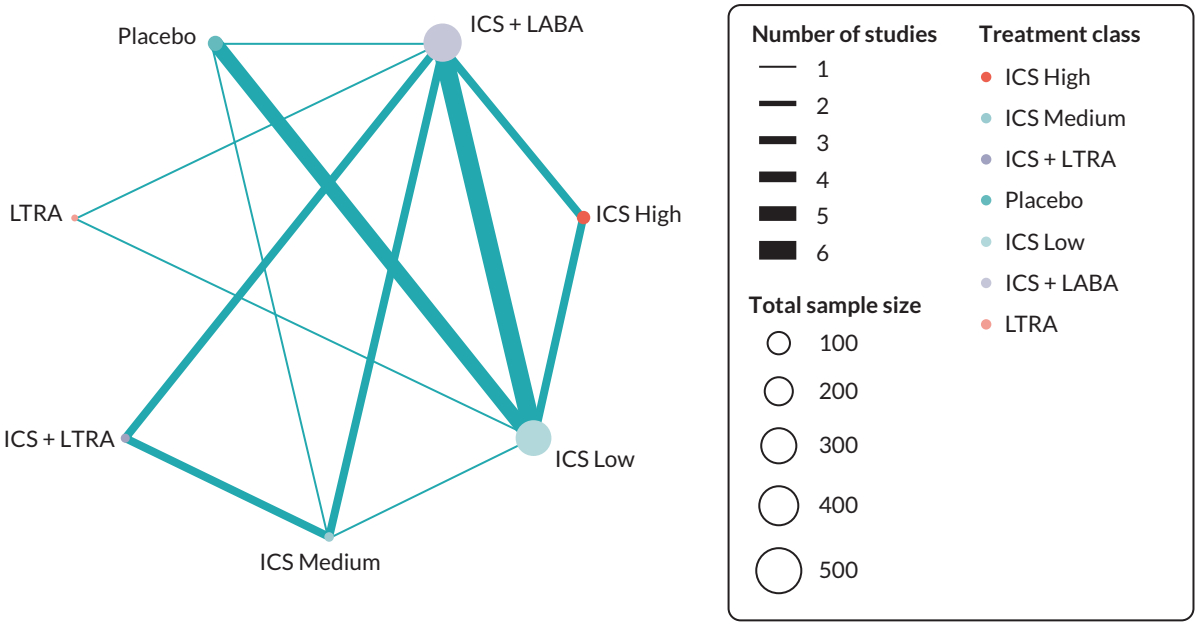

FIGURE 40 Network diagram of studies for the outcome asthma control and the covariate eosinophilia.

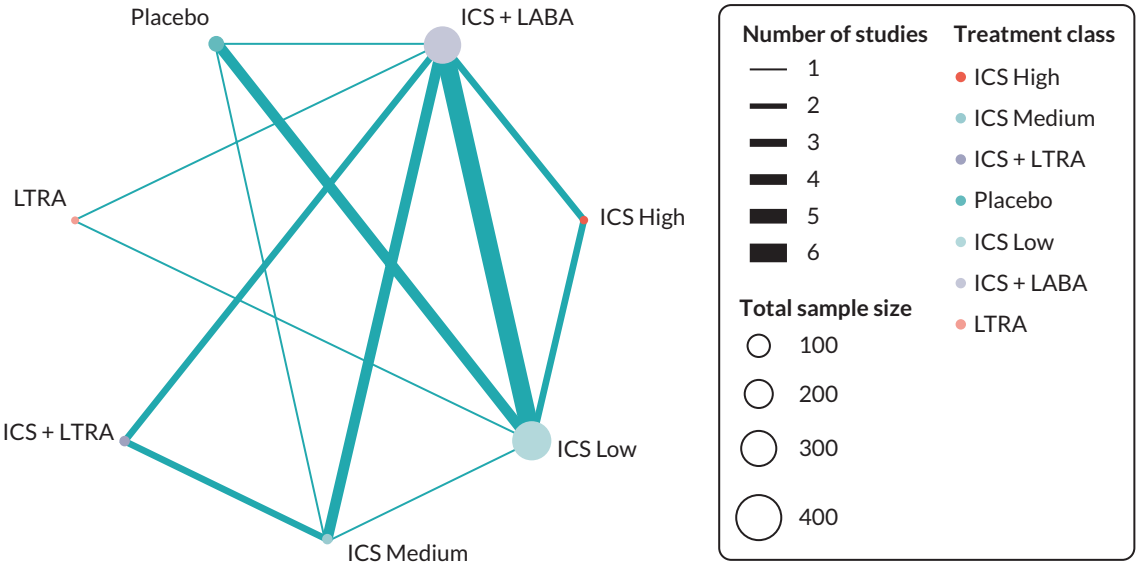

FIGURE 41 Network diagram of studies for the outcome asthma control and the covariate baseline severity (based on FEV_1).

TABLE 62 Covariate distributions for covariates for the outcome asthma control

Study	Comparison	Data type	Mean age (years)	Female (%)	Hispanic or Latino ethnicity (%)	Eczema (%)	Eosinophilic *eosinophilia* (%)	Baseline severity (based on FEV_1) (%)		
								Mild	Moderate	Severe
Bateman (2014)[47]	1	IPD	14.11	40	35	–	38	47	47	5
Bernstein (2015)[48]	1	IPD	14.65	38	48	–	46	0	76	24
Oliver (2016)[62]	1	IPD	8.01	41	71	–	41	47	20	33
Martin (2020)[58]	2	IPD	13.73	36	0	–	–	100	0	0
Stempel (2016)[67]	2	IPD	7.39	40	28	21	–	–	–	–
O'Byrne (2014)[61]	3	IPD	15.8	20	0	–	22	10	80	10
Oliver (2016)[63]	4	IPD	8.07	37	47	–	32	46	54	0
Woodcock (2014)[74]	13	IPD	14.69	38	23	–	71	24	52	24
Sorkness (2007)[66]	1, 16, 17	IPD	9.35	31	27	61	63	86	14	0
Stempel (2016)[68]	1, 2, 3, 12, 13, 14	IPD	14.2	44	30	14	–	–	–	–
Wechsler (2019)[72]	1, 3, 13	IPD	9.17	45	0	70	36	100	0	0
Lemanske (2010)[3]	2, 8, 10	IPD	10.61	26	45	23	45	87	13	0
Thomas (2014)[69]	2, 8, 10	IPD	11.09	36	0	48	18	52	42	6
Lötvall (2014)[57]	4, 5, 12	IPD	14	44	2	–	31	38	62	0
Bleecker (2014)[50]	4, 5, 6, 12, 13, 14	IPD	14.38	34	14	–	28	22	76	2

Comparison: 1 = ICS Low vs. ICS + LABA; 2 = ICS Medium vs. ICS + LABA; 3 = ICS High vs. ICS + LABA; 4 = ICS Low vs. placebo; 5 = ICS Medium vs. placebo; 6 = ICS High vs. placebo; 7 = ICS + LABA vs. placebo; 8 = ICS + LABA vs. ICS + LTRA; 9 = ICS Low vs. ICS + LTRA; 10 = ICS Medium vs. ICS + LTRA; 11 = ICS High vs. ICS + LTRA; 12 = ICS Low vs. ICS Medium; 13 = ICS Low vs. ICS High; 14 = ICS Medium vs. ICS High; 15 = ICS + theophylline vs. ICS + LTRA; 16 = ICS + LABA vs. LTRA; 17 = ICS Low vs. LTRA; 18 = ICS Low + LABA vs. ICS Medium + LABA.

TABLE 63 Model comparison assessments from NMA models including interactions for the outcome asthma control

Interaction	Model	Number of trials (no. of participants)	Number of data points	Residual deviance	Effective number of parameters (Pd)	DIC	Between trial SD
Treatment by *age*	Random-effects without interactions	15 (2998)	2998	2797.0	27.8	2824.8	0.43 (0.03, 1.02)
	Fixed-effect with interactions	15 (2998)	2998	2804.6	29.2	2833.9	–
	Random-effects with interactions	15 (2998)	2998	2790.8	36.7	2827.5	0.75 (0.19, 1.47)
Treatment by *sex*	Fixed-effect without interactions	15 (2998)	2998	2800.7	22.5	2823.2	–
	Fixed-effect with interactions	15 (2998)	2998	2799.2	28	2827.2	–
	Random-effects with interactions	15 (2998)	2998	2793.1	33	2826.1	0.44 (0.03, 1.06)
Treatment by *ethnicity*	Fixed-effect without interactions	15 (2998)	2998	2802.6	22.7	2825.3	–
	Fixed-effect with interactions	15 (2998)	2998	2805.2	28.9	2834.1	–
	Random-effects with interactions	15 (2998)	2998	2798.4	34.7	2833.1	0.49 (0.04, 1.11)
Treatment by *eczema*	Fixed-effect without interactions	6 (1968)	1968	1607.3	12.3	1619.5	–
	Fixed-effect with interactions	6 (1968)	1968	1610.0	17.6	1627.6	–
	Random-effects with interactions	6 (1968)	1968	1608.6	17.6	1626.2	0.29 (0.01, 0.87)
Treatment by *eosinophilia*	Fixed-effect without interactions	12 (1192)	1192	1326.2	19.5	1345.7	–
	Fixed-effect with interactions	12 (1192)	1192	1328.7	26.3	1355.0	–
	Random effect with interactions	12 (1192)	1192	1325.1	30	1355.1	0.54 (0.02, 1.52)

continued

TABLE 63 Model comparison assessments from NMA models including interactions for the outcome asthma control (*continued*)

Interaction	Model	Number of trials (no. of participants)	Number of data points	Residual deviance	Effective number of parameters (Pd)	DIC	Between trial SD
Treatment by *baseline severity (based on FEV_1)*	Fixed-effect without interactions	13 (1074)	1074	1187.2	20.5	1207.6	–
	Fixed-effect with interactions	13 (1074)	1074	1187.3	25.5	1212.7	–
	Random-effects with interactions	13 (1074)	1074	1177.8	30.8	1208.7	1.09 (0.08, 2.78)

TABLE 64 Parameter estimates from NMA models including interactions for the outcome asthma control

Model		Fixed-effect NMA with interactions		Random-effects NMA with interactions	
		Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)	Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)
Treatment by *age*	ICS High vs. ICS + LABA	−0.56 (−1.27 to 0.17)	0.01 (−0.15 to 0.17)	−0.98 (−2.36 to 0.22)	0.12 (−0.08 to 0.33)
	ICS Low vs. ICS + LABA	−0.20 (−0.55 to 0.15)	0.01 (−0.07 to 0.10)	−0.51 (−1.38 to 0.23)	0.04 (−0.07 to 0.16)
	ICS Medium vs. ICS + LABA	−0.09 (−0.37 to 0.20)	−0.07 (−0.15 to 0.01)	0.36 (−0.55 to 1.44)	−0.10 (−0.21 to 0.00)
	ICS + LTRA vs. ICS + LABA	0.06 (−1.69 to 1.96)	−0.04 (−0.45 to 0.43)	0.19 (−2.06 to 2.59)	−0.04 (−0.45 to 0.43)
	LTRA vs. ICS + LABA	−1.57 (−3.21 to 0.08)	−0.15 (−0.70 to 0.36)	−1.83 (−4.16 to 0.35)	−0.14 (−0.68 to 0.35)
	Placebo vs. ICS + LABA	−0.46 (−1.19 to 0.30)	−0.05 (−0.23 to 0.12)	−0.69 (−2.16 to 0.70)	−0.01 (−0.25 to 0.23)
Treatment by *sex*	ICS High vs. ICS + LABA	−0.43 (−0.98 to 0.15)	−0.08 (−1.05 to 0.86)	−0.45 (−1.27 to 0.37)	−0.04 (−1.00 to 0.92)
	ICS Low vs. ICS + LABA	−0.17 (−0.50 to 0.15)	0.48 (−0.03 to 1.00)	−0.30 (−0.90 to 0.19)	0.48 (−0.03 to 0.99)
	ICS Medium vs. ICS + LABA	−0.06 (−0.34 to 0.22)	0.14 (−0.34 to 0.63)	0.00 (−0.65 to 0.72)	0.14 (−0.35 to 0.62)
	ICS + LTRA vs. ICS + LABA	Not estimable	Not estimable	Not estimable	Not estimable
	LTRA vs. ICS + LABA	**−2.03 (−3.97 to −0.23)**	−1.85 (−5.50 to 1.16)	**−2.15 (−4.37 to −0.14)**	−1.85 (−5.63 to 1.26)
	Placebo vs. ICS + LABA	−0.48 (−1.12 to 0.18)	−0.49 (−1.57 to 0.58)	−0.58 (−1.58 to 0.35)	−0.56 (−1.65 to 0.53)

continued

TABLE 64 Parameter estimates from NMA models including interactions for the outcome asthma control (*continued*)

Model		Fixed-effect NMA with interactions		Random-effects NMA with interactions	
		Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)	Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)
Treatment by *ethnicity*	ICS High vs. ICS + LABA	−0.53 (−1.09 to 0.05)	0.43 (−0.86 to 1.68)	−0.51 (−1.39 to 0.36)	0.22 (−1.12 to 1.53)
	ICS Low vs. ICS + LABA	−0.17 (−0.49 to 0.16)	0.07 (−0.44 to 0.57)	−0.32 (−0.96 to 0.21)	0.15 (−0.39 to 0.69)
	ICS Medium vs. ICS + LABA	−0.05 (−0.32 to 0.23)	−0.05 (−0.61 to 0.49)	0.05 (−0.66 to 0.84)	−0.03 (−0.60 to 0.52)
	ICS + LTRA vs. ICS + LABA	0.49 (−1.51 to 2.92)	1.24 (−1.77 to 4.89)	0.51 (−1.67 to 3.12)	1.23 (−1.75 to 4.75)
	LTRA vs. ICS + LABA	−1.49 (−3.21 to 0.25)	−1.00 (−4.45 to 1.82)	−1.59 (−3.63 to 0.41)	−1.00 (−4.56 to 1.79)
	Placebo vs. ICS + LABA	−0.52 (−1.15 to 0.15)	0.94 (−0.22 to 2.10)	−0.69 (−1.77 to 0.28)	1.17 (−0.12 to 2.54)
Treatment by *eczema*	ICS High vs. ICS + LABA	**−0.82 (−1.45 to −0.18)**	−0.02 (−1.12 to 1.07)	−0.73 (−1.49 to 0.13)	−0.09 (−1.21 to 1.01)
	ICS Low vs. ICS + LABA	**−0.91 (−1.76 to −0.04)**	0.52 (−0.73 to 1.74)	−0.79 (−1.69 to 0.18)	0.45 (−0.84 to 1.70)
	ICS Medium vs. ICS + LABA	−0.06 (−0.35 to 0.22)	0.50 (−0.16 to 1.18)	0.04 (−0.48 to 0.81)	0.47 (−0.20 to 1.16)
	ICS + LTRA vs. ICS + LABA	0.16 (−1.64 to 2.14)	0.02 (−3.06 to 3.58)	0.22 (−1.53 to 2.11)	−0.03 (−2.67 to 2.96)
	LTRA vs. ICS + LABA	**−2.28 (−4.07 to −0.53)**	0.73 (−1.72 to 3.29)	**−1.98 (−3.79 to −0.21)**	0.55 (−1.70 to 2.89)

TABLE 64 Parameter estimates from NMA models including interactions for the outcome asthma control (*continued*)

Model		Fixed-effect NMA with interactions		Random-effects NMA with interactions	
		Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)	Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)
Treatment by *eosinophilia*	ICS High vs. ICS + LABA	0.22 (−0.60 to 1.08)	0.99 (−0.51 to 2.70)	0.11 (−1.30 to 1.35)	0.98 (−0.55 to 2.70)
	ICS Low vs. ICS + LABA	−0.05 (−0.39 to 0.31)	0.28 (−0.32 to 0.88)	−0.14 (−0.89 to 0.51)	0.27 (−0.32 to 0.87)
	ICS Medium vs. ICS + LABA	1.13 (−0.55 to 3.32)	−1.29 (−4.83 to 1.58)	1.23 (−0.66 to 3.64)	−1.30 (−4.82 to 1.67)
	ICS + LTRA vs. ICS + LABA	0.45 (−1.45 to 2.50)	1.32 (−1.69 to 4.85)	0.48 (−1.70 to 2.78)	1.32 (−1.63 to 4.96)
	LTRA vs. ICS + LABA	−1.78 (−3.70 to 0.08)	1.28 (−1.39 to 3.96)	−1.88 (−4.23 to 0.35)	1.30 (−1.43 to 4.05)
	Placebo vs. ICS + LABA	−0.33 (−1.05 to 0.40)	−0.36 (−1.62 to 0.89)	−0.38 (−1.52 to 0.77)	−0.42 (−1.71 to 0.87)
Treatment by *baseline severity (based on FEV_1)*	ICS High vs. ICS + LABA	0.34 (−1.53 to 2.30)	−0.51 (−3.16 to 2.03)	−0.04 (−2.86 to 2.55)	−0.23 (−3.04 to 2.62)
	ICS Low vs. ICS + LABA	−0.16 (−0.54 to 0.21)	0.22 (−0.22 to 0.65)	−0.66 (−2.10 to 0.36)	0.19 (−0.26 to 0.66)
	ICS Medium vs. ICS + LABA	0.52 (−0.90 to 2.09)	−0.77 (−3.04 to 1.59)	0.48 (−1.54 to 2.76)	−1.17 (−4.01 to 1.43)
	ICS + LTRA vs. ICS + LABA	Not estimable	Not estimable	Not estimable	Not estimable
	LTRA vs. ICS + LABA	**−2.51 (−5.01 to −0.37)**	−1.90 (−5.53 to 1.14)	−2.89 (−6.37 to 0.26)	−1.92 (−5.57 to 1.06)
	Placebo vs. ICS + LABA	−0.49 (−1.18 to 0.22)	−0.69 (−1.88 to 0.41)	−0.85 (−2.84 to 0.86)	−0.61 (−1.82 to 0.52)

Note
Posterior mean (95% CrI) presented. Bold indicates that zero is excluded from the CrI. The regression coefficient represents the change in the log OR per unit increase in the covariate value.

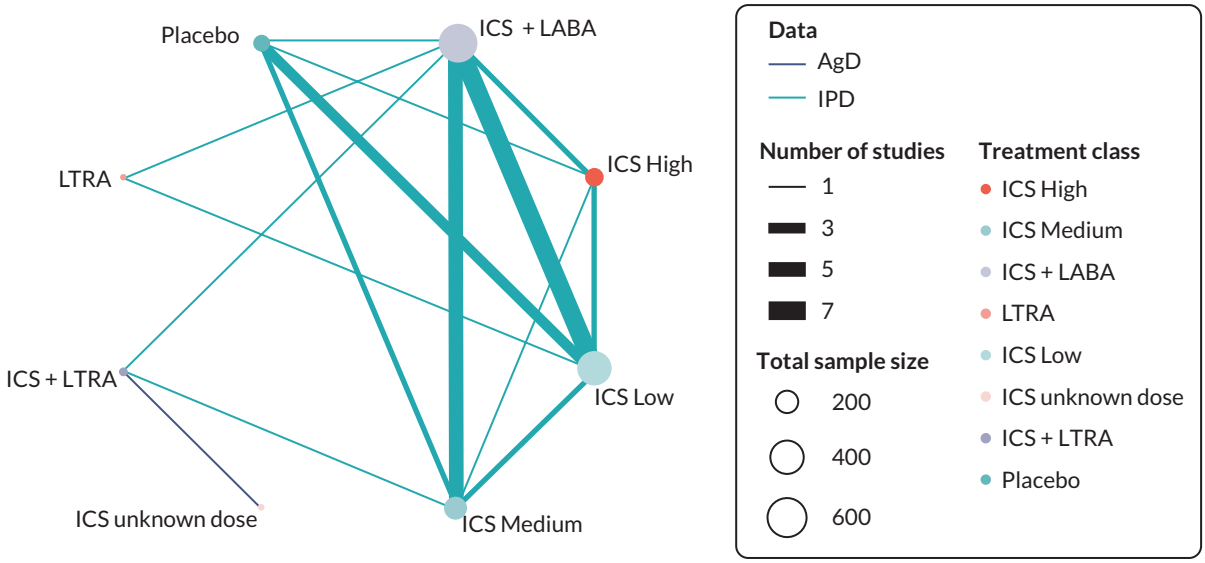

FIGURE 42 Network diagram of studies for the outcome FEV_1 and the covariate age.

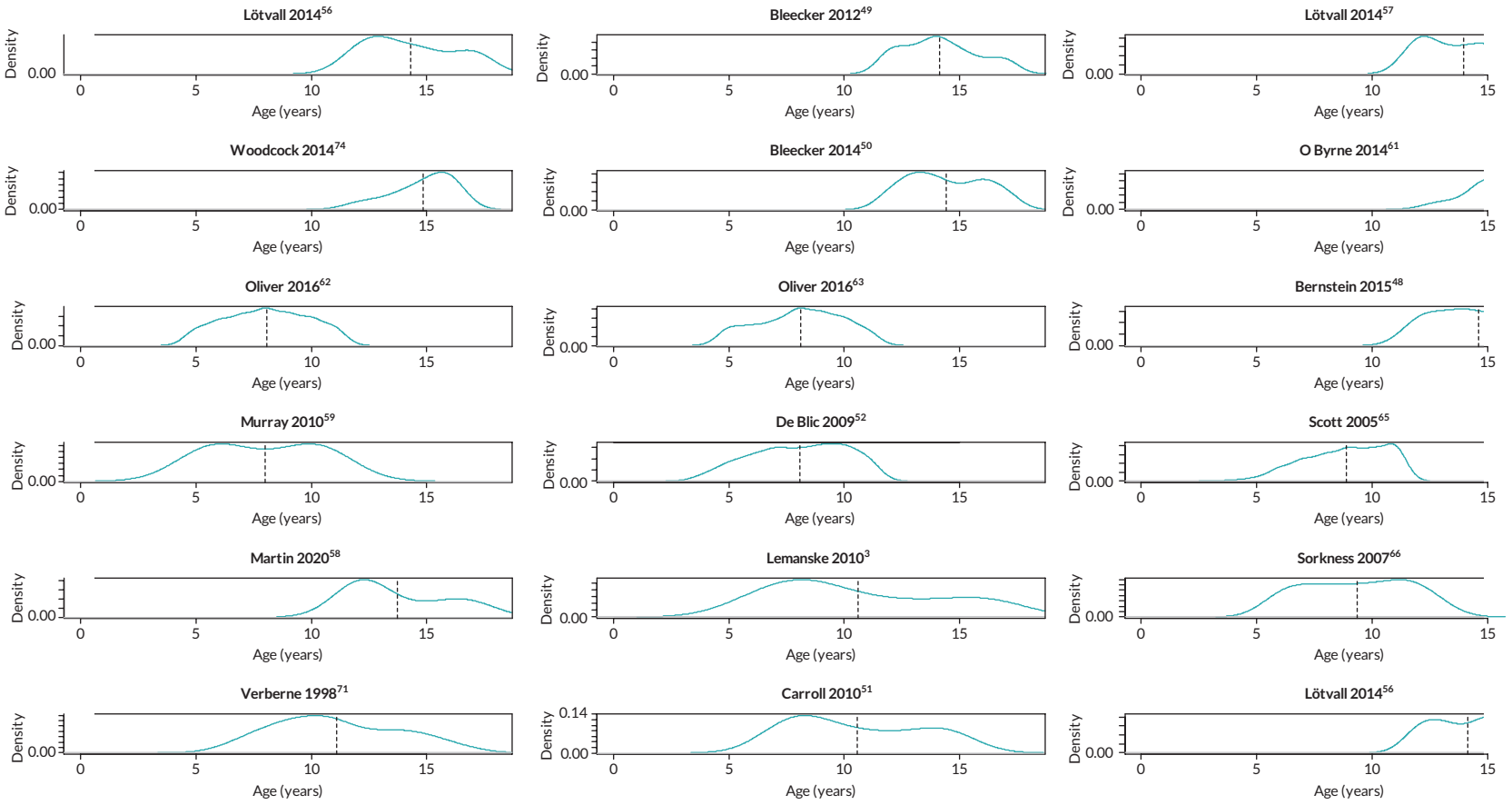

FIGURE 43 Covariate distributions for the continuous covariate age for the outcome FEV_1. Note: Dashed line represents the mean age.

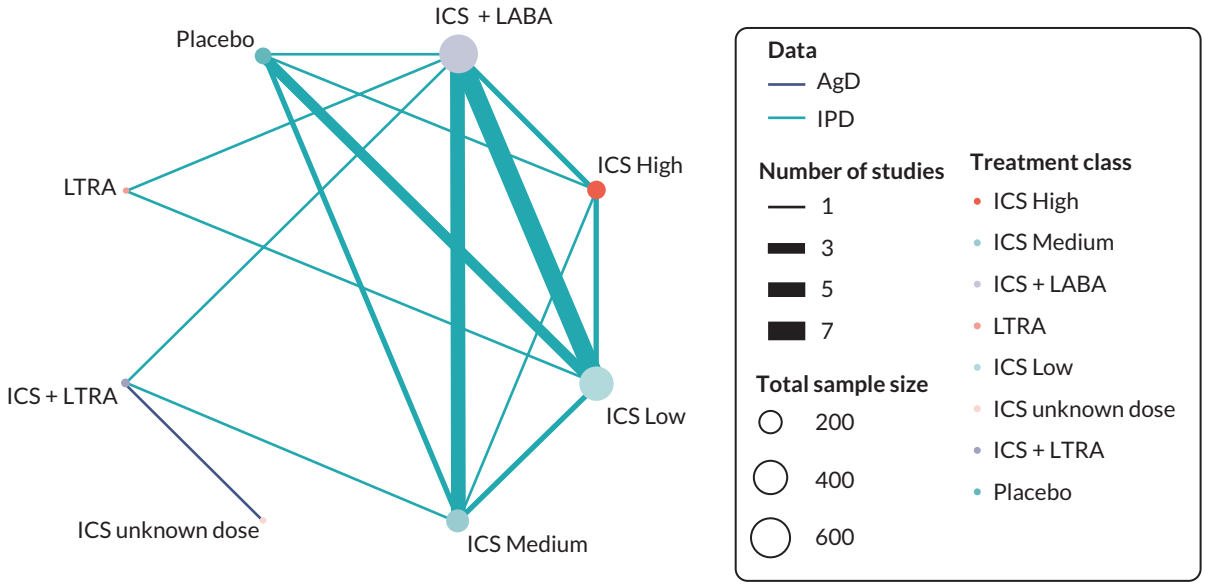

FIGURE 44 Network diagram of studies for the outcome FEV_1 and the covariate sex.

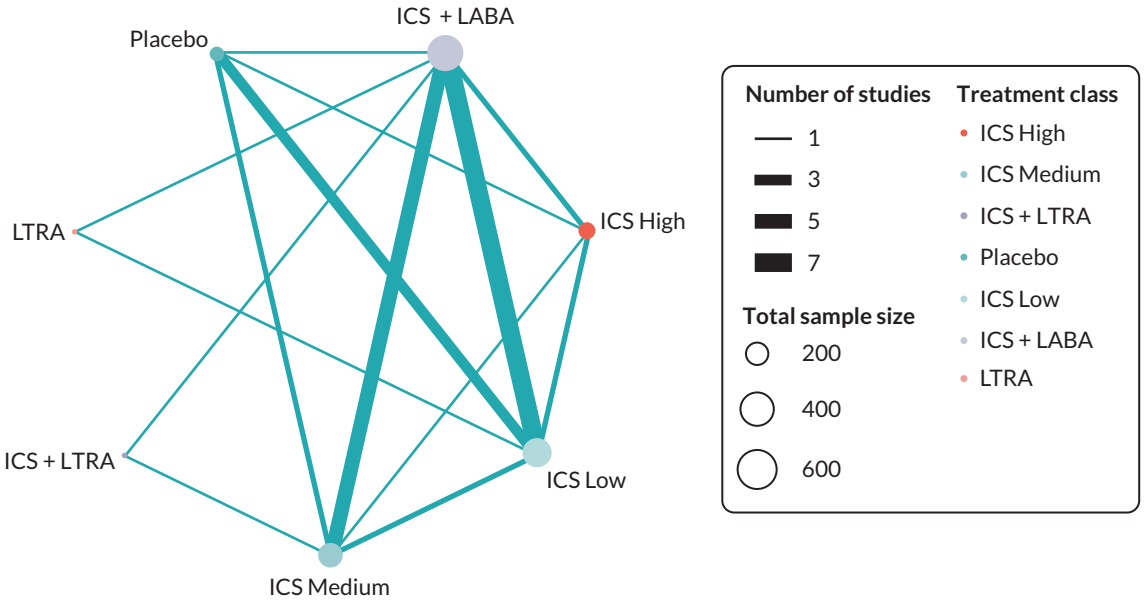

FIGURE 45 Network diagram of studies for the outcome FEV_1 and the covariate ethnicity.

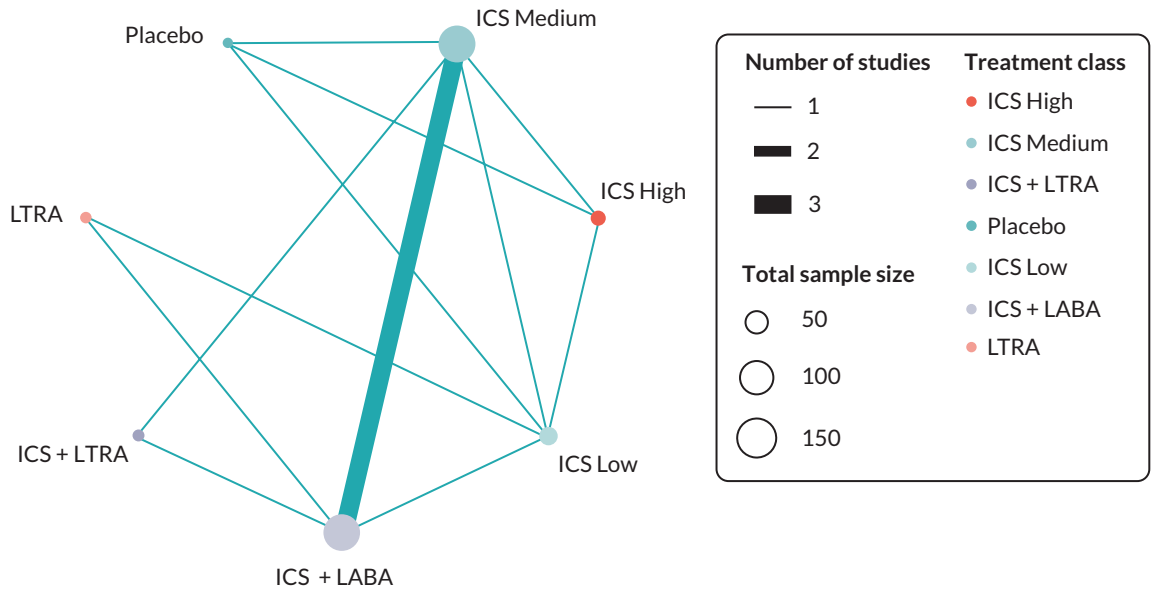

FIGURE 46 Network diagram of studies for the outcome FEV_1 and the covariate eczema.

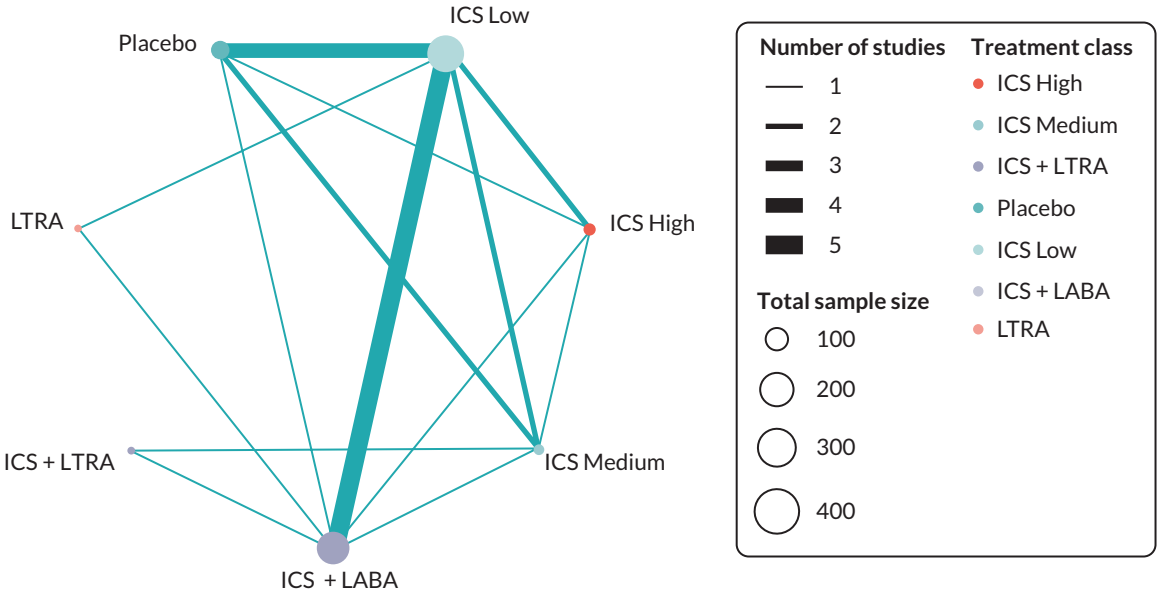

FIGURE 47 Network diagram of studies for the outcome FEV_1 and the covariate eosinophilia.

TABLE 65 Covariate distributions for covariates for the outcome FEV_1

Trial	Comparison	Type	Mean age	Female (%)	Hispanic or Latino ethnicity (%)	Eczema (%)	Eosinophilic *eosinophilia* (%)
Bernstein (2015)[48]	1	IPD	14.61	39	42	–	43
Carroll (2010)[51]	1	IPD	10.57	41	0	–	–
Oliver (2016)[62]	1	IPD	8.06	39	69	–	40
Scott (2005)[65]	1	IPD	8.87	39	9	–	54
de Blic (2009)[52]	2	IPD	8.06	36	4	88	–
Gappa (2009)[54]	2	IPD	–	31	0	–	–
Martin (2020)[58]	2	IPD	13.73	36	0	–	–
Murray (2010)[59]	2	IPD	8	71	0	100	–
O'Byrne (2014)[61]	3	IPD	15.8	20	0	–	22
Verberne (1998)[71]	3	IPD	11.11	32	0	–	–
Oliver (2016)[63]	4	IPD	8.1	36	49	–	33
Woodcock (2014)[74]	13	IPD	14.83	33	17	–	67
Visitsunthorn (2011)[91]	19	AgD	9	13	–	–	–
Sorkness (2007)[66]	1, 16, 17	IPD	9.35	31	27	61	63
Lötvall (2014)[56]	1, 2, 12	IPD	14.3	40	70	–	–
Lötvall (2014)[56]	1, 2, 12	IPD	14.16	60	48	–	–
Bleecker (2014)[50]	1, 4, 7	IPD	14.41	39	28	–	23
Lemanske (2010)[3]	2, 8, 10	IPD	10.61	26	45	23	45
Lötvall (2014)[57]	4, 5, 12	IPD	13.96	42	4	–	30
Bleecker (2012)[49]	4, 5, 6, 12, 13, 14	IPD	14.15	40	13	60	51

TABLE 66 Model comparison assessments from NMA models including interactions for the outcome FEV_1

Interaction	Model	Number of trials (no. of participants)	Number of data points	Residual deviance	Effective number of parameters (Pd)	DIC	Between trial SD
Treatment by *age*	Fixed-effect without interactions	18 (1657)	1659	1616.8	−2196	−579.2	-
	Fixed-effect with interactions	18 (1657)	1659	1616.2	−2330.5	−714.3	-
	Random-effects with interactions	18 (1657)	1659	1618.3	−2299.9	−681.6	0.05 (0.00, 0.14)
Treatment by *sex*	Random-effects without interactions	20 (1937)	1910	1864.3	−1193.8	670.6	0.04 (0.00, 0.12)
	Fixed-effect with interactions	20 (1937)	1910	1866.9	−1105.4	761.5	–
	Random-effects with interactions	20 (1937)	1910	1866.3	−1120	746.2	0.04 (0.00, 0.12)
Treatment by *ethnicity*	Random-effects without interactions	19 (1908)	1908	1865.7	−1205.8	659.8	0.04 (0.00, 0.12)
	Fixed-effect with interactions	19 (1908)	1908	1864.6	−1002.8	861.7	–
	Random-effects with interactions	19 (1908)	1908	1864.9	−1029.6	835.3	0.04 (0.00, 0.12)
Treatment by *eczema*	Fixed-effect without interactions	5 (455)	455	441.1	199.8	640.9	–
	Fixed-effect with interactions	5 (455)	455	441.0	205.7	646.7	–
	Random-effects with interactions	5 (455)	455	441.9	203.3	645.1	0.08 (0.00, 0.22)
Treatment by *eosinophilia*	Fixed-effect without interactions	11 (1024)	1024	996.9	121.4	1118.3	–
	Fixed-effect with interactions	11 (1024)	1024	996.2	128.6	1124.8	–
	Random-effects with interactions	11 (1024)	1024	998.8	137.5	1136.3	0.07 (0.00, 0.21)

TABLE 67 Parameter estimates from NMA models including interactions for the outcome FEV_1

Model		Fixed-effect NMA with interactions		Random-effects NMA with interactions	
		Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)	Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)
Treatment by *age*	ICS High vs. ICS + LABA	−0.04 (−0.15 to 0.06)	0.02 (0.00 to 0.04)	−0.03 (−0.16 to 0.12)	0.02 (0.00 to 0.04)
	ICS Low vs. ICS + LABA	−0.02 (−0.07 to 0.02)	0.00 (−0.02 to 0.01)	−0.02 (−0.09 to 0.06)	0.00 (−0.02 to 0.01)
	ICS Medium vs. ICS + LABA	−0.02 (−0.07 to 0.02)	−0.01 (−0.03 to 0.00)	−0.03 (−0.13 to 0.06)	−0.01 (−0.03 to 0.01)
	ICS unknown dose vs. ICS + LABA	−0.28 (−5.25 to 4.40)	−0.05 (−8.85 to 8.35)	−0.29 (−3.27 to 2.69)	−0.06 (−5.41 to 5.09)
	ICS + LTRA vs. ICS + LABA	**−0.10 (−0.18 to −0.01)**	0.01 (0.00 to 0.03)	−0.10 (−0.24 to 0.05)	0.01 (−0.01 to 0.03)
	LTRA vs. ICS + LABA	0.14 (−0.11 to 0.39)	0.04 (−0.05 to 0.13)	0.16 (−0.12 to 0.43)	0.04 (−0.05 to 0.13)
	Placebo vs. ICS + LABA	**−0.13 (−0.21 to −0.05)**	−0.02 (−0.04 to 0.01)	−0.13 (−0.27 to 0.00)	−0.02 (−0.05 to 0.01)
Treatment by *sex*	ICS High vs. ICS + LABA	0.02 (−0.08 to 0.12)	−0.02 (−0.15 to 0.12)	0.02 (−0.10 to 0.16)	−0.01 (−0.15 to 0.12)
	ICS Low vs. ICS + LABA	−0.02 (−0.07 to 0.03)	0.00 (−0.07 to 0.06)	−0.02 (−0.08 to 0.05)	0.00 (−0.06 to 0.07)
	ICS Medium vs. ICS + LABA	−0.01 (−0.05 to 0.02)	0.02 (−0.05 to 0.09)	−0.02 (−0.10 to 0.04)	0.02 (−0.05 to 0.09)
	ICS unknown dose vs. ICS + LABA	−0.37 (−2.74 to 2.04)	−0.14 (−9.96 to 9.57)	−0.32 (−2.79 to 1.99)	0.12 (−9.26 to 9.60)
	ICS + LTRA vs. ICS + LABA	**−0.20 (−0.32 to −0.08)**	−0.08 (−0.33 to 0.16)	**−0.20 (−0.37 to −0.05)**	−0.09 (−0.33 to 0.16)
	LTRA vs. ICS + LABA	0.22 (−0.01 to 0.44)	**0.67 (0.23 to 1.11)**	0.23 (−0.01 to 0.48)	**0.68 (0.21 to 1.14)**
	Placebo vs. ICS + LABA	**−0.12 (−0.21 to −0.03)**	0.04 (−0.11 to 0.18)	**−0.13 (−0.26 to −0.02)**	0.04 (−0.09 to 0.17)

Model		Fixed-effect NMA with interactions		Random-effects NMA with interactions	
		Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)	Log OR at the mean covariate value (95% CrI)	Regression coefficient for the treatment by covariate interaction (95% CrI)
Treatment by *ethnicity*	ICS High vs. ICS + LABA	0.05 (−0.10 to 0.20)	−0.10 (−0.56 to 0.34)	0.05 (−0.11 to 0.22)	−0.08 (−0.52 to 0.36)
	ICS Low vs. ICS + LABA	−0.02 (−0.07 to 0.02)	−0.05 (−0.12 to 0.03)	−0.02 (−0.09 to 0.05)	−0.04 (−0.12 to 0.04)
	ICS Medium vs. ICS + LABA	0.02 (−0.03 to 0.08)	−0.16 (−0.32 to 0.00)	0.01 (−0.08 to 0.09)	−0.16 (−0.32 to 0.00)
	ICS + LTRA vs. ICS + LABA	**−0.18 (−0.30 to −0.07)**	−0.08 (−0.23 to 0.06)	**−0.18 (−0.34 to −0.03)**	−0.07 (−0.21 to 0.07)
	LTRA vs. ICS + LABA	0.12 (−0.16 to 0.39)	0.23 (−0.32 to 0.77)	0.13 (−0.15 to 0.40)	0.23 (−0.32 to 0.77)
	Placebo vs. ICS + LABA	**−0.11 (−0.20 to −0.02)**	0.03 (−0.12 to 0.18)	**−0.13 (−0.27 to −0.01)**	0.04 (−0.11 to 0.19)
Treatment by *eczema*	ICS High vs. ICS Medium	0.14 (−0.15 to 0.44)	−0.01 (−0.37 to 0.35)	0.12 (−0.24 to 0.46)	0.00 (−0.37 to 0.35)
	ICS Low vs. ICS Medium	0.08 (−0.14 to 0.28)	−0.03 (−0.27 to 0.21)	0.05 (−0.25 to 0.30)	−0.03 (−0.27 to 0.20)
	ICS + LABA vs. ICS Medium	0.00 (−0.04 to 0.05)	0.03 (−0.10 to 0.15)	−0.01 (−0.17 to 0.13)	0.04 (−0.10 to 0.17)
	ICS + LTRA vs. ICS Medium	**−0.18 (−0.32 to −0.05)**	−0.03 (−0.20 to 0.13)	−0.19 (−0.42 to 0.04)	−0.02 (−0.19 to 0.14)
	LTRA vs. ICS Medium	0.24 (−0.11 to 0.59)	0.12 (−0.40 to 0.63)	0.22 (−0.22 to 0.62)	0.12 (−0.40 to 0.63)
	Placebo vs. ICS Medium	−0.30 (−0.78 to 0.19)	−0.51 (−1.20 to 0.17)	−0.30 (−0.80 to 0.19)	−0.49 (−1.14 to 0.19)
Treatment by *eosinophilia*	ICS High vs. ICS Low	0.16 (−0.08 to 0.39)	−0.14 (−0.45 to 0.18)	0.15 (−0.14 to 0.42)	−0.14 (−0.44 to 0.17)
	ICS Medium vs. ICS Low	0.03 (−0.12 to 0.19)	−0.08 (−0.34 to 0.16)	0.03 (−0.17 to 0.22)	−0.08 (−0.34 to 0.15)
	ICS + LABA vs. ICS Low	0.01 (−0.05 to 0.06)	**0.11 (0.03 to 0.19)**	0.00 (−0.12 to 0.10)	**0.10 (0.03 to 0.18)**
	ICS + LTRA vs. ICS Low	**−0.15 (−0.28 to −0.01)**	−0.05 (−0.22 to 0.11)	−0.15 (−0.39 to 0.08)	−0.05 (−0.22 to 0.11)
	LTRA vs. ICS Low	0.04 (−0.29 to 0.36)	0.26 (−0.32 to 0.81)	0.05 (−0.30 to 0.42)	0.25 (−0.29 to 0.79)
	Placebo vs. ICS Low	**−0.09 (−0.17 to −0.01)**	−0.03 (−0.18 to 0.13)	−0.11 (−0.28 to 0.01)	−0.03 (−0.18 to 0.12)

Note
Posterior mean (95% CrI) presented. Bold indicates that zero is excluded from the CrI. The regression coefficient represents the change in the MD per unit increase in the covariate value.

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