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Addition of long-acting beta2 agonists or long-acting muscarinic antagonists versus doubling the dose of inhaled corticosteroids (ICS) in adolescents and adults with uncontrolled asthma with medium dose ICS: a systematic review and network meta-analysis

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Abstract

Background

Inhaled corticosteroids (ICS) are the mainstay treatment for persistent asthma. Escalating treatment is required when asthma is not controlled with ICS therapy alone which would include, but not limited to, adding a long-acting beta2-agonist (LABA) or a long-acting muscarinic antagonist (LAMA) or doubling the dose of ICS.

Objectives

To assess the efficacy and safety of adding a LABA or LAMA to ICS therapy versus doubling the dose of ICS in adolescents and adults whose asthma is not well controlled on medium dose (MD)-ICS using a network meta-analysis (NMA), and to provide a ranking of these treatments according to their efficacy and safety

Search methods

We searched Cochrane Airways Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Global Health, ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform for pre-registered randomised controlled trials (RCTs) of at least 12 weeks of study duration from January 2008 to 19 December 2022.

Selection criteria

We searched studies including adolescents and adults with uncontrolled asthma who had been treated with or were eligible for MD-ICS comparing it to high dose (HD)-ICS, ICS/LAMA or ICS/LABA. We excluded cluster and crossover RCTs.

Data collection and analysis

We conducted a systematic review and network meta-analysis according to the previously published protocol. We used Cochrane's Screen4ME workflow to assess search results and Grading of Recommendations Assessment, Development and Evaluation to assess the quality of evidence. The primary outcome is asthma exacerbations (moderate and severe asthma exacerbations).

Main results

We included 38,276 participants from 35 studies (median duration 24 weeks [range 12 to 78]; mean age 44.1; male 38%; White 69%; mean forced expiratory volume in 1 second 2.1 litters and 68% of predicted).

MD- and HD-ICS/LABA likely reduce and MD-ICS/LAMA possibly reduces moderate to severe asthma exacerbations compared to MD-ICS (hazard ratio (HR) 0.70; 95% credible interval (CrI) 0.59 to 0.82; moderate certainty, HR 0.59; 95% CrI 0.46 to 0.76; moderate certainty, and HR 0.56; 95% CrI 0.38 to 0.82; low certainty, respectively) whereas HD-ICS probably does not (HR 0.94; 95% CrI 0.70 to 1.24; moderate certainty). There is no clear evidence to suggest any combination therapy or HD-ICS reduces severe asthma exacerbations compared to MD-ICS (low to moderate certainty).

This study suggests no clinically meaningful differences in the symptom or quality of life score between dual combinations and monotherapy (low to high certainty).

MD- and HD-ICS/LABA increase or likely increase the odds of Asthma Control Questionnaire (ACQ) responders at 6 and 12 months compared to MD-ICS (odds ratio (OR) 1.47; 95% CrI 1.23 to 1.76; high certainty and OR 1.59; 95% CrI 1.31 to 1.94; high certainty at 6 months and OR 1.61; 95%CrI 1.22 to 2.13; moderate certainty and OR 1.55; 95% CrI 1.20 to 2.00; high certainty at 12 months, respectively).

MD-ICS/LAMA probably increases the odds of ACQ responders at 6 months (OR 1.32; 95% CrI 1.11 to 1.57; moderate certainty). No data was available at 12 months. There is no clear evidence to suggest HD-ICS increases the odds of ACQ responders or improves the symptom or qualify of life score compared to MD-ICS [very low to high certainty].

There is no evidence to suggest that ICS/LABA or ICS/LAMA reduces asthma-related or all-cause serious adverse events compared to MD-ICS (very low to high certainty). HD-ICS results in or likely results in little or no difference in the included safety outcomes compared to MD-ICS as well as HD-ICS/LABA compared to MD-ICS/LABA.

The pairwise meta-analysis shows that MD-ICS/LAMA likely reduces all-cause adverse events (AEs) and results in a slight reduction in treatment discontinuation due to AEs compared to MD-ICS (risk ratio (RR) 0.86; 95% confidence interval (CI) 0.77 to 0.96; n=2238; 4 studies; moderate certainty and RR 0.51; 95% CI 0.26 to 0.99; n=2239; 4 studies; absolute risk reduction 10 fewer per 1000 subjects; moderate certainty, respectively). The NMA evidence is in agreement with the pairwise evidence on treatment discontinuation due to AEs, but very uncertain on all-cause AEs due to imprecision and heterogeneity.

Authors' conclusions

The review findings suggest MD- or HD-ICS/LABA and MD-ICS/LAMA reduce moderate to severe asthma exacerbations and increase the odds of ACQ responders compared to MD-ICS whereas HD-ICS probably does not. The evidence is generally stronger for MD- and HD-ICS/LABA than for MD-ICS/LAMA primarily due to larger evidence base. There is no evidence to suggest ICS/LABA, ICS/LAMA or HD-ICS/LABA reduces severe asthma exacerbations or SAEs compared to MD-ICS. MD-ICS/LAMA likely reduces all-cause AEs and results in a slight reduction in treatment discontinuation due to AEs compared to MD-ICS.

Above findings may assist deciding on a treatment option in the stepwise approach of asthma management. Longer-term safety of higher than medium dose ICS needs to be addressed in phase 4 or observational studies given the median duration of included studies was 6 months.

Plain language summary

Preferred treatment options for uncontrolled asthma on medium-dose inhaled corticosteroids.

Key messages

• Adding a long-acting beta2-agonist (LABA) or a long-acting muscarinic antagonist (LAMA) to medium-dose ICS likely reduces asthma attacks requiring treatment with oral steroids and increases the odds of satisfactory symptom control compared to ICS alone, whereas doubling the dose of inhaled corticosteroids (ICS) probably doesn't. The database we found was much larger for LABAs than for LAMAs.

• We need to learn more about the long-term side effects of high-dose ICS because the average duration of the included studies was 6 months. Using the lowest effective ICS doses is encouraged to minimise corticosteroid-associated side effects.

What is asthma, and how is it treated?

Asthma is a chronic respiratory condition characterised by inflammation and narrowing of the airways that causes symptoms such as wheezing, coughing, chest tightness, and shortness of breath. Treatment involves the use of inhalers, which are relievers (e.g., short-acting bronchodilators) and, if needed, preventers (e.g., ICS), as well as avoiding triggers and maintaining a healthy lifestyle.

What did we want to find out?

What would be the preferred option when asthma is not well controlled while on medium-dose ICS?

Why is the question important?

Uncontrolled asthma adversely affects quality of life and could lead to an emergency room or hospital visit. Reducing symptoms and complications of asthma is of paramount importance.

How did we do?

We collected and analysed data from 35 studies, which included a total of 38,276 people with uncontrolled asthma while on medium-dose ICS, using a special method called network meta-analysis. This enabled us to simultaneously compare multiple inhaler groups. We compared adding a LABA or a LAMA to medium dose ICS, versus doubling the dose of ICS or using medium dose ICS alone.

What did we find?

Adding a long-acting beta2-antagonist (LABA) or a long-acting muscarinic antagonist (LAMA) to medium-dose ICS likely reduces asthma attacks requiring treatment with oral steroids. It also increases the odds of satisfactory symptom control compared to ICS alone whereas doubling the dose of ICS probably does not. The database we found was much larger for LABAs than for LAMAs.

Adding a LABA or LAMA to medium-dose ICS or doubling the dose of ICS unlikely reduces asthma-related hospitalizations or serious side effects. The addition of a LAMA to ICS possibly reduces side effects and treatment discontinuation. However, the combination of ICS/LAMA therapy requires two separate inhalers whereas ICS/LABA combinations are available in a single inhaler.

What are the limitations of the evidence?

We need to learn more about the long-term side effects of high-dose ICS because the average duration of the included studies was 6 months. The study results might not be relevant to people who smoke or to individuals who experience side effects from anticholinergic treatment because those individuals were either not included or were very few in this review.

How up to date is this evidence?

This review is up-to-date to December 2022.

Summary of findings

Summary of findings 1

NMA Summary of Findings for severe exacerbations

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, LD-ICS/LABA, MD-ICS/LAMA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: Severe asthma exacerbation

Setting: Outpatient

Total studies: 17 RCTs **Total Participants: 22819**	**Hazard ratio**** **(95% CrI)**	**Anticipated absolute effect at the end of 1 year*** (95% CrI)**		**Certainty of the evidence**	**Ranking****** **(95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS**			
HD-ICS (Direct evidence; 4 RCTs; 3003 participants)	**1.28** (0.47 to 4.22)	83 per 1000	18 per 1000 more (from 35 fewer to 208 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**4.0** (1.0 to 6.0)	HD-ICS likely results in little to no difference in severe exacerbations compared to MD-ICS.
LD-ICS/LABA (Direct evidence; 0 RCTs; 0 participants)	**0.65** (0.07 to 6.18)	42 per 1000	23 per 1000 fewer (from 60 fewer to 334 more)	⊕⊕◯◯ **Low** Due to imprecision[2]	**2.0** (1.0 to 6.0)	The evidence suggests that LD-ICS/LABA results in little to no difference in severe exacerbations compared to MD-ICS.
MD-ICS/LAMA	**0.41** (0.01 to 8.62)	26 per 1000	39 per 1000 fewer	⊕⊕◯◯ **Low**	**1.0** (1.0 to 6.0)	The evidence suggests that MD-ICS/LAMA results in little to no

(Direct evidence; 1 RCT; 282 participants)			(from 64 fewer to 492 more)	Due to imprecision[2]		difference in severe exacerbations compared to MD-ICS.
MD-ICS/LABA (Direct evidence; 10 RCTs; 15651 participants)	**1.00** (0.50 to 2.34)	65 per 1000	0 per 1000 fewer (from 33 fewer to 86 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**5.0** (2.0 to 6.0)	MD-ICS/LABA likely results in little to no difference in severe exacerbations compared to MD-ICS.
HD-ICS/LABA (Direct evidence; 3 RCTs; 3319 participants)	**1.29** (0.52 to 3.98)	83 per 1000	18 per 1000 more (from 31 fewer to 192 more)	⊕⊕◯◯ **Low** Due to imprecision[1] and heterogeneity[3]	**3.0** (1.0 to 6.0)	The evidence suggests that HD-ICS/LAMA results in little to no difference in severe exacerbations compared to MD-ICS.
MD-ICS	Reference Comparator	65 per 1000[4]	Reference Comparator	Reference Comparator	**4.0** (1.0 to 6.0)	Reference Comparator

NMA-SoF table definitions

** Network Meta-Analysis estimates are reported as hazard ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect (exacerbation rate at 1 year). Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1] Downgraded one level for serious imprecision. Due to wide confidence intervals and/or suboptimal sample size in the direct and/or indirect estimate(s).

[2] Downgraded two levels for very serious imprecision. Due to wide confidence intervals and suboptimal sample sizes in the direct and/or indirect estimate(s).

[3] Downgraded one level for substantial heterogeneity I^2>= 50% to 90% in the direct pairwise comparison.

[4] Based on the average rate in patients treated with MD-ICS in the included studies.

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; RCT: randomised controlled trial.

Summary of findings 2

NMA Summary of Findings for moderate to severe exacerbations

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, LD-ICS/LABA, MD-ICS/LAMA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: Moderate-to-severe asthma exacerbation

Setting: Outpatient

Total studies: 25 RCTs **Total Participants: 25583**	**Hazard ratio**** **(95% CrI)**	**Anticipated absolute effect at the end of 1 year*** (95% CrI)**		**Certainty of the evidence**	**Ranking**** **(95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS**			
HD-ICS (Direct evidence; 4 RCTs; 1685 participants)	**0.94** (0.70 to 1.24)	214 per 1000	13 per 1000 fewer (from 68 fewer to 55 more)	⊕⊕⊕◯ **Moderate** Due to risk of bias[1]	**5.0** (4.0 to 6.0)	HD-ICS likely results in little to no difference in moderate to severe exacerbations compared to MD-ICS.
LD-ICS/LABA (Direct evidence; 0 RCTs; 0 participants)	**0.42** (0.15 to 1.11)	95 per 1000	132 per 1000 fewer (from 193 fewer to 25 more)	⊕⊕◯◯ **Low** Due to imprecision[2]	**1.0** (1.0 to 6.0)	The evidence suggests LD-ICS/LABA reduces moderate to severe exacerbations compared to MD-ICS
MD-ICS/LAMA (Direct evidence; 2 RCTs; 679 participants)	**0.56** (0.38 to 0.82)	127 per 1000	100 per 1000 fewer (from 141 fewer to 41 fewer)	⊕⊕◯◯ **Low** Due to imprecision[2]	**2.0** (1.0 to 4.0)	The evidence suggests MD-ICS/LAMA reduces moderate to severe exacerbations compared to MD-ICS

MD-ICS/LABA (Direct evidence; 12 RCTs; 7569 participants)	**0.70** (0.59 to 0.82)	159 per 1000	68 per 1000 fewer (from 93 fewer to 41 fewer)	⊕⊕⊕◯ **Moderate** Due to risk of bias[1]	**4.0** (2.0 to 4.0)	MD-ICS/LABA probably reduces moderate to severe exacerbations compared to MD-ICS
HD-ICS/LABA (Direct evidence; 2 RCTs; 1759 participants)	**0.59** (0.46 to 0.76)	134 per 1000	93 per 1000 fewer (from 122 fewer to 54 fewer)	⊕⊕⊕◯ **Moderate** Due to risk of bias[1]	**2.0** (1.0 to 4.0)	HD-ICS/LABA probably reduces moderate to severe exacerbations compared to MD-ICS
MD-ICS	Reference Comparator	227 per 1000[4]	Reference Comparator	Reference Comparator	**6.0** (5.0 to 6.0)	Reference Comparator

NMA-SoF table definitions

** Network Meta-Analysis estimates are reported as hazard ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect (exacerbation rate at 1 year). Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1] Downgraded one level: Serious risk of bias due to missing data and/or a lack of robustness in the direct and/or indirect estimate(s).

[2] Downgraded two levels for very serious imprecision. Due to wide confidence intervals and suboptimal sample sizes in the direct and/or indirect estimate(s).

[3] Based on the average rate in patients treated with MD-ICS in the included studies.

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; RCT: randomised controlled trial.

Summary of findings 3

NMA Summary of Findings for change from baseline in ACQ score at 12 months

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: Change from baseline in ACQ scores at 12 months

Setting: Outpatient

Total studies: 4 RCTs **Total Participants: 5681**	**Relative effect (95% CrI)**	**Anticipated absolute effect** (95% CrI)**		**Certainty of the evidence**	**Ranking*** (95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS[1]**			
HD-ICS (Direct evidence; 2 RCTs; 1005 participants)	**-0.05** (-0.15 to 0.04)	**0.98** (0.89 to 1.08)	Change from baseline in ACQ score was 0.05 higher (0.04 lower to 0.15 higher)	⊕⊕⊕⊕ **High**	**3.0** (3.0 to 4.0)	HD-ICS results in little to no difference in ACQ score at 12 months compared to MD-ICS
MD-ICS/LABA (Direct evidence; 1 RCT; 774 participants)	**-0.18** (-0.26 to -0.09)	**1.11** (1.03 to 1.19)	Change from baseline in ACQ score was 0.18 lower (0.09 lower to 0.26 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**2.0** (1.0 to 2.0)	MD-ICS/LABA is unlikely to result in clinically meaningful improvement in ACQ scores at 12 months compared to MD-ICS[3]
HD-ICS/LABA (Direct evidence; 2 RCTs; 2863 participants)	**-0.2** (-0.26 to -0.14)	**1.13** (1.07 to 1.19)	Change from baseline in ACQ score was 0.2 higher (0.14 higher to 0.26 higher)	⊕⊕⊕⊕ **High**	**1.0** (1.0 to 2.0)	HD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 12 months compared to MD-ICS[3]
MD-ICS	Reference Comparator[1]	**0.93**	Reference Comparator	Reference Comparator	**4.0** (3.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 The mean change from baseline in ACQ score was 0.93 with MD-ICS.
2 Downgraded one level for serious imprecision due to small sample sizes in the direct and/or indirect estimate(s).
3 Minimal clinically important difference is 0.5.

ACQ: Asthma Control Questionnaire; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose; RCT: randomised controlled trial.

Summary of findings 4

NMA Summary of Findings for change from baseline in AQLQ score at 6 months

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, LD-ICS/LABA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: Change from baseline in AQLQ scores at 6 months

Setting: Outpatient

Total studies: 6 RCTs **Total Participants: 4276**	**Relative effect (95% CrI)**	**Anticipated absolute effect** (95% CrI)**		**Certainty of the evidence**	**Ranking*** (95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS[1]**			
HD-ICS (Direct evidence; 0 RCTs; 0 participants)	**0.02** (-0.20 to 0.25)	**0.54** (0.31 to 0.76)	Change from baseline in AQLQ score was 0.02 higher (0.20 lower to 0.25 higher)	⊕◯◯◯ **Very low** Due to imprecision[2] and risk of bias[3]	**4.0** (1.0 to 5.0)	The evidence is very uncertain
LD-ICS/LABA (Direct evidence; 3 RCTs; 1719 participants)	**0.18** (0.08 to 0.29)	**0.70** (0.59 to 0.80)	Change from baseline in AQLQ score was 0.18 higher (0.08 higher to 0.29 higher)	⊕⊕⊕⊕ **High**	**1.0** (1.0 to 3.0)	LD-ICS/LABA results in no clinically important difference in CFB in AQLQ at 6 months compared to MD-ICS[4]
MD-ICS/LABA (Direct evidence; 3 RCTs; 1359 participants)	**0.11** (-0.09 to 0.30)	**0.64** (0.53 to 0.74)	Change from baseline in AQLQ score was 0.11 higher (0.09 lower to 0.30 higher)	⊕⊕⊕⊕ **High**	**2.0** (1.0 to 4.0)	MD-ICS/LABA results in no difference in CFB in AQLQ at 6 months compared to MD-ICS
HD-ICS/LABA (Direct evidence; 0 RCTs; 0 participants)	**0.07** (-0.07 to 0.21)	**0.58** (0.44 to 0.72)	Change from baseline in AQLQ score was 0.07 higher (0.07 lower to 0.21 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[5]	**3.0** (2.0 to 5.0)	HD-ICS/LABA likely results in little to no difference in CFB in AQLQ at 6 months compared to MD-ICS
MD-ICS	Reference Comparator[1]	**0.57**	Reference Comparator	Reference Comparator	**5.0** (3.0 to 5.0)	Reference Comparator

NMA-SoF table definitions
** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.
*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 The mean change from baseline in AQLQ score was 0.57 with MD-ICS.
2 Downgraded for two levels for very serious imprecision due to small sample sizes in the indirect estimate.
3 Downgraded one level for serious risk of bias due to high dropout rates in the indirect estimate and indirectness.
4 Minimal clinically important difference is 0.5.
5 Downgraded one level for serious imprecision due to small sample sizes in the indirect estimate.

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose; RCT: randomised controlled trial.

Summary of findings 5

NMA Summary of Findings for ACQ responders at 6 months

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, MD-ICS/LAMA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: ACQ response at 6 months

Setting: Outpatient

Total studies: 6 RCTs **Total Participants: 7252**	**Risk ratio**** **(95% CrI)**	**Anticipated absolute effect*** (95% CrI)**		**Certainty of the evidence**	**Ranking****** **(95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS**			
HD-ICS (Direct evidence; 1 RCT; 798 participants)	**1.09** (0.99 to 1.18)	679 per 1000	56 per 1000 more (from 6 fewer to 112 more)	⊕⊕◯◯ **Low** Due to imprecision[1]	**4.0** (1.0 to 5.0)	The evidence suggests that HD-ICS results in little to no difference in ACQ response at 6 months compared to MD-ICS
MD-ICS/LAMA (Direct evidence; 3 RCTs; 2219 participants)	**1.32** (1.11 to 1.57)	685 per 1000	62 per 1000 more (from 25 more to 100 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**3.0** (1.0 to 4.0)	MD-ICS/LAMA likely increases ACQ responders at 6 months compared to MD-ICS
MD-ICS/LABA (Direct evidence; 2 RCTs; 1853 participants)	**1.47** (1.23 to 1.76)	710 per 1000	87 per 1000 more (from 50 more to 118 more)	⊕⊕⊕⊕ **High**	**2.0** (1.0 to 4.0)	MD-ICS/LABA increases ACQ responders at 6 months compared to MD-ICS
HD-ICS/LABA (Direct evidence; 1 RCT; 1210 participants)	**1.59** (1.31 to 1.94)	723 per 1000	100 per 1000 more (62 more to 137 more)	⊕⊕⊕⊕ **High**	**1.0** (1.0 to 3.0)	HD-ICS/LABA increases ACQ responders at 6 months compared to MD-ICS
MD-ICS	Reference Comparator	623 per 1000[3]	Reference Comparator	Reference Comparator	**5.0** (4.0 to 5.0)	Reference Comparator

NMA-SoF table definitions

** Network Meta-Analysis estimates are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS/ group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Downgraded for two levels for very serious imprecision due to suboptimal sample size in the direct and/or indirect estimate(s).
2 Downgraded one level for serious imprecision due to suboptimal sample size in the direct and/or indirect estimate(s).
3 Based on the average rate in patients treated with MD-ICS in the included studies.

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: medium dose; RCT: randomised controlled trial.

Summary of findings 6

NMA Summary of Findings for ACQ responders at 12 months

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: ACQ response at 12 months

Setting: Outpatient

Total studies: 3 RCTs Total Participants: 3828	Risk ratio** (95% CrI)	Anticipated absolute effect*** (95% CrI)		Certainty of the evidence	Ranking**** (95% CrI)	Interpretation of Findings
		With intervention	Difference compared to MD-ICS			
HD-ICS (Direct evidence; 2 RCTs; 1011 participants)	**1.03** (0.94 to 1.11)	681 per 1000	20 per 1000 more (from 40 fewer to 73 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**3.0** (3.0 to 4.0)	Probably little or no difference
MD-ICS/LABA (Direct evidence; 1 RCT; 774 participants)	**1.15** (1.07 to 1.22)	760 per 1000	99 per 1000 fewer (from 46 more to 145 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**1.0** (1.0 to 2.0)	Probably superior
HD-ICS/LABA (Direct evidence; 1 RCT; 1167 participants)	**1.14** (1.06 to 1.20)	754 per 1000	93 per 1000 more (40 more to 132 more)	⊕⊕⊕⊕ **High**	**2.0** (1.0 to 2.0)	Superior
MD-ICS	Reference Comparator	661 per 1000[3]	Reference Comparator	Reference Comparator	**4.0** (3.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

** Network Meta-Analysis estimates are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

1 Downgraded one level for serious imprecision due to suboptimal sample size in the direct and/or indirect estimate(s).
2 Downgraded one level for substantial heterogeneity I2>= 50% to 90% in the direct estimate.
3 Based on the average rate in patients treated with MD-ICS in the included studies.

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose; RCT: randomised controlled trial.

Summary of findings 7

NMA Summary of Findings for dropouts due to AE

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, LD-ICS/LABA, MD-ICS/LAMA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: Dropouts due to adverse events

Setting: Outpatient

Total studies: 34 RCTs Total Participants: 32684	Risk ratio** (95% CrI)	Anticipated absolute effect*** (95% CrI)		Certainty of the evidence	Ranking**** (95% CrI)	Interpretation of Findings
		With intervention	Difference compared to MD-ICS			
HD-ICS (Direct evidence; 6 RCTs; 2211 participants)	**0.75** (0.41 to 1.36)	12 per 1000	5 per 1000 fewer (from 10 fewer to 6 more)	⊕⊕⊕⊕ **High**	**3.0** (1.0 to 6.0)	HD-ICS results in little to no difference in dropouts due to adverse event compared to MD-ICS
LD-ICS/LABA (Direct evidence; 1 RCT; 5846 participants)	**0.85** (0.43 to 1.69)	14 per 1000	3 per 1000 fewer (from 10 fewer to 11 more)	⊕⊕⊕⊕ **High**	**3.0** (1.0 to 6.0)	LD-ICS/LABA results in little to no difference in dropouts due to adverse event compared to MD-ICS
MD-ICS/LAMA (Direct evidence; 4 RCTs; 2239	**0.54** (0.24 to 1.09)	9 per 1000	8 per 1000 fewer (from 13 fewer to 1 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**1.0** (1.0 to 5.0)	MD-ICS/LAMA probably results in slight decrease in dropouts due to adverse event compared to MD-ICS

participants)						
MD-ICS/LABA (Direct evidence; 21 RCTs; 20326 participants)	**0.97** (0.73 to 1.28)	16 per 1000	1 per 1000 fewer (from 5 fewer to 4 more)	⊕⊕⊕⊕ **High**	**5.0** (2.0 to 6.0)	MD-ICS/LABA results in little to no difference in dropouts due to adverse event compared to MD-ICS
HD-ICS/LABA (Direct evidence; 4 RCTs; 2750 participants)	**0.82** (0.48 to 1.33)	14 per 1000	3 per 1000 fewer (from 9 fewer to 5 more)	⊕⊕⊕⊕ **High**	**3.0** (1.0 to 6.0)	HD-ICS/LABA results in little to no difference in dropouts due to adverse event compared to MD-ICS
MD-ICS	Reference Comparator	17 per 1000[2]	Reference Comparator	Reference Comparator	**5.0** (2.0 to 6.0)	Reference Comparator

NMA-SoF table definitions
** Network Meta-Analysis estimates of **random-effects model** are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.
*** Anticipated absolute effect. Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS group.
**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 Downgraded one level for serious imprecision due to confidence intervals crossing the null effect in the direct and/or indirect estimate(s).
2 Based on the average rate in patients treated with MD-ICS in the included studies.

AE: adverse event; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; RCT: randomised controlled trial.

Background

Description of the condition

Asthma is a chronic inflammatory airway disease that has a daily impact on the lives of millions of people. In 2018, it was estimated that asthma affects 334 million people worldwide and represents 13.2 million years lived with disability. Globally, asthma-related deaths were estimated at 420,000 in 2016, or more than 1000 deaths per day (Nurmagambetov 2018). Within the United States, asthma affects one in 13 Americans, or approximately 25 million people. Furthermore, the annual healthcare burden of asthma in the US accounts for 9.8 million ambulatory clinic visits, 1.8 million emergency room visits, and 188,968 hospitalisations (Zahran 2018). Asthma represents a large financial, social, and medical burden to society, and therefore it is imperative that providers who treat asthma take a robust, evidence-based approach.

Description of the intervention

Various expert panels, including the Global Initiative on Asthma (GINA 2022) and the National Asthma Education and Prevention Program's Expert Panel Review (NAEPP) (EPR-4 2020), have developed a series of stepwise recommendations in the management of asthma. The preferred approach for managing persistent asthma involves daily use of a combination of low-dose ICS and formoterol, which can also be used as needed for symptom relief. However, if this preferred treatment is not appropriate or effective for a particular individual, an alternative option is to use medium-dose ICS daily and rely on a short-acting beta-agonist on an as-needed basis for symptom relief.

The 2022 GINA guidelines recommend escalating therapy to a medium-dose ICS in conjunction with long-acting beta2-agonist (LABA) therapy, rather than daily use of a high-dose ICS or adding a long-acting muscarinic antagonist (LAMA), in cases where medium-dose ICS monotherapy has proven ineffective. The EPR-4 2020 concluded that adding a LAMA to ICS monotherapy was more effective than ICS monotherapy. When comparing LAMA with LABA, adding a LAMA to ICS monotherapy was not more efficacious than addition of a LABA to ICS monotherapy (Peters 2010; Wechsler 2015). The escalation of treatment described above can improve asthma symptoms and quality of life and reduce exacerbations (Thomas 2011).

Despite well-developed guidelines for the management of asthma, there is a lack of robust evidence which compares various doses of ICS monotherapy to each other and to combination therapies of ICS/LABA and ICS/LAMA.

How the intervention might work

Inhaled corticosteroids (ICS) represent a cornerstone in the management of asthma. The mechanism of ICS in the setting of asthma revolves around inhibition of steroid-sensitive genes which decreases the transcription of inflammatory cytokines, ultimately resulting in reduction of chronic airway inflammation (Barnes 1993; Barnes 2010).

The LABA class of medications works by stimulation of the $beta_2$-receptors on smooth muscles of the airways, which results in prolonged bronchodilation and a membrane stabilisation effect (Derom 1992; Kips 2001). LABA therapy plays a role in the treatment of asthma. However, it has long been established that LABA should play an adjunctive role with ICS as LABA was found to be inferior to ICS in the management of asthma when used as monotherapy (Haahtela 1991). Therefore, in the management of asthma, LABA medications are not utilised until failure with ICS monotherapy has been identified.

In addition to the use of ICS and LABA medications in asthma, there are also LAMAs. The mechanism of action of LAMA in the setting of asthma is via antagonism of the muscarinic M3 receptor, which, when stimulated, typically results in bronchoconstriction. Blockade of M3 receptors by LAMA medications results in promotion of bronchodilation. Additionally, LAMAs have been shown to mediate inflammatory cell chemotaxis and activation, resulting in an anti-inflammatory effect on respiratory smooth muscles (Lipworth 2014).

Why it is important to do this review

Multiple evidence-based guidelines exist to guide clinicians in the appropriate management of asthma. However, there are gaps in the current recommendations which would benefit from further investigation via systematic review and network meta-analysis (NMA).

The meta-analyses (examination of data from a number of independent studies) conducted in the past, which reviewed ICS alone compared to ICS/LABA and ICS/LAMA, did not subclassify ICS doses into low-, medium- and high-dose (Ducharme 2010a; Ducharme 2010b; Kew 2015; Sobieraj 2018). Moreover, multiple studies demonstrated a lack of a clinical response with escalation of ICS dosing from medium- to high-doses (Holt 2001; Masoli 2004; Zhang 2014). One such study evaluated the dose-response relationship of fluticasone and concluded that most of the therapeutic benefit of inhaled fluticasone was seen with a total daily dose of 100 to 250 µg, with minimal clinical benefit identified with the use of higher doses of fluticasone (Holt 2001). At this time, GINA 2022 guidelines may not be supported by concrete evidence. Furthermore, established literature demonstrated a reduction of asthma exacerbation rates when a LAMA is added, for those who are unable to maintain adequate asthma control while on ICS monotherapy (Kerstjens 2012; Kerstjens 2015).

Therefore, we conducted a systematic review and NMA to assess the efficacy and tolerability of combination inhaler therapies compared amongst each other and varying doses of inhaled corticosteroids in the combination inhalers in patients with asthma. We compared MD-ICS, HD-ICS, LABA/ICS, and LAMA/ICS to assess frequencies of moderate (requiring oral corticosteroids) and severe (requiring hospitalisation, intubation or death) asthma exacerbations.

Objectives

To conduct NMAs to compare the efficacy and tolerability of adding a LABA or LAMA to existing ICS therapy versus doubling the ICS dose in adolescents and adults with uncontrolled asthma who have been treated with, or are eligible for, medium-dose ICS monotherapy, and to provide a ranking of these treatments based on their efficacy and safety.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of at least 12 weeks duration. Studies can be either published or unpublished. To minimise publication bias and selective reporting, studies must be pre-registered. We did not consider cluster or crossover RCTs to minimise a unit of analysis error, overestimating the treatment effects, and residual effects of crossover ICS doses. Additionally, quasi-randomized trials were not considered due to the potential introduction of biased allocation of participants to treatment groups.

Types of participants

We included studies in adolescents (aged 12 years and older) and adults with uncontrolled asthma who had been treated with or were eligible for MD-ICS monotherapy. In this review, uncontrolled asthma is defined as: Asthma Control Questionnaire (ACQ) score equal to or greater than 1.5 (Juniper 2005); Asthma Control Test (ACT) score less than 20 (Schatz 2006); symptoms or rescue medication usage at least two days per week or nighttime awakenings at least three times per month; or at least one asthma exacerbation in the past 12 months prior to randomisation (Bateman 2014; Bernstein 2018; Kerstjens 2015; Peters 2010). When there were multiple treatment arms, we only included participants who received the intervention of interest, as described below.

Types of interventions

We included studies comparing at least two of the following therapies.

- Medium or high-dose ICS alone (budesonide, fluticasone furoate and propionate, mometasone)
- LABA/ICS, a fixed-dose (a combination of two or more active ingredients in a fixed ratio of doses) or free combination of two separate inhalers (formoterol plus beclomethasone, formoterol plus budesonide, formoterol plus ciclesonide, formoterol plus fluticasone formoterol plus mometasone, indacaterol plus mometasone, salmeterol plus fluticasone, vilanterol plus fluticasone)
- LAMA/ICS, a free combination of two separate inhalers (LAMA: aclidinium, glycopyrronium, tiotropium, umeclidinium). We did not find a fixed-dose combination for LAMA/ICS.

We classified doses of ICS in both single-agent and combination inhalers into low-, medium-, and high-dose, based on clinical comparability (BTS/SIGN 2019; GINA 2022). We considered fluticasone furoate 100 µg once daily a medium dose which was approximately equivalent to fluticasone propionate 250 µg twice daily, according to the manufacturer's summary of product characteristics (Bernstein 2018; NICE 2018). We considered fluticasone propionate/salmeterol (FP/SAL) multidose dry powder inhaler (MDPI) 100/12.5 and 200/12.5 µg twice daily as medium- and high-dose formulations because FP/SAL MDPI showed comparable results to FP/SAL dry powder inhaler (DPI) at lower drug dosages due to a cyclone design that facilitates efficient de-agglomeration and aerosolization of the drug particles from the lactose carrier (Bernstein 2017; Paik 2018).

We allowed the use of a short-acting bronchodilator, such as albuterol (salbutamol) and ipratropium as rescue treatment.

Types of outcome measures

We analysed the following outcomes in this study.

Primary outcomes

1. Asthma exacerbations (moderate defined as requiring a short course of oral corticosteroids and severe defined as resulting in hospitalisation, intubation requiring mechanical ventilation, or death).

Secondary outcomes

1. Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores (Juniper 1994)
2. ACQ responder: defined as someone who experiences a clinically meaningful improvement in their ACQ score that is defined as a reduction in the ACQ score by 0.5 or more points on the 7-point scale of the ACQ
3. Asthma-related serious adverse events (SAEs)
4. All-cause SAEs
5. All-cause adverse events (AEs)
6. Dropouts due to AEs

An SAE is defined by the US Food and Drug Administration (FDA) as any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalisation or causes prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; or requires intervention to prevent permanent impairment or damage (FDA 2016).

Search methods for identification of studies

Electronic searches

We identified studies from searches of the following databases and trial registries.

1. Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, 2008 to 19 December 2022
2. Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, 2008 to 19 December 2022
3. MEDLINE Ovid 2008 to 19 December 2022
4. Embase Ovid 2008 to 19 December 2022
5. Global Health Ovid 2008 to 19 December 2022
6. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
7. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch)

The search strategies are presented in Appendix 1. We adapted this for use in the other databases. The search strategy was structured to search for articles containing terms for asthma, a LABA or LAMA, and an ICS. This

structure facilitated searching for all the possible comparisons. The Cochrane Airways Information Specialist in collaboration with the authors developed the search strategy, and it was peer-reviewed by another Cochrane Information Specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist (McGowan 2016).

We searched all databases and trial registries from 2008, the year when the International Committee of Medical Journal Editors made trial registration a requirement for publication, to include only pre-registered studies up to 19 December 2022. There was no restriction on language or type of publication. We identified conference abstracts and grey literature through the Cochrane Airways Trials Register and the CENTRAL database.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We searched websites of relevant manufacturers for study information. We searched on PubMed for errata or retractions from included studies published in full text.

Data collection and analysis

Selection of studies

We conducted this review according to our previously published protocol (Oba 2020) and reported any deviations from it in the 'Differences between protocol and review' section of the systematic review.

We used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and labelled as an RCT or as Not an RCT; the RCT classifier – a machine-learning model that distinguishes RCTs from non-RCTs; and if appropriate, Cochrane Crowd (www.crowd.cochrane.org) -Cochrane's citizen science platform where the Crowd helps to identify and describe health evidence. More detailed information about the Screen4Me components can be found in these publications: Marshall 2018; McDonald 2017; Noel-Storr 2018; Thomas 2017.

Following this initial assessment, two review authors (YO, TP) independently screened the titles and abstracts of the remaining search results and coded them as 'retrieve' (eligible or potentially eligible or unclear) or 'do not retrieve'. We retrieved the full-text study reports of all potentially eligible studies and the two review authors (YO, TP) independently screened them for inclusion, recording the reasons for exclusion of ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a third review author (TM). We identified and excluded duplicates and collate multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We used a standardised data extraction form to extract the outcomes of interest, identifying effect modifiers, checking for accuracy and ensuring completeness of all relevant data. Three review authors (YO, TP, TM) extracted the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention (including dose or regimen), comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported. We used end-of-study data for dichotomous outcomes and change from baseline (CFB) data, the difference between baseline and post-treatment values at 3, 6 and 12 months, for continuous outcomes.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (YO, TP) independently extracted outcome data from included studies. We chose the estimated effects of intervention in the following order of preference: (1) full intention-to-treat analysis (ITT); (2) modified ITT; (3) per-protocol analysis. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third review author (TM). One review author (YO) transferred data into the Review Manager file (Review Manager 2020). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (TP) spot-checked study characteristics for accuracy.

Assessment of risk of bias in included studies

Two review authors (YO, TP) independently assessed risk of bias for outcome in each study using the criteria outlined in the revised Cochrane 'Risk of bias 2' (RoB 2) tool (Higgins 2019; Sterne 2019). We used the RoB 2 Excel tool to implement RoB 2, and presented consensus decisions for signalling questions in a general

repository as supplemental data to be transparent. We assessed the risk of bias according to the following domains in all the outcome measures and time points as necessary.

1. Randomisation processes
2. Deviations from intended interventions
3. Missing outcome data
4. Measurement of outcome
5. Selective outcome reporting

We categorised each domain as being 'high risk', 'low risk', or 'some concerns' using the algorithms proposed in RoB 2. We assessed overall risk of bias and consider an outcome to be at high risk of bias when at least one domain was judged as being at high risk; to be at low risk when all domains were judged as being at low risk; and to raise some concerns when at least one domain was judged to raise some concerns, but no domains were judged as being at high risk of bias. We resolved any disagreement through discussion or, if required, we consulted a third review author (TM). We used the overall risk of bias judgements in the GRADE approach and Summary of Finding tables.

Measures of treatment effect

Pairwise meta-analyses were carried out to compare pairs of interventions for which head-to-head evidence was available. A frequentist approach was used assuming a fixed effect size. This estimates the overall effect size by way of a weighted average and attributes differences between studies to stochastic variability. Network meta-analysis, was used to evaluate the efficacy of multiple treatments simultaneously, incorporating both direct and indirect evidence. A Bayesian approach was used to allow analyses of more complex data (time to event) and to explore random effects models by incorporating minimally informative prior distributions for the between-study heterogeneity (Dias 2018).

Minimum Clinically Important Difference (MCID), which is the smallest difference in a patient-reported outcome measure that is considered clinically meaningful or significant. For the ACQ and AQLQ, the MCID has been estimated to be a change of 0.5 points or more on a 7-point scale (Juniper 2005).

Relative treatment effects

We compared each pair of treatments by estimating a hazard ratio (HR) for time-to-event outcomes (e.g. asthma exacerbations), a mean difference for continuous outcomes, and an odds ratio (OR) for dichotomous outcomes, along with their 95% credible intervals (CrIs).

We used a shared parameter model for exacerbation outcomes, whereby data on the log hazard ratio (lnHR) were modelled with the assumption that continuous treatment differences (lnHR and standard error) had a normal likelihood. When lnHR data were not available, or when appropriate covariance matrices could not be extracted or calculated for studies with more than two arms, we modelled the dichotomous data at a given time as lnHR by using a binomial likelihood with a cloglog link. We used HR data in preference to dichotomous data when available and consider only the HR for the first event for exacerbation outcomes (Dias 2018).

For trials reporting lnHR data with three or more treatment arms, we calculated the covariance between differences taken with respect to the control arm using the following equation: $Cov(y_{ab},y_{ac}) = (Var(y_{ab}) + Var(y_{ac}) - Var(y_{bc}))/2$, where *a* is the control arm and *b* and *c* are the remaining two arms being compared.

We used a normal likelihood with an identity link for continuous outcomes and a binomial likelihood with a logit link for dichotomous outcomes.

Relative treatment ranking

We estimated the probability that each treatment group ranked at one of four to six possible positions and presented mean and median ranks along with their 95% CrIs for all the primary and secondary outcomes with rank one, meaning that group was best for that outcome. We presented specific methodological details for each analysis in the result sections.

Direct pairwise meta-analysis

We compared each pair of treatments by estimating a risk ratio (RR) or risk difference (RD) for dichotomous outcomes and a mean difference for continuous outcomes along with their 95% confidence intervals (CIs).

Differences on effect size between pairwise and network meta-analyses

We utilized different effect sizes for pairwise meta-analysis and NMA based on data selection and availability. For example, we employed time-to-event data for exacerbations in the NMA to incorporate a larger dataset, whereas dichotomous data was used for pairwise meta-analysis due to limited data availability. Furthermore, we preferred using risk ratio over odds ratio for pairwise meta-analyses because it facilitated a more straightforward assessment of precision.

Unit of analysis issues

For dichotomous outcomes, we used participants, rather than events, as the unit of analysis (i.e. number of subjects admitted to hospital, rather than number of admissions).

For network meta-analysis, the data from multi-arm studies was directly incorporated into the analysis using the statistical methods described above. Specifically, the direct and indirect evidence from the multi-arm study were combined with evidence from other studies in a network of evidence, allowing for indirect comparisons between treatments that were not directly compared in any individual study. For pairwise meta-analyses, the data from multi-arm studies was analysed by selecting a single comparison from the multi-arm study, or by combining data across multiple comparisons when appropriate.

Dealing with missing data

We contacted investigators or study sponsors in order to obtain missing numerical outcome data where possible (e.g. when a study was identified as an abstract only). When this was not possible and a large proportion of data was missing, we utilized the following methods to evaluate the extent to which the analysis results remained robust in the presence of missing data (Guyatt 2017).

We conducted a primary meta-analysis using complete case analysis, which included only participants with complete data. Then, sensitivity meta-analyses were conducted, where missing data was imputed in each study, and the results were pooled across studies. For binary outcomes, we used a "plausible worst-case" scenario. This involved assuming that participants with missing data in the treatment group had proportionally higher event rates than those who were successfully followed. For continuous outcomes, we obtained imputed mean values from other studies included in the systematic review. The standard deviation, on the other hand, was derived from the median standard deviations of the control arms across all studies.

Imputation data sets to assess the impact of missing outcomes are available at https://figshare.com/articles/dataset/Imputation_for_missing_data_for_selected_outcomes/23289740. If the results of the primary meta-analysis remained robust even when subjected to the most extreme assumptions that were considered plausible, the certainty of the evidence was not downgraded due to the risk of bias arising from missing participant outcome data. However, if the results did not hold up under these assumptions, we lowered the certainty of the evidence by one level. We accounted for the potential influence of missing data in the Summary of Findings tables.

Assessment of heterogeneity

Network meta-analysis

We assessed heterogeneity by comparing the between-trials standard deviation to the size of relative treatment effects, on the log-scale for HRs and ORs. We assessed consistency between direct and indirect estimates by fitting node splitting models (Dias 2010; van Valkenhoef 2016) and inspecting the resulting Bayesian p-values for inconsistency, as well as comparing the model fit and between-study heterogeneity to the standard NMA model. The consistency assumption asserts that the effect of an intervention is consistent across all direct and indirect comparisons. This means that if multiple treatments are being compared, the relative effect of each treatment should be the same across all trials, regardless of whether the comparison is direct or indirect. Violation of consistency may imply that there are differences in treatment effects that are not explicable by chance and may be due to bias or other confounding factors. The consistency was checked locally.

We assumed that the treatment effects of various interventions were consistent across different trials (transitivity). This implies that the study populations and interventions being compared are comparable across different trials, ensuring that the comparison of treatment effects is strong and reliable. If the distribution of effect modifiers is significantly different across different treatment comparisons, we question the validity of the comparison of treatment effects. In this case, transitivity may be compromised and may manifest as inconsistency between direct and indirect evidence included in the network. We extracted potential effect modifiers, such as age, gender, race, smoking status, baseline FEV1, and exacerbation history, which are factors that could influence the magnitude of treatment effects and only pooled studies that were sufficiently homogenous. Consistency of direct and indirect evidence was also formally checked.

We used informative, empirically derived prior distributions for the between-study heterogeneity for dichotomous outcomes (Turner 2015) and semi-informative half-normal prior distributions for exacerbation outcomes (Röver 2021). A non-informative uniform (0, 2) prior distribution was used for the between-study heterogeneity for continuous outcomes.

Direct pairwise meta-analysis

We embarked on a thorough examination of diverse heterogeneity modalities to ensure a stringent evaluation of consistency and generalisability of the findings across the included studies. Clinical heterogeneity was evaluated through the inspection of differences in the baseline characteristics of the study populations, as well as the type and dose of interventions and the outcomes being measured. Methodological heterogeneity was scrutinised by the examination of the types of study, the tools used to measure outcomes (e.g., self-report questionnaires, clinical exams), and the methods of data analysis employed (e.g., intention-to-treat, per-protocol).

The I^2 statistic was utilised in the measurement of statistical heterogeneity amongst the included studies in each analysis. The statistical heterogeneity was evaluated based on the following guidelines proposed by Deeks et al. (Deeks 2022): 0% to 40% were deemed insignificant heterogeneity; 30% to 60% were viewed as moderately

heterogeneous; 50% to 90% were indicative of substantial heterogeneity; while 75% to 100% were viewed as considerably heterogeneous. In cases where there were few studies, uncertainty around measures such as the I^2 statistic and Tau were indicated, while simple thresholds were avoided in the interpretation of statistical heterogeneity. Furthermore, forest plots were visually inspected, and P values from the Chi2 test were assessed to identify heterogeneity.

Assessment of reporting biases

We minimised reporting bias from unpublished studies or selective outcome reporting by using a broad search strategy and by checking references of included studies and relevant systematic reviews. For each outcome, we presented the total number of participants and the number of studies providing direct evidence contributing data to the NMA.

For pairwise meta-analyses, we created a funnel plot that was stratified by a comparison group when more than 10 studies were being pooled. We assessed evidence of publication bias through asymmetry of funnel plots and the Egger test (Egger 1997) and the results were interpreted in the context of the meta-analysis findings and any other relevant information. We assumed the presence of small study bias when the number of participants is fewer than 50 per study, 1000 per pooled analysis, or 100 per arm when no more than 10 studies could be pooled (Dechartres 2013; Nüesch 2010).

Data synthesis

We included all eligible studies for the primary analysis.

Network meta-analysis

We conducted NMAs using a Bayesian framework estimated through Markov chain Monte Carlo. The analysis codes are presented in Appendix 2. We assessed model convergence through inspection of Gelman-Rubin diagnostic plots. Both fixed-effect and random-effects models were fit to the data. We assessed model fit through mean total residual deviance and plots of residual deviance contribution per study arm.

We used R (version 4.2.0) with GeMTC package for continuous and dichotomous outcomes sampling over 100,000 iterations for 4 chains after a burn-in of 50,000 iterations. Where a continuity correction was needed for dichotomous outcomes due to sparse data, we used OpenBUGS as GeMTC does not allow the addition of a continuity-correction. We also used OpenBUGS for exacerbation outcomes as GeMTC does not have models that can conduct node-splitting for a shared parameter model. In OpenBUGS we sampled over 100,000 iterations for 3 chains after a burn-in of 50,000 iterations.

For studies with zero counts for events, we followed guidance provided in Dias 2018 to decide where continuity-corrections should be applied. No continuity correction was applied unless there were problems with model convergence or extreme results. In that case, the network was inspected with all studies with zero counts excluded, and a continuity-correction of 0.5 was added to studies comparing treatments that were now disconnected from the network, to make the models stable and ensure convergence. We included all eligible studies in the primary analysis as long as a trial was connected to the main network.

We based model comparisons on the Deviance Information Criterion (DIC) (Spiegelhalter 2002). Differences of three points or more were considered meaningful. If models differed by less than three points, we selected the simplest model. We also calculated the posterior mean of the residual deviance to assess model fit. We considered this adequate when the posterior mean of the residual deviance approximated the number of unconstrained data points (Dias 2013).

We provided network diagrams consisting of nodes and edges. Nodes represent the interventions being compared, and edges represent the direct comparisons between them. The size of the nodes indicates the sample sizes for each intervention, while the thickness of the edges indicates the number of studies directly comparing two interventions.

We created and presented rank plots, which are a graphical tool commonly used in NMA to compare the efficacy of multiple treatment arms. These plots show the probability that each treatment is ranked first, second, third, and so on based on their efficacy or safety outcomes. Rank plots provide information to help identify which treatments are most likely to be ranked highest for a given condition (Dias 2018; Neupane 2014).

Direct pairwise meta-analysis

We conducted direct pairwise meta-analyses using Review Manager 2020. We investigated clinical and methodological differences amongst studies and quantified heterogeneity using the statistical tests described in the methods section. We used a random-effects model when substantial heterogeneity was present and a fixed-effect model otherwise. We analysed studies of different durations separately for continuous outcomes. We undertook a pairwise meta-analysis only where this was meaningful; that is, if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

Subgroup analysis and investigation of heterogeneity

We classified ICS doses into low, medium, and high dose and the results were reported individually for each strength in all outcomes as well as all strengths combined for selected outcomes.

We conducted a subgroup analysis for exacerbation outcomes in the pairwise meta-analysis separating studies which required a history asthma exacerbation in the previous year from those which did not. We used the formal test for subgroup interactions provided in Review Manager 2020.

Sensitivity analysis

We conducted sensitivity analyses excluding studies that had a significant amount of missing data and/or used the methods described in the 'Dealing with Missing Data' section. For all outcomes in pairwise meta-analysis and for all outcomes except exacerbation outcomes in NMAs, sensitivity analyses were performed using either fixed-effect or random-effects model, whichever was not used in the primary analysis. Additionally, threshold analysis was conducted for exacerbation outcomes in the NMA, as outlined below.

Threshold analysis

We conducted threshold analyses at the contrast level for the exacerbation outcomes as part of a sensitivity analysis to examine the impact of potential bias on each treatment contrast of the group comparisons (Phillippo 2018; Phillippo 2019).

Summary of findings and assessment of the certainty of the evidence

We created 'Summary of findings' tables for all primary and secondary outcomes listed under Types of outcome measures. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it related to the studies that contributed data for the prespecified outcomes (Guyatt 2011). The RoB 2 assessment was used specifically to evaluate the risk of bias in the included RCTs. The results of the RoB 2 assessment were used to assess the certainty of the evidence and inform the GRADE approach to rating the quality of evidence and incorporated into Summary of Findings tables.

We used the methods and recommendations described in Chapter 14 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2019), using GRADEpro software (GRADEpro GDT) for pairwise meta-analyses. We estimated anticipated absolute effects from each reference comparator (active control). We justified all decisions to downgrade the quality of outcomes using footnotes and made comments to aid the reader's understanding of the review where necessary. We presented NMA Summary of Findings tables, proposed by Yepes-Nuñez and colleagues, for NMAs (Yepes-Nuñez 2019). It consists of details of questions and interventions for a specific outcome, relative effect estimates for each intervention, anticipated absolute effects, GRADE certainty of evidence, rank probabilities of the intervention, and interpretations of findings.

Results

Description of studies

Results of the search

We identified 11,410 records from the multiple databases. We searched all records using the search strategy in Appendix 1 up to 21 December 2022. We excluded 6,307 duplicates and 919 records by Crowd Known Assessments and Classifier. We reviewed the remaining 5,200 studies for further details and excluded additional 5,160 studies for various reasons. Forty and 35 studies were included respectively for the individual and grouped treatment comparisons as shown in Figure 1.

Included studies

We included 35 studies with a total of 38,276 participants for the grouped treatment comparisons. The study and patient characteristics are presented in Table 1. Details of each study are shown in Characteristics of included studies. The median duration of trials was 24 weeks (range 12 to 78 weeks). A history of at least one asthma exacerbation within the past year was required in 4 studies (Bateman 2014; Kerstjens 2020; Peters 2016; Stempel 2016). Five studies included intra group comparisons only and were used for the individual treatment comparisons (Bodzenta-Lukaszyk 2012; Busse 2008; Cukier 2013; Lotvall 2014; Papi 2007). The number of included studies varied with each outcome due to data availability which is summarised in Summary of Findings tables. All studies were industry funded and conducted in multiple centres.

Participants

The mean age and proportion of male and White participants were 44.1 years, 38 %, and 69 %, respectively. Six studies allowed current smokers (Brown 2012; Huchon 2009; Murphy 2015; Pedersen 2017; Peters 2016; Spector 2012) but excluded in the rest. Maximum pack-years allowed in ex-smokers was 10 in most studies, 20 in Peters 2008 and Stirbulov 2012, and not reported in CHIESI 2009, Hamelmann 2016, Pedersen 2017, and Spector 2012. The mean forced expiratory volume in 1 second (FEV1) and FEV1 % predicted at baseline were 2.1 litters and 68% which were reported in 33 and 30 studies.

Excluded studies

Among the 5,200 full-text articles evaluated for eligibility, 5,160 were excluded. The reasons for exclusion among the 42 key studies were documented in the Characteristics of excluded studies as follows: 15 studies did not meet the desired design criteria, 13 studies did not include the desired comparator, 13 studies did not involve the target population, and one study was not pre-registered.

Risk of bias in included studies

'Risk of bias' judgements for individual outcomes are presented at the side of all forest plots. Consensus decisions for signalling questions are available at https://doi.org/10.6084/m9.figshare.22318366.v1. There were no studies that we excluded from this review because of differences in baseline characteristics or a poor quality.

The randomization process in 30 studies was assessed for bias using a validated computerized system, while the remaining studies used an assumed industry-standard method. The risk of bias was considered low for random sequence generation and allocation concealment. However, some bias was noted in two studies that had open-label designs, which raised some concerns about the ACQ score outcomes. Nonetheless, most studies were double-blinded, reducing the risk of bias.

Bias resulting from missing outcome data was observed in several outcomes due to high or uneven attrition rates, leading to a high risk of bias or concerns.

To mitigate bias in the selection of reported results, only pre-registered trials were included, and all studies reported expected outcomes either in publications or industry-generated reports. Therefore, the risk of selective reporting bias was considered low for all outcomes.

The impact of these biases on the overall interpretation of the evidence was addressed in the Summary of Findings tables and Discussion section.

Other potential sources of bias in the NMAs

Study characteristics across the treatment groups are presented in Table 2. The proportion of participants with a history of asthma exacerbation in the previous 12 months before randomisation varied amongst treatment groups ranging from 1 to 83%. The baseline FEV1 was 1.9L for HD-ICS/LABA and 2.4L for LD-ICS/LABA while the mean value for all studies was 2.1L. Other clinical characteristics of participants were comparable amongst treatment groups. We rated down the certainty of evidence as necessary for NMAs considering the clinical heterogeneity.

Effects of interventions

We present grouped treatment comparisons only as there was insufficient evidence to allow for individual treatment comparisons.

1. EXACERBATION OUTCOMES

1.1 Severe Exacerbation

For this outcome, 17 trials including 22,819 participants provided dichotomous data comparing 6 treatment groups. A network diagram for the studies included in the NMA is presented as Figure 2. The data set used for the analysis is presented in Table S1.

1.1.1 Model Selection and Inconsistency Checking

A half-normal (0.5^2) prior was used to model the between-study heterogeneity in the random-effects model (Röver 2021). Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. The random-effects model fits the data better than the fixed-effect model. The DIC for the random-effects model is also much smaller than the DIC for the fixed-effect model, and so the random-effects model was chosen. There was moderate between-study heterogeneity, however the estimate has a wide credible interval. Results for the random-effects model are presented in Section 1.1.2.

A node-splitting model was fit to assess the inconsistency in the model. The results of the node-splitting model are presented in Appendix 4. There was no evidence to suggest there was any inconsistency in the model.

1.1.2 NMA Results

HRs for severe exacerbations are presented in Figure 3. The HRs for the comparison of all treatment groups against each other are reported in Table 3. An NMA summary of findings is presented in Summary of findings table 1. There is insufficient evidence to suggest that there is a change in hazards of severe exacerbations for any of the treatment comparisons. The estimates for the HRs were very uncertain due to the sparsity in the network. The HRs for the MD-ICS/LABA vs. MD-ICS/LAMA and HD-ICS/LABA vs. MD-ICS/LAMA comparisons in particular are very uncertain and should be treated with caution. The density plot for the between-study heterogeneity is presented in Figure S1.

The rank plot for severe exacerbations is presented in Figure S2 and the mean and median ranks with their corresponding 95% CrIs are presented in Table 4. Due to the uncertainty in the estimated HRs, treatment ranks were also uncertain with very wide intervals that imply that any of the treatment groups could rank anywhere from first to last. The rank probabilities for most of the treatments were under 50%.

1.1.3 Threshold Analysis

The forest plot for the threshold analysis is presented in Figure 4, and the threshold and new optimal treatments, based only on the relative effect, are presented in Table 5. The results of threshold analysis should be interpreted with caution as the results of the NMA were so uncertain. Additional evidence on a single comparison would not be very useful, but evidence on the entire network could change the conclusions of the NMA.

The credible intervals for the MD-ICS/LAMA vs. MD-ICS and MD-ICS/LABA vs. LD-ICS/LABA comparisons extend beyond the limits of the invariance intervals, suggesting that the recommended treatment (MD-ICS/LAMA) is sensitive to uncertainty in the data. The recommended treatment seemed to be sensitive to moderate potential bias in the negative direction for the MD-ICS/LABA vs. MD-ICS comparison as well as moderate potential bias in the positive direction for the MD-ICS/LAMA vs. MD-ICS and MD-ICS/LABA vs. MD-ICS/LABA comparisons. For all these comparisons, potential bias would make LD-ICS/LABA the recommended treatment. This is consistent with the ranks discussed in Section 1.1.2, where LD-ICS/LABA was ranked the second-best treatment (median rank 2.0 [95% CrI 1.0 to 6.0]). It should be pointed out, however, that the probability that LD-ICS/LABA was the best treatment is less than 25% (Figure S2). Clinical heterogeneity should also be considered because the LD-ICS/LABA group had the highest proportion of subjects with a history of asthma exacerbation (Table 2) which would affect the results in favour of the group.

1.1.4 Pairwise Meta-Analysis

The pairwise evidence suggests there is little or no difference in severe exacerbations for any of the treatment comparisons (low to moderate certainty, Analysis 1.1; Table 6) which is in accordance with the NMA. The results are unchanged when analysed combining all ICS strengths in mono- and combination therapies (Analysis 1.1.10). There was no difference in the results between fixed- and random-effects models.

The test for subgroup differences suggests that there is a statistically significant subgroup effect between high- and low risk-populations for HD-ICS/LABA vs. HD-ICS (Analysis 2.6). However, a paucity of data for the high-risk population would make the subgroup difference uncertain.

1.2 Moderate to Severe Exacerbation

For this outcome, 25 trials including 25,583 participants provided evidence comparing 6 treatment groups. Of these trials, 22 provided evidence as dichotomous data and 3 as lnHR data. A network diagram for the studies included in the NMA is presented as Figure 5. The data set used for the analysis is presented in Table S2.

1.2.1Model Selection and Inconsistency Checking

A half-normal (0.5^2) prior was used to model the between-study heterogeneity in the random-effects model (Röver 2021). Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. The random-effects model fit the data better than the fixed-effect model. As the DIC for the random-effects model was smaller than that for the fixed-effect model, by more than 3 units, the random-effects model was chosen. There was moderate between-study heterogeneity. Results for the random-effects model are presented in Section 1.2.2.

A node-splitting model was fit to assess the inconsistency in the model. The results of the node-splitting model are presented in Appendix 5. There was some evidence of conflict in the MD-ICS/LABA vs. HD-ICS comparison. However, as many nodes have been split resulting in several comparisons within the same network, it is possible that some p-values will be small by chance. As the comparison of MD-ICS/LABA vs. HD-ICS is directly linked to multiple loops in the network, any other comparisons in loops including MD-ICS/LABA vs. HD-ICS should be interpreted with caution. However, although the direct evidence for MD-ICS/LABA vs. HD-ICS estimates a lower HR than the indirect evidence, the treatment direction is consistent between these evidence sources.

1.2.2 NMA Results

HRs for moderate to severe exacerbations are presented in Figure 6. The HRs for the comparison of all treatments against each other are reported in Table 7. An NMA summary of findings is presented in Summary of findings table 2.

There is evidence to suggest that MD-ICS/LAMA, MD-ICS/LABA, and HD-ICS/LABA reduce the hazards of moderate to severe exacerbations compared to MD-ICS (HR 0.56; 95% CrI 0.38 to 0.82; low certainty, HR 0.70; 95% CrI 0.59 to 0.82; moderate certainty, and HR 0.59; 95% CrI 0.46 to 0.76; moderate certainty, respectively). There was also evidence to suggest that MD-ICS/LAMA and MD-ICS/LABA marginally reduce the hazards of moderate to severe exacerbations compared to HD-ICS (HR 0.60 ; 95% CrI 0.37 to 0.95; very low certainty and HR 0.75; 95% CrI 0.56 to 0.99; moderate certainty, respectively), and that HD-ICS/LABA reduces the hazard of moderate to severe exacerbations compared to HD-ICS (HR 0.63; 95% CrI 0.47 to 0.84; moderate certainty). The HRs for comparisons involving LD-ICS/LABA are very uncertain, this is due to the sparsity of evidence for LD-ICS/LABA, there was only one two-arm study that compared the treatment to MD-ICS/LABA (CHIESI 2009). The density plot for the between-study heterogeneity is presented in Figure S3.

The rank plot for moderate to severe exacerbations is presented in Figure S4, and the mean and median ranks with their corresponding 95% CrIs are presented in Table 8. LD-ICS/LABA had the highest probability of being ranked the best treatment (median rank 1.0 [95% CrI 1.0 to 6.0]). However, as mentioned earlier, the evidence for LD-ICS/LABA was very sparse and the resulting uncertainty in the estimates can make treatment ranks very unreliable as suggested by wide credible intervals.

1.2.3 Threshold Analysis

The forest plot for the threshold analysis is presented in Figure 7 and the threshold and new optimal treatments are presented in Table 9.

The credible interval for the MD-ICS/LABA vs. LD-ICS/LABA comparison extended beyond the lower limit of the invariance interval, suggesting that the recommended treatment (LD-ICS/LABA) is sensitive to uncertainty in the data. The recommended treatment seemed to be sensitive to moderate potential bias in the negative direction for the MD-ICS/LAMA vs. MD-ICS comparison and in the positive direction for the MD-ICS/LABA vs. MD-ICS. Potential bias in both these comparisons would make MD-ICS/LAMA the recommended treatment.

1.2.4 Pairwise Meta-Analysis

The pairwise evidence is very uncertain for the effect of HD-ICS on moderate to severe exacerbations compared to MD-ICS due to imprecision, a lack of robustness, and missing data (Analysis 1.2; Table 6). The pairwise evidence suggests little to no difference in moderate to severe exacerbations comparing HD-ICS/LABA vs. MD-ICS (RR 0.71; 95% CI 0.33 to 1.56; n=1759; 2 studies; low certainty; Analysis 1.2.4) while the NMA evidence suggests HD-ICS/LABA probably reduces the hazards of moderate to severe exacerbations compared to MD-ICS (HR 0.59; 95% CrI 0.46 to 0.76; moderate certainty). Otherwise, the results of pairwise meta-analysis are qualitatively similar to those of the NMA.

ICS/LABA probably reduces moderate to severe exacerbations compared to ICS alone when analysed combining all strengths of ICS in mono- and combination therapies (RR 0.69; 95% CI 0.60 to 0.79; n= 11,141; 16 studies; moderate certainty; Analysis 1.2.9).

There was no difference in the results between fixed- and random-effects models except for HD-ICS/LABA vs. MD-ICS for which the 95% CI crossed the line of no effect with the random-effects model but not with the fixed-effect model.

The test for subgroup differences suggests that there is a statistically significant subgroup effect between high- and low risk-populations in the MD-ICS/LABA vs. MD-ICS and ICS/LABA vs.ICS comparisons (Analysis 3.3; Analysis 3.9). However, the direction of effect is consistent between the high- and low-risk populations and a paucity of data for the high-risk population would make the subgroup differences uncertain.

2. CONTINUOUS OUTCOMES

2.1 Change From Baseline in ACQ Scores

2.1.1 Change From Baseline in ACQ Scores at 3 Months

For this outcome, 4 trials including 5261 participants were included in the NMA comparing 5 treatment groups (Figure 8). The data set used for the analysis is presented in Table S3.

2.1.1.1 Model Selection and Inconsistency Checking

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. Both fixed- and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed- and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 2.1.1.2.

A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Appendix 6. There was no evidence to suggest there was any inconsistency in the model.

2.1.1.2 NMA Results

The mean difference in CFB in ACQ scores at 3 months are presented in Figure 9. The mean difference in CFB in ACQ scores at 3 months comparing all treatment groups against each other are reported in Table 10.

There is evidence to suggest that MD-ICS/LABA and HD-ICS/LABA reduce the ACQ score at 3 months compared to MD-ICS (mean difference-0.21; 95% CrI -0.27 to -0.14; high certainty and mean difference -0.19; 95% CrI -0.27 to -0.11; high certainty, respectively), HD-ICS (mean difference -0.14; 95% CrI -0.22 to -0.07; high certainty and mean difference -0.13; 95% CrI -0.20 to -0.05; high certainty, respectively), and LD-ICS/LABA (mean difference -0.22; 95% CrI -0.35 to -0.09; moderate certainty and mean difference -0.20; 95% CrI -0.35 to -0.05; moderate certainty, respectively) but this evidence is borderline and the differences do not reach MCID of 0.5 (Juniper 2005). An NMA summary of findings is presented in Table 11.

The rank plot for CFB in ACQ scores at 3 months is presented in Figure S5, and the mean and median ranks are presented in Table 12. MD-ICS/LABA ranks higher than the other treatments (median rank 1.0 [95% CrI 1.0 to 2.0]), with HD-ICS/LABA also ranking highly (median rank 2.0 [95% CrI 1.0 to 2.0]) which is consistent with the results presented in Table 10. The remaining three treatment ranks have overlapping credible intervals, reflecting high uncertainty in treatment rankings. The results were consistent for the fixed- and random-effects models.

2.1.2 Change From Baseline in ACQ Scores at 6 Months

For this outcome, 9 trials including 9298 participants were included in the NMA comparing 5 treatment groups (Figure 10). The data set used for the analysis is presented in Table S4.

2.1.2.1 Model Selection and Inconsistency Checking

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. Both fixed- and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed and random-effects models was less than 3, the simpler fixed-effect model was chosen.

A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Appendix 7. There was no evidence to suggest inconsistency in the model.

2.1.2.2 NMA Results

The mean differences in CFB in ACQ scores at 6 months are presented in Figure 11. The mean difference in CFB in ACQ scores at 6 months for all treatment comparisons are reported in Table 13.

There is evidence to suggest that MD-ICS/LAMA, MD-ICS/LABA, and HD-ICS/LABA reduce the ACQ score at 6 months compared to MD-ICS (mean difference -0.13; 95 % CrI -0.20 to -0.07; high certainty, mean difference -0.17; 95 % CrI -0.22 to -0.12; high certainty, and mean difference -0.22; 95 % CrI -0.29 to -0.16; high certainty, respectively). There also is evidence to suggest that MD-ICS/LABA and HD-ICS/LABA compared to HD-ICS (mean difference -0.11; 95 % CrI -0.21 to -0.02; moderate certainty and mean difference -0.17; 95 % CrI -0.26 to -0.07; high certainty, respectively), and HD-ICS/LABA compared to MD-ICS/LAMA (mean difference -0.09; 95 % CrI -0.17 to -0.01; moderate certainty) reduce the ACQ score at 6 months. However, above evidence is borderline and the differences do not reach MCID of 0.5 (Juniper 2005). An NMA summary of findings is presented in Table 14.

The rank plot for CFB in ACQ scores at 6 months is presented in Figure S6, and the mean and median ranks are presented in Table 15. HD-ICS/LABA ranks higher than the other treatments (median rank 1.0 [95% CrI 1.0 to 2.0]). The results were consistent for the fixed- and random-effects models.

2.1.3 Change From Baseline in ACQ Scores at 12 Months

For this outcome, 4 trials including 5681 participants were included in the NMA comparing 4 treatment groups (Figure 12). The data set used for the analysis is presented in Table S5.

2.1.3.1 Model Selection and Inconsistency Checking

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. While the random-effects model appears to fit the data well, the total residual deviance for the fixed-effect model is slightly higher than the number of data points. The between-study heterogeneity was low, but had a wide credible interval. As the difference in DICs between the fixed- and random-effects models was less than 3, the simpler fixed-effect model was chosen, however due to the better fit of the random-effects model, results for the random-effects model are also presented in Section 2.1.3.2.

A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Appendix 8. There was no evidence to suggest inconsistency in the network.

2.1.3.2 NMA Results

The mean difference in CFB in ACQ scores at 12 months are presented in Figure 13. The mean difference in CFB in ACQ scores at 12 months comparing all treatment groups against each other are reported in Table 16.

Results for the fixed- and random-effects models are largely consistent in terms of mean differences. For the fixed-effect model, there also is evidence to suggest that MD-ICS/LABA reduces the ACQ score at 12 months compared to MD-ICS and HD-ICS (mean difference -0.18; 95% CrI -0.26 to -0.09; moderate certainty and mean difference -0.13; 95% CrI -0.23 to -0.03; moderate certainty, respectively), and HD-ICS/LABA reduces the ACQ score at 12 months compared to MD-ICS and HD-ICS (mean difference -0.20; 95% CrI -0.26 to -0.14; high certainty and mean difference -0.15; 95% CrI -0.24 to -0.06; high certainty, respectively). However, above evidence is borderline and the differences do not reach MCID of 0.5 (Juniper 2005). The credible intervals for these three comparisons include the “null” effect for the random-effects model. An NMA summary of findings is presented in Summary of findings table 3.

The density plot for the between-study heterogeneity is presented in Figure S7. Its peak close to zero is consistent with a fixed-effect model, although a higher value cannot be discarded.

The rank plot for grouped treatments is presented in Figure S8, and the mean and median ranks are presented in Table 17. HD-ICS/LABA ranks higher than the other treatments (median rank 1.0 [95% CrI 1.0 to 2.0]). All other treatment ranks display wide credible intervals, reflecting high uncertainty in treatment rankings.

2.1.4 Pairwise Meta-Analysis

2.1.4.1 Change From Baseline in ACQ Scores at 3, 6, and 12 Months.

There is insufficient evidence to suggest that there is a clinically meaningful difference in the ACQ scores at 3, 6, or 12 months for any of the treatment comparisons (Analysis 4.1; Analysis 4.2; Analysis 4.3). The certainty of evidence ranges from low to high (Table 18). There was no difference in the results between fixed- and random-effects models. Above results are in accordance with those of the NMA.

2.2 Change From Baseline in AQLQ Scores

2.2.1 Change From Baseline in AQLQ Scores at 3 Months

For this outcome, 6 trials including 2585 participants were included in the NMA comparing 4 treatment groups (Figure 14). The data set used for the analysis is presented in Table S6.

2.2.1.1 Model Selection and Inconsistency Checking

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. Both fixed- and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs

between the fixed and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 2.2.1.2.

There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

2.2.1.2 NMA Results

The mean difference in CFB in AQLQ scores at 3 months are presented in Figure 15. The mean difference in CFB in AQLQ scores at 3 months comparing all treatment groups against each other are reported in Table 19.

There is evidence to suggest that MD-ICS/LABA increases the AQLQ score at 3 months compared to MD-ICS and HD-ICS (mean difference 0.19; 95% CrI 0.09 to 0.30; low certainty and mean difference 0.14; 95% CrI 0.04 to 0.24; moderate certainty, respectively). However, the differences do not reach MCID of 0.5 (Juniper 2005). An NMA summary of findings is presented in Table 20.

The rank plot for CFB in AQLQ scores at 3 months is presented in Figure S9, and mean and median ranks are presented in Table 21. MD-ICS/LABA ranks the highest of all the treatments (median rank 1.0 [95% CrI 1.0 to 2.0]), but all treatment ranks display wide credible intervals except for MD-ICS/LABA, reflecting high uncertainty in treatment rankings. The results were consistent for the fixed- and random-effects models.

2.2.2 Change From Baseline in AQLQ Scores at 6 Months

For this outcome, 6 trials including 4276 participants were included in the NMA comparing 5 treatment groups (Figure 16). The data set used for the analysis is presented in Table S7.

2.2.2.1 Model Selection and Inconsistency Checking

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. While the random-effects model appears to fit the data well, the total residual deviance for the fixed-effect model is slightly higher than the number of data points. The between-study heterogeneity was low, but with a wide credible interval. As the difference in DICs between the fixed- and random-effects models was less than 3, the simpler fixed-effect model was chosen, however due to the better fit of the random-effects model, results for the random-effects model are also presented in Section 2.2.2.2.

A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Appendix 9. There was no evidence to suggest inconsistency in the network.

2.2.2.2 NMA Results

The mean difference in CFB in AQLQ scores at 6 months are presented in Figure 17. The mean difference in CFB in AQLQ scores at 6 months comparing all treatments against each other are reported in Table 22.

Results for the fixed- and random-effects models are largely consistent in terms of mean differences. For the fixed-effect model, LD-ICS/LABA and MD-ICS/LABA increase the AQLQ score at 12 months compared to MD-ICS (mean difference 0.18; 95% CrI 0.08 to 0.29; high certainty and mean difference 0.12; 95% CrI 0.02 to 0.23; high certainty, respectively). However, the differences do not reach MCID of 0.5 (Juniper 2005) and the credible intervals for these comparisons include the “null” effect for the random-effects model. An NMA summary of findings is presented in Summary of findings table 4.

The density plot for the between-study heterogeneity is presented in Figure S10. Its peak close to zero is consistent with a fixed-effect model, although a higher value cannot be discarded.

The rank plot for CFB in AQLQ scores at 6 months is presented in Figure S11, and mean and median ranks are presented in Table 23. LD-ICS/LABA ranks the highest of all the grouped treatments (median rank 1.0 [95% CrI 1.0 to 3.0]), but the credible intervals for all treatment ranks are very wide, indicating considerable uncertainty in treatment rankings.

2.2.3 Pairwise Meta-Analysis

2.2.3.1 Change From Baseline in AQLQ Scores at 6 and 12 Months.

There is insufficient evidence to suggest that there is a clinically meaningful difference in the AQLQ scores (MCID 0.5) at 6 or 12 months for any of the treatment comparisons (Analysis 5.1; Analysis 5.2). The certainty of evidence ranges from low to high (Table 24). There was no difference in the results between fixed- and random-effects models. Above results are in accordance with those of the NMA.

3. DICHOTOMOUS OUTCOMES

3.1. ACQ RESPONDER

3.1.1 ACQ Responder at 6 Months.

For this outcome, 6 trials including 7252 participants were included in the NMA comparing 5 treatment groups (Figure 18). The data set used for the analysis is presented in Table S8.

3.1.1.1 Model Selection and Inconsistency Checking

For this subjective outcome comparing pharmacological interventions, a Turner prior of log-normal (-2.93, 1.58^2) was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. Both fixed- and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed- and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.1.1.2.

A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Appendix 10. There was no evidence to suggest inconsistency in the network.

3.1.1.2 NMA Results

The ORs of ACQ responders at 6 months are presented in Figure 19. The ORs of ACQ responders at 6 months comparing all treatments against each other are reported in Table 25.

There is evidence to suggest that MD-ICS/LAMA, MD-ICS/LABA, and HD-ICS/LABA increase the odds of ACQ responders at 6 months compared to MD-ICS (OR 1.32; 95% CrI 1.11 to 1.57; moderate certainty, OR 1.47; 95% CrI 1.23 to 1.76; high certainty, and OR 1.59; 95% CrI 1.31 to 1.94; high certainty, respectively). An NMA summary of findings is presented in Summary of findings table 5.

The rank plot for ACQ response at 6 months is presented in Figure S12, and mean and median ranks are presented in Table 26. HD-ICS/LABA ranks higher than the other treatments (median rank 1.0 [95% CrI 1.0 to 3.0]), but there is considerable uncertainty in the rankings exhibited in the wide credible intervals. The results were consistent for the fixed- and random-effects models.

3.1.1.3 Pairwise Meta-Analysis

Results of pairwise meta-analysis are presented in Analysis 6.1 and Table 27. MD- and HD-ICS/LABA increase and MD-ICS/LAMA likely increases ACQ responders at 6 months compared to MD-ICS (RR 1.15; 95% CI 1.07 to 1.22; n=1853; 2 studies; absolute benefit increase (ABI) 93 more per 1000 subjects; high certainty, RR 1.14 [95% CI 1.05 to 1.23]; n=1210; 1 study; ABI 94 more per 1000 subjects; high certainty, RR 1.10; 95%CI 1.03 to 1.18; n=2219; 3 studies; ABI 60 more per 1000 subjects; moderate certainty, respectively). The evidence suggests little or no difference in ACQ responders at 6 months in other comparisons. Above results are in accordance with those of the NMA. There was no difference in the results between fixed- and random-effects models.

3.1.2 ACQ Responder at 12 Months.

For this outcome, 3 trials including 3828 participants were included in the NMA comparing 4 treatment groups (Figure 20). The data set used for the analysis is presented in Table S9.

3.1.2.1 Model Selection and Inconsistency Checking

For this subjective outcome comparing pharmacological interventions, a Turner prior of log-normal (-2.93, 1.58^2) was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. Both the fixed- and random-effects models fit the data similarly well. As the difference in DICs between the two models was less than 3, the simpler fixed-effect model was chosen. The between-study heterogeneity was low. The results for the fixed-effect model are presented in Section 3.1.2.2.

There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

3.1.2.2 NMA Results

The ORs of ACQ responders at 12 months are presented in Figure 21. The ORs of ACQ responders at 12 months comparing all treatment groups against each other are reported in Table 28.

There is evidence to suggest that MD-ICS/LABA and HD-ICS/LABA increase the odds of ACQ responders at 12 months compared to both MD-ICS (OR 1.61; 95% CrI 1.22 to 2.13; moderate certainty and 1.55; 95% CrI 1.20 to 2.00; high certainty, respectively) and HD-ICS (OR 1.48; 95% CrI 1.12 to 1.96; moderate certainty and 1.42; 95% CrI 1.10 to 1.84; moderate certainty, respectively). An NMA summary of findings is presented in Summary of findings table 6.

The rank plot for ACQ response at 12 months is presented in Figure S13, and mean and median ranks are presented in Table 29. MD-ICS/LABA ranked higher than all the other treatments (median rank 1.0 [95% CrI 1.0 to 2.0]). The results were consistent for the fixed- and random-effects models.

3.1.2.3 Pairwise Meta-Analysis

Results of pairwise meta-analysis are presented in Analysis 6.2 and Table 27. HD-ICS/LABA increases ACQ responders at 12 months compared to MD-ICS (RR 1.12; 95% CI 1.04 to 1.21; n=1167; 1 study; ABI 83 more per 1000 subjects; high certainty). MD-ICS/LABA likely increases ACQ responders at 12 months compared to MD- and HD-ICS (RR 1.19; 95% CI 1.09 to 1.29; n=774; 1 study; ABI 132 more per 1000 subjects; moderate certainty and RR 1.12; 95% CI 1.03 to 1.20; n=784; 1 study; ABI 88 more per 1000 subjects; moderate certainty, respectively). The evidence suggests little or no difference in ACQ responders at 12 months in other comparisons. There was no difference in the results between fixed- and random-effects models.

Above results are qualitatively similar to those of the NMA except for HD-ICS/LABA vs. HD-ICS for which the NMA evidence suggests that HD-ICS/LABA increases the odds of ACQ responders at 12 months compared to HD-ICS (OR 1.42; 95% CrI 1.10 to 1.84; moderate certainty) while the pairwise evidence does not (OR 1.23 [95%

CI 0.93 to 1.63]; n=1177; 1 study; moderate certainty). There was no difference in the results between fixed- and random-effects models.

3.2 SERIOUS ADVERSE EVENTS (SAEs)

3.2.1 Asthma-related SAE

For this outcome, 24 trials including 22,752 participants were included in the NMA comparing 6 treatment groups (Figure 22). The data set used for the analysis is presented in Table S10.

Fifteen out of the 24 trials included had zero counts of asthma-related SAEs in at-least one treatment arm. There were no trials where there were zero asthma-related SAEs in all treatment arms. Using the guidance from Dias 2018, we added a continuity-correction of 0.5 to CHIESI 2009 which would be disconnected from the network without the correction. We contacted the authors for missing data on this outcome but were not able to obtain it.

3.2.1.1 Model Selection and Inconsistency Checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a log-normal (-2.10, 1.58^2) prior, was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. The random-effects model fit the data better than the fixed-effect model. There was moderate between-study heterogeneity. The random-effects model had a smaller DIC than the fixed-effect model.

The model fit and DIC suggest that we choose the random-effects mode, however due to sparsity in the data, there is little evidence to inform the between-study heterogeneity. This can be seen in the density plot for the between-study standard deviation (Figure S14) where two peaks are observed. Therefore, we present results for the fixed-effect model alongside the random-effects model in Section 3.2.1.2.

A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Appendix 11. There was evidence to suggest inconsistency for the comparison between HD-ICS/LABA and HD-ICS. The p-value for the comparison between MD-ICS/LABA and MD-ICS was marginal, and the estimate for the indirect evidence was uncertain. Results for asthma-related SAEs for this comparison should be interpreted with caution.

3.2.1.2 NMA Results

As discussed in 3.2.1.1, all results in this section should be regarded with caution due to the inconsistency in the model. It is also important to note here that only one study (CHIESI 2009) provided evidence for LD-ICS/LABA to the network, and no asthma-related adverse events were observed in the LD-ICS/LABA arm. Therefore, the estimates for comparisons involving LD-ICS/LABA are very uncertain.

The ORs of asthma-related SAEs are presented in Figure 23. The ORs of asthma-related SAEs comparing all treatment groups against each other are reported in Table 30.

For the random-effects model, there is insufficient evidence to suggest a difference in odds of asthma-related SAEs for any treatment comparisons. Results obtained using the fixed-effect model are largely consistent with the random-effects model, but there is evidence that there are increased odds of asthma-related SAEs for treatment with MD-ICS/LABA and HD-ICS/LABA compared to LD-ICS/LABA (OR 2.97; 95% CrI 1.13 to 7.78; moderate certainty and OR 4.44; 95% CrI 1.53 to 12.91; moderate certainty, respectively). An NMA summary of findings is presented in Table 31.

Rank plots for the fixed- and random-effects model are presented in Figure S15, and mean and median ranks are presented in Table 32. LD-ICS/LABA had the highest probability of being ranked the best (median rank 1.0 [95% CrI 1.0 to 2.0] for the fixed-effect and 1.0 [95% CrI 1.0 to 5.0] for the random-effects model), but this is due to the sparse evidence for the treatment that forms the network.

3.2.1.3 Pairwise Meta-Analysis

The evidence suggests there is no or little difference in asthma-related SAEs for any of the treatment comparisons [low to high certainty] (Analysis 7.1, Table 33). There was no difference in the results between fixed- and random-effects models.

3.2.2 All-cause SAE

For this outcome, 33 trials including 26,875 participants were included in the NMA comparing 6 treatment groups (Figure 24). The data set used for the analysis is presented in Table S11.

3.2.2.1 Model Selection and Inconsistency Checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a log-normal (-2.10, 1.58^2) prior, was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. The random-effects model fit the data slightly better than the fixed-effect model. There was moderate between-study heterogeneity. The DIC for the random-effects model was more than 3 units smaller than the fixed-effect model.

The model fit and DIC suggest that we choose the random-effects mode, however due to sparsity in the data, there is little evidence to inform the between-study heterogeneity. This can be seen in the density plot for the

between-study standard deviation (Figure S16) where two peaks are observed. Therefore, we present results for the fixed-effect model alongside the random-effects model in Section 3.2.2.2.

A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Appendix 12. There was no evidence to suggest inconsistency in the network.

3.2.2.2 NMA Results

The ORs of all-cause SAEs are presented in Figure 25. The ORs of all-cause SAEs comparing all treatments are reported in Table 34. There is no evidence to suggest there is a change in odds of all-cause SAEs for any treatment comparisons. Results were consistent for the fixed- and random-effects models. Due to the sparsity of data in the network, the estimates for the LD-ICS/LABA vs. MD-ICS and LD-ICS/LABA vs. HD-ICS comparisons were highly uncertain for both models. The certainty of evidence was rated down accordingly. An NMA summary of findings is presented inTable 35.

Rank plots for the fixed- and random-effects models are presented in Figure S17, and mean and median ranks are presented in Table 36. There is a lot of uncertainty in treatment ranks, as suggested by the very wide 95% CrIs for both models.

3.2.2.3 Pairwise Meta-Analysis

The evidence suggests there is no or little difference in all-cause SAEs for any of the treatment comparisons [low to high certainty] (Analysis 7.2, Table 33). There was no difference in the results between fixed- and random-effects models.

3.3 ADVERSE EVENTS (AEs)

3.3.1 All-cause AE

For this outcome, 33 trials including 24,122 participants were included in the NMA comparing 6 treatment groups (Figure 26). The data set used for the analysis is presented in Table S12.

3.3.1.1 Model Selection and Inconsistency Checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a log-normal (-2.10, 1.58^2) prior, was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. While the random-effects model fit the data well, the fixed-effect model did not. Additionally, the DIC for the random-effects model was much smaller than the DIC for the fixed-effect model, therefore the random-effects model was chosen. There was moderate between-study heterogeneity. Results for the random-effects model are presented in Section 3.3.1.2.

A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Appendix 13. There was no evidence to suggest inconsistency in the network.

3.3.1.2 NMA Results

The ORs of all-cause AEs are presented in Figure 27. The ORs of all-cause AEs comparing all treatment groups against each other are reported in Table 37. There is no evidence to suggest that there is a change in odds of all-cause AEs for any of the treatment comparisons. An NMA summary of findings is presented in Table 38. The density plot for the between-study heterogeneity is presented in Figure S18.

The rank plot for all-cause AEs is presented in Figure S19, and mean and median ranks are presented in Table 39. While LD-ICS/LABA has the highest probability of being the best treatment (median rank 1.0 [95% CrI 1.0 to 6.0]), it only has a 50% probability. The treatment rankings overall are very uncertain as suggested by the very wide 95% CrIs. The results were consistent for the fixed- and random-effects models.

3.3.1.3 Pairwise Meta-Analysis

Results of pairwise meta-analysis are presented in Analysis 7.3 and Table 33. There is evidence that MD-ICS/LAMA probably reduces all-cause AEs compared to MD-ICS (RR 0.86; 95% CI 0.77 to 0.96; n=2238; 4 studies; absolute risk reduction (ARR) 55 fewer per 1000 subjects; moderate certainty) while the NMA evidence is very uncertain due to heterogeneity and imprecision. There also is evidence that MD-ICS/LABA probably reduces all-cause AEs compared to HD-ICS for the fixed-effect model (RR 0.92; 95% CI 0.85 to 0.99; n=2148; 5 studies; I^2=0%; moderate certainty) but not for the random-effects model (RR 0.93; 95% CI 0.87 to 1.00). The evidence suggests little or no difference in all-cause AEs in other comparisons.

3.3.2 Dropout Due to AEs

For this outcome, 34 trials including 32,684 participants were included in the NMA comparing 6 treatment groups (Figure 28). The data set used for the analysis is presented in Table S13.

3.3.2.1 Model Selection and Inconsistency Checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a Log-Normal(-2.10, 1.58^2) prior, was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. Both fixed- and random-effects models fit the data similarly. There was moderate between-study heterogeneity. While the DIC for the random-effects model was smaller than that for the fixed-effect model, the difference was marginal.

Additionally, the density plot for the between-study deviation shows two peaks (Figure S20) which suggests there is not a lot of evidence to inform the between-study heterogeneity due to the sparse data. Results for both fixed-effect and random-effects models are presented in Section 3.3.2.2.

A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Appendix 14. There was evidence of inconsistency for the comparisons of MD-ICS/LABA with MD-ICS/LAMA, which is directly linked to other loops in the network. Therefore, results for dropouts due to AEs should be interpreted with caution.

3.3.2.2 NMA Results

As discussed in 3.3.2.1, all results in this section should be regarded with caution due to the inconsistency in the model. The ORs of dropouts due to AEs are presented in Figure 29. The ORs of dropouts due to AEs comparing all treatment groups against each other are reported in Table 40. There is no evidence that any treatment reduces the odds of dropouts due to AEs for either the fixed-effect or random-effects model. An NMA summary of findings is presented in Summary of findings table 7 where MD-ICS/LAMA is judged likely to result in a slight reduction in dropouts due to AEs compared to MD-ICS (OR 0.57; 95% CrI 0.30 to 1.07; ARR 8 fewer per 1000 subjects ; 95% CrI 13 fewer to 1 more per 1000 subjects; moderate certainty) considering the pairwise evidence and inconsistency in the NMA model (Brignardello-Petersen 2018). The density plot for the between-study heterogeneity is presented in Figure 29.

The rank plots for the fixed- and random-effects models are presented in Figure S21, and mean and median ranks are presented in Table 41. MD-ICS/LAMA has the highest probability of being ranked the best treatment for both models (median rank 1.0 [95% CrI 1.0 to 6.0 for the fixed-effect and 1.0 to 5.0 for the random-effects model]) but there is a lot of uncertainty in these treatment ranks with wide credible intervals for both models.

3.3.2.3 Pairwise Meta-Analysis

Results of pairwise meta-analysis are presented in Analysis 7.4 and Table 33. There is evidence that MD-ICS/LAMA probably results in a slight reduction in dropouts due to AEs compared to MD-ICS (RR 0.51; 95% CI 0.26 to 0.99; n=2239; 4 studies; I^2=0; ARR 10 fewer per 1000 subjects; moderate certainty) for the fixed-effect model. However, the 95% CI for this comparison crosses the line of no effect for the random-effects model (RR 0.54 [95% CI 0.27 to 1.07]). The evidence suggests little or no difference in dropouts due to AEs in other comparisons.

Discussion

Summary of main results

We included 38,276 participants from 35 studies who had uncontrolled asthma and were eligible or had been treated with MD-ICS. The median duration of included studies was 24 weeks ranging from 12 to 78 weeks. Demographics of included population were as follows: mean age 44.1; male 38%; White 69%; mean FEV1 2.1 litters and 68% of predicted. The quality of included outcomes was high except for several outcomes in 8 studies due to high attrition rates.

The review findings suggest MD-ICS/LABA, HD-ICS/LABA, and MD-ICS/LAMA reduce moderate to severe asthma exacerbations (defined as moderate to severe in this study) compared to MD-ICS whereas HD-ICS probably does not. The certainty of evidence is low for MD-ICS/LAMA (HR 0.56 [95% CrI 0.38 to 0.82]) and moderate for MD- and HD-ICS/LABA (HR 0.70 [95% CrI 0.59 to 0.82] and 0.59 [0.46 to 0.76], respectively). There is no evidence to suggest any combination therapy or HD-ICS reduces severe asthma exacerbations (defined as severe exacerbation in this study) compared to MD-ICS [low to moderate certainty]. (Summary of findings table 1; Summary of findings table 2).

The efficacy of ICS/LABA or ICS/LAMA is less clear on symptom and quality of life scores (i.e., CFB in ACQ and AQLQ scores). The review findings suggest no clinically important differences in the symptom or quality of life score between MD-ICS and ICS/LABA or ICS/LAMA considering MCID [low to high certainty](Summary of findings table 3; Summary of findings table 4; Table 11; Table 14; Table 18; Table 20; Table 22; Table 24).

MD- and HD-ICS/LABA increase or likely increase the odds of ACQ responders at 6 and 12 months compared to MD-ICS at 12 months [moderate and high certainty]. MD-ICS/LAMA probably increases the odds of ACQ responder at 6 months, data was not available at 12 months, compared to MD-ICS [moderate certainty]. There is no evidence to suggest HD-ICS increases the odds of ACQ responders or improves the symptom or qualify of life score compared to MD-ICS [very low to high certainty] (Summary of findings table 5; Summary of findings table 6; Table 27).

There is no evidence to suggest ICS/LABA or ICS/LAMA reduces all-cause or asthma-related SAEs compared to MD-ICS [very low to high certainty]. There is moderate to high quality evidence that HD-ICS results in little or no difference in all the safety outcomes compared to MD-ICS and as well as HD-ICS/LABA compared to MD-ICS/LABA (Table 31; Table 33; Table 35). The median duration of included studies for the safety outcomes was 26 weeks (range 12 to 52 weeks).

The pairwise evidence indicates that MD-ICS/LAMA likely reduces all-cause AEs and results in a slight reduction in treatment discontinuation due to AEs compared to MD-ICS [moderate certainty]. The NMA evidence is in

agreement with the pairwise evidence on treatment discontinuation due to AEs but very uncertain for all-cause AEs due to imprecision and heterogeneity (Summary of findings table 7; Table 33; Table 38).

Overall completeness and applicability of evidence

The data is limited due to sparse evidence for LD-ICS/LABA treatment, as only one study provided evidence for LD-ICS/LABA in moderate to severe exacerbations and asthma-related SAEs. As a result, the reliability of treatment ranks, such as LD-ICS/LABA having the highest probability of being the best treatment for moderate to severe exacerbations and asthma-related SAEs in the NMA, is questionable due to the wide credible intervals caused by the uncertainty of the estimates. Therefore, the results should be interpreted with caution.

The evidence suggests little or no difference in the safety outcomes comparing HD-ICS to MD-ICS or HD-ICS/LABA to MD-ICS/LABA. However, longer-term side effects of higher than medium dose ICS need to be addressed in phase 4 or observational studies as the maximum study duration of the included studies for safety outcomes was 52 weeks and available evidence suggests higher ICS doses are associated with increased risk of clinically important systemic side effects (Beasley 2019).

Our results may not be applicable to active smokers as they were excluded in most of the included studies and cigarette smoking is known to impair the efficacy of ICS therapy (Shimoda 2016).

Individuals who were prone to side effects of anticholinergic treatment, such as narrow-angle glaucoma, urinary retention, and prostate hypertrophy, were excluded or restricted in the ICS/LAMA studies (Hamelmann 2016; Kerwin 2020). Therefore, the safety results of ICS/LAMA are not applicable to such individuals.

Quality of the evidence

The GRADE approach was used to assess the quality of evidence (Guyatt 2011). The results are presented in the Summary of Findings tables. Overall, the certainty of evidence for the different outcomes and treatment options varies from very low to high. Factors such as imprecision, risk of bias, heterogeneity, and limited data availability impact the ratings. The details of the risk assessment and evidence profile, along with the reasons for downgrading, are available at the following link: https://doi.org/10.6084/m9.figshare.22318363.

The certainty of evidence for severe exacerbations ranges from moderate to low, with imprecision being the main factor affecting the ratings. The certainty of evidence for moderate-to-severe exacerbations varies from very low to moderate, with factors such as risk of bias, imprecision, and paucity of data influencing the ratings.

The certainty of evidence for CFB in ACQ scores is generally high in most comparisons, supported by direct evidence from multiple RCTs with a significant number of participants. However, in a few comparisons, the certainty level is moderate due to imprecision.

The certainty of evidence for CFB in AQLQ scores is low due to imprecision at 3 months. However, at 6 months, the certainty varies from very low to high. LD-ICS/LABA and MD-ICS/LABA, when compared to MD-ICS, have high level of certainty. On the other hand, HD-ICS, MD-ICS/LABA, and HD-ICS/LABA, when compared to MD-ICS, have low to moderate levels of certainty primarily due to imprecision. Additionally, in the case of HD-ICS, there is also a concern regarding the risk of bias.

The overall certainty of evidence for ACQ responders varies across different comparisons, with a range from low to high certainty. At 6 months, MD-ICS/LABA and HD-ICS/LABA have a high level of certainty when compared to MD-ICS. At 12 months, HD-ICS and MD-ICS/LABA, when compared to MD-ICS, have a moderate level of certainty. Furthermore, at 6 months, MD-ICS/LAMA shows moderate certainty when compared to MD-ICS, while HD-ICS, in comparison to MD-ICS, has a low level of certainty primarily due to imprecision.

The certainty of evidence for SAEs varies across different treatment options, with HD-ICS/LABA, MD-ICS/LAMA, and MD-ICS/LABA, when compared to MD-ICS, having high level of certainty, LD-ICS/LABA, when compared to MD-ICS, having very low to low level of certainty, and HD-ICS, when compared to MD-ICS, having moderate level of certainty, primarily due to heterogeneity, imprecision, and limited data availability.

The certainty of evidence for all-cause AEs varies across different treatment options, with HD-ICS, when compared to MD-ICS, having moderate level of certainty, LD-ICS/LABA, MD-ICS/LABA, and HD-ICS/LABA, when compared to MD-ICS, having low level of certainty, and MD-ICS/LAMA, when compared to MD-ICS, having very low level of certainty, primarily due to imprecision and heterogeneity in the available data.

The evidence for Dropouts due to AEs varies in certainty, with HD-ICS, LD-ICS/LABA, MD-ICS/LABA, and HD-ICS/LABA, when compared to MD-ICS, having high level of certainty, and MD-ICS/LAMA, when compared to MD-ICS, having moderate level of certainty due to imprecision.

Overall, the varying levels of certainty highlight the importance of considering the quality of evidence when interpreting and making decisions about asthma treatment options.

Potential biases in the review process

The proportion of participants who had a history of asthma exacerbation in the previous year was 1% in the MD-ICS/LAMA group, 83% in the LD-ICS/LABA group, 32% in the HD-ICS group, and 51-53 % in the MD-ICS, MD-ICS/LABA, and HD-ICS/LABA groups. The mean FEV1 in the LD-ICS/LABA and MD-ICS/LAMA groups was relatively higher than in the other groups (Table 2). We took the clinical heterogeneity into consideration and

rated down the certainty of evidence as necessary for the clinical heterogeneity especially when there was inconsistency between the pairwise and NMA evidence.

There were no substantial differences in the decisions made by the review authors regarding study selection, data extraction, and data synthesis, which would have impacted the conclusions or interpretations of the data.

Agreements and disagreements with other studies or reviews

This study differs in several aspects from previous systematic reviews (Anderson 2015; Buhl 2018; Chipps 2020; Kew 2015; Rodrigo 2015; Sobieraj 2018).

This study was designed to compare treatment options in individuals who were still symptomatic or experiencing an asthma exacerbation despite being on ICS monotherapy (EPR-4 2020 or GINA 2022 Step 3 or higher). Therefore, clinical trials comparing treatment options in Step 3 and 4 were included (i.e., MD-ICS, HD-ICS, LD-ICS/LABA, MD-ICS/LAMA, MD-ICS/LABA, and HD-ICS/LABA). We did not consider add-on leukotriene receptor antagonists or as-needed plus daily ICS/formoterol to minimise complexity and intransitivity involving the NMA.

The previous studies included trials with shorter durations of less than 12 weeks, crossover design, and unavailable formulations/doses to make comparisons possible while such trials were excluded in this study to estimate the impact on patient-centered outcomes with a long enough duration, minimise residual effects of crossover ICS doses, and reflect the real-world practice.

We conducted both pairwise and network meta-analyses anchored by MD-ICS monotherapy which enabled us to provide direct and indirect comparisons between ICS/LABA and ICS/LAMA combination therapies unlike in the others. This study is in agreement with the previous studies comparing ICS/LABA to ICS/LAMA suggesting no robust evidence to favour one over the other. However, the certainty of evidence is generally greater for MD- or HD-ICS/LABA than for MD-ICS/LAMA primarily due to much larger evidence base for ICS/LABA which would support the current guidelines favouring a LABA over a LAMA as add-on therapy.

The pairwise evidence in this study indicates MD-ICS/LAMA likely reduces all-cause AEs and results in a slight reduction in treatment discontinuation due to AEs compared to MD-ICS while such outcomes were not reported in the previous studies.

We classified asthma exacerbations requiring systemic corticosteroids as moderate and a hospitalisation as severe and reported them separately while previous studies were either inconclusive on or did not report asthma-related hospitalisation primarily due to the paucity of data at the time of their reviews. This study would advance the evidence on asthma-related hospitalisation and other patient-centered outcomes with the addition of new data and NMA evidence.

We compared the impact of medium- vs. high-dose ICS and found no evidence to suggest that high-dose ICS improved efficacy or increased adverse events compared to medium-dose ICS either in mono- or combination therapy. The results were in accordance with Chipps 2020 in which the authors reported comparable effects across low, medium, and high ICS doses on rescue medication use, nighttime symptom score, FEV1, and withdrawal due to adverse events as well as a clinically insignificant small improvement in morning peak expiratory flow. A post hoc analysis in Lee 2020 showed HD-ICS containing groups had greater improvements in both FEV1 and annualised rates of moderate to severe exacerbations in subjects with higher blood eosinophils or fractional exhaled nitric oxide at baseline than did MD-ICS containing groups. A previous meta-analysis showed that treatment tailored using type 2 biomarkers resulted in fewer asthma exacerbations compared with traditional management but did not impact final daily ICS doses (Petsky 2018).

Authors' conclusions

Implications for practice

In summary, the review findings suggest that MD- or HD-ICS/LABA and MD-ICS/LAMA are effective in reducing moderate to severe asthma exacerbations and increasing the likelihood of ACQ responders compared to MD-ICS alone. However, HD-ICS is likely not as effective in this regard. The evidence is generally stronger for MD- and HD-ICS/LABA treatments, primarily due to a larger body of evidence supporting their efficacy. There is no evidence suggesting that ICS/LABA, ICS/LAMA, or HD-ICS/LABA reduce asthma-related or all-cause SAEs compared to MD-ICS. On the other hand, MD-ICS/LAMA treatment is likely to reduce all-cause AEs and slightly decrease treatment discontinuation due to AEs when compared to MD-ICS alone.

These findings can guide treatment decisions in the stepwise approach to asthma management, but longer-term safety studies are needed to assess the use of higher than medium dose ICS.

Implications for research

Although this study suggests higher than medium dose ICS in mono- or combination therapy provides no additional benefits in the population studied, the optimal approach to ICS dosing in subjects with the biomarker-high phenotype and active smokers remains to be established with further studies. Longer-term safety of higher than medium dose ICS needs to be addressed in phase 4 or observational studies given the median duration of included studies was 6 months.

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Data and analyses

Comparison 1

Exacerbations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Severe exacerbations	17		Risk Difference (M-H, Random, 95% CI)	Subtotals only
1.1.1 HD-ICS vs MD-ICS	4	3003	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.05, 0.03]
1.1.2 MD-ICS/LAMA vs MD-ICS	1	282	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.02]
1.1.3 MD-ICS/LABA vs MD-ICS	10	15651	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
1.1.4 HD-ICS/LABA vs MD-ICS	3	3319	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.12, 0.07]
1.1.5 MD-ICS/LABA vs HD-ICS	4	2954	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.02]
1.1.6 HD-ICS/LABA vs HD-ICS	6	5028	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]
1.1.7 MD-ICS/LABA vs LD-ICS/LABA	1	694	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
1.1.8 HD-ICS/LABA vs	5	4612	Risk Difference	0.00 [-0.01, 0.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
MD-ICS/LABA			(M-H, Random, 95% CI)	
1.1.9 ICS-LAMA vs ICS	1	282	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.02]
1.1.10 ICS-LABA vs ICS	11	19664	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]
1.2 Moderate to severe exacerbations	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 HD-ICS vs MD-ICS	4	1685	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.98]
1.2.2 MD-ICS/LAMA vs MD-ICS	2	679	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.24, 0.95]
1.2.3 MD-ICS/LABA vs MD-ICS	12	7569	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.56, 0.83]
1.2.4 HD-ICS/LABA vs MD-ICS	2	1759	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.33, 1.56]
1.2.5 MD-ICS/LABA vs HD-ICS	3	1386	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.52, 0.83]
1.2.6 HD-ICS/LABA vs HD-ICS	6	3434	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.53, 0.77]
1.2.7 MD-ICS/LABA vs LD-ICS/LABA	1	694	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.68, 3.85]
1.2.8 HD-ICS/LABA vs MD-ICS/LABA	5	4880	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.12]
1.2.9 ICS/LABA vs ICS	16	11141	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.79]

Comparison 2

Severe exacerbations (high and low risk subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 HD-ICS vs MD-ICS	4		Risk Difference (M-H, Random, 95% CI)	Subtotals only
2.1.1 High Risk	0	0	Risk Difference (M-H, Random, 95% CI)	Not estimable
2.1.2 Low Risk	4	3003	Risk Difference (M-H,	-0.01 [-0.05, 0.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
			Random, 95% CI)	
2.2 MD-ICS/LAMA vs MD-ICS	1	282	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.70]
2.2.1 High Risk	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2.2 Low Risk	1	282	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.70]
2.3 MD-ICS/LABA vs MD-ICS	10	15651	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
2.3.1 High Risk	3	11579	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.00]
2.3.2 Low Risk	7	4072	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.02]
2.4 HD-ICS/LABA vs MD-ICS	3	3319	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.12, 0.07]
2.4.1 High Risk	1	1560	Risk Difference (M-H, Random, 95% CI)	0.01 [0.01, 0.02]
2.4.2 Low Risk	2	1759	Risk Difference (M-H, Random, 95% CI)	-0.05 [-0.25, 0.16]
2.5 MD-ICS/LABA vs HD-ICS	4	2954	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.03, -0.00]
2.5.1 High Risk	1	1568	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.01, 0.00]
2.5.2 Low Risk	3	1386	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.06, 0.00]
2.6 HD-ICS/LABA vs HD-ICS	6	5028	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.02, 0.00]
2.6.1 High Risk	1	1970	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.00, 0.02]
2.6.2 Low Risk	5	3058	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.04, -0.00]
2.7 MD-ICS/LABA vs LD-ICS/LABA	1	694	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.01, 0.02]
2.7.1 High Risk	0	0	Risk Difference (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
2.7.2 Low Risk	1	694	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.01, 0.02]	
2.8 HD-ICS/LABA vs MD-ICS/LABA	5	4612	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.01, 0.01]	
2.8.1 High Risk	1	1562	Risk Difference (M-H, Fixed, 95% CI)	0.01 [0.00, 0.02]	
2.8.2 Low Risk	4	3050	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.02, 0.02]	
2.9 ICS/LAMA vs ICS	1	282	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]	
2.9.1 High Risk	0	0	Risk Difference (M-H, Fixed, 95% CI)	Not estimable	
2.9.2 Low Risk	1	282	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]	
2.10 ICS/LABA vs ICS	11	19664	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]	
2.10.1 High Risk	3	13549	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.00]	
2.10.2 Low Risk	8	6115	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.02]	

Comparison 3

Moderate to severe exacerbations (high and low risk subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
3.1 HD-ICS vs MD-ICS	4	1685	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.97]	
3.1.1 High Risk	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable	
3.1.2 Low Risk	4	1685	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.97]	
3.2 MD-ICS/LAMA vs MD-ICS	2	679	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.96]	
3.2.1 High Risk	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable	
3.2.2 Low Risk	2	679	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.96]	
3.3 MD-ICS/LABA vs MD-ICS	12	7569	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.62, 0.78]	

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
3.3.1 High Risk	1	2019	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]	
3.3.2 Low Risk	11	5550	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.55, 0.73]	
3.4 HD-ICS/LABA vs MD-ICS	2	1759	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.33, 1.56]	
3.4.1 High Risk	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	
3.4.2 Low Risk	2	1759	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.33, 1.56]	
3.5 MD-ICS/LABA vs HD-ICS	3	1386	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.44, 0.79]	
3.5.1 High Risk	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable	
3.5.2 Low Risk	3	1386	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.44, 0.79]	
3.6 HD-ICS/LABA vs HD-ICS	6	3434	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.54, 0.78]	
3.6.1 High Risk	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable	
3.6.2 Low Risk	6	3434	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.54, 0.78]	
3.7 MD-ICS/LABA vs LD-ICS/LABA	1	694	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.68, 3.85]	
3.7.1 High Risk	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable	
3.7.2 Low Risk	1	694	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.68, 3.85]	
3.8 HD-ICS/LABA vs MD-ICS/LABA	5	4880	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.12]	
3.8.1 High Risk	1	1830	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.14]	
3.8.2 Low Risk	4	3050	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.65, 1.25]	
3.9 ICS/LABA vs ICS	16	11141	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.62, 0.75]	
3.9.1 High Risk	1	2019	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]	
3.9.2 Low Risk	15	9122	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.57, 0.71]	

Comparison 4

CFB in ACQ

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 CFB in ACQ at 3 months	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1.1 HD-ICS vs MD-ICS	1	829	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.22, 0.01]
4.1.2 MD-ICS/LABA vs MD-ICS	2	2700	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.27, -0.14]
4.1.3 HD-ICS/LABA vs MD-ICS	1	1255	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.30, -0.11]
4.1.4 MD-ICS/LABA vs HD-ICS	2	1247	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.24, -0.07]
4.1.5 HD-ICA/LABA vs HD-ICS	2	1698	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.20, -0.05]
4.1.6 MD-ICS/LABA vs LD-ICS/LABA	1	658	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.35, -0.09]
4.1.7 HD-ICS/LABA vs MD-ICS/LABA	2	1689	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.05, 0.11]
4.2 CFB in ACQ at 6 months	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.2.1 HD-ICS vs MD-ICS	1	798	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.18, 0.04]
4.2.2 MD-ICS/LAMA vs MD-ICS	4	2116	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.20, -0.06]
4.2.3 MD-ICS/LABA vs MD-ICS	5	3909	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.23, -0.13]
4.2.4 HD-ICS/LABA vs MD-ICS	1	1210	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.31, -0.12]
4.2.5 MD-ICS/LABA vs HD-ICS	1	812	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.29, -0.06]
4.2.6 HD-ICS/LABA vs HD-ICS	1	1222	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.24, -0.05]
4.2.7 MD-ICS/LABA vs MD-ICS/LAMA	2	1483	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.11, 0.06]
4.2.8 HD-ICS/LABA vs MD-ICS/LABA	3	3762	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.10, 0.01]
4.3 CFB in ACQ at 12 months	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.3.1 HD-ICS vs	2	1005	Mean Difference	-0.09 [-0.19, 0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
MD-ICS			(IV, Fixed, 95% CI)	
4.3.2 MD-ICS/LABA vs MD-ICS	1	774	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.38, -0.15]
4.3.3 HD-ICS/LABA vs MD-ICS	2	2863	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.25, -0.12]
4.3.4 MD-ICS/LABA vs HD-ICS	1	784	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.08]
4.3.5 HD-ICS/LABA vs HD-ICS	1	1177	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.25, -0.05]
4.3.6 HD-ICS/LABA vs MD-ICS/LABA	2	2980	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.10, 0.04]

Comparison 5

CFB in AQLQ

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 CFB in AQLQ at 3 months	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1.1 HD-ICS vs MD-ICS	1	265	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.16, 0.25]
5.1.2 MD-ICS/LABA vs MD-ICS	3	880	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.08, 0.30]
5.1.3 HD-ICS/LABA vs MD-ICS	1	264	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.01, 0.40]
5.1.4 MD-ICS/LABA vs HD-ICS	2	680	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.03, 0.25]
5.1.5 HD-ICS/LABA vs HD-ICS	4	1500	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.01, 0.15]
5.1.6 HD-ICS/LABA vs MD-ICS/LABA	2	694	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.20, 0.02]
5.2 CFB in AQLQ at 6 months	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.2.1 LD-ICS/LABA vs MD-ICS	3	1605	Mean Difference (IV, Random, 95% CI)	0.24 [0.09, 0.40]
5.2.2 MD-ICS/LABA vs MD-ICS	3	1359	Mean Difference (IV, Random, 95% CI)	0.16 [0.05, 0.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2.3 HD-ICS/LABA vs HD-ICS	1	463	Mean Difference (IV, Random, 95% CI)	0.05 [-0.13, 0.22]
5.2.4 MD-ICS/LABA vs LD-ICS/LABA	2	1470	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.22, 0.03]
5.2.5 HD-ICS/LABA vs MD-ICS/LABA	1	1222	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.14, 0.04]

Comparison 6

ACQ responder

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 ACQ responder at 6 months	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1.1 HD-ICS vs MD-ICS	1	798	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.99, 1.19]
6.1.2 MD-ICS/LAMA vs MD-ICS	3	2219	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.03, 1.18]
6.1.3 MD-ICS/LABA vs MD-ICS	2	1853	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.07, 1.22]
6.1.4 HD-ICS/LABA vs MD-ICS	1	1210	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.05, 1.23]
6.1.5 MD-ICS/LABA vs HD-ICS	1	812	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.14]
6.1.6 HD-ICS/LABA vs HD-ICS	1	1222	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.98, 1.13]
6.1.7 MD-ICS/LABA vs MD-ICS/LAMA	1	1563	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.96, 1.11]
6.1.8 HD-ICS/LABAcs MD-ICS/LABA	3	3700	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.07]
6.2 ACQ responder at 12 months	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.2.1 HD-ICS vs MD-ICS	2	1011	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.85, 1.19]
6.2.2 MD-ICS/LABA vs MD-ICS	1	774	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.09, 1.29]
6.2.3 HD-ICS/LABA vs MD-ICS	1	1167	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.04, 1.21]
6.2.4 MD-ICS/LABA vs HD-ICS	1	784	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.03, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
6.2.5 HD-ICS/LABA vs HD-ICS	1	1177	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.98, 1.13]	
6.2.6 HD-ICS/LABA vs MD-ICS/LABA	2	2817	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.07]	

Comparison 7

Safety outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Asthma-related SAEs	24		Risk Difference (M-H, Random, 95% CI)	Subtotals only
7.1.1 HD-ICS vs MD-ICS	5	3324	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.02, 0.01]
7.1.2 MD-ICS/LAMA vs MD-ICS	4	2238	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.00]
7.1.3 MD-ICS/LABA vs MD-ICS	15	11971	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.00, 0.00]
7.1.4 HD-ICS/LABA vs MD-ICS	4	3610	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.02]
7.1.5 MD-ICS/LABA vs HD-ICS	5	3422	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.00]
7.1.6 HD-ICS/LABA vs HD-ICS	7	5063	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.01]
7.1.7 MD-ICS/LABA vs LD-ICS/LABA	1	695	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
7.1.8 MD-ICS/LABA vs MD-ICS/LAMA	2	1577	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.00]
7.1.9 HD-ICS/LABA vs MD-ICS/LABA	7	6652	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.01]
7.2 All cause SAEs	33		Risk Difference (M-H, Random, 95% CI)	Subtotals only
7.2.1 HD-ICS vs	7	3775	Risk Difference	-0.01 [-0.02, 0.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
MD-ICS			(M-H, Random, 95% CI)	
7.2.2 MD-ICS/LAMA vs MD-ICS	4	2238	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.02, 0.01]
7.2.3 MD-ICS/LABA vs MD-ICS	21	14588	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.01]
7.2.4 HD-ICS/LABA vs MD-ICS	5	4302	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
7.2.5 MD-ICS/LABA vs HD-ICS	6	3716	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]
7.2.6 HD-ICS/LABA vs HD-ICS	8	5814	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.01]
7.2.7 MD-ICS/LABA vs LD-ICS/LABA	1	695	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]
7.2.8 MD-ICS/LABA vs MD-ICS/LAMA	2	1577	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.02, 0.02]
7.2.9 HD-ICS/LABA vs MD-ICS/LABA	9	7919	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
7.3 All cause AEs	33		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.3.1 HD-ICS vs MD-ICS	6	2208	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.14]
7.3.2 MD-ICS/LAMA vs MD-ICS	4	2238	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.77, 0.96]
7.3.3 MD-ICS/LABA vs MD-ICS	20	13430	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.19]
7.3.4 HD-ICS/LABA vs MD-ICS	4	2742	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.05]
7.3.5 MD-ICS/LABA vs HD-ICS	5	2148	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.87, 1.00]
7.3.6 HD-ICS/LABA vs HD-ICS	8	4220	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.87, 1.00]
7.3.7 MD-ICS/LABA	1	695	Risk Ratio (M-H,	0.92 [0.75, 1.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
vs LD-ICS/LABA			Random, 95% CI)		
7.3.8 MD-ICS/LABA vs MD-ICS/LAMA	2	1577	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.87, 1.17]	
7.3.9 HD-ICS/LABA vs MD-ICS/LABA	8	6357	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.05]	
7.4 Dropouts due to adverse event	34		Risk Ratio (M-H, Random, 95% CI)	Subtotals only	
7.4.1 HD-ICS vs MD-ICS	6	2211	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.48, 3.48]	
7.4.2 LD-ICS/LABA vs MD-ICS	1	5846	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.38, 1.14]	
7.4.3 MD-ICS/LAMA vs MD-ICS	4	2239	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.27, 1.07]	
7.4.4 MD-ICS/LABA vs MD-ICS	21	20326	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.31]	
7.4.5 HD-ICS/LABA vs MD-ICS	4	2750	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.31, 2.27]	
7.4.6 MD-ICS/LABA vs HD-ICS	5	2465	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.67, 2.40]	
7.4.7 HD-ICS/LABA vs HD-ICS	8	3916	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.68, 2.17]	
7.4.8 MD-ICS/LABA vs LD-ICS/LABA	2	6542	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.62, 1.70]	
7.4.9 MD-ICS/LABA vs MD-ICS/LAMA	2	1577	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.19, 8.66]	
7.4.10 HD-ICS/LABA vs MD-ICS/LABA	8	6380	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.56, 1.19]	

Contributions of authors

Y. Oba: extracted data, assessed studies for methodological quality, constructed figures and tables for pairwise meta-analyses and otherwise constructed the review.

T Maduke: extracted data and assessed studies for methodological quality.

S Anwer: conducted the network meta-analyses, constructed tables and figures, and drafted the network meta-analysis results.

T Patel: extracted data and assessed studies for methodological quality.

S Dias: provided guidance and supervision of the network meta-analyses and their presentation and interpretation and drafted the network meta-analysis results.

All authors contributed to the writing of the review and approved the final version of the document.

Contributions of editorial team

Elizabeth Stovold (Information Specialist): designed the search strategy; arranged for peer review of the search strategy.

Declarations of interest

Y. Oba has provided consultation and received honoraria from Genentech unrelated to the current review. This author, who is a Cochrane Editor, was not involved in the editorail process.

T Patel: none known.

S Anwer: none known.

T Maduke: none known.

S Dias: none known.

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External sources

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Differences between protocol and review

- We presented grouped treatment comparisons only as there was insufficient evidence to allow for individual treatment comparisons.
- We did not combine ACQ, ACT and AQLQ scores using minimally important difference units to avoid indirectness in a pooled analysis.
- We did not perform a subgroup analysis on publication status as it was homogenous across the included studies.
- We used the GeMTC package in R as well as OpenBUGS for the NMAs.
- We used informative, empirically derived prior distributions for the dichotomous outcomes (Turner 2015) and semi-informative half-normal prior distributions for severe exacerbations (Röver 2021) to assess between-study heterogeneity in the NMAs.
- We used the node-splitting model (van Valkenhoef 2016) to assess inconsistency between direct and indirect estimates instead of an inconsistency model in the NMAs. This is a more sensitive method to detect inconsistency.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Bateman 2014

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: up to 76 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Australia, Germany, Japan, Mexico, Philippines, Poland, Romania, Russian Federation, Ukraine, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 2019

	Mean age: 41.7 (Ages Eligible for Study: 12 Years and older) **Male %**: 33 **White %:** 74 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Yes/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.1 **Baseline FEV1 % predicted**: 69 **Hx of asthma exacerbation**: Required **Inclusion Criteria:** • Clinical diagnosis of asthma • Reversibility FEV1 of twelve percent or greater and two hundred milliliters and greater approximately ten to forty minutes following two to four inhalations of albuterol • FEV1 of fifty to ninety percent of predicted • Currently using inhaled corticosteroid therapy • History of one or more asthma exacerbations requiring treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization in previous year **Exclusion Criteria:** • History of life threatening asthma in previous 5 years (requiring intubation, and/or associated with hypercapnia, hypoxic seizure or respiratory arrest • Respiratory infection or oral candidiasis • - Uncontrolled disease or clinical abnormality • Allergies • Taking another investigational medication or prohibited medication
Interventions	MD-ICS: FF 100 µg daily MD-ICS/LABA: FF/VI 100/25 µg daily
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event CFB in ACQ at 3 months CFB in ACQ at 6 months CFB in ACQ at 12 months
Notes	NCT01086384 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=SAS30040

Beasley 2015

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: up to 68 weeks **SPONSORSHIP SOURCE**: Novartis Pharmaceuticals **COUNTRY**: Brazil, Colombia, Czech Republic, Hungary, India, Korea, Republic of, Peru, Slovakia, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 1508 **Mean age:** 42.3 (Ages Eligible for Study: 12 Years to 70 years old) **Male %**: 42 **White %:** 62 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.3 **Baseline FEV1 % predicted**: 76 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Patients with a documented diagnosis of persistent asthma and who were currently treated with or qualified for treatment with both ICS and long-acting beta2-agonist (LABA) combination • Patients demonstrating an increase in forced expiration volume in 1 second (FEV1) of ≥ 12% or ≥ 200 mLs within 30 minutes after administration of short-acting beta2-agonist (SABA) • Patients with an FEV1 ≥ 50% of predicted normal **Exclusion Criteria:** • Patients with a previous diagnosis of chronic obstructive pulmonary disease (COPD)

	• Patients who had an asthma attack/exacerbation requiring hospitalization/emergency room visit or respiratory tract infection within 1 month prior to randomization • Patients who had ever required ventilator support for respiratory failure • Patients with diabetes Type I or uncontrolled diabetes Type II • Patients with concomitant pulmonary disease • Patients with certain cardiovascular co-morbid conditions • Patients with any significant medical condition that might compromise patient safety, interfere with evaluation or preclude completion of the study Other protocol-defined inclusion/exclusion criteria may apply
Interventions	MD-ICS: MF 400 µg qd MD-ICS/LABA: MF/IND 400/500 µg qd
Outcomes	All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	NCT00941798

Bernstein 2011

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Merck Sharp & Dohme **COUNTRY**: Canada, Colombia, Costa Rica, Czech Republic, Ecuador, Estonia, Finland, Former Serbia and Montenegro, Germany, Latvia, Lithuania, Netherlands, Puerto Rico, Romania, Russian Federation, Serbia, Slovenia, Ukraine, United
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 1705 **Mean age:** 44.9 (Ages Eligible for Study: 12 Years and older) **Male %**: 87 **White %:** 87 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.3 **Baseline FEV1 % predicted**: 74 **Hx of asthma exacerbation**: Not required **INCLUSION CRITERIA**: Participants must have a diagnosis of asthma for at least 12 months' duration. A participant must have been using a medium daily dose of inhaled glucocorticosteroids (alone or in combination with long-acting beta 2-agonist [LABA]) for at least 12 weeks and must have been on a stable regimen for at least 2 weeks prior to Screening. If there is no inherent harm in changing the participant's current asthma therapy, the participant must be willing to discontinue his/her prescribed inhaled glucocorticosteroid (ICS) or ICS/LABA prior to initiating MF MDI run-in medication. The diagnosis of asthma must be documented by either demonstrating an increase in absolute forced expiratory volume in 1 second (FEV1) of at least 12% and a volume increase of at least 200 mL within approximately 15 to 20 minutes after administration of 4 inhalations of albuterol/salbutamol or of nebulized short-acting beta 2-agonist (SABA) OR peak expiratory flow (PEF) variability of more than 20% OR a diurnal variation PEF of more than 20% based on the difference between pre-bronchodilator (before taking albuterol/salbutamol) morning value and the post-bronchodilator value (after taking albuterol/salbutamol) from the evening before, expressed as a percentage of the mean daily PEF value on any day during the open-label Run-in Period. A participant must have a history of >: 2 asthma-related unscheduled visits to a physician or to an emergency room within the past year AND >: 3 asthma-related unscheduled visits within the past 2 years. Prior to randomization participants must have used a total of 12 or more inhalations of SABA rescue medication during the last 10 days of run-in. Clinical laboratory tests (complete blood counts [CBC], blood chemistries, including serum pregnancy for females of child-bearing potential, and urinalysis) conducted at the Screening Visit must be within normal limits or clinically acceptable to the investigator/sponsor before the participant is instructed to start using open-label MF MDI run-in medication. An electrocardiogram (ECG) performed at the Screening Visit, using a centralized trans-telephonic technology, must be clinically acceptable to the investigator. A chest x-ray performed at the Screening Visit, or within 12 months prior to the Screening Visit, must be clinically acceptable to the investigator. A non-pregnant female participant of childbearing potential must be using a medically acceptable, adequate form of birth control. A female participant of childbearing potential must have a negative serum pregnancy test at Screening in order to be considered eligible for enrollment. **EXCLUSION CRITERIA**: A participant who demonstrates a change in absolute FEV1 of > 20% at any time between the Screening and Baseline Visits on any 2 consecutive days between the Screening and Baseline visits. A participant who requires the use of greater than 8 inhalations per day of SABA MDI or 2 or more nebulized treatments per day of 2.5 mg SABA on any 2 consecutive days between the Screening and Baseline Visits. A participant who experiences a decrease in AM or PM PEF below the Run-in Period stability limit on any 2 consecutive days prior to randomization. The average AM and average PM PEF respective values from the preceding 7 days are added, divided by the number of non-missing values, and multiplied by 0.70 to determine the stability limit. A participant who experiences a clinical asthma exacerbation: defined as a clinical deterioration of asthma as judged by the clinical investigator between the Screening and Baseline Visits, that results in emergency treatment, hospitalization due to asthma, or treatment with additional, excluded asthma medication (including oral or other systemic corticosteroids, but allowing SABA).
Interventions	MD-ICS: MF 200 µg bid (open label) MD-ICS/LABA: FP/SAL 250/50 µg bid; MF/FM 200/10 µg bid
Outcomes	All cause serious adverse events

	All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	NCT00424008

Bernstein 2015

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Chile, Germany, Mexico, Netherlands, Poland, Romania, Russian Federation, Sweden, Ukraine, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 1039 **Mean age:** 45.7 (Ages Eligible for Study: 12 Years and older) **Male %**: 35 **White %:** 86 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.0 **Baseline FEV1 % predicted**: 63 **Hx of asthma exacerbation**: Not required **INCLUSION CRITERIA**: Subjects must give their signed and dated (written) informed consent to participate. Written informed consent must be obtained if a subject's current medication is changed as a result of study participation Outpatient >:12 years of age at Visit 1 who have had a diagnosis of asthma, as defined by the National Institutes of Health. Countries with local restrictions prohibiting enrolment of adolescents will only enroll subjects >:18 years of age Male or an eligible female. Eligible female is defined as having non-childbearing potential or having childbearing potential and using an acceptable method of birth control consistently and correctly. Best pre-bronchodilator FEV1 of 40% to 80% of their predicted normal value. Demonstrate >:12% and >:200 mL reversibility of FEV1 within 10 to 40 minutes following 4 inhalations of albuterol/salbutamol inhalation aerosol (or an equivalent nebulized treatment with albuterol/salbutamol solution) or have documented reversibility testing within the 6 months prior to Visit 1 meeting this measure of reversibility. A spacer device may be used for testing, if required. If subject have received ICS for at least 12 weeks prior to Visit 1 and their treatment during the 4 weeks immediately prior to Visit 1 consisted of either of the two regimens (a or b).a.) A stable mid-dose or high-dose of ICS alone (e.g., >:FP 250 mcg twice daily) or b.) A stable dose of a mid-dose ICS/LABA combination (e.g., FP/Salmeterol [SALM] 250/50 mcg twice daily) or an equivalent combination via separate inhalers. Use of ICS/LABA are not permitted with LABA on the day of Visit 1. Must be able to replace current SABA treatment with albuterol/salbutamol aerosol inhaler at Visit 1 for use as needed, during the study. Subjects must be able to withhold albuterol/salbutamol for at least 6 hours prior to study visits **EXCLUSION CRITERIA**: History of life-threatening asthma, defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the last 5 years. Upper or lower respiratory tract, sinus, or middle ear that is: not resolved within 4 weeks of Visit 1 and led to a change in asthma management or, in the opinion of the investigator, expected to affect the subject's asthma status or the subject's ability to participate in the study. Any asthma exacerbation that required oral corticosteroids within the 12 weeks prior to Visit 1 or, resulted in an overnight hospitalization requiring additional treatment for asthma within 6 months prior to Visit 1. A subject must not have current evidence of atelectasis (segmental or larger), bronchopulmonary dysplasia, chronic obstructive pulmonary disease, Or any evidence of concurrent respiratory disease other than asthma A subject must not have any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the efficacy results if the condition/disease exacerbated during the study Chronic stable hepatitis B or C are acceptable provided their screening alanine transaminase (ALT) is <2x upper limit of normal (ULN) and the y otherwise meet the entry criteria. Chronic co-infection with both hepatitis B and hepatitis C are not eligible Clinical visual evidence of candidiasis at Visit 1 Use of any investigational drug within 30 days prior to Visit 1 or within five half-lives (t½), whichever is longer of the two. Allergies to drug or milk protein: any adverse reaction, to any beta2-agonist, sympathomimetic drug, or any intranasal, inhaled, or systemic corticosteroid therapy or known or suspected sensitivity to the constituents of the NDPI, or history of severe milk protein allergy Administration of medication that would significantly affect the course of asthma, or interact with study drug Use of immunosuppressive medications during the study. Use of potent CYP3A4 inhibitor within 4 weeks of Visit 1. A subject or his/her parent or legal guardian has any infirmity, disability, disease, or resides in a geographical location which seems likely, in the opinion of the Investigator, to impair compliance with any aspect of this study protocol, including visit schedule, and completion of the daily diaries. Current smoker or has a smoking history of 10 pack-years (20 cigarettes/day for 10 years). A subject may not have used inhaled tobacco products within the past 3 months (i.e., cigarettes, cigars, or pipe tobacco). If subject is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator. Subject previously randomized to treatment with FF/VI or FF in another Phase III study Subjects working on night shift a week prior to Visit 1 or during the study period. Adolescents who are wards of the state or government **SYMPTOM CRITERIA**: Asthma symptoms (a score of 3 on the combined day- and night-time asthma symptom scale) and/or daily salbutamol use on 4 of the last 7 days of the run-in period.
Interventions	MD-ICS: FF 100 µg qd MD-ICS/LABA: FF/VI 100/25 µg qd HD-ICS/LABA: FF/VI 200/25 µg qd
Outcomes	All cause serious adverse events All cause adverse events Dropouts due to adverse event

Notes	NCT01686633 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=116863

Bernstein 2017

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Teva Branded Pharmaceutical Products R&D **COUNTRY**: Australia, Bulgaria, Canada, Croatia, Germany, Greece, Hungary, Ireland, Israel, New Zealand, Poland, Romania, Russian Federation, Serbia, South Africa, Spain, Ukraine, United Kingdom, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 213 **Mean age:** 49.3 (Ages Eligible for Study: 12 Years and older) **Male %**: 35 **White %:** 86 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.0 **Baseline FEV1 % predicted**: 64 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** 1. Written informed consent/assent signed and dated by the subject and/or parent /legal guardian before conducting any study related procedure. 2. Male or female 12 years and older, as of the Screening Visit. Male or female 18 years and older, as of the Screening Visit, in countries where local regulations or the regulatory status of study medication permit enrollment of adults only. 3. General good health, and free of any concomitant conditions or treatment that could interfere with study conduct, influence the interpretation of study observations/results, or put the subject at increased risk during the study. 4. Asthma Diagnosis: Asthma as defined by the National Institutes of Health (NIH). 5. Severity of Disease:• A best forced expiratory volume in one second (FEV1) of 40%-85% of the predicted normal value during the Screening Visit. NHANES III predicted values will be used for subjects aged ≥12 years and adjustments to predicted values will be made for African American subjects. ATS/ERS 2005 criteria for acceptability, reproducibility, and end of test must be met for spirometry 6. Reversibility of Disease: Demonstrated a ≥12% reversibility of FEV1 within 30 minutes following 2 inhalations of albuterol/salbutamol inhalation aerosol (if required, spacers are permitted for reversibility testing only) at the Screening Visit. If a subject fails to demonstrate an increase in FEV1 ≥12% then the subject is not eligible for the study and will not be allowed to re-screen. Reversibility values of 11.50 - 11.99 will be rounded to 12. Documented historical reversibility of ≥ 12 % within 3 months of the Screening Visit will be accepted. 7. Current Asthma Therapy: Subjects will be required to be on a short acting β2 agonist and inhaled corticosteroid for a minimum of 8 weeks before the Screening Visit and have been maintained on a stable dose of inhaled corticosteroids for four weeks prior to the Screening Visit at one of the following doses:Fluticasone propionate HFA MDI ≥ 880 mcg/dayFluticasone propionate DPI≥ 1000 mcg/dayBeclomethasone dipropionate DPI ≥ 2000 mcg/dayBeclomethasone dipropionate HFA (QVAR)≥ 640 mcg/dayBeclomethasone dipropionate HFA (Clenil Modulite)≥ 2000 mcg/dayBudesonide DPI ≥ 1600 mcg/dayBudesonide MDI ≥ 1600 mcg/dayFlunisolide ≥ 2000 mcg/dayTriamcinolone acetonide ≥ 2000 mcg /dayMometasone furoate DPI ≥ 880 mcg/dayCiclesonide HFA MDI ≥ 640 mcg/dayException 1: Based upon the investigator's judgment that there is no inherent harm in changing the subject's current ICS/LABA therapy and the subject provides consent, subjects on inhaled Fluticasone propionate/salmeterol DPI ≥ 1000 mcg/day, or Fluticasone propionate/salmeterol HFA ≥ 880 mcg/day, or Fluticasone propionate/Formoterol ≥ 1000 mcg/day,or Beclomethasone dipropionate/Formoterol ≥ 400 mcg/day, or Budesonide/formoterol HFA ≥ 640 mcg/day, or Budesonide/formoterol DPI ≥ 800 mcg/day, or Mometasone furoate/formoterol MDI ≥ 800 mcg/day or subjects on a qualifying ICS dose plus a long-acting β2-agonists (LABA) administered via separate inhalers, may be switched to a qualifying dose of fluticasone propionate provided the subjects will not participate in the PK portion of the study.Exception 2: Subjects on a qualifying dose of fluticasone propionate who wish to participate in the PK portion of the study and who provide consent may have their fluticasone propionate switched to a different qualifying ICS (non-fluticasone propionate) at a pre-screening visit. The subject will be required to return to the clinic to complete the Screening Visit following a 1-week washout period. 8. Short-Acting β2-Agonists: All subjects must be able to replace their current short-acting β2-agonists with albuterol/salbutamol inhalation aerosol at the Screening Visit for use as needed for the duration of the study. The use of spacer devices with the metered dose inhaler (MDI) will not be allowed during the study with exception of it's use during reversibility testing at the Screening Visit. Nebulized albuterol/salbutamol will not be allowed at any time during the study. Subjects must be able to withhold all inhaled short-acting β2 sympathomimetic bronchodilators for at least 6 hours prior to all study visits. 9. If female, is currently not pregnant, breast feeding, or attempting to become pregnant, has a negative serum pregnancy test, and is ofNon-childbearing potential, defined as:Before menarche, or1 year post-menopausal, orSurgically sterile (tubal ligation, bilateral oophorectomy, or hysterectomy), orCongenital sterility, orDiagnosed as infertile and not undergoing treatment to reverse infertility or is ofChild-bearing potential, willing to commit to using a consistent and acceptable method of birth control as defined below for the duration of the study:Systemic contraception used for 1 month prior to screening, including birth control pills, transdermal patch (Ortho Evra®), vaginal ring (NuvaRing®), levonorgesterel (Norplant®), or injectable progesterone (Depo-Provera®), orDouble barrier methods (condoms, cervical cap, diaphragm, and vaginal contraceptive film with spermicide), orIntrauterine device (IUD) orMonogamous with a vasectomized male partner or is ofChild-bearing potential and not sexually active, willing

	to commit to using a consistent and acceptable method of birth control as defined above for the duration of the study, in the event the subject becomes sexually active 10. Capable of understanding the requirements, risks, and benefits of study participation, and, as judged by the investigator, capable of giving informed consent/assent and being compliant with all study requirements (visits, record-keeping, etc). **Exclusion Criteria:** 1. History of life-threatening asthma that is defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures. 2. Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that is not resolved within 2 weeks of the Screening Visit. In addition, the subject must be excluded if such infection occurs between the Screening Visit and the Randomization Visit. 3. Any asthma exacerbation requiring oral corticosteroids within 1 month of the Screening Visit. A subject must not have had any hospitalization for asthma within 2 month prior to the Screening Visit.Note: An exacerbation of asthma is defined as any worsening of asthma requiring any treatment other than rescue albuterol/salbutamol HFA MDI and/or the subject's regular inhaled corticosteroid maintenance treatment. This includes requiring the use of systemic corticosteroids and/or emergency room visit or hospitalization, a change in the subject's regular inhaled corticosteroid maintenance treatment, or the addition of other asthma medications. 4. Presence of glaucoma, cataracts, ocular herpes simplex, or malignancy other than basal cell carcinoma. 5. Historical or current evidence of a clinically significant disease including, but not limited to: cardiovascular (e.g., congestive heart failure, known aortic aneurysm, clinically significant cardiac arrhythmia or coronary heart disease), hepatic, renal, hematological, neuropsychological, endocrine (e.g., uncontrolled diabetes mellitus, uncontrolled thyroid disorder, Addison's disease, Cushing's syndrome), gastrointestinal (e.g., poorly-controlled peptic ulcer, GERD), or pulmonary (e.g., chronic bronchitis, emphysema, bronchiectasis with the need for treatment, cystic fibrosis, bronchopulmonary dysplasia, chronic obstructive pulmonary disease). Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which could affect the efficacy or safety analysis if the disease/condition exacerbated during the study. 6. Have any of the following conditions that, in the judgment of the investigator, might cause participation in this study to be detrimental to the subject, including, but not limited to:Current malignancy excluding basal cell carcinoma; History of malignancy is acceptable only if the subject has been in remission for one year prior to the Screening Visit. (Remission is defined as no current evidence of malignancy and no treatment for the malignancy in the 12 months prior to the Screening Visit)Current or untreated tuberculosis; History of tuberculosis is acceptable only if a subject has received an approved prophylactic treatment regimen or an approved active treatment regimen and has had no evidence of active disease for a minimum of 2 yearsUncontrolled hypertension (systolic BP ≥160 or diastolic BP >100)Stroke within 3 months prior to the Screening VisitImmunologic compromise 7. History of a positive test for HIV, hepatitis B or hepatitis C infection. 8. Untreated oral candidiasis at the Screening Visit. Subjects with clinical visual evidence of oral candidiasis and who agree to receive treatment and comply with appropriate medical monitoring may enter the study 9. History of any adverse reaction to any intranasal, inhaled or systemic corticosteroid therapy. Known or suspected sensitivity to the constituents of the dry powder inhalers (Spiromax or Diskus) used in the study (i.e., lactose). 10. History of severe allergy to milk protein. 11. Use of systemic, oral or depot corticosteroids within 4 weeks prior to the Screening VisitUse of topical corticosteroids (≤1% hydrocortisone cream) for dermatological disease is permittedUse of intranasal corticosteroids or ocular corticosteroids at a stable dose for at least 4 weeks prior to the Screening Visit and throughout the study is permitted 12. Use of immunosuppressive medications within 4 weeks prior to the Screening Visit and during the study. 13. Immunotherapy for the treatment of allergy at a stable maintenance dose for at least 90 days prior to the Screening Visit and which will remain at a stable dose without escalation throughout the study is permitted. 14. Use of Cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, ketoconazole, itraconazole) within 4 weeks prior to the Screening Visit. Strong and moderate CYP3A4 inhibitors are prohibited and weak CYP3A4 are allowed. 15. History of alcohol or drug abuse within two years preceding the Screening Visit. 16. Current smoker or a smoking history of 10 pack years or more (a pack year is defined as smoking 1 pack of cigarettes/day for 1 year). A subject may not have used tobacco products within the past one year (e.g., cigarettes, cigars, chewing tobacco, or pipe tobacco). 17. Study participation by clinical investigator site employees and/or their immediate relatives. 18. Study participation by more than one subject from the same household at the same time. However, after the study completion or discontinuation by one subject another subject from the same household may be screened. 19. Participation in any investigational drug study within the 30 days (starting at the final follow-up visit) preceding the Screening Visit or planned participation in another investigational drug study at any time during this study. 20. Pregnancy, nursing, or plans to become pregnant or donate gametes (ova or sperm) for in vitro fertilization during the study period or for 30 days following the subject's last study related visit (for eligible subjects only - if applicable). Eligible female subjects unwilling to employ appropriate contraceptive measures to ensure that pregnancy will not occur during the study will be excluded.
Interventions	FP 250 µg bid MD (open label) excluded MD-ICS: FP 200 µg bid HD-ICS: FP 400 µg bid
Outcomes	All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	NCT01576718

Bleecker 2014

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Germany, Japan, Poland, Romania, Ukraine, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 406 **Mean age:** 40.5 (Ages Eligible for Study: 12 Years and older) **Male %**: 40 **White %:** 84 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.3 **Baseline FEV1 % predicted**: 71 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Male and female; female subjects of childbearing potential must be willing to use birth control • Pre-bronchodilator FEV1 of 40-90% predicted normal • Reversibility FEV1 of at least 12% and 200mL • Current asthma therapy includes inhaled corticosteroid use for at least 12 weeks prior to first visit **Exclusion Criteria:** • History of life-threatening asthma during last 10 years • Respiratory infection or oral candidiasis • Asthma exacerbation requiring oral corticosteroids or that required overnight hospitalisation requiring additional asthma treatment • Uncontrolled disease or clinical abnormality • Allergies to study drugs or the excipients • Taking another investigational medication or prohibited medication • Night shift workers • Current smokers or subjects with a smoking history of at least 10 pack years
Interventions	MD-ICS: FF 100 µg qd MD-ICS/LABA: FF/VI 100/25 µg qd
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Dropouts due to adverse event CFB in AQLQ at 3 months
Notes	NCT01165138 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=106827

Bodzenta-Lukaszyk 2012

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Mundipharma Research Ltd **COUNTRY**: Bulgaria, Hungary, India, Poland, Romania
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 279 **Mean age:** 49 (Ages Eligible for Study: 12 Years and older) **Male %**: 32 **White %:** 96 **Current and Ex smoker excluded:** Yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** Not reported **Baseline FEV1 % predicted**: 64 **Hx of asthma exacerbation**: Not required. **Inclusion Criteria:**

	1. Male or female subjects at least 12 years old 2. Female subjects less than 1 year post-menopausal must have a negative urine pregnancy test recorded at the screening visit prior to the first dose of study medication, be non-lactating, & willing to use adequate & highly effective methods of contraception throughout the study. A highly effective method of birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently & correctly such as sterilisation, implants, injectables, combined oral contraceptives, some IUDs (Intrauterine Device, hormonal), sexual abstinence or vasectomised partner. 3. Known history of moderate to severe persistent, reversible asthma for ≥ 6 months prior to the Screening Visit characterised by:Treatment with an inhaled corticosteroid (ICS) at a dose of 250 - 1000 µg fluticasone or equivalent OR Treatment with ICS at a dose of 200-500 µg fluticasone or equivalent in combination with a Long Acting β2-Agonist (LABA). 4. Demonstrated a FEV1 of ≥ 50% to ≤ 80% for predicted normal values (Quanjer et al., 1993 (adults), & 1995 (adolescents)) during the Screening Period (Visit 1 or Visit 2) following appropriate withholding of asthma medications (if applicable).No β2-agonist use on day of testingNo use of inhaled combination asthma therapy on day of testing.Inhaled corticosteroids are allowed on day of testing. 5. Documented reversibility of ≥ 15% in FEV1 at visit 1 or visit 2. 6. Demonstrated satisfactory technique in the use of the study medications i.e. pMDI and Dry Powder Inhaler (DPI) devices. 7. Willing & able to enter information in the electronic diary & attend all study visits. 8. Willing & able to substitute study medication for their pre study prescribed asthma medication for the duration of the study. 9. Written informed consent obtained. Inclusion criteria required following run-in: Subject has used rescue medication for at least 3 days & had at least 1 night with sleep disturbance (i.e., sleep disturbance score of ≥ 1) during the last 7 days of the run in period,OR subject has used rescue medication for at least 3 days & had at least 3 days with asthma symptoms (i.e., a symptom score of ≥ 1) during the last 7 days of the run-in period. **Exclusion criteria:** 1. Near fatal or life-threatening (including intubation) asthma within the past year. 2. Hospitalisation or an emergency visit for asthma within the 4 weeks before the Screening Visit. 3. Known history of systemic (injectable or oral) corticosteroid medication use within 1 month of the Screening Visit. 4. Known history of omalizumab use within the past 6 months. 5. Current evidence or known history of any clinically significant disease or abnormality including uncontrolled coronary artery disease, congestive heart failure, myocardial infarction, or cardiac dysrhythmia. 'Clinically significant' is defined as any disease that, in the opinion of the Investigator, would put the subject at risk through study participation, or which would affect the outcome of the study. 6. In the investigator's opinion a clinically significant upper or lower respiratory infection within 4 weeks prior to the Screening Visit. 7. Significant, non-reversible, active pulmonary disease (e.g., chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, tuberculosis). 8. Known Human Immunodeficiency Virus (HIV)-positive status. 9. Subject has a smoking history equivalent to "10 pack years" (i.e., at least 1 pack of 20 cigarettes/day for 10 years or 10 packs/day for 1 year, etc.). 10. Current smoking history within 12 months prior to the Screening Visit. 11. Current evidence or known history of alcohol and/or substance abuse within 12 months prior to the Screening Visit. 12. Subject has taken B-blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, astemizole (Hismanal), quinidine type antiarrhythmics, or potent CYP 3A4 inhibitors such as ketoconazole within the past week. 13. Current use of medications other than those allowed in the protocol that will have an effect on bronchospasm &/or pulmonary function. 14. Current evidence or known history of hypersensitivity or idiosyncratic reaction to test medications or components. 15. Subject has received an investigational drug within 30 days of the Screening Visit (12 weeks if an oral or injectable steroid). 16. Subject is currently participating in a clinical stud
Interventions	FP/FM 250/10 µg bid BUD/FM 400/12 µg bid
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Dropouts due to adverse event
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. NCT01099722

Brown 2012

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group

	DURATION OF THE STUDY: 52 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 742 **Mean age:** 37.2 (Ages Eligible for Study: 12 Years and older) **Male %:** 35 **White %:** 0 **Current smoker excluded/maximum PYs allowed for ex-smokers:** N/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.3 **Baseline FEV1 % predicted**: 78 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Male or Female, African American (self-reported), ≥12 years of age • Moderate to severe asthma requiring treatment with an inhaled corticosteroid • Diagnosis of asthma for at least 6 months **Exclusion Criteria:** • Subjects requiring treatment with systemic corticosteroids (e.g., oral, parenteral, ocular) • Any significant disease or disorder that may jeopardize a subject's safety
Interventions	MD-ICS: BUD 320 µg bid MD-ICS/LABA: BUD/FM 320/9 µg bid
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	NCT00419952

Busse 2008

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: USA
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 833 **Mean age:** 39.1 (Ages Eligible for Study: 12 Years and older) **Male %**: 38 **White %:** 83 **Current and Ex smoker excluded:** Yes. > 20 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 2.55 **Baseline FEV1 % predicted**: 78.6 **Hx of asthma exacerbation**: Not required. **Inclusion Criteria:** • Diagnosis of asthma • Baseline lung function tests as determined by protocol • Required and received treatment with inhaled corticosteroids within timeframe and doses specified in protocol **Exclusion Criteria:** • Has required treatment with any non-inhaled corticosteroid within previous 30 days, sensitivity to drugs specified in the protocol, or requires treatment with a beta-blockers • Had cancer within previous 5 years or currently has any other significant disease or disorder as judged by the investigator
Interventions	FP/SAL 250/50 µg bid BUD/FM 320/9 µg bid
Outcomes	Moderate to severe exacerbations Severe exacerbations Dropouts due to adverse event

	CFB in ACQ at 6 months
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. NCT00646594 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=106839

CHIESI 2009

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Chiesi Farmaceutici S.p.A. **COUNTRY**: Germany
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review: 696** **Mean age:** Not reported (Ages Eligible for Study: 12 Years and older) **Male %:** 42 **White %:** Not reported **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.0 **Baseline FEV1 % predicted**: 64 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Written informed consent • Outpatients of both sexes, aged > 12 years • Moderate to severe symptomatic asthma • Forced expiratory volume in the first second (FEV1) > 40% and < 80% of the predicted normal values • Reversibility test • "Partly controlled" asthma (GINA revised 2006) • Patients free of long-acting beta2-agonists (LABAs) treatment • Under inhaled corticosteroids (ICS) treatment • A minimum inspiratory flow ≥ 40 L/min 10. • Non-smokers or ex smokers • Asthma Control Questionnaire ACQ score ≥ 1.5 **Exclusion Criteria:** • Pregnant or nursing (lactating) women • Women of child-bearing potential, UNLESS they are menopausal or have acceptable methods of contraception • Significant seasonal variation in asthma or asthma occurring only during episodic exposure to an allergen or a chemical sensitizer • History of near fatal asthma • Occurrence of asthma exacerbations or respiratory tract infections in the 6 weeks preceding the screening visit • Diagnosis COPD • History of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency • Diagnosis of restrictive lung disease • Patients treated with oral or parenteral corticosteroids in the previous 2 months (3 months for parenteral depot corticosteroids) • Intolerance or contra-indication to treatment with beta2-agonists and/or inhaled corticosteroids • Allergy to any component of the study treatments • Any change in the dose, schedule, formulation or product of an inhaled corticosteroid in the 4 weeks prior to screening visit • Significant medical history of and/or treatments for cardiac, renal, neurological, hepatic, endocrine diseases, or any laboratory abnormality ; • Patients with abnormal QTc
Interventions	LD-ICS/LABA: BDP/FM 100/6 µg DPI bid; BDP/FM 100/6 µg pMDI bid MD-ICS/LABA: BDP/FM 200/12 µg DPI bid; BDP/FM 200/12 µg pMDI bid
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event

	CFB in ACQ at 3 months
Notes	NCT00862394 https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-000401-11/results

Corren 2013

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: SkyePharma AG **COUNTRY**: Puerto Rico, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 223 **Mean age:** 43.3 (Ages Eligible for Study: 12 Years and older) **Male %:** 43 **White %:** 81 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.5 **Baseline FEV1 % predicted**: Not reported. **Hx of asthma exacerbation**: Not required. **Inclusion Criteria**: • History of asthma for at least 12 months. • Documented use of inhaled corticosteroid for at least 4 weeks prior to Screening Visit Demonstrate FEV-1 of 40-80% of predicted normal values at Screening and Baseline Visit. • Documented reversibility of 15% within 12 months of Screening visit or at Screening Visit (15% increase from pre-FEV-1 levels following albuterol inhalation or nebulized albuterol administration). • Symptoms of Asthma during Run-in. • Females of childbearing potential must have a negative urine pregnancy test at Screening and Baseline Visits. Females are eligible only if they are not pregnant or lactating, and are either sterile or using acceptable methods of contraception • Must otherwise be healthy. • Provide written informed consent. Wishes of minors must be respected. **Exclusion Criteria**: • Life-threatening asthma within past year or during Run-In Period. • History of systemic corticosteroid medication within 3 months before Screening Visit. • History of omalizumab use within past 6 months. • History of leukotriene receptor antagonist use, e.g. montelukast, within past week. • Current evidence or history of any clinically significant disease or abnormality including uncontrolled hypertension, uncontrolled coronary artery disease, congestive heart failure, myocardial infarction, or cardiac dysrhythmia. • Upper or lower respiratory infection within 4 weeks prior to Screening visit or during Run-In Period • Significant, non-reversible, pulmonary disease (e.g., chronic obstructive pulmonary disease [COPD], cystic fibrosis, bronchiectasis). • Known Human Immunodeficiency Virus (HIV)-positive status. • Smoking history equivalent to "10 pack years". • Current smoking history within 12 months prior to Screening Visit. • Current evidence or history of alcohol and/or substance abuse within 12 months prior to Screening visit. • Patients who are confined in institution.
Interventions	MD-ICS: FP 250 µg bid MD-ICS/LABA: FP/FM 250/10 µg bid
Outcomes	Moderate to severe exacerbations All cause serious adverse events All cause adverse events Dropouts due to adverse event
Notes	NCT00393952

Cukier 2013

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group

	DURATION OF THE STUDY: 12 weeks **SPONSORSHIP SOURCE**: Libbs Pharmaceutical Ltd **COUNTRY**: 11 research centers in Brazil
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 196 **Mean age:** 35.1 (Ages Eligible for Study: 12 to 65 Years old) **Male %**:26 **White %:** 69 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.5 **Baseline FEV1 % predicted**: 85.3 **Hx of asthma exacerbation**: Not required. **Inclusion criteria** 1. Male or female from 18 to 65 years old with known history of asthma according to Global Initiative for Asthma (GINA) update 2008 criteria for at least three months. 2. Patients with partially controlled or non-controlled asthma using therapeutic doses of inhaled corticosteroid combined with long-acting bronchodilator (daily doses equal or more than 400 mcg of budesonide or similar drugs) for at least four weeks 3. Forced Expiratory Volume in 1 second (FEV1) > 60 % of predicted normal value 4. Willing and able to keep diary and attend all visits 5. Written informed consent obtained **Exclusion criteria** 1. Pregnant or nursing women 2. Females of childbearing potential without an effective method of birth control 3. Use of systemic corticosteroid within 30 days before randomization 4. Three or more treatments with oral corticosteroid or history of asthma hospitalization in the previous six months 5. Use of the following drugs within two weeks before randomization: 5.1. meltixantines 5.2. monoaminurias 5.3. beta-blockers 5.4. acetylcysteine 5.5. carbocisteine 5.6. tricyclic antidepressive 5.7. sodium channel blockers 5.8. leukotriene 5.9. anticholinergic 5.10. phenothiazines 5.11. immunotherapy 5.12. levodopa 5.13. ritonavir 5.14. oral ketoconazole 6. Current evidence of history of hypersensitivity to the study drug 7. Evidence of non-adhesion to the treatment during run-in phase 8. A smoking history equivalent to "10 pack years" (i.e., at least 1 pack of 20 cigarettes/day for 10 years or 10 packs/day for 1 year, etc) 9. Clinically significant laboratory test results during the screening phase 10. Morning serum level of cortisol < 5 mcg/dL 11. Inability to perform the lung function test 12. Current evidence of other pulmonary disease 13. Patients with asthma exacerbation during the run-in period 14. Evidence of clinically significant oral candidiasis
Interventions	FP/FM 250/12 µg bid BUD/FM 400/12 µg bid
Outcomes	Moderate to severe exacerbations All cause serious adverse events All cause adverse events Dropouts due to adverse event CFB in ACQ at 3 months
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. ISRCTN60408425

Hamelmann 2016

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: Boehringer Ingelheim/Pfizer **COUNTRY**: Chile, Germany, Hungary, Italy, Korea, Republic of, Latvia, Mexico, Russian Federation, Slovakia, Spain, Ukraine, United States
Participants	**BASELINE CHARACTERISTICS:**

No. of participants included in this review: 397

Mean age: 14.3 (Ages Eligible for Study: 12 to 17 Years old)

Male %: 66

White %: Not reported

Current smoker excluded/maximum PYs allowed for ex-smokers: Y/Not reported
Baseline FEV1 (L) pre-bronchodilator: 2.8
Baseline FEV1 % predicted: 83
Hx of asthma exacerbation: Not required

Inclusion criteria:

1. All patients and their parents (or legally accepted caregiver) must sign and date an informed consent consistent with ICH-GCP guidelines and local legislation prior to participation in the trial.
2. Male or female patients between 12 and 17 years of age.
3. All patients must have at least a 3 months history of asthma at the time of enrolment into the trial. The diagnosis of asthma has to be confirmed at visit 1 with a bronchodilator reversibility test.
4. All patients must have been on maintenance treatment with inhaled corticosteroids at a stable medium dose for at least 4 weeks before Visit 1.
5. All patients must be symptomatic (partly controlled) at Visit 1 (screening) and at randomisation defined by an Asthma Control Questionnaire (ACQ) mean score of more than or equal to 1.5.
6. All patients must have a pre-bronchodilator FEV1 more than or equal to 60% and less than or equal to 90% of predicted normal at Visit 1. Variation of absolute FEV1 values of Visit 1 as compared to Visit 2 must be within ± 30%.
7. All patients must have an increase in FEV1 of equal or above 12% and 200 mL after 400 µg salbutamol (albuterol) at Visit 1. If patients in the lower age range (e.g., 12 to 14 year olds) exhibit a very small total lung volume, positive reversibility testing might be based solely on the relative (12%) post-bronchodilator response.
8. All patients should be never-smokers or ex-smokers who stopped smoking at least one year prior to enrolment.
9. Patients should be able to use the Respimat® inhaler correctly.
10. Patients must be able to perform all trial related procedures including technically acceptable spirometric manoeuvres.

Exclusion criteria:

1. Patients with a significant disease other than asthma.
2. Patients with clinically relevant abnormal screening haematology or blood chemistry
3. Patients with a history of congenital or acquired heart disease, and/or have been hospitalised for cardiac syncope or failure during the past year.
4. Patients with any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy within the past year.
5. Patients with malignancy for which the patient has undergone resection, radiation therapy or chemotherapy within the last five years.
6. Patients with lung diseases other than asthma (e.g. Cystic Fibrosis). In case of ex-premature infants, a history of significant bronchopulmonary dysplasia will be regarded as exclusion criterion.
7. Patients with known active tuberculosis.
8. Patients with significant alcohol or drug abuse within the past two years.
9. Patients who have undergone thoracotomy with pulmonary resection.
10. Patients who are currently in a pulmonary rehabilitation program or have completed a pulmonary rehabilitation program in the 6 weeks prior to the screening visit (Visit 1).
11. Patients with known hypersensitivity to anticholinergic drugs, Benzalkonium chloride (BAC), Ethylenediaminetetraacetic acis (EDTA) or any other components of the tiotropium inhalation solution.
12. Pregnant or nursing adolescent female patients
13. Sexually active female patients of child-bearing potential not using a highly effective method of birth control.
14. Patients who have taken an investigational drug within 4 weeks prior to Visit 1.
15. Patients who have been treated with long-acting anticholinergics (e.g. tiotropium -Spiriva) within four weeks prior to screening (Visit 1).
16. Patients who are unable to comply with pulmonary medication restrictions prior to randomisation.
17. Patients who have been treated with Anti-IgE treatment (Omalizumab Xolair) within the last 6 months prior to screening.
18. Patients who have been treated with systemic (oral or intravenous) corticosteroids within 4 weeks prior to screening (Visit 1).
19. Patients who have been treated with long-acting theophylline preparations within 2 weeks prior to screening (Visit 1) or during the run-in period
20. Patients who have been treated with other non-approved and according to international guidelines not recommended ¿experimental¿ drugs for routine asthma therapy.
21. Patients with any acute asthma exacerbation or respiratory tract infection in the 4 weeks prior to Visit 1.
22. Patients requiring 10 or more puffs of rescue medication (salbutamol/albuterol) per day on more than 2 consecutive days during the run-in period.
23. Patients who have previously been randomised in this trial or are currently participating in another study.
24. Patients who are being treated with oral beta-blocker medication.

	25. Patients with a known narrow-angle glaucoma, or any other disease where anticholinergic treatment is contraindicated. 26. Patients with renal impairment, as defined by a creatinine clearance less than 50 mL/min/1.73 m2 Body Surface Area as calculated by Schwartz formula.
Interventions	MD-ICS MD-ICS + Tio 2.5 µg qd MD-ICS +Tio 5 µg qd
Outcomes	Moderate to severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months CFB in ACQ at 6 months
Notes	NCT01257230

Huchon 2009

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: Chiesi Farmaceutici S.p.A. **COUNTRY**: Belgium, France, Hungary, Poland, Romania, and Russia
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 645 **Mean age:** 47.3 (Ages Eligible for Study: 18 Years and older) **Male %:** 35 **White %:** Not reported **Current smoker excluded/maximum PYs allowed for ex-smokers:** N/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.0 **Baseline FEV1 % predicted**: 65 **Hx of asthma exacerbation**: Not required. **Inclusion Criteria**: • Clinical diagnosis of moderate to severe persistent asthma (according to GINA 2002 guidelines) • FEV1 > 40% and < 80% of predicted normal post-bronchodilator (and at least 0.7 L absolute value) • Patients already treated for at least 2 months with an association of inhaled corticosteroids plus LABA at doses of:750 - 1000 µg beclomethasone dipropionate or equivalent (ICSs) 24 µg formoterol or 100 µg salmeterol (LABAs) • Or patients naïve of LABA already treated for at least 2 months with inhaled corticosteroids (doses as above) associated with a daily use of SABA and/or with clinical symptoms > 3 times in the week prior to inclusion • A documented positive response to the reversibility test. **Exclusion Criteria**: • Pregnant or lactating females or women of childbearing potential without any efficient contraception. • Heavy smokers defined as smoking for > 10 pack years. • Evidence of asthma exacerbation causing an hospitalisation or requiring treatment with oral/parenteral corticosteroids or evidence of symptomatic airways infection in the 4 weeks prior to inclusion (3 months for slow-release corticosteroids). • Seasonal asthma or asthma occurring only during episodic exposure to an allergen or occupational chemical sensitizer. • Clinically significant or unstable concomitant diseases, including clinically significant laboratory abnormalities. • Patients with an abnormal QTc interval value in the ECG test, defined as > 450 msec in males or > 470 msec in females. • Evidence of asthma worsening during the week preceding randomisation (e.g. PEF variability > 30% during 2 consecutive days, SABA use > 8 puffs/day during 2 consecutive days, nocturnal awakenings due to asthma symptoms during 3 consecutive days
Interventions	MD-ICS: BDP 500 µg bid MD-ICS/LABA: BDP 500 µg + FM 24 µg bid ; xf-BDP/FM 200/12 µg bid
Outcomes	Moderate to severe exacerbations All cause serious adverse events All cause adverse events Dropouts due to adverse event
Notes	NCT00476268

Katial 2011

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 52 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Brazil, Canada, Philippines, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 621 **Mean age:** 38.1 (Ages Eligible for Study: 12 Years and older) **Male %:** 37 **White %:** 65 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.2 **Baseline FEV1 % predicted**: 69 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Subjects eligible for enrollment in the study must meet all of the following criteria: • Consent: A signed and dated written informed consent must be obtained from the subject and/or subject's legally acceptable representative prior to study participation. • Type of Subject: Outpatient • Gender: Male or female Females are eligible to participate only if they are currently non-pregnant and non-lactating. A female is eligible to enter and participate in the study if she is: 1. of non-child-bearing potential; OR 2. of child-bearing potential but has a negative urinary pregnancy test at Screening (Visit 1 and when specified in Appendix 1) and agrees to take contraceptive precautions (including abstinence) which are adequate to prevent pregnancy during the study.Acceptable methods of contraception [Hatcher, 2004] are:- Abstinenceoral contraceptive (either combined or progestogen only)injectable progestogenimplants of levonorgestrelestrogenic vaginal ringpercutaneous contraceptive devicesintrauterine device (IUD) or intrauterine system (IUS) with published data showing that the lowest expected failure rate is less than 1% per yearmale partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study and is the sole sexual partner for that female subjectdouble barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agentAge: A subject must be 12 years of age at Visit 1 (screening).Asthma Diagnosis: A documented diagnosis of persistent asthma, for at least six months, as defined by the following American Thoracic Society definition:Asthma is a clinical syndrome characterized by increased responsiveness of the airways to a variety of stimuli. The major symptoms of asthma are episodes of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting (status asthmaticus). The primary physiological manifestation of this hyperresponsiveness is variable airway obstruction. This can take the form of spontaneous fluctuations in the severity of obstruction, substantial improvements in the severity of obstruction following bronchodilators or corticosteroids, or increased obstruction caused by drugs or other stimuli [American Thoracic Society, 1987].Asthma Medication History: A subject must be using a low to medium dose of an ICS (Table 1) OR a combination of controller medications (Table 2), containing a low (total daily) dose ICS (as defined in Table 1) for at least 4 weeks preceding screening.Table 1 (ICS Dosage Table) Inhaled Corticosteroid (Dosage (mcg/day))(LowMedium) Beclomethasone dipropionate CFC(168 = 504> 504 = 840) Beclomethasone dipropionate HFA (80 = 240>240 = 640) Triamcinolone acetonide(400 = 1000>1000 = 2000) Flunisolide (500 = 1000> 1000 = 2000) Fluticasone propionate inhalation aerosol (176 = 220> 220 = 440) Fluticasone propionate inhalation powder (100 = 250> 250 = 500) Budesonide1 (200 = 600> 600 =1200) Mometasone (200 = 400> 400 = 800) Ciclesonide (80 = 160>160 = 320)1.Respules are allowed at a dosage of 250-500mcg/day.Table 2 (Asthma Controller Medications) Asthma Controller Medication(s) Low dose ICS + Leukotriene modifiers Low dose ICS + Theophylline products Low Dose ICS + Inhaled anticholinergics or combination products (e.g., Atrovent or Combivent) Low Dose ICS + Long acting inhaled anticholinergic (e.g. Spiriva) Low dose ICS+ long acting beta agonist or combination products containing a low dose ICS and a long-acting beta-agonists (e.g. ADVAIR™/SERETIDE™1 100/50 mcg BID or Symbicort 160/9 mcg BID (i.e 80/4.5 mcg two inhalations BID)1) ADVAIR/SERETIDE =250/50 mcg BID or Symbicort 320/9 mcg BID (i.e 160/4.5 mcg two inhalation BID) are not permitted.Pulmonary function: A pre-albuterol (salbutamol) FEV1 of 50% and 85% of predicted normal value at screening (Visit 1) after withholding asthma medications as detailed in the protocol (Section 6.8.1). Predicted FEV1 will be based on the National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older [Hankinson, 1999].Reversibility: An increase in FEV1 of 12% over the pre-albuterol (salbutamol) FEV1 within 30 minutes after the inhalation of 2-4 puffs of albuterol (salbutamol). Historical documentation of reversibility will not be permitted.Asthma symptom criteria: Each subject must have experienced asthma symptoms requiring albuterol (salbutamol) use within the 4 weeks preceding screening (Visit 1).Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational product that may impact subject eligibility is provided in the IB and the product labels. **Exclusion Criteria:** - Subjects meeting any of the following criteria must not be enrolled in the study: 1. Life-Threatening Asthma: A subject must not have life-threatening asthma. Life-threatening asthma is defined for this protocol as a history of significant asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, or hypoxic seizures, or asthma-related syncopal episode(s) within the 12 months prior to screening (Visit 1). 2. Worsening of Asthma: A subject must not have experienced a worsening of asthma which involved an ER visit, hospitalization or use of oral/parenteral corticosteroids within 4 weeks of screening (Visit 1).

	3. Intermittent, Seasonal, or Exercise-Induced Asthma Alone: Subjects with only intermittent or seasonal or exercise-induced asthma are excluded from participation in this study. 4. Concurrent Respiratory Disease: A subject must not have current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or other respiratory abnormalities other than asthma. 5. Concurrent Conditions/Diseases: A subject with historical or current evidence of any clinically significant, co-morbid or uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the results if the condition/disease exacerbated during the study. The list of excluded conditions/diseases includes, but is not limited to: congestive heart failure known aortic aneurysm clinically significant coronary clinically significant cardiac arrhythmia heart disease stroke within 3 months of screening (Visit 1) uncontrolled hypertension coronary artery disease hematologic, hepatic, or renal disease cystic fibrosis poorly controlled peptic ulcer dyspnea by any other cause than asthma gastroesophageal reflux disease (GERD) not controlled by pharmacotherapy and may be causing/contributing to subject's respiratory symptoms thyrotoxicosis hypokalemia immunologic compromise current malignancy1 tuberculosis (current or quiescent) Cushing's or Addison's disease pneumonia, pneumothorax, chronic bronchitis or atelectasis uncontrolled diabetes mellitus recent history of drug or alcohol abuse 1) history of malignancy is acceptable only if subject has been in remission for one year prior to screening (Visit 1; remission = no treatment for the malignancy in the 12 months prior to screening [Visit 1]) • Drug Allergy: A subject must not have had any immediate or delayed hypersensitivity to any beta2-agonist; sympathomimetic drug; any intranasal; inhaled or systemic corticosteroid therapy; lactose; or have a severe milk protein allergy. • Respiratory Tract Infections: A subject must not have had any sinus, middle ear, oropharyngeal, upper or lower respiratory tract infection symptoms that have not resolved at least 7 days immediately preceding screening (Visit 1).3. Asthma Medications: Asthma medications listed below must not have been used prior to screening (Visit 1) for the required exclusion period as indicated below: Medication (Exclusion Period Prior to screening (Visit 1)) Oral or parenteral systemic corticosteroids (4 weeks) Omalizumab (Xolair) (6 months) 1. Concurrent Medications: A subject must not have the concurrent use of any of the following medications that interact with any of the study drugs used in this study, or that may affect the course of asthma or interact with sympathomimetic amines, such as:- beta-adrenergic receptor blocking agents- monoamine oxidase (MAO) inhibitors- tricyclic antidepressants- ritonavirketoconazole 2. Concurrent use of asthma medications: Concurrent use of all asthma medications (other than protocol defined study and rescue medications and oral/parenteral corticosteroids) are prohibited during the study. 3. Concomitant use of leukotriene modifiers (LTM) for allergies is prohibited. A subject must not be on LTM for treatment of nasal allergies that requires regular maintenance therapy. Substitution with any other antihistamine is permitted. 4. Immunosuppressive Medications: A subject must not be using, or require the use of, immunosuppressive medications during the study. 5. Immunotherapy for the treatment of allergies is not allowed during the study unless the subject has used a constant dose for 4 weeks prior to Screening (Visit 1) and the same dose will be continued throughout the study. 6. Tobacco Use: >10 pack year history or use of any tobacco products within 1 year of screening (Visit 1). This includes cigarettes, cigars, pipe, chewing tobacco, and snuff. 7. Questionable Validity of Consent: A subject must not have any infirmity or disability that would limit the subject's consent. 8. Positive Pregnancy Test (for all females who have had menarche): A current positive pregnancy test. 9. Investigational Medications: A subject must not have had use of any investigational drug within 30 days of screening (Visit 1). 10. Site Affiliation: A subject may not participate if he/she is a participating investigator, sub-investigator, study coordinator, employee of a participating investigator or is in any way associated with the administration of the study. Immediate family members of these individuals are also excluded. 11. Compliance with Study Requirements: A subject may not participate if, in the opinion of the investigator, there are present or anticipated circumstances that will prohibit the subject from being compliant with study visits and procedures (e.g. geographic location that will prohibit subject from required clinic visit schedule)
Interventions	MD-ICS: FP 250 µg bid MD-ICS/LABA: FP/SAL 250/50 µg bid
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	NCT00452699 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=ADA109055

Kerstjens 2015

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks

	SPONSORSHIP SOURCE: Boehringer Ingelheim/Pfizer **COUNTRY**: Brazil, China, Guatemala, India, Japan, Latvia, Mexico, Peru, Poland, Russian Federation, United States for Kerstjens 2015a Brazil, China, Colombia, Germany, India, Japan, Mexico, Peru, Poland, Romania, United States for Kerstjens 2015b
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 2100 **Mean age:** 43.1 (Ages Eligible for Study: 18 to 75 Years old) **Male %:** 41 **White %:** 48 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.3 **Baseline FEV1 % predicted**: 73 **Hx of asthma exacerbation:** Not required See Kerstjens 2015a and Kerstjens 2015b for inclusion and exclusion criteria.
Interventions	MD-ICS MD-ICS +Tio 2.5 µg qd MD-ICS +Tio 5 µg qd MD-ICS + SAL 50 µg bid
Outcomes	All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months CFB in ACQ at 6 months CFB in AQLQ at 6 months
Notes	NCT01172808, NCT01172821

Kerstjens 2015a

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: Boehringer Ingelheim/Pfizer **COUNTRY**: Brazil, China, Guatemala, India, Japan, Latvia, Mexico, Peru, Poland, Russian Federation, United States
Participants	**BASELINE CHARACTERISTICS:** See Kerstjens 2015 **Inclusion criteria**: 1. All patients must sign and date an Informed Consent Form consistent with International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guidelines and local legislation prior to participation in the trial (i.e. prior to any trial procedures, including any pre-trial washout of medications and medication restrictions for pulmonary function test at Visit 1). 2. Male or female patients aged at least 18 years but not more than 75 years. 3. All patients must have at least a 3 month history of asthma at the time of enrolment into the trial. The diagnosis should be confirmed at Visit 1 by fulfilling inclusion criterion 5. 4. The initial diagnosis of asthma must have been made before the patient's age of 40. 5. The diagnosis of asthma has to be confirmed at Visit 1 with a bronchodilator reversibility (15 minutes after 400 mcg salbutamol (albuterol)) resulting in a Forced Expiratory Volume in one second (FEV1) increase of at least 12% and at least 200mL. 6. All patients must have been on maintenance treatment with a medium, stable dose of inhaled corticosteroids for at least for 4 weeks prior to Visit 1. 7. All patients must be symptomatic at Visit 1 (screening) and prior to randomisation at Visit 2 as defined by an Asthma Control Questionnaire (ACQ) mean score of at least 1.5. 8. All patients must have a pre-bronchodilator FEV1 at least 60% and less than or equal to 90% of predicted normal at Visit 1. 9. Variation of absolute FEV1 values of Visit 1 (pre-bronchodilator) as compared to Visit 2 (pre-dose) must be within ± 30%. 10. Patients must be never-smokers or ex-smokers who stopped smoking at least one year prior to enrolment (Visit 0) and who have a smoking history of less than 10 pack years. 11. Patients must be able to use the Respimat® inhaler and metered dose inhaler correctly. 12. Patients must be able to perform all trial related procedures including technically acceptable pulmonary function tests and use of electronic diary/peak flow meter. **Exclusion criteria**: 1. Patients with a significant disease other than asthma. A significant disease is defined as a disease which, in the opinion of the investigator, may (i) put the patient at risk because of participation in the trial, or (ii) influence the results of the trial, or (iii) cause concern regarding the patient's ability to participate in the trial.

	2. Patients with a clinically relevant abnormal screening (Visit 1) haematology or blood chemistry if the abnormality defines a significant disease as defined in exclusion criterion 1. 3. Patients with a recent history (i.e. six months or less) of myocardial infarction. 4. Patients who have been hospitalised for cardiac failure during the past year. 5. Patients with any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy within the past year. 6. Patients with lung diseases other than asthma (e.g. Chronic Obstructive Pulmonary Disease (COPD)). 7. Patients with known active tuberculosis. 8. Patients with malignancy for which the patient has undergone resection, radiation therapy or chemotherapy within the last five years. Patients with treated basal cell carcinoma are allowed. 9. Patients who have undergone thoracotomy with pulmonary resection. Patients with a history of thoracotomy for other reasons should be evaluated as per exclusion criterion no. 1. 10. Patients with significant alcohol or drug abuse within the past two years. 11. Patients who are currently in a pulmonary rehabilitation program or have completed a pulmonary rehabilitation program in the 6 weeks prior to Visit 1 (screening). 12. Patients with known hypersensitivity to anticholinergic drugs, benzalkonium chloride (BAC), ethylenediamineteraacetic acid (EDTA), salmeterol xinafoate or any other components of the study medication delivery systems. 13. Pregnant or nursing woman. 14. Women of childbearing potential not using a highly effective method of birth control. 15. Patients who have taken an investigational drug within four weeks prior to Visit 1. 16. Patients who have been treated with beta-blocker medication within four weeks prior to Visit 1 and/or during the screening period. Topical cardio-selective beta-blocker eye medications for non-narrow angle glaucoma are allowed. 17. Patients who have been treated with the long-acting anticholinergic tiotropium (Spiriva®) within four weeks prior to Visit 1 and/or during the screening period. 18. Patients who have been treated with oral or patch beta-adrenergics within four weeks prior to Visit 1 and/or during the Screening period. 19. Patients who have been treated with oral corticosteroids within four weeks prior to Visit 1 and/or during the screening period. 20. Patients who have been treated with anti-IgE antibodies, e.g. omalizumab (Xolair®), within 6 months prior to Visit 1 and/or during the screening period. 21. Patients who have been treated with cromone within two weeks prior to Visit 1 and/or during the screening period. 22. Patients who have been treated with methylxanthines or phosphodiesterase 4 inhibitors within two weeks prior to Visit 1 and/or during the screening period. 23. Patients who have been treated with other non-approved and according to international guidelines not recommended "experimental" drugs for routine asthma therapy within four weeks prior to Visit 1 and/or during the screening period. 24. Patients with any asthma exacerbation or any respiratory tract infection iin the four weeks prior to Visit 1 and/or during the screening period. 25. Patients who have previously been randomised in this trial or in the respective twin trial (205.419) or are currently participating in another trial.
Interventions	MD-ICS MD-ICS +Tio 2.5 µg qd MD-ICS +Tio 5 µg qd MD-ICS + SAL 50 µg bid
Outcomes	All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months CFB in ACQ at 6 months CFB in AQLQ at 6 months
Notes	NCT01172808

Kerstjens 2015b

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: Boehringer Ingelheim/Pfizer **COUNTRY**: Brazil, China, Colombia, Germany, India, Japan, Mexico, Peru, Poland, Romania, United States
Participants	**BASELINE CHARACTERISTICS:** See Kerstjens 2015 **Inclusion criteria:** 1. All patients must sign and date an Informed Consent Form consistent with International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guidelines and local legislation prior to participation in the trial (i.e.

prior to any trial procedures, including any pre-trial washout of medications and medication restrictions for pulmonary function test at Visit 1).

2. Male or female patients aged at least 18 years but not more than 75 years.
3. All patients must have at least a 3 month history of asthma at the time of enrolment into the trial. The diagnosis should be confirmed at Visit 1 by fulfilling inclusion criterion 5.
4. The initial diagnosis of asthma must have been made before the patient's age of 40.
5. The diagnosis of asthma has to be confirmed at Visit 1 with a bronchodilator reversibility (15 minutes after 400 mcg salbutamol (albuterol)) resulting in a Forced Expiratory Volume in one second (FEV1) increase of at least 12% and at least 200mL.
6. All patients must have been on maintenance treatment with a medium, stable dose of inhaled corticosteroids for at least for 4 weeks prior to Visit 1. 7. All patients must be symptomatic at Visit 1 (screening) and prior to randomisation at Visit 2 as defined by an Asthma Control Questionnaire (ACQ) mean score of at least 1.5.

8. All patients must have a pre-bronchodilator FEV1 at least 60% and less than or equal to 90% of predicted normal at Visit 1.

9. Variation of absolute FEV1 values of Visit 1 (pre-bronchodilator) as compared to Visit 2 (pre-dose) must be within ± 30%.

10. Patients must be never-smokers or ex-smokers who stopped smoking at least one year prior to enrolment (Visit 0) and who have a smoking history of less than 10 pack years.

11. Patients must be able to use the Respimat® inhaler and metered dose inhaler correctly.

12. Patients must be able to perform all trial related procedures including technically acceptable pulmonary function tests and use of electronic diary/peak flow meter.

Exclusion criteria:

1. Patients with a significant disease other than asthma. A significant disease is defined as a disease which, in the opinion of the investigator, may (i) put the patient at risk because of participation in the trial, or (ii) influence the results of the trial, or (iii) cause concern regarding the patient's ability to participate in the trial.
2. Patients with a clinically relevant abnormal screening (Visit 1) haematology or blood chemistry if the abnormality defines a significant disease as defined in exclusion criterion 1.
3. Patients with a recent history (i.e. six months or less) of myocardial infarction.
4. Patients who have been hospitalised for cardiac failure during the past year.
5. Patients with any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy within the past year.
6. Patients with lung diseases other than asthma (e.g. Chronic Obstructive Pulmonary Disease (COPD)).
7. Patients with known active tuberculosis.
8. Patients with malignancy for which the patient has undergone resection, radiation therapy or chemotherapy within the last five years. Patients with treated basal cell carcinoma are allowed.
9. Patients who have undergone thoracotomy with pulmonary resection. Patients with a history of thoracotomy for other reasons should be evaluated as per exclusion criterion no. 1.
10. Patients with significant alcohol or drug abuse within the past two years.
11. Patients who are currently in a pulmonary rehabilitation program or have completed a pulmonary rehabilitation program in the 6 weeks prior to Visit 1 (screening).
12. Patients with known hypersensitivity to anticholinergic drugs, benzalkonium chloride (BAC), ethylenediamineteraacetic acid (EDTA), salmeterol xinafoate or any other components of the study medication delivery systems.
13. Pregnant or nursing woman.
14. Women of childbearing potential not using a highly effective method of birth control.
15. Patients who have taken an investigational drug within four weeks prior to Visit 1.
16. Patients who have been treated with beta-blocker medication within four weeks prior to Visit 1 and/or during the screening period. Topical cardio-selective beta-blocker eye medications for non-narrow angle glaucoma are allowed.
17. Patients who have been treated with the long-acting anticholinergic tiotropium (Spiriva®) within four weeks prior to Visit 1 and/or during the screening period.
18. Patients who have been treated with oral or patch beta-adrenergics within four weeks prior to Visit 1 and/or during the Screening period.
19. Patients who have been treated with oral corticosteroids within four weeks prior to Visit 1 and/or during the screening period.
20. Patients who have been treated with anti-IgE antibodies, e.g. omalizumab (Xolair®), within 6 months prior to Visit 1 and/or during the screening period.
21. Patients who have been treated with cromone within two weeks prior to Visit 1 and/or during the screening period.
22. Patients who have been treated with methylxanthines or phosphodiesterase 4 inhibitors within two weeks prior to Visit 1 and/or during the screening period.
23. Patients who have been treated with other non-approved and according to international guidelines not recommended "experimental" drugs for routine asthma therapy within four weeks prior to Visit 1 and/or during the screening period.
24. Patients with any asthma exacerbation or any respiratory tract infection iin the four weeks prior to Visit 1 and/or during the screening period.
25. Patients who have previously been randomised in this trial or in the respective twin trial (205.418) or are currently participating in another trial.

Interventions	MD-ICS MD-ICS +Tio 2.5 µg qd

	MD-ICS +Tio 5 µg qd MD-ICS + SAL 50 µg bid
Outcomes	All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months CFB in ACQ at 6 months CFB in AQLQ at 6 months
Notes	NCT01172821

Kerstjens 2020

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 26-52 weeks **SPONSORSHIP SOURCE**: Novartis **COUNTRY**: Argentina, Austria, Belgium, Bulgaria, Canada, Chile, China, Colombia, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Jordan, Latvia, Lebanon, Lithuania, Mexico, Netherlands, Peru, Philippines, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Thailand, United Kingdom, Vietnam
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 1853 **Mean age:** 52.2 (Ages Eligible for Study: 18 to 75 Years old) **Male %:** 37 **White %:** 74 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 1.6 **Baseline FEV1 % predicted**: 55 **Hx of asthma exacerbation**: Required **Inclusion Criteria:** • Patients with a diagnosis of asthma, (GINA 2015) for a period of at least 1 year prior to Visit 1 (Screening). • Patients who have used medium or high dose of ICS/LABA combinations for asthma for at least 3 months and at stable medium or high doses of ICS/LABA for at least 1 month prior to Visit 1. • Patients must be symptomatic at screening despite treatment with mid or high stable doses of ICS/LABA. Patients with ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (before randomization). • Patients with documented history of at least one asthma exacerbation which required medical care from a physician, ER visit (or local equivalent structure) or hospitalization in the 12 months prior to Visit 1, and required systemic corticosteroid treatment. • Pre-bronchodilator FEV1 of < 80 % of the predicted normal value for the patient according to ATS/ERS guidelines after withholding bronchodilators at both visits 101 and 102. • Withholding period of bronchodilators prior to spirometry: SABA for ≥ 6 hrs, Twice daily LABA (or FDC of ICS/LABA) for ≥ 12 hrs, Once daily LABA (or FDC of ICS/LABA) for ≥ 24 hrs, SAMA for ≥ 8 hrs, Short acting xanthines for 12 hrs, Long acting xanthines for 24 hrs, . • Washout period of each drug should be kept as close as possible as above and should not be longer. If longer washout period is needed due to scheduling issues, please contact Novartis Medical monitor. • A one-time repeat of percentage predicated FEV1 (Pre-bronchodilator) at Visit 101 and/or Visit 102 is allowed in an ad-hoc visit. Repeat of Visit 101 spirometry should be done in an ad-hoc visit to be scheduled on a date that would provide sufficient time to receive confirmation from the spirometry data central reviewer of the validity of the assessment before randomization. Run-in medication should be dispensed once spirometry assessment met inclusion criteria (ATS/ERS quality criteria, FEV1 % predicted normal value, and reversibility) as per equipment • A one-time rescreen is allowed in case the patient fails to meet the criteria at the repeat, provided the patient returned to the required treatment as per inclusion criteria 4 • Patients who demonstrate an increase in FEV1 of 12% and 200 mL within 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101.All patients must perform a reversibility test at Visit 101. If reversibility is not demonstrated at Visit 101 then one of the following criteria need to be met. • Reversibility should be repeated once. • Patients may be permitted to enter the study with historical evidence of reversibility that was performed according to ATS/ERS guidelines within 2 years prior to Visit 1. • Alternatively, patients may be permitted to enter the study with a historical positive bronchoprovocation test that was performed within 2 years prior to Visit 1. If reversibility is not demonstrated at Visit 101 (or after repeated assessment in an ad-hoc visit) and historical evidence of reversibility/bronchoprovocation is not available (or was not performed according to the ATS/ERS guidelines patients must be screen failed • Spacer devices are permitted during reversibility testing only. The Investigator or delegate may decide whether or not to use a spacer for the reversibility testing **Exclusion Criteria:**

	• Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1 (Screening). If patients experience an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit between Visit 1 and Visit 102 they may be re-screened 6 weeks after recovery from the exacerbation. • Patients who have ever required intubation for a severe asthma attack/exacerbation. • Patients who have a clinical condition which is likely to be worsened by ICS administration (e.g. glaucoma, cataract and fragility fractures) who are according to investigator's medical judgment at risk participating in the study. • Patients treated with a LAMA for asthma within 3 months prior Visit 1 (Screening). • Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia (BPH) or bladder-neck obstruction or severe renal impairment or urinary retention. BPH patients who are stable on treatment can be considered). • Patients who have had a respiratory tract infection or asthma worsening as determined by investigator within 4 weeks prior to Visit 1 (Screening) or between Visit 1 and Visit 102. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening. • Patients with evidence upon visual inspection (laboratory culture is not required) of clinically significant (in the opinion of investigator) oropharyngeal candidiasis at Visit 102 or earlier, with or without treatment. Patients may be re-screened once their candidiasis has been treated and has resolved. • Patients with any chronic conditions affecting the upper respiratory tract (e.g. chronic sinusitis) which in the opinion of the investigator may interfere with the study evaluation or optimal participation in the study. • Patients with a history of chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis. • Patients with Type I diabetes or uncontrolled Type II diabetes. • Patients who, either in the judgment of the investigator or the responsible Novartis personnel, have a clinically significant condition such as (but not limited to) unstable ischemic heart disease, New York Heart Association (NYHA) Class III/IV left ventricular failure arrhythmia, uncontrolled hypertension, cerebrovascular disease, psychiatric disease, neurodegenerative diseases, or other neurological disease, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder or patients with a medical condition that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study. • Patients with paroxysmal (e.g., intermittent) atrial fibrillation are excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., selective beta blockers, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, atrial fibrillation must be present at the run-in visit (Visit 101) with a resting ventricular rate < 100/min. At Visit 101 the atrial fibrillation must be confirmed by central reading. • Patients with a history of myocardial infarction (this should be confirmed clinically by the investigator) within the previous 12 months. • Concomitant use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of study • Patients with a history of long QT syndrome or whose QTc measured at Visit 101 (Fridericia method) is prolonged (> 450 msec for males and > 460 msec for females) and confirmed by a central assessor (these patients should not be rescreened). • Patients with a history of hypersensitivity to lactose, any of the study drugs or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof. • Patients who have not achieved an acceptable spirometry result at Visit 101 in accordance with ATS/ERS criteria for acceptability and repeatability. A one-time repeat spirometry is allowed in an ad-hoc visit scheduled as close as possible from the first attempt (but not on the same day) if the spirometry did not qualify due to ATS/ERS criteria at Visit 101 and/or Visit 102. If the patient fails the repeat assessment, the patient may be rescreened once, provided the patient returns to the required treatment as per inclusion criteria 4. • Patients unable to use the Concept1 dry powder inhaler, Accuhaler or a metered dose inhaler. Spacer devices are not permitted. • History of alcohol or other substance abuse. • Patients with a known history of non-compliance to medication or who were unable or unwilling to complete a patient diary or who are unable or unwilling to use Electronic Peak Flow with e-diary device. • Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).
Interventions	MD-ICS/LABA: MF/IND 160/150 µg qd HD-ICS/LABA: MF/IND 320/150 µg qd, FP/SAL 500/50 µg bid
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months ACQ responder at 12 months CFB in ACQ at 6 months CFB in ACQ at 12 months CFB in AQLQ at 12 months
Notes	NCT02571777

Kerwin 2011

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 52 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Brazil, Canada, Philippines, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 628 **Mean age:** 40.2 (Ages Eligible for Study: 12 Years and older) **Male %:** 42 **White %:** 82 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator: 2.3** **Baseline FEV1 % predicted**: 69 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Subjects eligible for enrollment in the study must meet all of the following criteria:Consent: A signed and dated written informed consent must be obtained from the subject and/or subject's legally acceptable representative prior to study participation.Type of Subject: OutpatientGender: Male or female Females are eligible to participate only if they are currently non-pregnant and non-lactating. A female is eligible to enter and participate in the study if she is: 1. of non-child-bearing potential; OR 2. of child-bearing potential but has a negative urinary pregnancy test at Screening (Visit 1 and when specified in Appendix 1) and agrees to take contraceptive precautions (including abstinence) which are adequate to prevent pregnancy during the study.Acceptable methods of contraception [Hatcher, 2004] are:- Abstinenceoral contraceptive (either combined or progestogen only)injectable progestogenimplants of levonorgestrelestrogenic vaginal ringpercutaneous contraceptive devicesintrauterine device (IUD) or intrauterine system (IUS) with published data showing that the lowest expected failure rate is less than 1% per yearmale partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study and is the sole sexual partner for that female subjectdouble barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agentAge: A subject must be 12 years of age at Visit 1 (screening).Asthma Diagnosis: A documented diagnosis of persistent asthma, for at least six months, as defined by the following American Thoracic Society definition:Asthma is a clinical syndrome characterized by increased responsiveness of the airways to a variety of stimuli. The major symptoms of asthma are episodes of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting (status asthmaticus). The primary physiological manifestation of this hyperresponsiveness is variable airway obstruction. This can take the form of spontaneous fluctuations in the severity of obstruction, substantial improvements in the severity of obstruction following bronchodilators or corticosteroids, or increased obstruction caused by drugs or other stimuli [American Thoracic Society, 1987].Asthma Medication History: A subject must be using a low to medium dose of an ICS (Table 1) OR a combination of controller medications (Table 2), containing a low (total daily) dose ICS (as defined in Table 1) for at least 4 weeks preceding screening.Table 1 (ICS Dosage Table) Inhaled Corticosteroid (Dosage (mcg/day))(LowMedium) Beclomethasone dipropionate CFC (168 = 504> 504 = 840) Beclomethasone dipropionate HFA (80 = 240>240 = 640) Triamcinolone acetonide (400 = 1000>1000 = 2000) Flunisolide (500 = 1000> 1000 = 2000) Fluticasone propionate inhalation aerosol (176 = 220> 220 = 440) Fluticasone propionate inhalation powder (100 = 250> 250 = 500) Budesonide1 (200 = 600> 600 =1200) Mometasone (200 = 400> 400 = 800) Ciclesonide (80 = 160>160 = 320)1.Respules are allowed at a dosage of 250-500mcg/day.Table 2 (Asthma Controller Medications) Asthma Controller Medication(s) Low dose ICS + Leukotriene modifiers Low dose ICS + Theophylline products Low Dose ICS + Inhaled anticholinergics or combination products (e.g., Atrovent or Combivent) Low Dose ICS + Long acting inhaled anticholinergic (e.g. Spiriva) Low dose ICS+ long acting beta agonist or combination products containing a low dose ICS and a long-acting beta-agonists (e.g. ADVAIR™/SERETIDE™1 100/50 mcg BID or Symbicort 160/9 mcg BID (i.e 80/4.5 mcg two inhalations BID)1.ADVAIR/SERETIDE =250/50 mcg BID or Symbicort 320/9 mcg BID (i.e 160/4.5 mcg two inhalation BID) are not permitted.Pulmonary function: A pre-albuterol (salbutamol) FEV1 of 50% and 85% of predicted normal value at screening (Visit 1) after withholding asthma medications as detailed in the protocol (Section 6.8.1). Predicted FEV1 will be based on the National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older [Hankinson, 1999].Reversibility: An increase in FEV1 of 12% over the pre-albuterol (salbutamol) FEV1 within 30 minutes after the inhalation of 2-4 puffs of albuterol (salbutamol). Historical documentation of reversibility will not be permitted.Asthma symptom criteria: Each subject must have experienced asthma symptoms requiring albuterol (salbutamol) use within the 4 weeks preceding screening (Visit 1).Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational product that may impact subject eligibility is provided in the IB and the product labels. **Exclusion Criteria:** The list of excluded conditions/diseases includes, but is not limited to:congestive heart failure known aortic aneurysm clinically significant coronary clinically significant cardiac arrhythmia heart disease stroke within 3 months of screening (Visit 1) uncontrolled hypertension coronary artery disease hematologic, hepatic, or renal disease cystic fibrosis poorly controlled peptic ulcer dyspnea by any other cause than asthma gastroesophageal reflux disease (GERD) not controlled by pharmacotherapy and may be causing/contributing to subject's respiratory symptoms thyrotoxicosis hypokalemia immunologic compromise current malignancy1 tuberculosis (current or quiescent) Cushing's or Addison's disease pneumonia, pneumothorax, chronic bronchitis or atelectasis uncontrolled diabetes mellitus recent history of drug or alcohol abuse 1.history of malignancy is acceptable only if subject has been in remission for one year prior to screening (Visit 1;

	remission = no treatment for the malignancy in the 12 months prior to screening [Visit 1])Drug Allergy: A subject must not have had any immediate or delayed hypersensitivity to any beta2-agonist; sympathomimetic drug; any intranasal; inhaled or systemic corticosteroid therapy; lactose; or have a severe milk protein allergy.Respiratory Tract Infections: A subject must not have had any sinus, middle ear, oropharyngeal, upper or lower respiratory tract infection symptoms that have not resolved at least 7 days immediately preceding screening (Visit 1).Asthma Medications: Asthma medications listed below must not have been used prior to screening (Visit 1) for the required exclusion period as indicated below:Medication (Exclusion Period Prior to screening (Visit 1)) Oral or parenteral systemic corticosteroids (4 weeks) Omalizumab (Xolair) (6 months)Concurrent Medications: A subject must not have the concurrent use of any of the following medications that interact with any of the study drugs used in this study, or that may affect the course of asthma or interact with sympathomimetic amines, such as:- beta-adrenergic receptor blocking agents- monoamine oxidase (MAO) inhibitors- tricyclic antidepressants- ritonavirketoconazoleConcurrent use of asthma medications: Concurrent use of all asthma medications (other than protocol defined study and rescue medications and oral/parenteral corticosteroids) are prohibited during the study.Concomitant use of leukotriene modifiers (LTM) for allergies is prohibited. A subject must not be on LTM for treatment of nasal allergies that requires regular maintenance therapy. Substitution with any other antihistamine is permitted.Immunosuppressive Medications: A subject must not be using, or require the use of, immunosuppressive medications during the study.Immunotherapy for the treatment of allergies is not allowed during the study unless the subject has used a constant dose for 4 weeks prior to Screening (Visit 1) and the same dose will be continued throughout the study.Tobacco Use: >10 pack year history or use of any tobacco products within 1 year of screening (Visit 1). This includes cigarettes, cigars, pipe, chewing tobacco, and snuff.Questionable Validity of Consent: A subject must not have any infirmity or disability that would limit the subject's consent.Positive Pregnancy Test (for all females who have had menarche): A current positive pregnancy test.Investigational Medications: A subject must not have had use of any investigational drug within 30 days of screening (Visit 1).Site Affiliation: A subject may not participate if he/she is a participating investigator, sub-investigator, study coordinator, employee of a participating investigator or is in any way associated with the administration of the study. Immediate family members of these individuals are also excluded.Compliance with Study Requirements: A subject may not participate if, in the opinion of the investigator, there are present or anticipated circumstances that will prohibit the subject from being compliant with study visits and procedures (e.g. geographic location that will prohibit subject from required clinic visit schedule).
Interventions	MD-ICS: FP 250 µg bid MD-ICS/LABA: FP/SAL 250/50 µg bid
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	NCT00452348 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=ADA109057

Kerwin 2020

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Canada, Poland, Romania, Russian Federation, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 282 **Mean age:** 48.9 (Ages Eligible for Study: 18 Years and older) **Male %:** 27 **White %:** 93 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.2 **Baseline FEV1 % predicted**: 69 **Hx of asthma exacerbation**: Not required **Inclusion Criteria**: • 18 years of age or older at the time of signing the informed consent. • Subjects with a diagnosis of asthma as defined by the National Institutes of Health at least 6 months prior to Visit 0. • Asthma Control Questionnaire (ACQ)-6 total score of >0.75 at Visit 1. • Subjects are eligible if they have required daily Inhaled Corticosteroids (ICS) therapy >=100 milligram per day (mg/day) fluticasone propionate (FP) or equivalent with or without Long-Acting Beta-2-Agonists (LABA) or Long-Acting Muscarinic Antagonist (LAMA) for at least 12 weeks prior to Visit 0 and there have been no changes in maintenance asthma medications during the 4 weeks immediately prior to Visit 0. Dosing regimen (once or twice daily to equal the total daily dose) should be restricted to the current local product labels. • A best pre-bronchodilator morning FEV1 <=85% of the predicted normal value. Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative. A best post-bronchodilator FEV1/ forced vital capacity (FVC) >=0.7 at Visit 1. • Airway reversibility is defined as >=12% and >=200 mL increase in FEV1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1. Note: If the subject does not meet the above reversibility criteria at Visit 1 then the reversibility assessment may be repeated once within 7 days of Visit 1 if either criteria are met: The >=9% increase in FEV1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1;

Documented evidence of a reversibility assessment within 1 year prior to Visit 1 which demonstrated a post-bronchodilator increase in FEV1 of >=12% and >=200 milliliter (mL). Should the subject successfully demonstrate airway reversibility (defined as >=12% and >=200 mL increase in FEV1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol) at the second attempt then, provided that all other eligibility criteria assessed at Visit 1 are met, the subject may enter the 2-week run-in period.

- All subjects must be able to replace their current Short-Acting Beta-2-Agonists (SABA) inhaler with albuterol/salbutamol aerosol inhaler at Visit 1 as needed for the duration of the study. Subjects must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.
- Both male and female subjects are eligible to participate in the study. A female subject is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: Not a woman of childbearing potential (WOCBP) or a WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 5 days after the last dose of study treatment.
- Able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form and in this protocol. Subjects must be able to read, comprehend, and write at a level sufficient to complete study related materials.

Inclusion Criteria (for randomization)

- ACQ-6 total score of >0.75 at Visit 2.
- Spirometry: A best pre-bronchodilator morning FEV1 <=85% of the predicted normal value at Visit 2. Predicted values will be based upon the ERS Global Lung Function Initiative.
- Alanine aminotransferase (ALT) <=2 x upper limit of normal (ULN). Alkaline phosphatase <=1.5 x ULN. Bilirubin <=1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
- Compliance with completion of the Daily electronic diary (eDiary) reporting defined as completion of all questions/assessments on >=4 of the last 7 days during the run-in period.

Exclusion Criteria:

- Chest X-ray documented pneumonia in the 12 weeks prior to Visit 1.
- Any severe asthma exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (oral, parenteral or depot) within 12 weeks of Visit 1, or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids within 12 weeks of Visit 1.
- Current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, lung cancer, or other respiratory abnormalities other than asthma.
- Women who are pregnant or lactating or are planning to become pregnant during the study.
- Immune suppression (e.g., Human Immunodeficiency Virus [HIV], Lupus) or other risk factors for pneumonia (e.g., neurological disorders affecting control of the upper airway, such as Parkinson's disease, Myasthenia Gravis). Subjects at potentially high risk (e.g., very low Body Mass Index [BMI], severely malnourished, or very low FEV1) will only be included at the discretion of the Investigator
- Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
- Unstable liver disease as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice, cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Note: Chronic stable hepatitis B and C is acceptable if the subject otherwise meets entry criteria.
- Evidence of a clinically significant abnormality in the 12-lead ECG performed during screening or run-in. The Principal Investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude subjects who would be at undue risk by participating in the trial. An abnormal and clinically significant finding is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following: Atrial fibrillation (AF) with rapid ventricular rate >120 beats per minute (BPM); Sustained or nonsustained ventricular tachycardia (VT); Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted); QT interval corrected for heart rate by Fridericia's formula (QTcF) >=500 millisecond (msec) in subjects with QRS <120 msec and QTcF >=530 msec in subjects with QRS >=120 msec.
- Subjects with any of the following at Screening (Visit 1) would be excluded: Myocardial infarction or unstable angina in the last 6 months; Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months; New York Heart Association (NYHA) Class IV Heart failure.
- Subjects with a medical condition such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy or bladder neck obstruction should only be included if in the opinion of the Investigator the benefit outweighs the risk and that the condition would not contraindicate study participation.
- Subjects with carcinoma that has not been in complete remission for at least 5 years. Subjects who have had carcinoma in situ of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 5 year waiting period if the subject has been considered cured by treatment.
- Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.
- Subjects who are medically unable to withhold their albuterol/salbutamol for the 6-hour period required prior to spirometry testing at each study visit.
- Current smoker or a smoking history of >=10 pack years (e.g., 20 cigarettes/day for 10 years). A subject may not have used inhaled tobacco products within the past 12 months (i.e., cigarettes, e-cigarettes/vaping, cigars or pipe tobacco).

	• Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years. This includes marijuana, which is considered an abused drug. • A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate. • Subjects at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits. • Study investigators, sub-investigators, study coordinators, employees of a participating investigator or study site, or immediate family members of the aforementioned that is involved with this study. • In the opinion of the Investigator, any subject who is unable to read and/or would not be able to complete study related materials. Exclusion Criteria (for randomization) • Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study. • Evidence of a moderate asthma exacerbation leading to a change in therapy or severe exacerbation during screening or the run-in period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. • Changes in asthma medication (excluding changes after Visit 0 or run-in medication and albuterol/salbutamol inhalation aerosol provided at Visit 1). • Evidence of clinically significant abnormal laboratory tests during screening or run-in, which are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. Each Investigator will use his/her own discretion in determining the clinical significance of the abnormality
Interventions	FF 100 µg qd FF 100 µg qd+UMEC 62.5 µg qd
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months CFB in ACQ at 6 months CFB in AQLQ at 6 months
Notes	NCT03012061 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=205832

Lee 2020

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24-52 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Australia, Canada, Germany, Italy, Japan, Korea, Republic of, Netherlands, Poland, Romania, Russian Federation, South Africa, Spain, United Kingdom, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 813 **Mean age:** 53.6 (Ages Eligible for Study: 18 Years and older) **Male %:** 38 **White %:** 79 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 1.7 **Baseline FEV1 % predicted**: 59 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Age: 18 years of age or older at the time of signing the informed consent. • Diagnosis: Subjects with a diagnosis of asthma as defined by the National Institutes of Health at least one year prior to Visit 0. • Symptomatic: Subjects with inadequately controlled asthma (ACQ-6 score >=1.5) despite ICS/LABA maintenance therapy at Visit 1. Asthma Control: In the 1 year prior to Visit 1 • A documented healthcare contact for acute asthma symptoms or • A documented temporary change in asthma therapy for acute asthma symptoms, according to a pre-specified asthma action plan (or equivalent) • Current Asthma Maintenance Therapy: Subjects are eligible if they have required daily ICS/LABA for at least 12 weeks prior to Visit 0 with no changes to maintenance asthma medications during the 6 weeks immediately prior to

Visit 0 (including no changes to a stable total dose of ICS of >250 mcg/day fluticasone proprionate [FP, or equivalent]).

- Spirometry: A best pre-bronchodilator morning (ante meridian [AM]) FEV1 >=30% and <85% of the predicted normal value at Visit 1. Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative.
- Reversibility of Disease: airway reversibility defined as >=12% and >=200 milliliter (mL) increase in FEV1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1.
- If the subject does not meet the above reversibility criteria at Visit 1 then the reversibility assessment may be repeated once within 7 days of Visit 1 if either criteria a) or b) are met: a) >=9% increase in FEV1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1. b) Documented evidence of a reversibility assessment within 1 year prior to Visit 1 which demonstrated a post-bronchodilator increase in FEV1 of >=12% and >=200 mL.

Should the subject successfully demonstrate airway reversibility (defined as >=12% and >=200 mL increase in FEV1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol) at the second attempt then, provided that all other eligibility criteria assessed at Visit 1 are met, the subject may enter the 3-week run-in period.

- Short-Acting beta2 Agonists (SABAs): All subjects must be able to replace their current SABA inhaler with albuterol/salbutamol aerosol inhaler at Visit 1 as needed for the duration of the study. Subjects must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.
- Male or eligible Female, defined as having documentation of non-reproductive potential or reproductive potential as follows:

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test), not lactating, is not planning on becoming pregnant during the study and at least one of the following conditions applies: Non-reproductive potential defined as pre-menopausal females with documented tubal ligation or documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion or hysterectomy or documented bilateral oophorectomy; Postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile (e.g., age appropriate, >45 years, in the absence of hormone replacement therapy). In questionable cases for women <60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's postmenopausal reference range is confirmatory. Females under 60 years of age, who are on hormone replacement therapy (HRT) and whose menopausal status is in doubt, are required to use a highly effective method to avoid pregnancy if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, subjects can resume use of HRT during the study without use of a highly effective method to avoid pregnancy; Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) from the screening visit until after the last dose of study medication and completion of the follow-up visit. The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

- Informed Consent: Able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form and in this protocol. Subjects must be able to read, comprehend, and write at a level sufficient to complete study related materials.

Exclusion Criteria:

- Pneumonia: Chest X-ray documented pneumonia in the 6 weeks prior to Visit 1.
- Asthma Exacerbation: Any asthma exacerbation requiring a change in maintenance asthma therapy in the 6 weeks prior to Visit 1. Note: Subjects requiring a temporary change in asthma therapy (e.g., oral corticosteroids or increased dose of ICS) to treat an exacerbation in the 6 weeks prior to Visit 1 are not explicitly excluded at Visit 1 provided that, at the Investigator's discretion, the subject's condition is stable after they have resumed their pre-exacerbation maintenance asthma therapy (without modification) and they are considered appropriate for enrolment into this study of up to 12 month's duration.
- Chronic Obstructive Pulmonary Disease: Subjects with the diagnosis of chronic obstructive pulmonary disease, as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, including history of exposure to risk factors (i.e., especially tobacco smoke, occupational dusts and chemicals, smoke from home cooking and heating fuels) and a post-albuterol/salbutamol FEV1/Forced Vital Capacity (FVC) ratio of <0.70 and a post-albuterol/salbutamol FEV1 of =<70% of predicted normal values and onset of disease >=40 years of age.
- Concurrent respiratory disorders: Subjects with current evidence of pneumonia, active tuberculosis, lung cancer, significant bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases or abnormalities other than asthma.
- Risk Factors for Pneumonia: Immune suppression (e.g., human immunodeficiency virus, Lupus) or other risk factors for pneumonia (e.g., neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis).
- Patients at potentially high risk (e.g., very low body mass index (BMI), severely malnourished, or very low FEV1) will only be included at the discretion of the Investigator.
- Other diseases/abnormalities: Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
- Unstable liver disease as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices or persistent jaundice, cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Note: Chronic stable hepatitis B and C are acceptable if the subject otherwise meets entry criteria.

- Clinically significant Electrocardiogram abnormality: Evidence of a clinically significant abnormality in the 12-lead ECG performed during screening. The Investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude subjects who would be at undue risk by participating in the trial. An abnormal and clinically significant finding is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following: Atrial fibrillation (AF) with rapid ventricular rate >120 Beats Per Minute (BPM); sustained or non-sustained ventricular tachycardia (VT); Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted); QT interval corrected for heart rate by Fridericia's formula (QTcF) >=500 milliseconds (msec) in subjects with QRS <120 msec and QTcF >=530 msec in subjects with QRS >=120 msec.
- Unstable or life threatening cardiac disease: Subjects with any of the following at Screening (Visit 1) would be excluded: Myocardial infarction or unstable angina in the last 6 months; Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months; New York Heart Association (NYHA) Class IV Heart failure.
- Antimuscarinic effects: Subjects with a medical condition such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy or bladder neck obstruction should only be included if in the opinion of the Investigator the benefit outweighs the risk and that the condition would not contraindicate study participation.
- Cancer: Subjects with carcinoma that has not been in complete remission for at least 5 years. Subjects who have had carcinoma in situ of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 5 year waiting period if the subject has been considered cured by treatment.
- Questionable validity of consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.
- Medication prior to spirometry: Subjects who are medically unable to withhold their albuterol/salbutamol for the 6-hour period required prior to spirometry testing at each study visit.
- Tobacco Use: Subjects who are: Current smokers (defined as subjects who have used inhaled tobacco products within the 12 months prior to Visit 1 [i.e., cigarettes, e-cigarettes/vaping, cigars or pipe tobacco]) or former smokers with a smoking history of >=10 pack years (e.g., >=20 cigarettes/day for 10 years).
- Drug/alcohol abuse: Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years.
- Allergy or Hypersensitivity: A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate.
- Non-compliance: Subjects at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
- Affiliation with Investigator site: Study Investigators, sub-Investigators, study coordinators, employees of a participating Investigator or study site, or immediate family members of the aforementioned that is involved with this study.
- Inability to read: In the opinion of the Investigator, any subject who is unable to read and/or would not be able to complete study related materials.

Inclusion Criteria for Enrolment

- Inadequately controlled asthma: Subjects with inadequately controlled asthma (ACQ-6 score >=1.5) at Visit 2.
- Percent-predicted FEV1: A best pre-bronchodilator morning (AM) FEV1 >=30% and <90% of the predicted normal value at Visit 2. Predicted values will be based upon the ERS Global Lung Function Initiative
- Liver function tests at Visit 1: alanine aminotransferase (ALT) <2 x upper limit of normal (ULN); alkaline phosphatase <=1.5xULN; bilirubin <=1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
- Compliance with completion of the Daily eDiary reporting defined as completion of all questions/assessments on >=4 of the last 7 days during the run-in period.

Exclusion Criteria for Enrolment

- Respiratory Infection: Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study.
- Severe asthma exacerbation: Evidence of a severe exacerbation during screening or the run-in period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
- Asthma medication: Changes in asthma medication (excluding run-in medication and albuterol/salbutamol inhalation aerosol provided at Visit 1).
- Laboratory test abnormalities: Evidence of clinically significant abnormal laboratory tests during screening or run-in which are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. Each Investigator will use his/her own discretion in determining the clinical significance of the abnormality.

Inclusion Criteria for Randomization

- Compliance with completion of the Daily eDiary reporting defined as completion of all questions/assessments on >=4 of the last 7 days during the stabilization period.

Exclusion Criteria for Randomization

- Respiratory Infection: Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the stabilization period that led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study.
- Severe asthma exacerbation: Evidence of a severe exacerbation during enrolment or the stabilization period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3

	days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. • Asthma medication: Changes in asthma medication (excluding stabilization period medication provided at Visit 2 and albuterol/salbutamol inhalation aerosol provided at Visit 1).
Interventions	MD-ICS/LABA: FF/VI 100/25 µg qd HD-ICS/LABA: FF/VI 200/25 µg qd
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months CFB in ACQ at 6 months
Notes	NCT02924688 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=205715

Lin 2015

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: China, Korea, Republic of Philippines
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 309 **Mean age:** 47.8 (Ages Eligible for Study: 12 to 100 Years old) **Male %:** 41 **White %:** 0 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 1.8 **Baseline FEV1 % predicted**: 68 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** 1. Informed Consent: All subjects must be able and willing to give written informed consent to take part in the study 2. Type of Subject: Outpatients, of Asian ancestry, 12 years of age or older at Visit 1 (or ≥18 years of age or older if local regulations or the regulatory status of study medication permit enrolment of adults only) with a diagnosis of asthma as defined by the Global Initiative for Asthma [GINA, 2009] at least 12 weeks prior to Visit 1. 3. Gender: Male or Eligible Female, defined as non-childbearing potential or childbearing potential using an acceptable method of birth control consistently and correctly 4. Severity of Disease: A best FEV1 of 40%-90% of the predicted normal value at the Visit 1 Screening visit. Predicted values will be based upon NHANES III using the Asian adjustment 5. Reversibility of Disease: Demonstrated ≥12% and ≥200mL reversibility of FEV1 within 10-40minutes following 2-4 inhalations of albuterol/salbutamol inhalation aerosol (or one nebulized treatment with albuterol/salbutamol solution) at the Screening Visit. 6. Current Anti-Asthma Therapy: All subjects must be using an ICS, with or without LABA, for at least 12 weeks prior to Visit 1. 7. Short-Acting Beta2-Agonists: All subjects must be able to replace their current short-acting beta2-agonists with albuterol/salbutamol inhaler at Visit 1 for use as needed for the duration of the study. Subjects must be able to withhold albuterol/salbutamol for at least 4 hours prior to study visits. **Exclusion Criteria:** 1. History of Life-threatening asthma: Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures within the last 10 years. 2. Respiratory Infection: Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of Visit 1 and led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study. 3. Asthma Exacerbation: Any asthma exacerbation requiring oral corticosteroids within 12 weeks of Visit 1 or that resulted in overnight hospitalization requiring additional treatment for asthma within 6 months prior to Visit 1. 4. Concurrent Respiratory Disease: A subject must not have current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or other respiratory abnormalities other than asthma.

	5. Other Concurrent Diseases/Abnormalities: A subjects must not have any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the patient at risk through study participation or would confound the interpretation of the efficacy results if the condition/disease exacerbated during the study. 6. Oropharyngeal Examination: A subject will not be eligible for the Run-in if he/she has clinical visual evidence of candidiasis at Visit 1. 7. Allergies:Drug Allergy: Any adverse reaction including immediate or delayed hypersensitivity to any beta2-agonist, sympathomimetic drug, or any intranasal, inhaled, or systemic corticosteroid therapy. Known or suspected sensitivity to the constituents of the new powder inhalerMilk Protein Allergy: History of severe milk protein allergy. 8. Concomitant Medications: Use of the protocol defined prohibited medications within the prohibited time intervals prior to Screening (Visit 1) or during the study. 9. Tobacco Use: Current smoker or a smoking history of 10 pack years (e.g., 20 cigarettes/day for 10 years). A subject may not have used inhaled tobacco products within the past 3 months (i.e., cigarettes, cigars, smokeless or pipe tobacco). 10. Affiliation with Investigator's Site: A subject will not be eligible for this study if he/she is an immediate family member of the participating Investigator, sub Investigator, study coordinator, or employee of the participating Investigator. 11. Previous Participation: A subject may not have previously been randomized to treatment in another Phase III FF/VI combination product study 12. Compliance: A subject will not be eligible if he/she or his/her parent or legal guardian has any infirmity, disability, disease, or geographical location which seems likely (in the opinion of the Investigator) to impair compliance with any aspect of this study protocol, including visit schedule and completion of the daily diaries
Interventions	HD-ICS: FP 500 µg twice daily HD-ICS/LABA: FF/VI 200/25 µg daily
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event CFB in AQLQ at 3 months
Notes	NCT01498653 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=113714

Lotvall 2014

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Belgium, Germany, Poland, Romania, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 228 **Mean age:** 40.8 (Ages Eligible for Study: 12 Years and older) **Male %:** 41 **White %:** 79 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.4 **Baseline FEV1 % predicted**: 73 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Signed informed consent • Outpatient at least 12 years of age • Both genders; females of child bearing potential must be willing to use approved birth control method • Pre-bronchodilator FEV1 of 40-90% predicted • Reversibility FEV1 of at least 12% and 200mLs • Current asthma therapy that includes an inhaled corticosteroid for at least 4 weeks prior to first visit **Exclusion Criteria:** • History of life threatening asthma • Respiratory infection or candidiasis • Asthma exacerbation within 6 months prior to first visit • Concurrent respiratory disease or other disease that would confound study participation or affect subject safety • Allergies to study drugs, study drug excipients, medications related to study drugs • Taking another investigational medication or medication prohibited for use during this study

Interventions	FF 100 µg daily FP 250 µg twice daily
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Dropouts due to adverse event CFB in AQLQ at 3 and 6 months
Notes	NCT01159912 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=112059

Mansfield 2017

Study characteristics	
Methods	**DESIGN**: Multicenter randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 26 weeks **SPONSORSHIP SOURCE**: Teva Branded Pharmaceutical **COUNTRY**: United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 674 **Mean age:** 43.4 (Ages Eligible for Study: 12 Years and older) **Male %:** 40 **White %:** 78 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.5 **Baseline FEV1 % predicted**: Not reported **Hx of asthma exacerbation**: Not required **Inclusion Criteria**: 1. Best pre-bronchodilator forced expiratory volume in 1 second (FEV1) of greater than 40% of their predicted normal value. 2. Patients must have a treatment regimen that includes a short-acting β2 agonist (SABA) (albuterol) for use as needed and either an inhaled corticosteroid (ICS) or an ICS/long-acting β2 agonist (LABA) as a preventative treatment for a minimum of 8 weeks before the SV. Patients currently taking low-dose ICS without LABA are not eligible for this study. Patients currently taking low-dose ICS/LABA may only be entered into the mid ICS strength. All patients must have been maintained on a stable dose of ICS or ICS/LABA for 4 weeks prior to the SV (or pre-SV if necessary) at 1 qualifying doses 3. To meet reversibility of disease criteria, the patient must demonstrate a ≥12% reversibility of FEV1 (and 200 mL for patients aged18 years and older) within 30 minutes following 4 inhalations of albuterol at the SV. Historic reversibility within the past 12 months of the SV may be used to meet this criterion. 4. Written informed consent/assent is obtained. For adult patients (aged 18 years and older, or as applicable per local regulations), the written informed consent form (ICF) must be signed and dated by the patient before conducting any study-related procedure. For minor patients (aged 12 to 17 years, or as applicable per local regulations), the written ICF must be signed and dated by the parent/legal guardian and the written assent form must be signed and dated by the patient (if applicable) before conducting any study-related procedure. Note: Age requirements are as specified by local regulations. 5. Outpatient >: 12 years of age on the date of consent/assent. . 6. Asthma diagnosis: The patient has a diagnosis of asthma as defined by the National Institutes of Health (NIH). The asthma diagnosis has been present for a minimum of 3 months and has been stable (defined as no exacerbations and no changes in medication) for at least 30 days before providing informed consent. 7. The patient is able to perform acceptable and repeatable spirometry. 8. The patient is able to perform peak expiratory flow (PEF) with a handheld peak flow meter. 9. The patient is able to use a metered-dose inhaler (MDI) device without a spacer device and a MDPI device. 10. The patient is able to withhold (as judged by the investigator) his or her regimen of ICS or study drug, and rescue medication for at least 6 hours before the SV and before all treatment visits where spirometry is performed. 11. The patient/parent/legal guardian/caregiver is capable of understanding the requirements, risks, and benefits of study participation, and, as judged by the investigator, capable of giving informed consent/assent and being compliant with all study requirements. 12. SABAs: All patients must be able to replace their current SABA with albuterol/salbutamol HFA inhalation aerosol at the SV for use as needed for the duration of the study. 13. Female patients may not be pregnant, breastfeeding, or attempting to become pregnant.-Other criteria may apply, please contact the investigator for more information **Exclusion Criteria**: 1. The patient has a history of a life-threatening asthma exacerbation that is defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest, or hypoxic seizures. 2. The patient is pregnant or lactating, or plans to become pregnant during the study period or for 30 days after the study.

	3. The patient has participated as a randomized patient in any investigational drug study within the 30 days preceding the SV (or prescreening visit, as applicable) or plans to participate in another investigational drug study at any time during this study. 4. The patient has previously participated in an Fp MDPI or FS MDPI study. 5. The patient has a known hypersensitivity to any corticosteroid, salmeterol, or any of the excipients in the study drug or rescue medication formulation (ie, lactose). 6. The patient has been treated with any known strong cytochrome P450 (CYP) 3A4 inhibitors (eg, azole antifungals, ritonavir, or clarithromycin) within 30 days before the SV or plans to be treated with any strong CYP3A4 inhibitor during the study. 7. The patient has been treated with any of the prohibited medications during the prescribed (per protocol) washout periods before the SV. 8. The patient currently smokes or has a smoking history of 10 pack-years or more (a pack-year is defined as smoking 1 pack of cigarettes/day for 1 year). The patient may not have used tobacco products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco). 9. The patient has a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that has not resolved at least 2 weeks before the SV. 10. The patient has a history of alcohol or drug abuse within 2 years preceding the SV. 11. The patient has had an asthma exacerbation requiring systemic corticosteroids within 30 days before the SV, or has had any hospitalization for asthma within 2 months before the SV. 12. Initiation or dose escalation of immunotherapy (administered by any route) is planned during the study period. However, patients who initiated immunotherapy 90 days or more before the SV and have been on a stable (maintenance) dose for 30 days or more before the SV may be considered for inclusion. 13. The patient has used immunosuppressive medications within 4 weeks before the SV. 14. The patient is unable to tolerate or unwilling to comply with the appropriate washout periods and withholding of all applicable medications. (Patients that require continuous treatment with β-blockers, monoamine oxidase inhibitors, tricyclic antidepressants, anticholinergics, and/or systemic corticosteroids are excluded). 15. The patient has untreated oral candidiasis at the SV. Patients with clinical visual evidence of oral candidiasis who agree to receive treatment and comply with appropriate medical monitoring may enter the study. 16. The patient has a history of a positive test for human immunodeficiency virus, active hepatitis B virus, or hepatitis C infection. 17. The patient is either an employee or an immediate relative of an employee of the clinical investigational center. 18. A member of the patient's household is participating in the study at the same time. However, after the enrolled patient completes or discontinues participation in the study, another patient from the same household may be screened. 19. The patient has a disease/condition that in the medical judgment of the investigator would put the safety of the patient at risk through participation or that could affect the efficacy or safety analysis if the disease/condition worsened during the study.Other criteria may apply, please contact the investigator for more information
Interventions	MD-ICS: FP 220 µg bid; FP 200 µg bid HD-ICS: FP 440 µg bid LD-ICS/LABA: FP/SAL 100/12.5 µg bid MD-ICS/LABA: FP/SAL 250/50 µg bid, FP/SAL 200/12.5 µg bid HD-ICS/LABA: FP/SAL 500/50 µg bid
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	NCT02175771

Murphy 2015

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: Bulgaria, Hungary, Russian Federation, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 214 **Mean age:** 42.7 (Ages Eligible for Study: 12 Years and older) **Male %:** 44 **White %:** 83 **Current smoker excluded/maximum PYs allowed for ex-smokers:** N/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.1

	Baseline FEV1 % predicted: Not reported **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Male or female 12 years and above • Clinical diagnosis of asthma according to the American Thoracic Society definition at least 6 months • Pre-bronchodilator FEV1 ≥ 45% and ≤ 85% of predicted normal • Patients with reversible airway obstruction • Documented daily use of inhaled corticosteroids for ≥ 3 months **Exclusion Criteria:** • History of life-threatening asthma, defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures during the 2 years prior to Visit 2 • Hospitalized during previous 6 months for asthma • Required emergency treatment more than once during previous 6 months for an asthma-related condition • Intake of oral, rectal or parenteral glucocorticosteroid within 30 days of enrolment • Respiratory infection affecting the asthma within 30 days
Interventions	MD-ICS: BUD 320 µg bid MD-ICS/LABA: BUD/FM Breath actuated metered dose inhaler (BA MDI) 320/9 µg bid, BUD/FM pressured metered dose inhaler (pDMI) 320/9 µg bid
Outcomes	All cause serious adverse events All cause adverse events Dropouts due to adverse event
Notes	NCT01360021

Nathan 2010

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 26 weeks **SPONSORSHIP SOURCE**: Merck Sharp & Dohme Corp **COUNTRY**: Canada, Colombia, Costa Rica, Croatia, Denmark, Ecuador, Estonia, Guatemala, Hungary, Mexico, Poland, Russian Federation, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 384 **Mean age:** 42.9 (Ages Eligible for Study: 12 Years and older) **Male %:** 46 **White %:** 71 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.4 **Baseline FEV1 % predicted**: 73 **Hx of asthma exacerbation**: Not required **Key Inclusion Criteria** Include - A subject must have been using a medium daily dose of inhaled glucocorticosteroid (ICS) (either alone or in combination with a long-acting beta agonist (LABA)) for at least 12 weeks and must have been on a stable regimen (daily dose unchanged) for at least 2 weeks prior to Screening. Medium daily doses of ICS are defined as follows: • >500 to 1000 mcg beclomethasone chlorofluorocarbon (CFC) • >250 to 500 mcg beclomethasone hydrofluoroalkane (HFA) • >600 to 1000 mcg budesonide dry powder inhaler (DPI) • >1000 to 2000 mcg flunisolide • >250 to 500 mcg fluticasone • 400 mcg MF • >1000 to 2000 mcg triamcinolone acetonide Note: Dose delivery by method or modality other than those noted above must be equivalent. • If, based upon the medical judgment of the investigator, there is no inherent harm in changing the subject's current asthma therapy, then the subject (and parent/guardian, if applicable) must be willing to discontinue his/her prescribed ICS or ICS/LABA combination at the Screening Visit, and be transferred to open-label treatment with MF MDI 200 mcg BID for 2 to 3 weeks prior to the Baseline/Randomization Visit. • To document the diagnosis of asthma and assure the subject's responsiveness to bronchodilators before randomization one of the following methods can be used at the Screening Visit, Day -14, or thereafter, but prior to the Baseline Visit:The subject must demonstrate an increase in absolute FEV1 of at least 12% and at least 200 mL within 15 minutes after administration of four inhalations of albuterol/salbutamol (total dose of 360 to 400 mcg) or of nebulized SABA (2.5 mg) if confirmed as standard office practice, ORThe subject must demonstrate a peak expiratory flow (PEF) variability of more than 20% expressed as a percentage of the highest and lowest morning

	prebronchodilator PEF over at least 1 week, ORThe subject must demonstrate a diurnal variation in PEF of more than 20% based on the difference between the prebronchodilator morning value and the postbronchodilator value from the evening before, expressed as a percentage of the mean daily PEF value. • At the Screening Visit, the subject's FEV1 must be ≥60% and ≤90% predicted. • At the Baseline Visit, the subject's FEV1 must be ≥60% and ≤85% predicted when all restricted medications have been withheld for the appropriate intervals. • Clinical laboratory tests (complete blood counts [CBC], blood chemistries, and urinalysis) conducted at the Screening Visit must be within normal limits or clinically acceptable to the investigator/sponsor. An electrocardiogram (ECG) using a centralized trans-telephonic technology at the Screening Visit must be clinically acceptable to the investigator. A chest x-ray performed at the Screening Visit, or within 12 months prior to the Screening Visit, must be clinically acceptable to the investigator. • A female subject of childbearing potential must have been using a medically acceptable, adequate form of birth control. This includes: 1) hormonal contraceptives as prescribed by a physician (oral combined, hormonal implant); 2) medically prescribed intra-uterine device (IUD); 3) condom in combination with a spermicide (double barrier method); 4) monogamous relationship with a male partner who has had a vasectomy. The subject must have started this birth control method at least 3 months prior to Screening (with the exception of condom in combination with spermicide), and must agree to continue its use for the duration of the study. A female subject of childbearing potential who is not currently sexually active must agree and consent to using a medically acceptable birth control method should she become sexually active during the course of this study. Women who have been surgically sterilized or are at least 1 year postmenopausal are not considered to be of childbearing potential. A female subject of childbearing potential must have a negative serum pregnancy test at Screening in order to be considered eligible for enrollment. **Key Exclusion Criteria** Include • A subject who demonstrates a change (increase or decrease) in absolute FEV1 of >20% at any time from the Screening Visit up to and including the Baseline Visit. • A subject who requires the use of greater than eight inhalations per day of SABA MDI, or two or more nebulized treatments per day of 2.5 mg SABA, on any 2 consecutive days from the Screening Visit up to and including the Baseline Visit. • A subject who experiences a decrease in AM or PM PEF below the Screening Period stability limit on any 2 consecutive days prior to Randomization. • A subject who experiences an occurrence of any clinical deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with additional, excluded asthma medication (other than SABA) as judged by the clinical investigator at any time from the Screening Visit up to and including the Baseline Visit. • A subject who is a smoker or ex-smoker and has smoked within the previous year or has had a cumulative smoking history >10 pack-years
Interventions	MD-ICS: MF 200 µg bid MD-ICS/LABA: MF/FM 200/10 µg bid
Outcomes	Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event CFB in ACQ at 6 months CFB in AQLQ at 6 months
Notes	NCT00383240

O'Byrne 2014

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Germany, Japan, Poland, Romania, Russian Federation, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 586 **Mean age:** 46.2 (Ages Eligible for Study: 12 Years and older) **Male %:** 41 **White %:** 84 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.1 **Baseline FEV1 % predicted**: 67 **Hx of asthma exacerbation**: Not reported **Inclusion Criteria:** • Outpatient at least 12 years of age • Both genders; females of childbearing potential must be willing to use birth control method • Pre-bronchodilator FEV1 of 40-90% predicted • Reversibility FEV1 of at least 12% and 200mls

	• Current asthma therapy that includes an inhaled corticosteroid for at least 12 weeks prior to first visit **Exclusion Criteria:** • History of life-threatening asthma • Respiratory infection or oral candidiasis • Asthma exacerbation within 12 weeks • Concurrent respiratory disease or other disease that would confound study participation or affect subject safety • Allergies to study drugs, study drugs' excipients, medications related to study drugs • Taking another investigational medication or medication prohibited for use during this study
Interventions	HD-ICS: FP 500 µg bid, FF 200 µg qd HD-ICS/LABA: FF/VI 200/25 µg qd
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event CFB in AQLQ at 3 months CFB in AQLQ at 6 months
Notes	NCT01134042 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=106829

Paggiaro 2016b

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Chiesi Farmaceutici S.p.A. **COUNTRY**: Italy
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 359 **Mean age:** 49.3 (Ages Eligible for Study: 18 Years and older) **Male %:** 41 **White %:** Not reported **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/5 **Baseline FEV1 (L) pre-bronchodilator:** 2.0 **Baseline FEV1 % predicted**: 65 **Hx of asthma exacerbation**: Not required **Main Inclusion Criteria:** • Male or female patients aged > 18 years. • Patients with persistent asthma not optimally controlled (GINA 2010) on high doses of ICS or medium dose of ICS+LABA at a stable dose for at least 4 weeks prior to screening. • Patients with FEV1 >= 40% and < 80% of predicted for the patient normal value and at least 0.9 L. • Patients with a documented positive response to the reversibility test, defined as ΔFEV1 >= 12% and >= 200 mL over baseline, within 30 minutes after administration of 400 µg of salbutamol pMDI. • At screening and at the end of the run-in period, patients with not adequately controlled asthma according to GINA 2010 and with score at the Asthma Control Questionnaire (ACQ)> 0.75 **Main Exclusion Criteria:** • History of near fatal asthma or of a past hospitalisation for asthma in Intensive Care Unit or of frequent exacerbations (3 or more asthma exacerbations/ year). • Hospitalisation, Emergency Room admission or use of systemic steroids (more than 3 days) for asthma exacerbation in the 4 weeks prior to screening visit and during the run-in period. • Symptomatic infection of the lower airways in the 4 weeks before the screening visit. • Current or ex-smokers with total cumulative exposure equal or more than 5 pack-years and /or having stopped smoking one year or less prior to screening visit. • Patients with a clinically significant abnormality at 12-lead ECG or presenting a QTcB interval value in ECG > 450 msec in males or > 470 msec in females).
Interventions	HD-ICS: extrafine-BDP 800 µg qd HD-ICS/LABA: extrafine-BDP/FM 800/24 µg qd
Outcomes	Moderate to severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event

Notes	NCT01577082

Papi 2007

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Chiesi Farmaceutici **COUNTRY**: Poland, Ukraine
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 228 **Mean age:** 48.5 (Ages Eligible for Study: 18 to 65 Years old) **Male %**: 44 **White %:** Not reported **Current and Ex smoker excluded:** Yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 2.0 **Baseline FEV1 % predicted**: 67 **Hx of asthma exacerbation**: Not required. **Inclusion Criteria:** • Clinical diagnosis of moderate to severe persistent asthma for at least 6 months, according to GINA revised version 2002 guidelines (11):Forced expiratory volume (FEV1) or peak expiratory flow rate (PEFR) ^{3} 50% and £ 80% of the predicted normal;Asthma not adequately controlled with the current therapies, defined as presence of daily asthma symptoms > once a week and night-time asthma symptoms > twice a month, and daily use of short-acting β2-agonists. These findings are to be based on recent medical history and are to be confirmed in the 2-week run-in period. • Treatment with inhaled corticosteroids at a daily dose ≤ 1000 µg of BDP or equivalent. The daily dose of inhaled corticosteroids taken at visit 1 will be assessed taking into account the following ratios between the doses of the different steroids: fluticasone propionate : BDP CFC : 1 : 2; budesonide : BDP CFC : 4 : 5; flunisolide : BDP CFC : 1 : 1. The ratios between inhaled steroids are irrespective of the formulations (i.e. spray aerosol or powder) used. When BDP is given in the new extra-fine HFA-134a formulation (as QVAR®, 3M Healthcare), the ratio with BDP CFC is set as 2 : 5. Therefore, the maximum allowed daily dose of inhaled corticosteroids at study entry will be: budesonide 800 µg, fluticasone propionate 500 µg, flunisolide 1000 µg, BDP 1000 mg, BDP HFA extra-fine 400 µg. • Positive response to the reversibility test in the screening visit, defined as an increase of at least 12% (or, alternatively, of 200mL) from baseline value in the measurement of FEV1 30 minutes following 2 puffs (2 ´ 100 µg) of inhaled salbutamol administered via pMDI. The reversibility test can be avoided in patients having a documented positive response in the previous 6 months. • A co-operative attitude and ability to be trained to correctly use the metered dose inhalers and to complete the diary cards. • Written informed consent obtained. • At the end of the 2-week run-in period, the presence of daily asthma symptoms (of at least mild intensity) and nighttime asthma symptom (of at least mild intensity) > once a week, as well as of daily use of relief salbutamol is to be confirmed by reviewing the diary cards for run-in. **Exclusion Criteria:** • Inability to carry out pulmonary function testing; • Diagnosis of Chronic Obstructive Pulmonary Disease (COPD) as defined by the National Heart Lung and Blood Institute/World Health Organisation (NHLBI/WHO) Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (30); • History of near fatal asthma; • Evidence of severe asthma exacerbation or symptomatic infection of the airways in the previous 8 weeks; • Three or more courses of oral corticosteroids or hospitalisation due to asthma during the previous 6 months; • Patients treated with long-acting β2-agonists, anticholinergics and antihistamines during the previous 2 weeks, with topical or intranasal corticosteroids and leukotriene antagonists during the previous 4 weeks; • Patients who have changed their dose of inhaled corticosteroids during the previous 4 weeks, or treatment with inhaled corticosteroids at a daily dose > 1000 µg of BDP or equivalent (except for extra-fine formulations, see inclusion criteria); • Current smokers or recent (less than one year) ex-smokers, defined as smoking at least 10 cigarettes/day; • History or current evidence of heart failure, coronary artery disease, myocardial infarction, severe hypertension, cardiac arrhythmias; • Diabetes mellitus; • Percutaneous transluminal coronary angioplasty (PTCA) or coronary artery by-pass graft (CABG) during the previous six months; • Patients with an abnormal QTc interval value in the ECG test, defined as > 450 msec in males or > 470 msec in females; • Other haemodynamic relevant rhythm disturbances (including atrial flutter or atrial fibrillation with ventricular response, bradycardia (≤ 55 bpm), evidence of atrial-ventricular (AV) block on ECG of more than 1st degree;

	• Clinically significant or unstable concurrent diseases: uncontrolled hyperthyroidism, significant hepatic impairment, poorly controlled pulmonary (tuberculosis, active mycotic infection of the lung), gastrointestinal (e.g. active peptic ulcer), neurological or haematological autoimmune diseases; • Cancer or any chronic diseases with prognosis < 2 years; • Pregnant or lactating females or females at risk of pregnancy, i.e. those not demonstrating adequate contraception (i.e. barrier methods, intrauterine devices, hormonal treatment or sterilization). A pregnancy test is to be carried out in women of a fertile age. • History of alcohol or drug abuse; • Patients treated with monoamine oxidase inhibitors, tricyclic antidepressants or beta-blockers as regular use; • Allergy, sensitivity or intolerance to study drugs and/or study drug formulation ingredients; • Patients unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study; • Patients who received any investigational new drug within the last 12 weeks; • Patients who have been previously enrolled in this study; • At the end of the run-in period, patients will not be admitted to the treatment period in the case of an increase of PEFR (L/sec) measured at the clinics at the end of the run-in period ^{3} 15% in respect of values measured at the start of the run-in period; • Patients with asthma exacerbations during the run-in period will also be excluded from the study.
Interventions	FP/SAL 250/50 µg bid BDP/FM 200/12 µg bid
Outcomes	Moderate to severe exacerbations
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. NCT00394368

Pedersen 2017

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 52 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: Argentina, Brazil, Germany, Israel, Russian Federation
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 247 **Mean age:** 45.0 (Ages Eligible for Study: 12 to 70 Years old) **Male %:** 36 **White %:** 92 **Current smoker excluded/maximum PYs allowed for ex-smokers:** N/Not reported **Baseline FEV1 (L) pre-bronchodilator:** Not reported **Baseline FEV1 % predicted**: 73 **Hx of asthma exacerbation**: Not required **Inclusion Criteria**: • Written informed consent was provided • History of persistent bronchial asthma for at least 6 months • Current treatment with an Inhaled Corticosteroid (ICS) at a stable dose in the dose range of 200-1000 µg Fluticasone Propionate (FP)/day or equivalent for a minimum of 12 weeks • Good inhalation technique • Under the current ICS pre-treatment the ACQ score ranges between ≥ 0.75 and ≥ 2 **Exclusion Criteria**: • Clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation • Concomitant severe diseases (e.g. malignant diseases during the past 5 years [other than basal or squamous cell carcinoma], hepatitis C, acquired immune deficiency syndrome [AIDS]) • Diseases which are contraindications for the use of ICS (e.g. active or inactive pulmonary tuberculosis or relevant fungal, bacterial or viral infections of the lower respiratory tract demanding specific treatment) • Use of systemic glucocorticosteroids within 4 weeks (injectable depot steroids 6 weeks) before entry into the baseline period, or more than 3 times during the last 6 months
Interventions	MD-ICS: CIC 160 µg bid HD-ICS: CIC 320 µg bid
Outcomes	Moderate to severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event

	ACQ responder at 12 months CFB in ACQ at 12 months
Notes	NCT01455194

Pertseva 2013

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: SkyePharma AG **COUNTRY**: Argentina, Chile, Hungary, Mexico, Peru, Poland, Romania, South Africa, Ukraine, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 434 **Mean age:** 42.1 (Ages Eligible for Study: 12 Years and older) **Male %:** 35 **White %:** 77 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 1.9 **Baseline FEV1 % predicted**: 63 **Hx of asthma exacerbation**: Not required **Main Inclusion Criteria:** • ≥ Age 12 years at the Screening Visit. • History of asthma for 12 months prior to the Screening Visit. • Documented use of an inhaled corticosteroid for at least 4 weeks prior to the Screening Visit. • Steroid-requiring patient • patients must demonstrate (1) an FEV1 of 40% to 80% (inclusive) of predicted normal values at both the Screening and Baseline Visits and (2) documented reversibility within 12 months of the Screening Visit, defined as a ≥ 15% **Main Exclusion Criteria:** • Life-threatening asthma within the past year or during the Run-In Period. • History of systemic (oral or injectable) corticosteroid medication within 3 months before the Screening Visit. • An upper or lower respiratory infection within 4 weeks prior to the Screening Visit or during the Run-In Period. • Significant, non-reversible, pulmonary disease (e.g., chronic obstructive pulmonary disease [COPD], cystic fibrosis, bronchiectasis). • A smoking history equivalent to "10 pack years" (i.e., at least 1 pack of 20 cigarettes /day for 10 years or 10 packs/day for 1 year, etc.). • Current smoking history within 12 months prior to the Screening Visit. • Previous exposure to FlutiForm
Interventions	MD-ICS: FP 250 µg bid MD-ICS/LABA: FP/FM 250/10 µg bid
Outcomes	Moderate to severe exacerbations All cause serious adverse events All cause adverse events Dropouts due to adverse event
Notes	NCT00649025

Peters 2008

Study characteristics	
Methods	**DESIGN**: Multicenter randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 52 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 708 **Mean age:** 40.3 (Ages Eligible for Study: 12 Years and older) **Male %:** 37 **White %:** 87 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/20 **Baseline FEV1 (L) pre-bronchodilator:** 2.4

	Baseline FEV1 % predicted: 74 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Diagnosis of asthma and baseline lung function tests, symptoms and medication use as determined by the protocol • Required and received treatment with inhaled corticosteroids within the timeframe and doses specified in the protocol **Exclusion Criteria:** • Has required treatment with non-inhaled corticosteroids within previous 30 days, has sensitivity to drugs specified in the protocol or requires treatment with a beta-blocker. • Has had cancer within previous 5 years or has a condition that may put the patient at risk in this study.
Interventions	HD-ICS: BUD 640 µg bid MD-ICS/LABA: BUD/FM 320/9 µg bid HD-ICS/LABA: BUD/FM 640/18 µg bid
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Dropouts due to adverse event
Notes	NCT00651768 Clinical Study Report available at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=964

Peters 2016

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 26 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: Argentina, Brazil, Bulgaria, Chile, Colombia, Czech Republic, France, Germany, India, Italy, Korea, Republic of, Mexico, Panama, Peru, Philippines, Poland, Puerto Rico, Romania, Russian Federation, Slovakia, South Africa, Thailand, Ukraine, United Kingdom, United States, Vietnam
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 10047 **Mean age:** 44.0 (Ages Eligible for Study: 12 Years and older) **Male %:** 34 **White %:** 69 **Current smoker excluded/maximum PYs allowed for ex-smokers:** N/10 **Baseline FEV1 (L) pre-bronchodilator:** Not reported **Baseline FEV1 % predicted**: Not reported **Hx of asthma exacerbation**: Not required **Inclusion Criteria**: • Provision of signed informed consent/ paediatric assent (if applicable) prior to any study specific procedures including medication withdrawal • Male or Female, ≥12 years of age • Documented clinical diagnosis of asthma for at least 1 year prior to Visit 2 • Patient must have history of at least 1 asthma exacerbation including one of the following:requiring treatment with systemic corticosteroidsan asthma-related hospitalization between 4 weeks and 12 months prior to randomization • Current Asthma Therapy: Patients must be appropriately using one of the treatments for asthma listed in the protocol combined with achieving certain results when recording an Asthma Control Questionnaire **Exclusion Criteria**: • Patient has a history of life-threatening asthma. Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea requiring non-invasive ventilatory support. • Patient has required treatment with systemic corticosteroids (tablets, suspensions or injectable) for any reason within 4 weeks prior to Visit 2 • Patient has an ongoing exacerbation, defined as a worsening of asthma that requires treatment with systemic corticosteroids (tablets, suspension, or injectable) • An asthma exacerbation within 4 weeks of randomization or more than 4 separate exacerbations in the 12 months preceding randomization or more than 2 hospitalizations for treatment of asthma in the 12 months preceding randomization • Patient has a respiratory infection or other viral/bacterial illness, or is recovering from such an illness at the time of Visit 2 that, in the investigator's opinion, will interfere with the patient's lung function • Patient must not meet unstable asthma severity criteria as listed in the protocol • Peak expiratory flow must not be below 50% o predicted normal

	• Pregnancy, breast-feeding or planned pregnancy during the study
Interventions	MD-ICS: BUD 320 µg bid LD-ICS/LABA: BUD/FM 160/4.5 µg bid MD-ICS/LABA: BUD/FM 320/9 µg bid
Outcomes	Severe exacerbations Dropouts due to adverse event
Notes	NCT00651768

Sher 2017

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Teva Branded Pharmaceutical **COUNTRY**: Canada, Czechia, Hungary, Poland, Russian Federation, South Africa, Thailand, Ukraine, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 583 **Mean age:** 44.8 (Ages Eligible for Study: 12 Years and older) **Male %:** 40 **White %:** 80 **Current smoker excluded/maximum PYs allowed for ex-smokers: Y/10** **Baseline FEV1 (L) pre-bronchodilator:** 2.2 **Baseline FEV1 % predicted**: 65 **Hx of asthma exacerbation**: Required **Inclusion Criteria**: 1. Best pre-bronchodilator forced expiratory volume in 1 second (FEV1) of 40 to 85% of their predicted normal value. 2. Current Asthma Therapy: Patients must have a short-acting β2-agonist (for rescue use) for a minimum of 8 weeks before the Screening Visit (SV) and a qualifying dose of an inhaled corticosteroid (ICS). The ICS may be either as ICS monotherapy or as an ICS/long-acting beta agonist (LABA) combination. The ICS component of the patient's asthma therapy should be stable for a minimum of 1 month before providing consent. 3. Reversibility of Disease: Patients must have at least 15% reversibility (all patients) and at least a 200 mL increase from baseline FEV1 (patients age 18 and older) within 30 minutes after 2 to 4 inhalations of albuterol/salbutamol at the SV. Note: Patients who do not qualify for the study due to failure to meet reversibility will be permitted to perform a retest once within 7 days. 4. Patients must provide written informed consent/assent.. For minor patients (ages 12 to 17 years, or as applicable per local regulations), the written ICF must be signed and dated by the parent/legal guardian and the written assent form must be signed and dated by the patient (if applicable). Note: Age requirements are as specified by local regulations. 5. Outpatient >= 12 years of age on the date of consent/assent. In countries where the local regulations permit enrollment of adult patients only, patients must be 18 years of age and older. 6. Asthma diagnosis: The patient has a diagnosis of asthma as defined by the National Institute of Health (NIH). The asthma diagnosis has been present for a minimum of 3 months and has been stable (defined as no exacerbations and no changes in asthma medication) for at least 30 days. 7. The patient is able to perform acceptable and repeatable spirometry. 8. The patient is able to perform peak expiratory flow (PEF) with a handheld peak flow meter. 9. The patient is able to use a metered dose inhaler (MDI) device without a spacer device and a multidose dry powder inhaler (MDPI) device. 10. The patient is able to withhold (as judged by the investigator) his or her regimen of ICS or study drug, and rescue medication for at least 6 hours before the screening visit (SV) and before all treatment visits. 11. The patient/parent/legal guardian/caregiver is capable of understanding the requirements, risks, and benefits of study participation, and, as judged by the investigator, capable of giving informed consent/assent and being compliant with all study requirements. 12. SABAs: All patients must be able to replace their current SABA with albuterol/salbutamol HFA MDI inhalation aerosol for the duration of the study. 13. Female patients may not be pregnant, breastfeeding, or attempting to become pregnant.other criteria may apply, please contact the investigator for more information **Exclusion Criteria**: 1. A history of a life-threatening asthma exacerbation (an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest, or hypoxic seizures). 2. The patient is pregnant or lactating, or plans to become pregnant during the study period or for 30 days after the study. 3. The patient has participated as a randomized patient in any investigational drug study within 30 days of the SV. 4. The patient has previously participated as a randomized patient in a study of Fp MDPI or FS MDPI. 5. The patient has a known hypersensitivity to any corticosteroid, salmeterol, or any of the excipients in the study drug or rescue medication formulation (ie, lactose).

	6. The patient has been treated with any known strong cytochrome P450 (CYP) 3A4 inhibitors (eg, azole antifungals, ritonavir, or clarithromycin) within 30 days before the SV. 7. The patient has been treated with any of the prohibited medications during the prescribed (per protocol) washout periods before the SV. 8. The patient currently smokes or has a smoking history of 10 pack years or more (a pack year is defined as smoking 1 pack of cigarettes/day for 1 year). The patient must not have used tobacco products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco). 9. The patient has a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that has not resolved at least 2 weeks before the SV. 10. The patient has a history of alcohol or drug abuse within 2 years preceding the SV. 11. The patient has had an asthma exacerbation requiring systemic corticosteroids within 30 days before the SV, or has had any hospitalization for asthma within 2 months before the SV. 12. Initiation or dose escalation of immunotherapy (administered by any route) is planned during the study period. However, patients on stable immunotherapy may be considered for inclusion. 13. The patient has used immunosuppressive medications within 4 weeks before the SV. 14. The patient is unable to tolerate or unwilling to comply with the appropriate washout periods and withholding of all applicable medications. 15. The patient has untreated oral candidiasis at the SV. Patients with clinical visual evidence of oral candidiasis who agree to receive treatment and comply with appropriate medical monitoring may enter the study. 16. The patient has a history of a positive test for human immunodeficiency virus (HIV), active hepatitis B virus, or hepatitis C infection. 17. The patient is either an employee or an immediate relative of an employee of the clinical investigational center. 18. A member of the patient's household is participating in the study at the same time. However, after the enrolled patient completes or discontinues participation in the study, another patient from the same household may be screened. 19. The patient has a disease/condition that in the medical judgment of the investigator would put the safety of the patient at risk through participation or that could affect the efficacy or safety analysis if the disease/condition worsened during the study.other criteria may apply, please contact the investigator for more information
Interventions	MD-ICS: FP 200 µg bid LD-ICS/LABA: FP/SAL 100/12.5 µg bid MD-ICS/LABA: FP/SAL 200/12.5 µg bid
Outcomes	All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event CFB in AQLQ at 3 months
Notes	NCT02141854

Spector 2012

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 301 **Mean age:** 39.2 (Ages Eligible for Study: 12 Years and older) **Male %:** 35 **White %:** 0 **Current smoker excluded/maximum PYs allowed for ex-smokers:** N/Not reported **Baseline FEV1 (L) pre-bronchodilator:** 2.0 **Baseline FEV1 % predicted**: 69 **Hx of asthma exacerbation**: Not required **Inclusion Criteria**: • African American (self-reported) • Documented clinical diagnosis of asthma as defined by the American Thoracic Society (ATS) for at least 6 months prior to Visit 2 and be in stable condition. • FEV1, measured ≥6 hours after the last dose of short-acting β2-agonist and at least 48 hours after LABA, of 45%-85%, inclusive, of predicted normal. **Exclusion Criteria**: • Has been hospitalized at least once for an asthma related condition during the 6 months prior to Visit 2, or has required emergency treatment due to an asthma related condition more than once in the 3 months prior to Visit 2. • Has required treatment with systemic corticosteroids (eg, oral, parenteral, ocular, or rectal) for any reason within the 30 days prior to Visit 2.

	• Has a respiratory infection or other viral/bacterial illness, or is recovering from such an illness at the time of Visit 3 that, in the Investigator's opinion, will interfere with the subject's lung function and/or ability to perform spirometry
Interventions	MD-ICS: BUD 360 µg bid MD-ICS/LABA: BUD/FM 320/9 µg bid
Outcomes	Moderate to severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event CFB in AQLQ at 3 months
Notes	NCT00702325

Stempel 2016

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 26 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Croatia, Czechia, Denmark, Germany, Hungary, Indonesia, Italy, Korea, Republic of, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Taiwan, Ukraine, United Kingdom, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 3128 **Mean age:** 43.4 (Ages Eligible for Study: 12 Years and older) **Male %:** 34 **White %:** 75 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** Not reported **Baseline FEV1 % predicted**: Not reported **Hx of asthma exacerbation**: Required **Inclusion Criteria:** • Provided consent to participate in the study • Male or female, 12 years of age and older • Clinical diagnosis of asthma for at least 1 year prior to the randomization • Clinic PEF of greater than or equal to 50% of predicted normal value • Subject must be appropriately using one of the treatments for asthma listed in the protocol • Subject must be able to complete the asthma control questionnaire, daily questions about asthma, and use a DISKUS inhaler • Subject must have history of at least 1 asthma exacerbation including one of the following in the year prior to randomization: • requiring treatment with systemic corticosteroids • an asthma-related hospitalization **Exclusion Criteria**: • History of life threatening asthma defined for this protocol as asthma episode that required intubation and/or was associated with hypercapnea requiring non-invasive ventilatory support • Concurrent respiratory disease other than asthma • Current evidence of, or ever been told by a physician that they have chronic bronchitis, emphysema, or chronic obstructive pulmonary disease. • Exercise induced asthma (as the only asthma-related diagnosis) not requiring daily asthma control medicine • Presence of a bacterial or viral respiratory infection that is not resolved at randomization • An asthma exacerbation requiring systemic corticosteriods within 4 weeks of randomization or more than 4 separate exacerbations in the 12 months preceding randomization • More than 2 hospitalizations for treatment of asthma in the 12 months preceding randomization • Subject must not meet unstable asthma severity criteria as listed in the protocol • Potent cytochrome P450 3A4 (CYP3A4) inhibitors within the last 4 weeks (e.g., ritonavir, ketoconazole, itraconzole) • Pregnancy, breast-feeding or planned pregnancy during the study • A Child in Care (CiC) is a child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation.
Interventions	MD-ICS: FP 250 µg bid HD-ICS: FP 500 µg bid MD-ICS/LABA: FP/SAL 250/50 µg bid HD-ICS/LABA: FP/SAL 500/50 µg bid
Outcomes	

	Severe exacerbations All cause serious adverse events Asthma-related serious adverse events
Notes	NCT01475721 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=115359

Stirbulov 2012

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Ache Laboratorios Farmaceuticos **COUNTRY**: Brazil
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 175 **Mean age:** Not reported (Ages Eligible for Study: 18 to 77 Years old) **Male %:** Not reported **White %:** Not reported **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/20 **Baseline FEV1 (L) pre-bronchodilator:** 2.3 **Baseline FEV1 % predicted**: 76 **Hx of asthma exacerbation**: Not required **Inclusion Criteria**: • Diagnosis of uncontrolled asthma • Age ranged from 18 to 77 years • Nonsmokers **Exclusion Criteria**: • Use of oral corticosteroids, anti-leukotrienes, immunoglobulins, beta blockers, digitalis, amiodarone, antifungals, antidepressants, monoamine oxidase inhibitors and tricyclics during the standardization • Atrial fibrillation, Flutter, severe and complex tachyarrhythmias atrioventricular block 1,2 and 3 • Diabetes mellitus • Pregnancy • Neuropsychiatric diseases • Pulmonary malformations, tuberculosis, Cystic fibrosis • Immunosuppressive treatment • Hospitalization for asthma or respiratory infection in last 30 days • Severe systemic disease
Interventions	MD-ICS: BUD 400 µg bid MD-ICS/LABA: BUD/FM 400/12 µg bid
Outcomes	Dropouts due to adverse event
Notes	NCT01676987

van Zyl-Smit 2020

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 26-52 weeks **SPONSORSHIP SOURCE**: Novartis **COUNTRY**: Bulgaria, China, Croatia, Czechia, Egypt, Estonia, Germany, Guatemala, Hungary, India, Ireland, Japan, Korea, Republic of, Latvia, Lithuania, Mexico, Poland, Romania, Russian Federation, Serbia, Slovakia, South Africa, United Kingdom, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 2216 **Mean age:** 47.9 (Ages Eligible for Study: 12 to 75 Years old) **Male %:** 41 **White %:** 70 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.1 **Baseline FEV1 % predicted**: 67 **Hx of asthma exacerbation**: Not rquired

	Inclusion Criteria: • Participants with a diagnosis of asthma, for a period of at least 1 year prior to Visit 1 (Screening) • Participants who have used medium or high dose inhaled corticosteroids (ICS) or low dose of long acting beta-2 agonist (LABA)/ICS combinations for asthma for at least 3 months and at stable doses for at least 1 month prior to Visit 1 • Participants must have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (prior to double-blind treatment) and qualify for treatment with medium or high dose LABA/ICS • Pre-bronchodilator ≥ 50% Forced expiratory volume in 1 second (FEV1) of < 85 % of the predicted normal value for the participants after withholding bronchodilators at both Visit 101 and 102, according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria. • Withholding period of bronchodilators prior to spirometry: short acting beta-2 agonist (SABA) for ≥ 6 hours and FDC or free combinations of ICS/LABA for ≥ 48 hours, short acting anticholinergics (SAMA) for ≥ 8 hours, xanthines >:07 days • A one-time repeat/re-testing of percent predicted FEV1 (prebronchodilator FEV1) is allowed at Visit 101 and at Visit 102. Spacer devices are permitted for reversibility testing only. -Participants who demonstrate an increase in FEV1 of 12% and 200 mL within 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101 All participants must perform a reversibility test at Visit 101 If reversibility is not demonstrated at Visit 101: • Reversibility should be repeated once- • Participants may be permitted to enter the study with historical evidence of reversibility that was performed according to ATS/ERS guidelines within 2 years prior to Visit 1 • Alternatively, participants may be permitted to enter the study with a historical positive bronchoprovocation test that was performed within 2 years prior to Visit 1. **Exclusion Criteria:** • Participants who have smoked or inhaled tobacco products within the 6 month period prior to Visit 1, or who have a smoking history of greater than 10 pack years. This includes use of nicotine inhalers such as e-cigarettes at the time of Visit 1 • Participants who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1 (Screening) • Participants who have ever required intubation for a severe asthma attack/exacerbation. • Participants who have a clinical condition which is likely to be worsened by ICS administration (e.g. glaucoma, cataract and fragility fractures) who are according to investigator's medical judgment at risk participating in the study). • Participants who have had a respiratory tract infection or asthma worsening as determined by the investigator within 4 weeks prior to Visit 1 (Screening) or between Visit 1 and Visit 102. Participants may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening. • Participants with a history of chronic lung diseases other than asthma, including (but not limited to) Chronic Obstructive Pulmonary Disease (COPD), sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis. • Participants with severe narcolepsy and/or insomnia. • Participants who have a clinically significant electrocardiogram (ECG) abnormality at Visit 101 (Start of Run- In epoch) and at any time between Visit 101 and Visit 102 (including unscheduled ECG). ECG evidence of myocardial infarction at Visit 101 (via central reader) should be clinically assessed by the investigator with supportivedocumentation • Participants with a history of hypersensitivity to lactose, any of the study drugs or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof • Participants who have not achieved an acceptable spirometry results at Visit 101 in accordance with ATS/ERS criteria for acceptability and repeatability (rescreening allowed only once).
Interventions	MD-ICS: MF 400 µg qd HD-ICS: MF 400 µg bid MD-ICS/LABA: MF/IND 160/150 µg qd HD-ICS/LABA: MF/IND 320/150 µg qd, FP/SAL 500/50 µg bid
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months ACQ responder at 12 months CFB in ACQ at 3 months CFB in ACQ at 6 months CFB in ACQ at 12 months CFB ixn AQLQ at 6 months (MD-ICS/LABA and HD-ICS/LABA only)
Notes	NCT02554786

Weinstein 2010

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Merck Sharp & Dohme **COUNTRY:** North America, Latin America, Russia, Ukraine, and Europe
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 728 **Mean age:** 48.0 (Ages Eligible for Study: 12 Years and older) **Male %:** 44 **White %:** 90 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.0 **Baseline FEV1 % predicted**: 67 **Hx of asthma exacerbation**: not required **Inclusion Criteria**: • A subject must be at least 12 years of age, of either sex, and of any race, with a diagnosis of asthma of at least 12 months duration that is consistent with the following definition:The diagnosis of asthma is based upon clinical history and examination, pulmonary function parameters, and response to beta2-agonists, according to international guidelines. • A subject must have been using a high dose of inhaled glucocorticosteroid (ICS) either alone or in combination with a long-acting beta2 agonist (LABA) for at least 12 weeks prior to Screening, with no use of oral glucocorticosteroids within 30 days prior to Screening. A subject must have been on a stable asthma regimen (daily dose unchanged) for at least 2 weeks prior to Screening. High daily doses of ICS are defined as follows:>1000 mcg beclomethasone chlorofluorocarbon (CFC)>500 mcg beclomethasone hydrofluoroalkane (HFA)>1000 mcg budesonide dry powder inhaler (DPI)>2000 mcg flunisolide>500 mcg fluticasone>400 mcg MF>2000 mcg triamcinolone acetonide>320 mcg ciclesonide Note: Dose delivery by method or modality other than those noted above must be equivalent. • A subject must have experienced at least one severe exacerbation requiring a course of oral glucocorticosteroid 2 to 12 months prior to Screening. • If, based upon the medical judgment of the investigator, there is no inherent harm in changing the subject's current asthma therapy, then the subject (and parent/guardian, if applicable) must be willing to discontinue his/her prescribed ICS or ICS/LABA prior to initiating MF MDI run-in medication. • To document the diagnosis of asthma and assure the subject's responsiveness to bronchodilators before randomization, one of the following methods can be used at the Screening Visit, Day-14, or thereafter, but prior to the Baseline Visit:The subject must demonstrate an increase in absolute FEV1 of at least 12% and at least 200 mL within approximately 15 to 20 minutes after administration of four inhalations of albuterol/salbutamol (total dose of 360 to 400 mcg).The subject must demonstrate a peak expiratory flow (PEF) variability of more than 20% expressed as a percent of the best and lowest morning pre-bronchodilator PEF over at least 1 week.The subject must demonstrate a diurnal variation in PEF of more than 20% based on the difference between the prebronchodilator (before taking albuterol/salbutamol) morning value and the postbronchodilator value (after taking albuterol/salbutamol) from the evening before, expressed as a percentage of the mean daily PEF value. Note: If a subject is to qualify using diurnal variation, the subject should be instructed to perform his/her PEF evaluation after using his/her bronchodilator in the evening. • At the Screening Visit, the subject's FEV1 must be >:50% predicted when all restricted medications have been withheld for the appropriate intervals. • At the Baseline Visit, the subject's FEV1 must be >:50% and <:85% predicted when all restricted medications have been withheld for the appropriate intervals. • The subject (and parent/guardian for a subject under the age of legal consent) must be willing to give written informed consent and be able to adhere to dose and visit schedules. • A female subject of childbearing potential must be using a medically acceptable, adequate form of birth control. This includes:hormonal contraceptive as prescribed by a physician (oral combined, hormonal vaginal ring, hormonal implant or depot-injectable);medically prescribed intra-uterine device (IUD);medically prescribed topically-applied transdermal contraceptive patch;condom in combination with a spermicide (double-barrier method);monogamous relationship with a male partner who has had a vasectomy. The subject must have started this birth control method at least 3 months prior to Screening (with the exception of condom in combination with spermicide), and must agree to continue its use for the duration of the study. A female subject of childbearing potential who is not currently sexually active must agree and consent to using a medically acceptable method should she become sexually active during the course of this study. Women who have been surgically sterilized or are at least 1 year postmenopausal are not considered to be of childbearing potential. A female subject of childbearing potential must have a negative serum pregnancy test at Screening in order to be considered eligible for the open-label MF MDI Run-in Period. **Exclusion Criteria**: • A subject who demonstrates a change (increase or decrease) in absolute FEV1 of >20% at any time from the Screening Visit up to and including the Baseline Visit. Pulmonary function tests (PFTs) will be performed in the morning. • A subject who requires the use of >8 inhalations per day of short-acting beta agonists (SABA) MDI or >:2 nebulized treatments per day of 2.5 mg SABA, on any 2 consecutive days from the Screening Visit up to and including the Baseline Visit. • A subject who experiences a decrease in AM or PM peak expiratory flow (PEF) below the Run-in Period stability limit on any 2 consecutive days prior to randomization.

	• A subject who experiences a clinical asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with additional, excluded asthma medication [including oral or other systemic corticosteroids, but allowing SABAs]), at any time from the Screening Visit up to and including the Baseline Visit. • A subject who has been treated in the emergency room (for a severe asthma exacerbation), or admitted to the hospital for management of airway obstruction, within the last 3 months. • A subject who has ever required ventilator support for respiratory failure secondary to asthma. • A subject who has experienced an upper or lower respiratory tract infection (viral or bacterial) within the previous 2 weeks prior to Screening and Baseline Visits. Visits can be rescheduled 2 weeks after complete resolution of the event to re-assess eligibility. • A subject who is a smoker or ex-smoker and has smoked within the previous year or has had a cumulative smoking history >10 pack-years. • A subject with a clinically significant abnormal vital sign. • A subject with evidence (upon visual inspection, laboratory culture is not required) of clinically significant oropharyngeal candidiasis at Baseline (Visit 3) with or without treatment. If there is evidence of oropharyngeal candidiasis at Screening or Pre-Baseline Visit, the subject may be treated as appropriate and the Baseline Visit can be scheduled upon resolution. If there is evidence of oropharyngeal candidiasis at the Baseline Visit, the subject may be treated as appropriate and the visit can be rescheduled upon resolution. • A subject with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular, or other significant medical illness or disorder which, in the judgment of the investigator, could interfere with the study, or require treatment that might interfere with the study. Specific examples include (but are not limited to) insulin-dependent diabetes, hypertension being treated with beta blockers, active hepatitis, coronary artery disease, arrhythmia, stroke, severe rheumatoid arthritis, chronic open-angle glaucoma or posterior subcapsular cataracts, acquired immune deficiency syndrome (AIDS), or conditions that may interfere with respiratory function such as clinically diagnosed chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis, etc. Other conditions that are well-controlled and stable (eg, hypertension not requiring beta blockers) will not prohibit participation if deemed appropriate per the investigator's judgment. • A subject who is known to be allergic to or intolerant of ICS, beta2 agonists, or any of the excipients present in the medications used in this study. • A female subject who is breast-feeding, pregnant, or intends to become pregnant while participating in this study. • A subject who is a known illicit drug user. • A subject who is known to be human immunodeficiency virus (HIV) positive (HIV testing will not be conducted in this study). • A subject who is unable to correctly use an oral MDI inhaler. • A subject who has been taking any of the restricted medications prior to Screening without meeting the required washout timeframes. • A subject who cannot adhere to the permitted concomitant medications and prohibited medications. • A subject participating in this study may not participate in this same study at another investigational site. In addition, a subject cannot participate in a different investigational study at any site, during the same timeframe of this study. • A subject must not be randomized into this study more than once. • No person directly associated with the administration of the study may participate as a study subject. No family member of the investigational study staff may participate in this study. • A subject who previously participated in a trial with MF/F. • Subjects with a history of significant QTC prolongation (ie, QTc>500 msec) are excluded from participation in the study.
Interventions	HD-ICS: MF 400 µg bid MD-ICS/LABA: MF/FM 200/10 µg bid HD-ICS/LABA: MF/FM 400/10 µg bid
Outcomes	All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event CFB in ACQ at 3 months CFB in AQLQ at 3 months
Notes	NCT00381485

Woodcock 2013

Study characteristics	
Methods	**DESIGN**: Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY:** Argentina, Chile, Korea, Republic of, Netherlands, Philippines, United States.
Participants	**BASELINE CHARACTERISTICS:**

	No. of participants included in this review: 806 **Mean age**: 42.9 (Ages Eligible for Study: 12 Years and older) **Male %**: 39 **White %**: 59 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator**: 2.0 **Baseline FEV1 % predicted**: 68.4 **Hx of asthma exacerbation**: Not required **Inclusion Criteria:** • Clinical diagnosis of asthma • Reversibility of at least 12% and at least 200mLs within 10-40 minutes following 2-4 inhalations of albuterol • FEV1 of 40-85% predicted normal • Currently using inhaled corticosteroid therapy **Exclusion Criteria**: • History of life-threatening asthma within previous 5 years (requiring intubation and/or was associated with hypercapnoea, respiratory arrest or hypoxic seizures) • Respiratory infection or oral candidiasis • Asthma exacerbation requiring oral corticosteroids or that resulted in overnight hospitalisation requiring additional asthma treatment • Uncontrolled disease or clinical abnormality • Allergies • Taking another investigational medication or prohibited medication • Night shift workers • Current smokers or subjects with smoking history of at least 10 pack years
Interventions	MD-ICS/LABA: FP/SAL 250/50 µg bid, FF/VI 100/25 µg qd
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event AQLQ responder at 6 months CFB in AQLQ at 6 months
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. NCT01147848 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=113091

Woodcock 2014

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Chile, France, Mexico, Russian Federation, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 238 **Mean age:** 45.9 (Ages Eligible for Study: 12 Years and older) **Male %:** 33 **White %:** 85 **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.1 **Baseline FEV1 % predicted**: 68 **Hx of asthma exacerbation**: Not required **Inclusion Criteria**: • Signed informed consent • Outpatient at least 12 years of age with diagnosis of asthma at least 12 weeks prior to first visit • Both genders; females of child bearing potential must be willing to use appropriate contraception • Pre-bronchodilator FEV1 of 40-90% predicted • Reversibility FEV1 of at least 12% and 200mLs

	• Current asthma therapy that includes inhaled corticosteroid for at least 4 weeks prior to first visit **Exclusion Criteria**: • History of life threatening asthma • Respiratory infection or candidiasis • Asthma exacerbation requiring OCS within last 4 weeks or overnight hospital stay within the last 3 months • Concurrent respiratory disease or other disease that would confound study participation of affect subject safety • Allergies to study drugs, study drug excipients, medications related to study drugs • Taking another investigational medication or medication prohibited for use during the study • Previous treatment with FF or FF/VI in a phase II or III study • Night shift workers • Children in care
Interventions	MD-ICS: FF 100 µg qd HD-ICS: FF 200 µg qd
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Dropouts due to adverse event
Notes	NCT01431950 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=114496

Zangrilli 2011

Study characteristics	
Methods	**DESIGN:** Randomized controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: Puerto Rico, United States
Participants	**BASELINE CHARACTERISTICS:** **No. of participants included in this review:** 250 **Mean age:** 38.4 (Ages Eligible for Study: 12 Years and older) **Male %:** 34 **White %:** Not reported **Current smoker excluded/maximum PYs allowed for ex-smokers:** Y/10 **Baseline FEV1 (L) pre-bronchodilator:** 2.2 **Baseline FEV1 % predicted**: 72 **Hx of asthma exacerbation**: Not required **Inclusion Criteria**: • Male or Female, Hispanic (self-reported), > 12 years of age • Moderate to severe asthma requiring treatment with an inhaled corticosteroid • Diagnosis of asthma for at least 6 months **Exclusion Criteria**: • Subjects requiring treatment with systemic corticosteroids (e.g., oral, parenteral, ocular) • Any significant disease or disorder that may jeopardize a subject's safety
Interventions	MD-ICS: BUD 320 µg bid MD-ICS/LABA: BUD/FM 320/9 µg bid
Outcomes	Moderate to severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	NCT00419757

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Amar 2016	Not interevention of interest. Low-dose ICS.
Antilla 2014	Not population of interest. Controlled asthma in 60-70% of the included.
Barnes 2013	Not design of interest. Participants were stable at the study entry
Bateman 2011	No breakdown on ICS dosing

Study	Reason for exclusion
Berger 2010	Not population of interest
Bernstein 2018	Not population of interest. Participants had to be symptom free
Bodzenta-Lukaszyk 2011	Not design of interest. No breakdown on ICS doses
Bodzenta-Lukaszyk 2013	Not study design of interest. Fixed-dose vs. free combination of FP/FM
Boyd 1995	Salmeterol xinafoate 100 micrograms twice daily is not approved or available for clinical use.
Busse 2013	Not population of interest. Asthma symptoms were not required.
Busse 2018	Not design of interest. No breakdown on ICS doses
Corradi 2016	Not design of interest.
Devillier 2018	Not design of interest. No breakdown on ICS doses
Hamelmann 2017	Not design of interest. Low-dose ICS included.
Hoshino 2016	Not pre-registered
Kerwin 2009	Not population of interest. Participants were asymptomatic at study entry
Kerwin 2017	Wrong comparator. Low-dose ICS
Koenig 2008	Not design of interest. No breakdown on ICS doses
Kornmann 2020	Not population of interest. Low-dose ICS included
Lenney 2013	Not population of interest. Low-dose ICS
Lötvall 2014	Not study design of interest. No breakdown on ICS doses
Maspero 2010	Not study design of interest. Patients were stratified (Figure 1) according to their previous ICS doses
Murphy 2012	Not population/study design of interest. Severe asthma with or without fixed airflow obstruction
Murphy 2015x	Not population of interest. Stable asthma
Nathan 2012	Not population of interest. Low-dose ICS
NCT00529529	Not population of interest.
NCT01001364	Formulation is not available or approved for clinical use
NCT01202084	Not population of interest. Controlled asthma
NCT01609478	Not study design of interest. Low-dose ICS
NCT01720069	Not population of interest. Steroid dependent asthma.
NCT01845025	Not study design of interest.
NCT02094937	Not population of interest. Well controlled asthma
NCT04677959	Not study design of interest.
Ohta 2015	Not study design of interest. 54 to 61% of participants also received LABA
Paggiaro 2016a	Not population of interest
Peters 2010	Crossover design. Not population of interest (LD-ICS combinations)
Renzi 2010	Not population of interest. Low dose ICS included
Tashkin 2016	Not study design of interest. Severe asthma with or without fixed airflow obstruction
Wechsler 2016	Not population of interest. Low dose ICS in 87% of the participants
Wechsler 2019	Crossover design
Weinstein 2019	Not population of interest. Participants were clinically stable at study entry
Woodcock 2017	Not study design of interest. No breakdown on ICS dosing

Characteristics of ongoing studies [ordered by study ID]

NCT03248128

Study name	GSK107116
Methods	Randomized, Parallel Assignment, Double-blind
Participants	Aged 5 to 17 Years Old (Inclusive) Currently Uncontrolled on Inhaled Corticosteroids
Interventions	FDC of FF/VI inhalation powder compared to FF inhalation powder
Outcomes	Lung function, ACQ, adverse events,
Starting date	August 14, 2017
Contact information	GlaxoSmithKline
Notes	

NCT03387241

Study name	FLT13-CN-301
Methods	Double Blind, Double Dummy, Randomised, Multicentre, Two Arm Parallel Group Study
Participants	Aged ≥12 Years With Moderate to Severe Persistent, Reversible Asthma
Interventions	FLUTIFORM® pMDI (2 Puffs Bid) vs Seretide® pMDI (2 Puffs Bid)
Outcomes	Lung function, ACQ, symptom scores
Starting date	January 2, 2018
Contact information	Ling Li 8610 65636891 ling.li@mundipharma.com.cn
Notes	

NCT04191434

Study name	EMS0219 - FLAMBOYANT125/12
Methods	Multicenter, Randomized, Double-blind, Double-dummy, National, Phase III Clinical Trial
Participants	Adults With Moderate Asthma
Interventions	Flamboyant 125/12 capsule vs. Budesonid/formoterol 200/6 capsule
Outcomes	Lung function and adverse events
Starting date	December 9, 2019
Contact information	Alexandra Dumont Alves, MD+551938879851 pesquisa.clinica@ncfarma.com.br
Notes	

NCT04191447

Study name	EMS0319 - FLAMBOYANT200/12
Methods	Multicenter, Randomized, Double-blind, Double-dummy, National, Phase III Clinical Trial
Participants	Adults With Severe Asthma
Interventions	Flamboyant 200/12 vs. Budesonide / Formoterol 400/12
Outcomes	Lung function and adverse events
Starting date	December 9, 2019
Contact information	Alexandra Dumont Alves, MD +551938879851 pesquisa.clinica@ncfarma.com.br
Notes	

NCT05202262 (VATHOS)

Study name	VATHOS
Methods	Randomized, Double-Blind, Parallel Group, Multicenter 24 Week Study
Participants	Adult and Adolescent Participants With Inadequately Controlled Asthma
Interventions	Budesonide and Formoterol Fumarate Metered Dose Inhaler
Outcomes	
Starting date	January 21, 2022
Contact information	AstraZeneca Clinical Study Information Center1-877-240-9479 information.center@astrazeneca.com
Notes	NCT05202262

Risk of bias

Risk of bias for analysis 1.1 Severe exacerbations

Study	Bias									
	Randomisation process		Deviations from intended interventions		Missing outcome data		Measurement of the outcome		Selection of the reported results	
	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement	Authors' judgement	Support for judgemer
Subgroup 1.1.1 HD-ICS vs MD-ICS										
Mansfield 2017	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Stempel 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Woodcock 2014	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
van Zyl-Smit 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Subgroup 1.1.2 MD-ICS/LAMA vs MD-ICS										
Kerwin 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Subgroup 1.1.3 MD-ICS/LABA vs MD-ICS										
Bateman 2014	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Bleecker 2014	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Brown 2012	Low risk of bias	No significant	Low risk of bias	No significant	High risk of bias	High dropout	Low risk of bias	No significant	Low risk of bias	No significant

		issues		issues		rates in both groups (~40%)		issues		issues
Katial 2011	Low risk of bias	No significant issues	Low risk of bias	No significant issues	High risk of bias	High dropout rates in both groups (23-26 %)	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Kerwin 2011	Low risk of bias	No significant issues	Low risk of bias	No significant issues	High risk of bias	High dropout rates in both groups (25-26%)	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Mansfield 2017	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Nathan 2010	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Peters 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Stempel 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
van Zyl-Smit 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Subgroup 1.1.4 HD-ICS/LABA vs MD-ICS										
Mansfield 2017	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Stempel 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
van Zyl-Smit 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Subgroup 1.1.5 MD-ICS/LABA vs HD-ICS										
Mansfield 2017	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Peters 2008	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Stempel 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
van Zyl-Smit 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Subgroup 1.1.6 HD-ICS/LABA vs HD-ICS										
Lin 2015	Low risk of bias	No significant issues	Low risk of bias	No significant issues	High risk of bias	Dropout rates were high and uneven between the groups (23% vs 12%)	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Mansfield 2017	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
O'Byrne 2014	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Peters 2008	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Stempel 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
van Zyl-Smit 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Subgroup 1.1.7 MD-ICS/LABA vs LD-ICS/LABA										

CHIESI 2009	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Subgroup 1.1.8 HD-ICS/LABA vs MD-ICS/LABA										
Lee 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Mansfield 2017	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Peters 2008	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Stempel 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
van Zyl-Smit 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Subgroup 1.1.9 ICS-LAMA vs ICS										
Kerwin 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Subgroup 1.1.10 ICS-LABA vs ICS										
Bateman 2014	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Katial 2011	Low risk of bias	No significant issues	Low risk of bias	No significant issues	High risk of bias	High dropout rates in both groups (23-26 %)	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Kerwin 2011	Low risk of bias	No significant issues	Low risk of bias	No significant issues	High risk of bias	High dropout rates in both groups (25-26%)	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Lin 2015	Low risk of bias	No significant issues	Low risk of bias	No significant issues	High risk of bias	Dropout rates were high and uneven between the groups (23% vs 12%)	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Mansfield 2017	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Nathan 2010	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
O'Byrne 2014	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Peters 2008	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Peters 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Stempel 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
van Zyl-Smit 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues

Risk of bias for analysis 2.1 HD-ICS vs MD-ICS

Study	Bias									
	Randomisation process		Deviations from intended interventions		Missing outcome data		Measurement of the outcome		Selection of the reported results	
	Authors' judgement	Support for	Authors' judgement	Support for	Authors' judgement	Support for	Authors' judgement	Support for	Authors' judgement	Support for

		judgement		judgement		judgement		judgement		judgemer
						Subgroup 2.1.1 High Risk				
Subgroup 2.1.2 Low Risk										
Mansfield 2017	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Stempel 2016	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
Woodcock 2014	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues
van Zyl-Smit 2020	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues	Low risk of bias	No significant issues

Appendices

Appendix 1. Database search strategy

Airway Register Search

#	1	MESH DESCRIPTOR Asthma EXPLODE ALL AND INSEGMENT
#	2	asthma*:ti,ab AND INSEGMENT
#	3	#1 OR #2
#	4	MESH DESCRIPTOR Formoterol Fumarate AND INSEGMENT
#	5	MESH DESCRIPTOR Salmeterol Xinafoate AND INSEGMENT
#	6	formoterol:ti,ab AND INSEGMENT
#	7	salmeterol:ti,ab AND INSEGMENT
#	8	indacaterol:ti,ab AND INSEGMENT
#	9	vilanterol:ti,ab AND INSEGMENT
#	10	#4 OR #5 OR #6 OR #7 OR #8 OR #9
#	11	MESH DESCRIPTOR Tiotropium Bromide AND INSEGMENT
#	12	MESH DESCRIPTOR Glycopyrrolate AND INSEGMENT
#	13	tiotropium:ti,ab AND INSEGMENT
#	14	glycopyrronium:ti,ab AND INSEGMENT
#	15	umeclidinium:ti,ab AND INSEGMENT
#	16	aclidinium:ti,ab AND INSEGMENT
#	17	#11 OR #12 OR #13 OR #14 OR #15 OR #16
#	18	MESH DESCRIPTOR Budesonide AND INSEGMENT
#	19	MESH DESCRIPTOR Fluticasone AND INSEGMENT
#	20	MESH DESCRIPTOR Mometasone Furoate AND INSEGMENT
#	21	MESH DESCRIPTOR Beclomethasone AND INSEGMENT
#	22	budesonide:ti,ab AND INSEGMENT
#	23	fluticasone:ti,ab AND INSEGMENT
#	24	mometasone:ti,ab AND INSEGMENT
#	25	beclomethasone:ti,ab AND INSEGMENT
#	26	ciclesonide:ti,ab AND INSEGMENT
#	27	(inhal* NEAR3 (steroid* or corticosteroid* or glucocorticoid*)):ti,ab AND INSEGMENT
#	28	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#	29	MESH DESCRIPTOR Budesonide, Formoterol Fumarate Drug Combination AND INSEGMENT
#	30	MESH DESCRIPTOR Mometasone Furoate, Formoterol Fumarate Drug Combination AND INSEGMENT
#	31	MESH DESCRIPTOR Fluticasone-Salmeterol Drug Combination AND INSEGMENT
#	32	#29 OR #30 OR #31
#	33	(#10 or #28) or #32
#	34	#17 AND #28
#	35	#33 OR #34
#	36	#3 AND #35
#	37	(2008 or 2009 or 2010 or 2011 or 2012 or 2013 or 2014 or 2015 or 2016 or 2017 or 2018 or 2019 or 2020):yr AND INSEGMENT
#	38	#36 AND #37
#	39	INREGISTER
#	40	#38 AND #39

CENTRAL

#	1	MESH DESCRIPTOR Asthma EXPLODE ALL AND CENTRAL:TARGET
#	2	asthma*:ti,ab AND CENTRAL:TARGET
#	3	#1 OR #2 AND CENTRAL:TARGET

#	4	MESH DESCRIPTOR Formoterol Fumarate AND CENTRAL:TARGET
#	5	MESH DESCRIPTOR Salmeterol Xinafoate AND CENTRAL:TARGET
#	6	formoterol:ti,ab AND CENTRAL:TARGET
#	7	salmeterol:ti,ab AND CENTRAL:TARGET
#	8	indacaterol:ti,ab AND CENTRAL:TARGET
#	9	vilanterol:ti,ab AND CENTRAL:TARGET
#	10	#4 OR #5 OR #6 OR #7 OR #8 OR #9 AND CENTRAL:TARGET
#	11	MESH DESCRIPTOR Tiotropium Bromide AND CENTRAL:TARGET
#	12	MESH DESCRIPTOR Glycopyrrolate AND CENTRAL:TARGET
#	13	tiotropium:ti,ab AND CENTRAL:TARGET
#	14	glycopyrronium:ti,ab AND CENTRAL:TARGET
#	15	umeclidinium:ti,ab AND CENTRAL:TARGET
#	16	aclidinium:ti,ab AND CENTRAL:TARGET
#	17	#11 OR #12 OR #13 OR #14 OR #15 OR #16 AND CENTRAL:TARGET
#	18	MESH DESCRIPTOR Budesonide AND CENTRAL:TARGET
#	19	MESH DESCRIPTOR Fluticasone AND CENTRAL:TARGET
#	20	MESH DESCRIPTOR Mometasone Furoate AND CENTRAL:TARGET
#	21	MESH DESCRIPTOR Beclomethasone AND CENTRAL:TARGET
#	22	budesonide:ti,ab AND CENTRAL:TARGET
#	23	fluticasone:ti,ab AND CENTRAL:TARGET
#	24	mometasone:ti,ab AND CENTRAL:TARGET
#	25	beclomethasone:ti,ab AND CENTRAL:TARGET
#	26	ciclesonide:ti,ab AND CENTRAL:TARGET
#	27	(inhal* NEAR3 (steroid* or corticosteroid* or glucocorticoid*)):ti,ab AND CENTRAL:TARGET
#	28	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 AND CENTRAL:TARGET
#	29	MESH DESCRIPTOR Budesonide, Formoterol Fumarate Drug Combination AND CENTRAL:TARGET
#	30	MESH DESCRIPTOR Mometasone Furoate, Formoterol Fumarate Drug Combination AND CENTRAL:TARGET
#	31	MESH DESCRIPTOR Fluticasone-Salmeterol Drug Combination AND CENTRAL:TARGET
#	32	#29 OR #30 OR #31 AND CENTRAL:TARGET
#	33	(#10 or #28) or #32 AND CENTRAL:TARGET
#	34	#17 AND #28 AND CENTRAL:TARGET
#	35	#33 OR #34 AND CENTRAL:TARGET
#	36	#3 AND #35 AND CENTRAL:TARGET
#	37	(2008 or 2009 or 2010 or 2011 or 2012 or 2013 or 2014 or 2015 or 2016 or 2017 or 2018 or 2019 or 2020):yr AND CENTRAL:TARGET
#	38	#36 AND #37 AND CENTRAL:TARGET

MEDLINE

#	1	exp Asthma/
#	2	asthma$.tw.
#	3	1 or 2
#	4	Formoterol Fumarate/
#	5	Salmeterol Xinafoate/
#	6	formoterol.tw.
#	7	salmeterol.tw.
#	8	indacaterol.mp.
#	9	vilanterol.mp.
#	10	or/4-9
#	11	Tiotropium Bromide/
#	12	Glycopyrrolate/
#	13	tiotropium.tw.
#	14	glycopyrronium.mp.
#	15	umeclidinium.mp.
#	16	aclidinium.mp.
#	17	or/11-16
#	18	Budesonide/
#	19	Fluticasone/
#	20	Mometasone Furoate/
#	21	Beclomethasone/
#	22	budesonide.tw.
#	23	fluticasone.tw.
#	24	mometasone.tw.
#	25	beclomethasone.tw.
#	26	ciclesonide.mp.
#	27	(inhal$ adj3 (steroid$ or corticosteroid$ or glucocorticoid$)).tw.
#	28	or/18-27
#	29	Budesonide, Formoterol Fumarate Drug Combination/
#	30	Mometasone Furoate, Formoterol Fumarate Drug Combination/

#	31	Fluticasone-Salmeterol Drug Combination/
#	32	or/29-31
#	33	(10 and 28) or 32
#	34	17 and 28
#	35	33 or 34
#	36	3 and 35
#	37	(controlled clinical trial or randomized controlled trial).pt.
#	38	(randomized or randomised).ab,ti.
#	39	placebo.ab,ti.
#	40	dt.fs.
#	41	randomly.ab,ti.
#	42	trial.ab,ti.
#	43	groups.ab,ti.
#	44	or/37-43
#	45	Animals/
#	46	Humans/
#	47	45 not (45 and 46)
#	48	44 not 47
#	49	36 and 48
#	50	limit 49 to yr="2008 -Current"

.tw= text word
.mp.= title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms
.ab.ti.= abstract, title
.pt.= publication type
.fs.= floating sub-heading

EMBASE

1	asthma/
2	asthma$.tw.
3	1 or 2
4	formoterol fumarate/
5	formoterol/
6	salmeterol xinafoate/ or salmeterol/
7	formoterol.tw.
8	salmeterol.tw.
9	indacaterol/
10	indacaterol.tw.
11	vilanterol/
12	vilanterol.tw.
13	or/4-12
14	tiotropium bromide/
15	glycopyrronium/
16	tiotropium.tw.
17	glycopyrronium.tw.
18	umeclidinium/
19	umeclidinium.tw.
20	aclidinium.tw.
21	aclidinium bromide/
22	or/14-21
23	budesonide/
24	fluticasone/
25	mometasone furoate/
26	beclometasone/
27	ciclesonide/
28	budesonide.tw.
29	fluticasone.tw.
30	mometasone.tw.
31	beclomethasone.tw.
32	ciclesonide.mp.
33	(inhal$ adj3 (steroid$ or corticosteroid$ or glucocorticoid$)).tw.
34	or/23-33
35	budesonide plus formoterol/
36	formoterol fumarate plus mometasone furoate/
37	fluticasone propionate plus salmeterol/
38	or/35-37

39	(13 and 34) or 38
40	22 and 34
41	39 or 40
42	3 and 41
43	Randomized Controlled Trial/
44	randomization/
45	controlled clinical trial/
46	Double Blind Procedure/
47	Single Blind Procedure/
48	Crossover Procedure/
49	(clinica$ adj3 trial$).tw.
50	((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw.
51	exp Placebo/
52	placebo$.ti,ab.
53	random$.ti,ab.
54	((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw.
55	(crossover$ or cross-over$).ti,ab.
56	or/43-55
57	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
58	human/ or normal human/ or human cell/
59	57 and 58
60	57 not 59
61	56 not 60
62	42 and 61
63	limit 62 to yr="2008 -Current"

Global Health

1	exp Asthma/
2	asthma$.tw.
3	1 or 2
4	formoterol.tw.
5	salmeterol.tw.
6	indacaterol.mp.
7	vilanterol.mp.
8	or/4-7
9	tiotropium.tw.
10	glycopyrronium.tw.
11	umeclidinium.tw.
12	aclidinium.tw.
13	or/9-12
14	budesonide.tw.
15	fluticasone.tw.
16	mometasone.tw.
17	beclomethasone.tw.
18	ciclesonide.tw.
19	(inhal$ adj3 (steroid$ or corticosteroid$ or glucocorticoid$)).tw.
20	or/14-19
21	8 and 20
22	13 and 20
23	21 or 22
24	3 and 23
25	randomized controlled trials/
26	(randomized or randomised).ab,ti.
27	placebo.ab,ti.
28	randomly.ab,ti.
29	trial.ab,ti.
30	or/25-29
31	24 and 30
32	limit 31 to yr="2008 -Current"

ClinicalTrials.gov

Study type	Interventional
Condition	asthma
Intervention	(budesonide OR fluticasone OR mometasone OR beclomethasone OR ciclesonide) AND ((formoterol OR salmeterol OR indacaterol OR vilanterol) OR (tiotropium OR glycopyrronium OR umeclidinium OR aclidinium))

WHO ICTRP

Condition	asthma
Intervention	(budesonide OR fluticasone OR mometasone OR beclomethasone OR ciclesonide) AND ((formoterol OR salmeterol OR indacaterol OR vilanterol) OR (tiotropium OR glycopyrronium OR umeclidinium OR aclidinium))

Appendix 2. Analysis Codes

Continuous Outcomes

Outcome: ACQ at 3 months

```
###########

## Outcome: ACQ at 3 months
## The same code was used for all continuous outcomes: ACQ at 3,6 and 12 months and
## AQLQ at 3 and 6 months

###########

# Load packages
library(gemtc)

dat_ACQ3M <- read.csv("ACQ_3M.csv")  # Load the data-file
net_ACQ3M <- mtc.network(dat_ACQ3M) # Create an mtc.network

# Generate a fixed-effect network meta-analysis model:
mod_FE <- mtc.model(net_ACQ3M,type="consistency", n.chain=4, linearModel = "fixed")

# Run the NMA model using an MCMC sampler:
res_FE <- mtc.run(mod_FE, n.adapt=50000, n.iter= 100000)
summary(res_FE)

# Generate a random-effect NMA using a Uniform(0,2) prior for the between-study heterogeneity:

mod_RE <- mtc.model(net_ACQ3M, type="consistency", n.chain=4,
 linearModel = "random",
 hy.prior=mtc.hy.prior("std.dev", "dunif", 0, 2))

res_RE <- mtc.run(mod_RE, n.adapt=50000, n.iter= 100000)
summary(res_RE)

# History and Gelman Plots

plot(res_FE) # History plot
gelman.diag(res_FE) # Gelman plot
plot(res_RE) # History plot
gelman.diag(res_RE) # Gelman plot

# Create a table for the relative effects where the baseline is treatment 1

tbl_res <- relative.effect.table(res_FE, t1="1")
tbl_res

# Calculate the rank-probabilities for each treatment, where the lower values of the estimate are preferred
(preferredDirection = -1), i.e. a higher ACQ score is a bad outcome:

rank_probs <- rank.probability(res_FE, preferredDirection =-1)
rank_probs

# Calculate the quantiles for the treatment ranks
rank_quant <- rank.quantiles(rank_probs)

# Conducting node-splitting to assess consistency

nodesplit <- mtc.nodesplit(net_ACQ3M)
res_nodesplit <- summary(nodesplit)
```

Dichotomous Outcomes

Outcome: ACQ Response at 6 months

```
# Load packages
library(gemtc)

###########

## Outcome: ACQ Response at 6 months
## The same code was used for ACQ Response at 6 and 12 months
```

```
###########
dat_ACQR6M <- read.csv("ACQR_6M.csv") # Load the data-file
net_ACQR6M <- mtc.network(dat_ACQR6M) # Create an mtc.network

# Generate a fixed-effect network meta-analysis model:
mod_FE <- mtc.model(net_ACQR6M,type="consistency", n.chain=4,
 linearModel = "fixed")

# Run the NMA model using an MCMC sampler:
res_FE <- mtc.run(mod_FE, n.adapt=50000, n.iter= 100000)
summary(res_FE)

# Generate a random-effect NMA using a Turner prior of LN(-2.93, 1.58^2) for the between-study heterogeneity:

mod_RE <- mtc.model(net_ACQR6M, type="consistency", n.chain=4,
 linearModel = "random",
 hy.prior=mtc.hy.prior(type="std.dev",
  distr="dlnorm", -2.93, 0.4006))

res_RE <- mtc.run(mod_RE, n.adapt=50000, n.iter= 100000)
summary(res_RE)

# History and Gelman Plots

plot(res_FE) # History plot
gelman.diag(res_FE) # Gelman plot
plot(res_RE) # History plot
gelman.diag(res_RE) # Gelman plot

# Create a table for the relative effects where the baseline is treatment 1

tbl_res <- relative.effect.table(res_FE, t1="1")
tbl_res

# Calculate the rank-probabilities for each treatment, where the higher values of the estimate are preferred
(preferredDirection = 1), i.e. a higher ACQ response is a good outcome:

rank_probs <- rank.probability(res_FE, preferredDirection =1)
rank_probs

# Calculate the quantiles for the treatment ranks
rank_quant <- rank.quantiles(rank_probs)

# Conducting node-splitting to assess consistency
nodesplit <- mtc.nodesplit(net_ACQR6M)
res_nodesplit <- summary(nodesplit)
```

Outcome: Total Adverse Events (AEs)

```
# Load packages
library(gemtc)

###########

## Outcome: Total Adverse Events
## The same code was used for Total SAEs, Dropouts due to AEs

###########

dat_AE <- read.csv("TotalAEs.csv") # Load the data-file
net_AE <- mtc.network(dat_AE) # Create an mtc.network

# Generate a fixed-effect network meta-analysis model:
mod_FE <- mtc.model(net_AE,type="consistency", n.chain=4,
 linearModel = "fixed")

# Run the NMA model using an MCMC sampler:
res_FE <- mtc.run(mod_FE, n.adapt=50000, n.iter= 100000)
summary(res_FE)

# Generate a random-effect NMA using a Turner prior of LN(-2.10, 1.58^2) for the between-study heterogeneity:

mod_RE <- mtc.model(net_AE, type="consistency", n.chain=4,
 linearModel = "random",
 hy.prior=mtc.hy.prior(type="std.dev",
  distr="dlnorm", -2.10, 0.4006))

res_RE <- mtc.run(mod_RE, n.adapt=50000, n.iter= 100000)
summary(res_RE)

# History and Gelman Plots
```

```
plot(res_FE) # History plot
gelman.diag(res_FE) # Gelman plot
plot(res_RE) # History plot
gelman.diag(res_RE) # Gelman plot

# Create a table for the relative effects where the baseline is treatment 1

tbl_res <- relative.effect.table(res_FE, t1="1")
tbl_res

# Calculate the rank-probabilities for each treatment, where lower values of the estimate are preferred
(preferredDirection = -1), i.e. more AEs are a bad outcome:

rank_probs <- rank.probability(res_FE, preferredDirection =1)
rank_probs

# Calculate the quantiles for the treatment ranks
rank_quant <- rank.quantiles(rank_probs)

# Conducting node-splitting to assess consistency
nodesplit <- mtc.nodesplit(net_ACQR6M)
res_nodesplit <- summary(nodesplit)

###########

## Outcome: Asthma SAEs (in OpenBUGS)

###########

# Adding a continuity-correction to CHIESI (2009)

# Burn-in: 50,000 iterations
# Sampled: 100, 000 iterations
# Chains: 3

# FE Model:

model{  # *** PROGRAM STARTS

for(i in 1:ns){ # Loop through STUDIES

 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines

 for (k in 1:na[i]) { # Loop through ARMS

 r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood

 # Model for linear predictor:

 logit(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]]

 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators

# Deviance contribution:

 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))

 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

 }

  # summed residual deviance contribution for this trial

resdev[i] <- sum(dev[i,1:na[i]])

}

totresdev <- sum(resdev[])  # Total Residual Deviance

d[1]<- 0 # treatment effect is zero for reference treatment

for (k in 2:nt) { d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

# pairwise ORs and LORs for all possible pair-wise comparisons

for (c in 1:(nt-1)) { for (k in (c+1):nt) {

 or[c,k] <- exp(d[k] - d[c])

 lor[c,k] <- (d[k]-d[c])

 }

}

# ranking

for (k in 1:nt) {

 rk[k] <- rank(d[],k) # assumes events are “bad”

 best[k] <- equals(rk[k],1) #calculate probability that treat k is best
```

```
 # calculates probability that treat k is h-th best
 for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
}} #*** PROGRAM ENDS

# RE Model:
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # Loop through STUDIES
 w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
 delta[i,1] <- 0 # treatment effect is zero for control arm
 mu[i] ~ dnorm(0,.1) # vague priors for all trial baselines
 for (k in 1:na[i]) { # Loop through ARMS
 r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
 # model for linear predictor:
 logit(p[i,k]) <- mu[i] + delta[i,k]
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
 # Deviance contribution
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 # summed residual deviance contribution for this trial
 resdev[i] <- sum(dev[i,1:na[i]])
 for (k in 2:na[i]) { # Loop through ARMS
 # trial-specific LOR distributions:
 delta[i,k] ~ dnorm(md[i,k],taud[i,k]) #
 # mean of LOR distributions (with multi-arm correction):
 md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
 # precision of LOR distributions (with multi-arm correction):
 taud[i,k] <- tau *2*(k-1)/k
 # Adjustment for multi-arm RCTs:
 w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
 # Cumulative adjustment for multi-arm trials1:
 sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<- 0 # Treatment effect is zero for reference treatment
for (k in 2:nt) { d[k] ~ dnorm(0,.01)} # Vague priors for treatment effects
sd ~ dlnorm(-2.10, prec) # Log-normal (-2.10, 1.58^2) prior for SD
prec <- pow(1.58,-2)
tau <-pow(sd,-2)
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) { for (k in (c+1):nt) {
 or[c,k] <- exp(d[k] - d[c])
 lor[c,k] <- (d[k]-d[c])
 }
}
# ranking
for (k in 1:nt) {
 rk[k] <- rank(d[],k) # assumes events are “bad”
 best[k] <- equals(rk[k],1) #calculate probability that treat k is best
```

```
}} # *** PROGRAM ENDS
# Data:
list(nt=6,ns=24)
t[,1] r[,1] n[,1] t[,2] r[,2] n[,2] t[,3] r[,3] n[,3] t[,4] r[,4] n[,4] na[]
1 9 1010 5 11 1009 NA NA NA NA NA NA 2 # Bateman 2014
1 9 759 5 2 749 NA NA NA NA NA NA 2 # Beasley 2015
1 0 983 5 2 722 NA NA NA NA NA NA 2 # Bernstein 2011
1 4 365 5 1 377 NA NA NA NA NA NA 2 # Brown 2012
3 0.5 346 5 1.5 351 NA NA NA NA NA NA 2 # CHIESI 2009
1 0 138 4 1 259 NA NA NA NA NA NA 2 #Hammelmann 2016
1 0 315 5 3 306 NA NA NA NA NA NA 2 # Katial 2011
1 1 269 4 1 526 5 0 275 NA NA NA 3 # Kerstjens 2015a
1 2 254 4 3 510 5 1 266 NA NA NA 3 # Kerstjens 2015b
5 8 608 6 21 1231 NA NA NA NA NA NA 2 # Kerstjens 2020
1 0 318 5 1 310 NA NA NA NA NA NA 2 # Kerwin 2011
1 2 143 4 0 139 NA NA NA NA NA NA 2 # Kerwin 2020
5 7 407 6 6 406 NA NA NA NA NA NA 2 # Lee 2020
2 1 154 6 1 155 NA NA NA NA NA NA 2 # Lin 2015
1 10 252 2 0 83 5 4 161 6 10 177 4 # Mansfield 2017
1 1 192 5 0 191 NA NA NA NA NA NA 2 # Nathan 2010
2 1 389 6 0 197 NA NA NA NA NA NA 2 # O'Byrne 2014
1 1 122 2 0 126 NA NA NA NA NA NA 2 # Pedersen 2017
1 0 146 2 0 146 5 0 143 6 1 145 4 # Sher 2017
1 1 155 5 0 156 NA NA NA NA NA NA 2 # Spector 2012
1 0 578 2 6 988 5 2 580 6 11 982 4 # Stempel 2016
1 8 443 2 6 440 5 2 437 6 5 887 4 # van Zyl-Smit 2020
2 0 240 5 0 233 6 1 255 NA NA NA 3 # Weinstein 2010
1 0 123 5 1 127 NA NA NA NA NA NA 2 # Zangrilli 2011
END
# Initial Values (FE Model):
list(d = c(NA,0,0,0,0, 0),
 mu = c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0),
 delta = structure(.Data = c(NA,0,NA,NA, NA,0, NA,NA, NA, 0, NA,NA,
 NA,0,NA,NA, NA,0,NA,NA, NA,0,NA,NA,
 NA,0,NA,NA, NA,0,0,NA, NA,0,0,NA,
 NA,0,NA,NA, NA,0, NA,NA, NA,0,NA,NA,
 NA,0,NA,NA, NA,0,NA,NA, NA,0,0,0,
 NA,0,NA,NA, NA,0,NA,NA,  NA,0, NA,NA,
 NA,0,0,0, NA,0,NA,NA, NA,0,0,0,
 NA,0,0,0, NA,0,0,NA, NA,0,NA,NA),
 .Dim = c(24,4)))
list(d = c(NA,1,-1,1,-1, 1),
 mu = c(1,-1,1,-1,1, -1,1,-1,-1,1, -1,1,-1,1,-1, 1,-1,1,-1,1, -1,1,-1,1),
 delta = structure(.Data = c(NA,1,NA,NA,  NA,-1, NA,NA, NA, 1, NA,NA,
 NA,-1,NA,NA,  NA,1,NA,NA, NA,-1,NA,NA,
   NA,1,NA,NA, NA,-1,1,NA, NA,-1,1,NA,
 NA,-1,NA,NA, NA,1, NA,NA, NA,-1,NA,NA,
  NA,1,NA,NA, NA,-1,NA,NA, NA,-1,1,-1,
```

```
 NA,1,NA,NA, NA,-1,NA,NA, NA,1, NA,NA,
  NA,-1,1,-1, NA,1,NA,NA, NA,-1,1,-1,
  NA,1,-1,1, NA,-1,1,NA, NA,-1,NA,NA),
 .Dim = c(24,4)))
list(d = c(NA,1,2,3,2, 1),
 mu = c(1,2,3,2,1, 2,3,1,2,3, 1,2,3,2,1, 2,3,1,2,3, 2,3,1,2),
 delta = structure(.Data = c(NA,1,NA,NA, NA,2, NA,NA,  NA, 3, NA,NA,
  NA,1,NA,NA, NA,2,NA,NA, NA,3,NA,NA,
  NA,1,NA,NA, NA,2,3,NA, NA,1,2,NA,
  NA,3,NA,NA, NA,1, NA,NA, NA,2,NA,NA,
   NA,3,NA,NA, NA,1,NA,NA, NA,2,3,1,
 NA,2,NA,NA, NA,3,NA,NA, NA,1, NA,NA,
  NA,2,3,1, NA,2,NA,NA, NA,3,1,2,
   NA,3,1,2, NA,3,1,NA, NA,2,NA,NA),
 .Dim = c(24,4)))
# Initial Values (RE Model):
list(d = c(NA,0,0,0,0, 0),
 mu = c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0),
 delta = structure(.Data = c(NA,0,NA,NA, NA,0, NA,NA, NA, 0, NA,NA,
 NA,0,NA,NA, NA,0,NA,NA, NA,0,NA,NA,
  NA,0,NA,NA, NA,0,0,NA, NA,0,0,NA,
 NA,0,NA,NA, NA,0, NA,NA, NA,0,NA,NA,
 NA,0,NA,NA, NA,0,NA,NA, NA,0,0,0,
 NA,0,NA,NA, NA,0,NA,NA,  NA,0, NA,NA,
 NA,0,0,0, NA,0,NA,NA, NA,0,0,0,
 NA,0,0,0, NA,0,0,NA, NA,0,NA,NA),
 .Dim = c(24,4)), sd=0.5)
list(d = c(NA,1,-1,1,-1, 1),
 mu = c(1,-1,1,-1,1, -1,1,-1,-1,1, -1,1,-1,1,-1, 1,-1,1,-1,1, -1,1,-1,1),
 delta = structure(.Data = c(NA,1,NA,NA,  NA,-1, NA,NA, NA, 1, NA,NA,
 NA,-1,NA,NA,  NA,1,NA,NA, NA,-1,NA,NA,
  NA,1,NA,NA, NA,-1,1,NA, NA,-1,1,NA,
 NA,-1,NA,NA, NA,1, NA,NA, NA,-1,NA,NA,
  NA,1,NA,NA, NA,-1,NA,NA, NA,-1,1,-1,
 NA,1,NA,NA, NA,-1,NA,NA, NA,1, NA,NA,
  NA,-1,1,-1, NA,1,NA,NA, NA,-1,1,-1,
  NA,1,-1,1, NA,-1,1,NA, NA,-1,NA,NA),
  .Dim = c(24,4), sd = 0.7))
list(d = c(NA,1,2,3,2, 1),
 mu = c(1,2,3,2,1, 2,3,1,2,3, 1,2,3,2,1, 2,3,1,2,3, 2,3,1,2),
 delta = structure(.Data = c(NA,1,NA,NA, NA,2, NA,NA,  NA, 3, NA,NA,
  NA,1,NA,NA, NA,2,NA,NA, NA,3,NA,NA,
  NA,1,NA,NA, NA,2,3,NA, NA,1,2,NA,
  NA,3,NA,NA, NA,1, NA,NA, NA,2,NA,NA,
   NA,3,NA,NA, NA,1,NA,NA, NA,2,3,1,
  NA,2,NA,NA, NA,3,NA,NA, NA,1, NA,NA,
  NA,2,3,1, NA,2,NA,NA, NA,3,1,2,
   NA,3,1,2, NA,3,1,NA, NA,2,NA,NA),
```

```
.Dim = c(24,4)), sd = 0.2)
```

Exacerbation Outcomes

```
# Outcome: Moderate-Severe Exacerbations (FE and RE Models)
# Shared parameter model:
# Binomial likelihood and cloglog link (for dichotomous data)
# Normal likelihood and identity link (for time to event data)
# Burn-in: 50,000 iterations
# Sample: 100, 000 iterations
# Chains: 3
# FE Model:
model{
for(i in 1:nsBi){ # Loop through studies with BINOMIAL DATA
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # Loop through arms
 r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
 # model for linear predictor
 cloglog(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
 # Deviance contribution
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 # summed residual deviance contribution for each trial
 resdev[i] <- sum(dev[i,1:na[i]])
 }
# Normal likelihood, identity link for TIME TO EVENT DATA
for(i in 1:nsNo){ # Loop through 2-ARM STUDIES
 y[i,2] ~ dnorm(delta[i+nsBi,2],prec[i,2]) # normal likelihood for 2-arm trials
 # Deviance contribution for trial i
 resdev[i+nsBi]<- (y[i,2]-delta[i+nsBi,2])*(y[i,2]-delta[i+nsBi,2])*prec[i,2]
 }
#
for(i in (nsNo+1):(nsNo+ns4)){ # Loop through 4-ARM STUDIES
 for (k in 1:(naNo[i]-1)){ # set variance-covariance matrix
 for (j in 1:(naNo[i]-1)){
 Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
 }
 }
 # Precision matrix
 Omega2[i,1:(naNo[i]-1),1:(naNo[i]-1)] <- inverse(Sigma2[i,,])
 # multivariate normal likelihood for 4-arm trials
 y[i,2:naNo[i]] ~ dmnorm(delta[i+nsBi,2:naNo[i]],Omega2[i,1:(naNo[i]-1),1:(naNo[i]-1)])
 # Deviance contribution for trial i
 for (k in 1:(naNo[i]-1)){ # multiply vector & matrix
 ydiff2[i,k]<- y[i,(k+1)] - delta[i+nsBi,(k+1)]
 z2[i,k]<- inprod(Omega2[i,k,1:(naNo[i]-1)], ydiff2[i,1:(naNo[i]-1)])
 }
 resdev[i+nsBi]<- inprod(ydiff2[i,1:(naNo[i]-1)], z2[i,1:(naNo[i]-1)])
 }
#
```

```
for(i in 1:(nsNo+ns4)){ # Loop through ALL STUDIES (Normal likelihood)
 w[i+nsBi,1] <- 0 # adjustment for multi-arm trials is zero for control arm
 delta[i+nsBi,1] <- 0 # treatment effect is zero for control arm
 for (k in 2:naNo[i]){ # Loop through arms
 var[i,k] <- pow(se[i,k],2) # calculate variances
 prec[i,k] <- 1/var[i,k] # set precisions
 }
 for (k in 2:naNo[i]){ # LOOP THROUGH ARMS
 # trial-specific treat effects distributions
 delta[i+nsBi,k] <- d[tNo[i,2]] - d[tNo[i,1]]
 }
 }
#

totresdevBi <- sum(resdev[1:nsBi]) # res dev for Binomial data
totresdevNo <- sum(resdev[nsBi+1:nsBi+nsNo]) # res dev for Normal data
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment

# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
for (c in 1:(nt-1)){
 for (k in (c+1):nt){
 lhr[c,k] <- (d[k]-d[c])
 log(hr[c,k]) <- lhr[c,k]
 }
 }
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k)  # assumes events are "good"
 rk[k] <- rank(d[],k)  # assumes events are "bad"
 best[k] <- equals(rk[k],1)  # Rank 1 is best
 # calculates probability that treat k is h-th best
 for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
 }
} # *** PROGRAM ENDS

# RE Model:
model{
for(i in 1:nsBi){ # Loop through studies with BINOMIAL DATA
 w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
 delta[i,1] <- 0 # treatment effect is zero for control arm
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # Loop through arms
 r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
 # model for linear predictor
 cloglog(p[i,k]) <- mu[i] + delta[i,k]
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
```

```
 # Deviance contribution
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 # summed residual deviance contribution for each trial
 resdev[i] <- sum(dev[i,1:na[i]])
 for (k in 2:na[i]) { # LOOP THROUGH ARMS
 # trial-specific LOR distributions
 delta[i,k] ~ dnorm(md[i,k],taud[i,k])
 # mean of RE distributions, with multi-arm trial correction
 md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
 # precision of RE distributions (with multi-arm trial correction)
 taud[i,k] <- tau *2*(k-1)/k
 # adjustment, multi-arm trials
 w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
 # cumulative adjustment for multi-arm trials
 sw[i,k] <- sum(w[i,1:k-1])/(k-1)
 }
 }
# Normal likelihood, identity link for TIME TO EVENT DATA
for(i in 1:nsNo){ # Loop through 2-ARM STUDIES
 y[i,2] ~ dnorm(delta[i+nsBi,2],prec[i,2]) # normal likelihood for 2-arm trials
 # Deviance contribution for trial i
 resdev[i+nsBi]<- (y[i,2]-delta[i+nsBi,2])*(y[i,2]-delta[i+nsBi,2])*prec[i,2]
 }
#
for(i in (nsNo+1):(nsNo+ns4)){ # Loop through 4-ARM STUDIES
 for (k in 1:(naNo[i]-1)){ # set variance-covariance matrix
 for (j in 1:(naNo[i]-1)){
 Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
 }
 }
 # Precision matrix
 Omega2[i,1:(naNo[i]-1),1:(naNo[i]-1)] <- inverse(Sigma2[i,,])
 # multivariate normal likelihood for 4-arm trials
 y[i,2:naNo[i]] ~ dmnorm(delta[i+nsBi,2:naNo[i]],Omega2[i,1:(naNo[i]-1),1:(naNo[i]-1)])
 # Deviance contribution for trial i
 for (k in 1:(naNo[i]-1)){ # multiply vector & matrix
 ydiff2[i,k]<- y[i,(k+1)] - delta[i+nsBi,(k+1)]
 z2[i,k]<- inprod(Omega2[i,k,1:(naNo[i]-1)], ydiff2[i,1:(naNo[i]-1)])
 }
 resdev[i+nsBi]<- inprod(ydiff2[i,1:(naNo[i]-1)], z2[i,1:(naNo[i]-1)])
 }
#
for(i in 1:(nsNo+ns4)){ # Loop through ALL STUDIES (Normal likelihood)
 w[i+nsBi,1] <- 0 # adjustment for multi-arm trials is zero for control arm
 delta[i+nsBi,1] <- 0 # treatment effect is zero for control arm
 for (k in 2:naNo[i]){  # LOOP THROUGH ARMS
```

```
 var[i,k] <- pow(se[i,k],2) # calculate variances
 prec[i,k] <- 1/var[i,k] # set precisions
 }
 for (k in 2:naNo[i]){ # LOOP THROUGH ARMS
 # trial-specific treat effects distributions
 delta[i+nsBi,k] ~ dnorm(md[i+nsBi,k],taud[i+nsBi,k])
 # mean of RE distributions (with multi-arm trial correction)
 md[i+nsBi,k] <- d[tNo[i,k]] - d[tNo[i,1]] + sw[i+nsBi,k]
 # precision of RE distributions (with multi-arm trial correction)
 taud[i+nsBi,k] <- tau *2*(k-1)/k
 # adjustment for multi-arm trials
 w[i+nsBi,k] <- (delta[i+nsBi,k] - d[tNo[i,k]] + d[tNo[i,1]])
 # cumulative adjustment for multi-arm trials
 sw[i+nsBi,k] <- sum(w[i+nsBi,1:k-1])/(k-1)
 }
 }
#
totresdevBi <- sum(resdev[1:nsBi]) # resdev for Binomial data
totresdevNo <- sum(resdev[nsBi+1:nsBi+nsNo]) # resdev for Normal data
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

prior.prec <- pow(0.5, -2)
sd ~ dnorm(0, prior.prec)I(0,) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
#
# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
 for (k in (c+1):nt) {
 lhr[c,k] <- (d[k]-d[c])
 log(hr[c,k]) <- lhr[c,k]
 }
 }
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k)  # assumes events are "good"
 rk[k] <- rank(d[],k)  # assumes events are "bad"
 best[k] <- equals(rk[k],1)  # calculate probability that treat k is best
 # calculates probability that treat k is h-th best
 for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
 }
} # *** PROGRAM ENDS

# Initial Values (FE Model):
list(d = c(NA,0,0,0,0, 0),
 mu = c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0))
list(d = c(NA,1,-1,1,-1, 1),
 mu = c(1,-1,1,-1,1, -1,1,-1,1,-1, 1,-1,1,-1,1, -1,1,-1,1,-1, 1,-1))
```

```
list(d = c(NA,1,2,3,1, 2),
 mu = c(1,2,3,2,1, 2,3,1,2,3, 1,2,3,2,1, 2,3,1,2,3, 2,1))
# Initial values (RE Model):
list(d = c(NA,0,0,0,0, 0),
 mu = c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0), sd=0.5)
list(d = c(NA,1,-1,1,-1, 1),
 mu = c(1,-1,1,-1,1, -1,1,-1,1,-1, 1,-1,1,-1,1, -1,1,-1,1,-1, 1,-1), sd=0.2)
list(d = c(NA,1,2,3,1, 2),
 mu = c(1,2,3,2,1, 2,3,1,2,3, 1,2,3,2,1, 2,3,1,2,3, 2,1), sd=0.7)
# Data
list(nsBi=22, nsNo=2, ns4=1, nt=6)
# lnHR data
tNo[,1] tNo[,2] tNo[,3] tNo[,4] y[,2] y[,3] y[,4] se[,2] se[,3] se[,4] V[] naNo[]
1 5 NA NA -0.229 NA NA 0.109 NA NA NA 2 # Bateman (2014)
1 5 NA NA -0.173 NA NA 0.066 NA NA NA 2 # Peters (2016)
1 4 4 5 -0.693 -0.329 -0.288 0.2627 0.2371 0.2295 0.023 4 # Kerstjens (2015)
END
# Binomial data (time not needed)
t[,1] r[,1] n[,1] t[,2] r[,2] n[,2] t[,3] r[,3] n[,3] t[,4] r[,4] n[,4] na[]
1 4 205 5 1 201 NA NA NA NA NA NA 2 # Bleecker (2014)
1 51 364 5 29 377 NA NA NA NA NA NA 2 # Brown (2012)
3 8 346 5 13 348 NA NA NA NA NA NA 2 # CHIESI (2009)
1 5 109 5 4 108 NA NA NA NA NA NA 2 # Corren (2013)
1 9 138 4 7 259 NA NA NA NA NA NA 2 # Hamelmann (2016)
1 9 213 5 11 432 NA NA NA NA NA NA 2 # Huchon (2009)
1 80 315 5 48 306 NA NA NA NA NA NA 2 # Katial (2011)
5 166 607 6 324 1223 NA NA NA NA NA NA 2 # Kerstjens (2020)
1 69 318 5 60 310 NA NA NA NA NA NA 2 # Kerwin (2011)
1 11 143 4 6 139 NA NA NA NA NA NA 2 # Kerwin (2020)
5 106 407 6 73 406 NA NA NA NA NA NA 2 # Lee (2020)
2 3 154 6 1 155 NA NA NA NA NA NA 2 # Lin (2015)
1 12 252 2 1 83 5 3 161 6 10 177 4 # Mansfield (2017)
2 3 389 6 0 197 NA NA NA NA NA NA 2 # O'Byrne (2014)
2 6 184 6 4 192 NA NA NA NA NA NA 2 # Paggiaro (2016b)
1 11 122 2 10 126 NA NA NA NA NA NA 2 # Pedersen (2017)
1 3 292 5 1 146 NA NA NA NA NA NA 2 # Pertseva (2013)
2 29 133 5 19 132 6 54 443 NA NA NA 3 # Peters (2008)
1 3 155 5 3 156 NA NA NA NA NA NA 2 # Spector (2012)
1 144 443 2 115 440 5 74 437 6 151 887 4 # van Zyl-Smit (2020)
1 14 108 2 13 111 NA NA NA NA NA NA 2 # Woodcock (2014)
1 2 123 5 7 127 NA NA NA NA NA NA 2 # Zangrilli (2011)
END
```

 # Outcome: Severe Exacerbations (FE and RE Models)

```
#
# Binomial likelihood and cloglog link as there only was dichotomous data
# Burn-in: 50,000 iterations
# Sample: 100, 000 iterations
# Chains: 3
# FE Model:
model{  # *** PROGRAM STARTS
```

```
for(i in 1:ns){  # Loop through STUDIES
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # Loop through ARMS
 r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor:
 cloglog(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]]
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
# Deviance contribution:
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
# Summed residual deviance contribution for this trial:
 resdev[i] <- sum(dev[i,1:na[i]])
 totresdev <- sum(resdev[]) #Total Residual Deviance
 d[1]<- 0 #Treatment effect is zero for reference treatment
 for (k in 2:nt){
 d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) { for (k in (c+1):nt) {
 hr[c,k] <- exp(d[k] - d[c])
 lhr[c,k] <- (d[k]-d[c])
 }}
# ranking
for (k in 1:nt) {
 rk[k] <- rank(d[],k) # assumes events are “bad”
 best[k] <- equals(rk[k],1) #calculate probability that treat k is best
 # calculates probability that treat k is h-th best
 for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
}} # *** PROGRAM ENDS
```

RE Model

```
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # Loop through STUDIES
 w[i,1] <- 0 # Adjustment for multi-arm trials is zero for control arm
 delta[i,1] <- 0 # Treatment effect is zero for control arm
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # Loop through ARMS
 r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# Model for linear predictor:
 cloglog(p[i,k]) <- mu[i] + delta[i,k]
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
# Deviance contribution:
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
# Summed residual deviance contribution for this trial:
 resdev[i] <- sum(dev[i,1:na[i]])
```

```
 for (k in 2:na[i]) { # Loop through ARMS
# Trial-specific LOR distributions
 delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm correction)
 md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm correction)
 taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
 w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
 sw[i,k] <- sum(w[i,1:k-1])/(k-1)
 }}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<- 0 # treatment effect is zero for reference treatment
for (k in 2:nt) { d[k] ~ dnorm(0,.0001)} # vague priors for treatment effects
tau <-pow(sd,-2)
prior.prec <- pow(0.5, -2) # between-trial precision
sd~dnorm(0, prior.prec)I(0,) # vague prior for between-trial SD

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) { for (k in (c+1):nt) {
 hr[c,k] <- exp(d[k] - d[c])
 lhr[c,k] <- (d[k]-d[c])
 }
}
# ranking
for (k in 1:nt) {
 rk[k] <- rank(d[],k) # assumes events are “bad”
 best[k] <- equals(rk[k],1) #calculate probability that treat k is best
 # calculates probability that treat k is h-th best
 for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
}}  # *** PROGRAM ENDS
# Data
list(nt=6,ns=15)
t[,1] r[,1] n[,1] t[,2] r[,2] n[,2] t[,3] r[,3] n[,3] t[,4] r[,4] n[,4] na[]
1 9 1010 5 8 1009 NA NA NA NA NA NA 2 # Bateman (2014)
1 4 364 5 0 377 NA NA NA NA NA NA 2 # Brown (2012)
# 1 0 205 5 0 201 NA NA NA NA NA NA 2 # Bleecker (2014)
3 4 346 5 6 348 NA NA NA NA NA NA 2 # CHIESI (2009)
1 0 315 5 3 306 NA NA NA NA NA NA 2 # Katial (2011)
1 0 318 5 1 310 NA NA NA NA NA NA 2 # Kerwin (2011)
1 2 143 4 1 139 NA NA NA NA NA NA 2 # Kerwin (2020)
5 7 407 6 5 406 NA NA NA NA NA NA 2 # Lee (2020)
2 1 154 6 0 155 NA NA NA NA NA NA 2 # Lin (2015)
1 1 252 2 0 83 5 0 161 6 2 177 4 # Mansfield (2017)
1 1 192 5 2 191 NA NA NA NA NA NA 2 # Nathan (2010)
2 1 389 6 0 197 NA NA NA NA NA NA 2 # O' Byrne (2014)
2 0 133 5 2 132 6 2 443 NA NA NA 3 # Peters (2008)
```

```
1 32 4201 5 36 4201 NA NA NA NA NA NA 2 # Peters (2016)
1 0 578 2 7 988 5 1 580 6 14 982 2 # Stempel (2016)
1 89 443 2 64 440 5 43 437 6 89 887 2 # van Zyl-Smit (2020)
# 1 0 108 2 0 111 NA NA NA NA NA NA 2 # Woodcock (2014)
END
#############################################################################
# Exacerbations Outcomes: Node-Splitting using R2OpenBUGS
#
#
#
#Node-splitting FIXED EFFECTS MODEL EXAMPLE
# R script to run node-split for the MTC FE model using OpenBUGS
#
# 1. Need to include in the working directory the following files:
# Data2.txt --- text file with data
# SharedParFE.txt --- text file holding OpenBUGS code.
# This code is included in the following section.
# For severe outcomes, this file would be called DichotRE.txt as the model is a
# dichotomous RE model.
#
# 2. Output files will be
# coda1.txt --- holds coda output
# codaIndex.txt --- holds indexes to coda output
# data.txt --- holds all data as used by OpenBUGS
# log.odc and log.txt --- hold OpenBUGS output
# inits1.txt --- holds initial values as read by OpenBUGS
# script.txt --- OpenBUGS script file with all commands to execute
#
# 3. Output files for each node should be transferred to a new directory
# as they will be overwritten in each new run
#
# 4. You may need to edit the WinBUGS directory 'bd'
#
# 5. You will need to edit the working directory 'pathname'
# to suit your computer settings
#
# 6. Run script file
#
# 7. To repeat for other node-splits need to change variable 'pair'
# and edit output file names
#
#############################################################################
#
#
# Declare the directory where OpenBUGS is found in this computer

bd <- "C:/Program Files (x86)/OpenBUGS/OpenBUGS323/OpenBUGS.exe"
#
# Declare working directory
```

```
pathname <- "C:/Users/sa1842/OneDrive - University of York/Desktop/OBA-2/Exacerbation Outcomes/Node-Splitting/ "
setwd(pathname)
#
# load package to call OpenBUGS
library(R2OpenBUGS)
library(coda)
#
# LOAD DATA MANIPULATING FUNCTIONS:
#
PairXY <- function(treat, pair)
 # Check if pair(X,Y) in row i of data
 # and give baseline for data row i
{
 N <- nrow(treat)
 out <- cbind(split=rep(0,N), b=rep(0,N))
 for (i in 1:N) {
 # returns positions of matches to elements of pair in t[i,]
 # or zero if not present
 pos <- match(pair, treat[i,], nomatch=0) # length = length(pair) = 2
 out[i,1] <- ifelse(prod(pos)>0, 1, 0) # 1 if pair in line i, 0 o.w.
 out[i,2] <- ifelse(prod(pos)==0, 1, pos[1])
 }
 out
}
#
NonbaseSweep <- function(index, na)
 # gives na-1 indexes to sweep non-baseline arms only
{
 N <- NROW(na)
 C <- max(na)
 out <- matrix(nrow=N, ncol=C)
 for (i in 1:N) {
 for (k in 2:na[i]) {
 out[i,k] <- k - (index[i,"b"] >= k)
 }
 }
 out
}
#
Sweeptreat <- function(treat, m)
 # Builds matrix with non-baseline treatments
{
 N <- NROW(treat)
 C <- NCOL(m)
 out <- matrix(nrow=N, ncol=C)
 for (i in 1:N) {
 for (k in 2:C) {
 out[i,k] <- treat[i,m[i,k]]
```

```
 }
 }
 out
}
#
Basetreat <- function(treat, b)
 # Builds vector with baseline treatments
{
 N <- nrow(treat)
 out <- rep(0,N)
 for (i in 1:N) {
 out[i] <- treat[i,b[i]]
 }
 out
}
#
# Setup subdirectory to hold results for each of node-split.
# Use GeMTC to find out which nodes to split the nodes on. In the code presented we # split nodes on the (1,2) comparison. Repeat the following code for each node that # needs to be split.
dir.create("Node12")
#
#
################################################################################
# load data for MTC
MTCData <- read.table("Data2.txt", header=TRUE)
nsBi <- 22
ns2 <-2
ns3 <- 1
r <- data.matrix(MTCData[,c("r1", "r2", "r3", "r4")])
n <- data.matrix(MTCData[,c("n1", "n2", "n3", "n4")])
t <- data.matrix(MTCData[,c("t1", "t2", "t3", "t4")])
y <- data.matrix(cbind(NA, MTCData[,c("y.T2", "y.T3")]))
se <- data.matrix(cbind(NA, MTCData[,c("se.T2", "se.T3")]))
V <- MTCData[,c("V")]
na <- data.matrix(MTCData[,"na"])
nt <- max(t, na.rm=TRUE)
ns <- nrow(r)
#
# define initial values
initv1 <- list(direct=0, d=c(NA,0,0,0,0,0), mu=rep(0,nsBi))
# create file with initial values for checking
bugs.inits(list(initv1), n.chains = 1, digits = 4)
#
################################################################################
# NODE-SPLITTING ROUTINE - DICHOTOMOUS + NORMAL DATA
################################################################################
#
#
# Define node to split: (1,2)
```

```
pair <- c(1,2)
#
# BUILD EXTRA INPUT VARIABLES
# Calculate split (1 if node to split is present) and b (baseline position)
checkPair <- PairXY(t, pair)
# Build vector bi[i] with baseline treatment: t[i, b[i]]
bi <- Basetreat(t, checkPair[,"b"])
# Indexes to sweep non-baseline arms only
m <- NonbaseSweep(checkPair, na)
# Build matrix si[i,k] with non-baseline treatments: t[i, m[i,k]]
si <- Sweeptreat(t,m)
#
# Build data file: stored in the working directory as "data.txt"
bugs.data(list("r"=r,"n"=n,"t"=t, "y"=y, "se"=se,
  "na"=na[,1], "nt"=nt, "ns"=ns, "nsBi"=nsBi, "ns2"=ns2, "ns3"=ns3, "V"=V,
 "split" = checkPair[,"split"], "m" =m,
 "bi" = bi, "si" = si, "pair" = pair) )
#
# Call OpenBUGS
split12 <- bugs(data = "data.txt",
 inits = list(initv1),
 parameters.to.save = c("direct", "d", "prob","totresdev","lhr"),
 model.file = "SharedParFE.txt",
 n.chains = 1,
 n.iter = 150000,
 n.burnin = 50000,
 n.thin = 1,
 OpenBUGS.pgm = bd,
 working.directory = getwd(),
 save.history = TRUE,
 debug = TRUE )
#
# Copy input and output files to relevant directory
file.copy(c("data.txt", "inits1.txt", "log.odc", "script.txt", "CODAchain1.txt",
 "CODAindex.txt"), c("Node12/data.txt", "Node12/inits1.txt",
 "Node12/log.odc", "Node12/script.txt",
  "Node12/CODAchain1.txt",
 "Node12/CODAindex.txt"), overwrite=TRUE,
 copy.date = TRUE)
file.remove(c("data.txt", "inits1.txt", "log.odc", "script.txt", "log.txt", "CODAchain1.txt", "CODAindex.txt"))
# Import coda output
coda12 <- read.bugs("Node12/CODAchain1.txt")
summary(coda12)
```

 # Nodesplitting: Code for SharedParFE.txt for Moderate-Severe Exacerbations

```
model{ # *** PROGRAM STARTS
# Binomial likelihood, cloglog link model for number of events data
# node-split specific items
for(i in 1:ns){ # LOOP THROUGH ALL STUDIES
 delta[i,bi[i]] <- 0 # Treatment effect is zero for control arm
```

```
 w[i, bi[i]] <- 0 # Adjustment for multi-arm trials is zero for control arm

 # LOOP THROUGH ALL ARMS
 for (k in 1:na[i]){ index[i,k] <- split[i] * (equals(t[i,k], pair[1]) + equals(t[i,k], pair[2])) }
 for (k in 2:na[i]) {
 # trial-specific LHR distributions, split into direct and indirect (through MTC)
 delta[i,si[i,k]] <- (d[si[i,k]] - d[bi[i]])*(1-index[i,m[i,k]]) + direct*index[i,m[i,k]]
 }
 }
for(i in 1:nsBi){ # LOOP THROUGH STUDIES WITH BINOMIAL DATA
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # LOOP THROUGH ARMS
 r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # Binomial likelihood
 cloglog(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]] # Model for linear pred
 rhat[i,k] <- p[i,t[i,k]] * n[i,k] # expected value of the numerators
 # Deviance contribution
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
  + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for each trial
 }
# Normal likelihood, identity link for data given as lnHR
# two arm studies only
for(i in (nsBi+1):(nsBi+ns2)){ # LOOP THROUGH 2-ARM STUDIES WITH NORMAL DATA
 prec[i,2] <- pow(se[i,2],-2) # set precisions
 # normal likelihood for 2-arm trials
 y[i,2] ~ dnorm(delta[i,t[i,2]],prec[i,2])
 # Deviance contribution for trial i
 dev[i,2] <- (y[i,2] - delta[i,t[i,2]]) * (y[i,2] - delta[i,t[i,2]]) * prec[i,2]
 resdev[i] <- dev[i,2]
 }
# Three arm studies
for(i in (nsBi+ns2+1):(nsBi+ns2+ns3)){ # LOOP THROUGH 3-ARM STUDIES
 for (k in 2:na[i]){ var[i,k] <- pow(se[i,k],2) }
 for (k in 1:(na[i]-1)){ # set variance-covariance matrix
 for (j in 1:(na[i]-1)){
 Sigma2[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
 }
 }
 # Precision matrix
 Omega2[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma2[i,,])
  # multivariate normal likelihood for 3-arm trials
 y[i,2:na[i]] ~ dmnorm(delta[i+nsBi,2:na[i]],Omega2[i,1:(na[i]-1),1:(na[i]-1)])
 # Deviance contribution for trial i
 for (k in 1:(na[i]-1)){ # multiply vector & matrix
 ydiff2[i,k]<- y[i,(k+1)] - delta[i+nsBi,(k+1)]
 z2[i,k]<- inprod(Omega2[i,k,1:(na[i]-1)], ydiff2[i,1:(na[i]-1)])
 }
```

```
 resdev[i+nsBi]<- inprod(ydiff2[i,1:(naNo[i]-1)], z2[i,1:(naNo[i]-1)])
 }
totresdevBi <- sum(resdev[1:nsBi]) # res dev for Binomial data
totresdevNo <- sum(resdev[nsBi+1:nsBi+ns2+ns3]) # res dev for Normal data
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment
direct ~ dnorm(0, 1.0E-6) # vague prior for direct comparison parameter
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
for (c in 1:(nt-1)){ # pairwise LHR and HR
 for (k in (c+1):nt){
 lhr[c,k] <- (d[k]-d[c])
 log(hr[c,k]) <- lhr[c,k]
 }
 }
# Calculate p-value
prob <- step(direct-lhr[pair[1], pair[2]])
} # *** PROGRAM ENDS
```

 # Nodesplitting: Code for DichotRE.txt for Severe Exacerbations

```
model{
# MTC Random effects model
# Binomial Likelihood, Cloglog link model for number of events data

for(i in 1:ns){
 w[i,1] <-0
 j[i,1] <-0
 delta[i,bi[i]] <- 0
 mu[i] ~ dnorm(0,.0001) # vague priors for 24 trial baselines
 for (k in 1:na[i]) {
  r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
  cloglog(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]] # model
  index[i,k] <- split[i] * (equals(t[i,k], pair[1]) + equals(t[i,k], pair[2])) #Deviance contribution
  rhat[i,k] <- p[i,t[i,k]] * n[i,k] # expected value of the numerators
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 resdev[i]<-sum(dev[i,1:na[i]])
 for (k in 2:na[i]) {
# trial-specific LHR distributions:
 delta[i,si[i,k]] ~ dnorm(md[i,si[i,k]],taud[i,si[i,k]])
# mean of LHR distributions, split into direct and indirect (through MTC):
 md[i,si[i,k]] <- (d[si[i,k]] - d[bi[i]] + sw[i,k])*(1-index[i,m[i,k]]) + direct*index[i,m[i,k]]
# adjustment for multi-arm RCTs with correction for arms removed to split node:
  j[i,k] <- k - (equals(1, split[i]) * step(k-3))
 taud[i,si[i,k]] <- tau *2*(j[i,k]-1)/j[i,k] # precision of LHR dist.
# adjustment, multi-arm RCTs
 w[i,k] <- (delta[i,si[i,k]] - d[si[i,k]] + d[bi[i]]) * (1-index[i,k])
# cumulative adjustment for multi-arm trials:
```

```
 sw[i,k] <- sum(w[i,1:k-1])/(j[i,k]-1) }
 }
d[1]<-0
direct ~ dnorm(0,1.0E-6) # vague prior for direct comparison parameter
for (k in 2:nt){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
sd~dunif(0,2) # vague prior for random effects standard deviation
var <- pow(sd,2)
tau <-1/var
totresdev<-sum(resdev[]) #Total Deviance
# pairwise HRs
for (c in 1:(nt-1)) { for (k in (c+1):nt) { hr[c,k] <- exp(d[k] - d[c] )
 lhr[c,k]<-(d[k]-d[c])} }
# calculate p-value
prob <- step(direct - lhr[pair[1], pair[2]])
}
```

Appendix 3. Model fit parameters

	Fixed-Effect Model	Random-Effects Model
Severe exacerbations- group (37 DPs)		
DIC	192.5	171.9
Total Residual Deviance, Mean	75.29	46.8
Between-study SD, Median (95% CrI)	--	0.477 (0.027, 1.246)
Moderate to severe exacerbations (54 DPs)		
DIC	296.4	288.0
Total Residual Deviance, Mean	72.47	54.88
Between-study SD, Median (95% CrI)	--	0.172 (0.067, 0.333)
Change from baseline in ACQ score at 3 months (11 DPs)		
DIC	17.43	19.07
Total Residual Deviance, Mean	9.42	9.78
Between-study SD, Median (95% CrI)	--	0.039 (0.002, 0.297)
Change from baseline in ACQ score at 6 months (22 DPs)		
DIC	33.83	35.41
Total Residual Deviance, Mean	20.82	20.06
Between-study SD, Median (95% CrI)	--	0.028 (0.001, 0.097)
Change from baseline in ACQ score at 12 months (10 DPs)		
DIC	20.85	19.49
Total Residual Deviance, Mean	13.84	10.08
Between-study SD, Median (95% CrI)	--	0.103 (0.009, 0.617)
Change from baseline in AQLQ scores at 3 months (14 DPs)		
DIC	21.10	22.07
Total Residual Deviance, Mean	11.11	11.68
Between-study SD, Median (95% CrI)	--	0.038 (0.002, 0.155)
Change from baseline in AQLQ scores at 6 months (14 DPs)		
DIC	28.38	27.38
Total Residual Deviance, Mean	18.38	14.54
Between-study SD, Median (95% CrI)	--	0.121 (0.009, 0.293)
ACQ response at 6 months (15 DPs)		
DIC	28.38	27.50
Total Residual Deviance, Mean	18.38	14.48
Between-study SD, Median (95% CrI)	--	0.130 (0.010, 0.511)
ACQ response at 12 months (8 DPs)		
DIC	18.68	17.44
Total Residual Deviance, Mean	12.65	10.07
	--	0.105 (0.003, 0.646)

Between-study SD, Median (95% CrI)		
Asthma-related SAEs (58 DPs)		
DIC	115.36	110.35
Total Residual Deviance, Mean	85.55	73.99
Between-study SD, Median (95% CrI)	--	0.507 (0.012, 1.448)
All-cause SAEs (79 DPs)		
DIC	163.99	150.19
Total Residual Deviance, Mean	124.58	96.49
Between-study SD, Median (95% CrI)	--	0.418 (0.047, 0.748)
All-cause AEs (77 DPs)		
DIC	267.37	138.89
Total Residual Deviance, Mean	229.25	73.77
Between-study SD, Median (95% CrI)	--	0.362 (0.271, 0.489)
Dropouts due to AEs (80 DPs)		
DIC	142.59	138.94
Total Residual Deviance, Mean	102.32	91.72
Between-study SD, Median (95% CrI)	--	0.265 (0.012, 0.643)

ACQ: Asthma Control Questionnaire, AE: adverse event, AQLQ: Asthma Quality of Life Questionnaire, CrI: credible interval; DIC: deviance information criterion; DP: data point, SAE: serious adverse event, SD: standard deviation.

Appendix 4. Node-splitting results for severe exacerbations

Comparison	Model	*p*	Mean LHR (95% CrI)
HD-ICS vs. MD-ICS			
	Direct	0.825	0.115 (-1.687, 2.118)
	Indirect		0.516 (-2.530, 3.670)
	Network		0.247 (-0.766, 1.440)
HD-ICS/LABA vs. MD-ICS			
	Direct	0.250	0.655 (-0.768, 2.532)
	Indirect		0.732 (-2.986, 1.421)
	Network		0.253 (-0.652, 1.382)
MD-ICS/LABA vs. HD-ICS			
	Direct	0.649	-0.489 (-2.132, 1.070)
	Indirect		-0.029 (-1.902, 1.656)
	Network		-0.246 (-1.318, 0.792)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LHR: Log hazard ratio; MD: medium dose.

Appendix 5. Node-splitting results for moderate to severe exacerbations for grouped treatments

Comparison	Model	*p*	Mean LHR (95% CrI)
HD-ICS vs. MD-ICS			
	Direct	0.246	-0.083 (-0.290, 0.121)

	Indirect		0.183 (-0.248, 0.588)
	Network		-0.034 (-0.227, 0.153)
MD-ICS/LABA vs. MD-ICS			
	Direct	0.377	-0.295 (-0.384, -0.207)
	Indirect		-0.407 (-0.655, -0.156)
	Network		-0.301 (-0.390, -0.213)
HD-ICS/LABA vs. MD-ICS			
	Direct	0.807	-0.506 (-0.709, -0.304)
	Indirect		-0.475 (-0.643, -0.307)
	Network		-0.483 (-0.621, -0.347)
MD-ICS/LABA vs. HD-ICS			
	Direct	**0.007**	-0.487 (-0.750, -0.237)
	Indirect		-0.157 (-0.355, 0.049)
	Network		-0.267 (-0.451, -0.078)
HD-ICS/LABA vs. HD-ICS			
	Direct	0.446	-0.478 (-0.684, -0.272)
	Indirect		-0.384 (-0.633, -0.129)
	Network		-0.449 (-0.635, -0.260)
MD-ICS/LABA vs. MD-ICS/LAMA			
	Direct	0.380	0.405 (-0.249, 0.461)
	Indirect		0.458 (-0.240, 1.199)
	Network		0.178 (-0.159, 0.513)
HD-ICS/LABA vs. MD-ICS/LABA			
	Direct	0.458	-0.181 (-0.300, -0.063)
	Indirect		-0.580 (-1.766, 0.436)
	Network		-0.182 (-0.303, -0.062)

Comparisons in **bold** exhibit evidence of inconsistency. Negative valued LHRs favour the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; lnHR: log hazard ratio; MD: medium dose.

Appendix 6. Node-splitting results for CFB in ACQ score at 3 months

Comparison	Model	*P*	Mean Difference (95% CrI)
HD-ICS vs. MD-ICS			
	Direct	0.552	-0.101 (-0.377, 0.171)
	Indirect		-0.007 (-0.376, 0.360)
	Network		-0.063 (-0.211, 0.079)
HD-ICS/LABA vs. MD-ICS			

	Direct	0.855	-0.206 (-0.476, 0.064)
	Indirect		-0.178 (-0.553, 0.197)
	Network		-0.191 (-0.338, -0.055)

Mean differences less than zero favour the first named treatment. Crl: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose

Appendix 7. Node-splitting results for CFB in ACQ score at 6 months.

Comparison	Model	*p*	Mean Difference (95% Crl)
HD-ICS/LABA vs. MD-ICS			
	Direct	0.739	-0.215 (-0.346, -0.082)
	Indirect		-0.241 (-0.356, -0.126)
	Network		-0.221 (-0.307, -0.136)
MD-ICS/LABA vs. MD-ICS/LAMA			
	Direct	0.523	-0.023 (-0.130, 0.089)
	Indirect		-0.082 (-0.240, 0.076)
	Network		-0.039 (-0.123, 0.044)

Mean differences less than zero favour the first named treatment. Crl: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose

Appendix 8. Node-splitting results for CFB in ACQ scores at 12 months

Comparison	Model	*p*	Mean Difference (95% Crl)
MD-ICS/LABA vs. MD-ICS			
	Direct	0.358	-0.267 (-0.583, 0.057)
	Indirect		-0.079 (-0.507, 0.313)
	Network		-0.196 (-0.425, 0.007)
MD-ICS/LABA vs. HD-ICS			
	Direct	0.303	-0.190 (-0.492, 0.113)
	Indirect		0.069 (-0.457, 0.593)
	Network		-0.126 (-0.363, 0.115)
HD-ICS/LABA vs. HD-ICS			
	Direct	0.754	-0.146 (-0.491, 0.198)
	Indirect		-0.066 (-0.572, 0.437)
	Network		-0.142 (-0.356, 0.086)

Mean differences less than zero favour the first named treatment. Crl: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose

Appendix 9. Node-splitting results for CFB in AQLQ scores at 6 months

Comparison	Model	*p*	Mean Difference (95% CrI)
MD-ICS/LABA vs. HD-ICS/LABA			
	Direct	0.277	-0.095 (-0.356, 0.165)
	Indirect		0.169 (-0.360, 0.690)
	Network		-0.052 (-0.274, 0.186)

Mean differences greater than zero favour the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; HD: high dose; MD: medium dose.

Appendix 10. Node-splitting results for ACQ Response at 6 months

Comparison	Model	*p*	LORs (95% CrI)
HD-ICS/LABA vs. MD-ICS			
	Direct	0.930	0.459 (-0.035, 0.954)
	Indirect		0.486 (-0.079, 1.066)
	Network		0.469 (0.186, 0.757)
MD-ICS/LABA vs. MD-ICS/LAMA			
	Direct	0.867	0.096 (-0.379, 0.575)
	Indirect		0.153 (-0.479, 0.792)
	Network		0.115 (-0.169, 0.407)

Negative LORs favour the second named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; LOR: log odds ratio; MD: medium dose.

Appendix 11. Node-splitting results for asthma-related SAEs

Comparison	Model	*p*	LOR (95% CrI)
HD-ICS vs. MD-ICS			
	Direct	0.617	-0.376 (-2.272, 1.226)
	Indirect		0.436 (-2.682, 3.770)
	Network		-0.211 (-1.530, 1.048)
MD-ICS/LABA vs. MD-ICS			
	Direct	**0.051**	-0.195 (-1.200, 0.984)
	Indirect		-24.883 (-86.119, -0.199)
	Network		-0.265 (-1.061, 0.612)
HD-ICS/LABA vs. MD-ICS			
	Direct	0.510	0.781 (-0.925, 3.167)
	Indirect		-0.111 (-2.451, 2.229)
	Network		0.296

			(-0.700, 1.560)
MD-ICS/LABA vs. HD-ICS			
Direct			-0.121 (-2.108, 2.159)
	Indirect	0.985	-0.071 (-3.415, 3.291)
	Network		-0.051 (-1.254, 1.286)
HD-ICS/LABA vs. HD-ICS			
Direct			0.634 (-0.631, 2.251)
	Indirect	**0.060**	25.889 (0.321, 84.455)
	Network		0.516 (-0.592, 1.911)
MD-ICS/LABA vs. MD-ICS/LAMA			
Direct			-1.303 (-5.304, 1.643)
	Indirect	0.328	0.953 (-2.639, 5.275)
	Network		0.027 (-1.804, 1.868)
HD-ICS/LABA vs.MD-ICS/LABA			
Direct			0.653 (-0.401, 2.101)
	Indirect	0.346	-1.174 (-6.028, 2.586)
	Network		0.562 (-0.368, 1.663)

Negative LORs favour the second named treatment. Comparisons in bold exhibit evidence of inconsistency. Crl: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; LOR: log odds ratio; MD: medium dose; SAE: serious adverse event.

Appendix 12. Node-splitting results for all-cause SAEs

Comparison	Model	*p*	LORs (95% Crl)
HD-ICS vs. MD-ICS			
	Direct	0.960	-0.366 (-1.104, 0.313)
	Indirect		-0.334 (-1.432, 0.759)
	Network		-0.291 (-0.842, 0.208)
MD-ICS/LABA vs. MD-ICS			
	Direct	0.252	0.049 (-0.290, 0.426)
	Indirect		-0.850 (-2.536, 0.674)
	Network		0.045 (-0.286, 0.395)
HD-ICS/LABA vs. MD-ICS			
	Direct	0.761	0.090 (-0.685, 0.866)
	Indirect		-0.076 (-0.936, 0.734)
	Network		0.026 (-0.451, 0.496)
MD-ICS/LABA vs. HD-ICS			
	Direct	0.083	0.058 (-0.605, 0.769)

	Indirect		1.201 (0.117, 2.383)
	Network		0.338 (-0.154, 0.888)
HD-ICS/LABA vs. HD-ICS			
	Direct	0.268	0.268 (-0.296, 0.858)
	Indirect		1.235 (-0.397, 3.004)
	Network		0.319 (-0.185, 0.856)
MD-ICS/LABA vs. MD-ICS/LAMA			
	Direct	0.704	-0.119 (-1.238, 0.969)
	Indirect		0.216 (-1.219, 1.625)
	Network		0.084 (-0.685, 0.849)
HD-ICS/LABA vs. MD-ICS/LABA			
	Direct	0.813	0.003 (-0.580, 0.539)
	Indirect		0.221 (-1.672, 2.018)
	Network		-0.017 (-0.471, 0.401)

Negative LORs favour the second named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; LOR: log odds ratio; MD: medium dose; SAE: serious adverse event.

Appendix 13. Node-splitting results for all-cause AEs

Comparison	Model	*p*	LOR (95% CrI)
HD-ICS vs. MD-ICS			
	Direct	0.434	-0.001 (-0.392, 0.394)
	Indirect		0.258 (-0.264, 0.794)
	Network		0.110 (-0.195, 0.420)
MD-ICS/LABA vs. MD-ICS			
	Direct	0.498	0.063 (-0.150, 0.277)
	Indirect		-0.231 (-1.067, 0.605)
	Network		0.040 (-0.146, 0.228)
HD-ICS/LABA vs. MD-ICS			
	Direct	0.212	-0.260 (-0.698, 0.185)
	Indirect		0.120 (-0.294, 0.542)
	Network		-0.047 (-0.338, 0.248)
MD-ICS/LABA vs. HD-ICS			
	Direct	0.438	-0.214 (-0.662, 0.226)
	Indirect		0.038 (-0.436, 0.506)
	Network		-0.069 (-0.381, 0.234)
HD-ICS/LABA vs. HD-ICS			

	Direct	0.913	-0.165 (-0.509, 0.177)
	Indirect		-0.120 (-0.912, 0.672)
	Network		-0.157 (-0.459, 0.144)
MD-ICS/LABA vs. MD-ICS/LAMA			
	Direct	0.718	0.013 (-0.575, 0.605)
	Indirect		0.176 (-0.504, 0.852)
	Network		0.167 (-0.240, 0.581)
HD-ICS/LABA vs. MD-ICS/LABA			
	Direct	0.486	-0.002 (-0.327, 0.324)
	Indirect		-0.278 (-0.994, 0.438)
	Network		-0.087 (-0.366, 0.191)

Negative LORs favour the second named treatment. AE: adverse event; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; LOR: log odds ratio; MD: medium dose.

Appendix 14. Node-splitting results for dropouts due to AEs for grouped treatments

Comparison	Model	*p*	LOR (95% CrI)
HD-ICS vs. MD-ICS			
	Direct	0.380	0.147 (-0.986, 1.249)
	Indirect		-0.466 (-1.356, 0.401)
	Network		-0.259 (-0.930, 0.388)
LD-ICS/LABA vs. MD-ICS			
	Direct	0.351	-0.445 (-1.555, 0.658)
	Indirect		0.430 (-1.148, 2.048)
	Network		-0.138 (-0.942, 0.698)
MD-ICS/LABA vs. MD-ICS			
	Direct	0.291	-0.033 (-0.385, 0.315)
	Indirect		0.834 (-0.760, 2.561)
	Network		-0.030 (-0.365, 0.297)
HD-ICS/LABA vs. MD-ICS			
	Direct	0.779	-0.109 (-1.213, 0.989)
	Indirect		-0.278 (-0.999, 0.390)
	Network		-0.204 (-0.789, 0.353)
MD-ICS/LABA vs. HD-ICS			
	Direct	0.981	0.260 (-0.606, 1.157)
	Indirect		0.249

			(-0.823, 1.256)
	Network		0.232 (-0.396, 0.863)
HD-ICS/LABA vs. HD-ICS			
	Direct	0.247	0.216 (-0.540, 0.962)
	Indirect		-0.864 (-2.659, 0.800)
	Network		0.056 (-0.586, 0.693)
MD-ICS/LABA vs. MD-ICS/LAMA			
	Direct	**0.002**	0.181 (-0.909, 1.270)
	Indirect		17.794 (2.566, 54.043)
	Network		0.634 (-0.164, 1.516)
HD-ICS/LABA vs. MD-ICS/LABA			
	Direct	0.159	-0.339 (-0.958, 0.224)
	Indirect		0.900 (-0.760, 2.558)
	Network		-0.173 (-0.693, 0.334)

Negative LORs favour the second named treatment. AE: adverse event; Crl: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; LOR: log odds ratio; MD: medium dose.

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Additional tables

Table 1

Study characteristics of included trials in the grouped treatment comparison

Study, year	Arms included Dose in micrograms	Duration (weeks)	No. of participants included	Mean age	Male %	White %	Current smoker excluded: maximum PYs allowed for ex-smokers	Baseline FEV1 (L) prebronchodilator (% predicted)	History of at least one asthma exacerbation
Bateman 2014	FF 100 µg qd	24-78	1010	42.3	32	74	Y/10	2.1 (69)	Required
	FF/VI 100/25 µg qd		1009	41.1	34	73		2.1 (69)	
Beasley 2015	MF 400 µg qd	68	759	42.3	41	63	Y/10	2.3 (76)	Not required
	MF/IND 400/500 µg qd		749	42.4	42	61		2.3 (75)	
Bernstein 2011	MF 200 µg bid (open label)	12	983	NR	NR	NR	Y/10	NR	Not required
	MF/FM 200/10 µg bid		371	44.8	87	87		2.3 (74)	
	FP/SAL 250/50 µg bid		351	45.1	86	86		2.4 (74)	
Bernstein 2015	FF 100 µg qd	12	347	44.7	43	88	Y/10	2.0 (61)	Not required
	FF/VI 100/25 µg qd		346	45.9	41	89		2.0 (63)	
	FF/VI 200/25 µg qd		346	46.6	35	87		2.0 (62)	
Bernstein 2017	FP 200 µg bid	12	106	47.7	38	88	Y/10	2.0 (63)	Not required
	FP 400 µg bid		107	50.9	33	85		2.0 (65)	
Bleecker 2014	FF 100 µg qd	12	205	40.4	39	83	Y/10	2.3 (70)	Not required
	FF/VI 100/25 µg qd		201	40.7	42	86		2.3 (71)	
Brown 2012	BUD 320 µg bid	52	365	38.4	36	0	N/10	2.3 (78)	Not required
	BUD/FM 320/9 µg bid		377	36.2	34	0		2.3 (77)	
CHIESI 2009	BDP/FM 100/6 µg DPI bid Arm B	12	173	NR	42	NR	Y/NR	2.4 (NR)	Not required
	BDP/FM 100/6 µg pMDI bid Arm A		173	NR	36	NR		2.3 (NR)	
	BDP/FM 200/12 µg DPI bid Arm D		174	NR	43	NR		2.5 (NR)	
	BDP/FM 200/12 µg pMDI bid Arm C		176	NR	48	NR		2.5 (NR)	
Corren 2013	FP 250 µg bid	12	113	41.9	44	79	Y/10	2.1 (66)	Not required
			110	44.8	42	84		2.1 (65)	

	FP/FM 250/10 µg bid								
Hamelmann 2016	MD-ICS	24	138	14.2	64	NR	Y/NR	2.7 (83)	Not required
	MD-ICS + Tio 2.5 µg qd		125	14.2	65	NR		2.7 (82)	
	MD-ICS +Tio 5 µg qd		134	14.5	66	NR		2.8 (83)	
Huchon 2009	BDP 500 µg bid	24	213	47.3	37	NR	N/10	2.0 (65)	Not required
	BDP 500 µg + FM 24 µg bid		220	47.4	35	NR		2.0 (66)	
	xf-BDP/FM 200/12 µg bid		212	47.3	35	NR		2.0 (65)	
Katial 2011	FP 250 µg bid	52	315	39.3	36	66	Y/10	2.2 (69)	Not required
	FP/SAL 250/50 µg bid		306	36.8	38	64		2.2 (69)	
Kerstjens 2015	MD-ICS	24	523	42.8	41	48	Y/10	2.3 (73)	Not required
	MD-ICS +Tio 2.5 µg qd		519	43.4	39			2.3 (73)	
	MD-ICS +Tio 5 µg qd		517	44.3	42			2.2 (72)	
	MD-ICS + SAL 50 µg bid		541	42.1	42			2.3 (73)	
Kerstjens 2020	MF/IND 160/150 qd	52	617	51.8	39	73	Y/10	1.6 (55)	Required
	MF/IND 320/150 qd		618	52	39	73		1.6 (54)	
	FP/SAL 500/50 bid		618	52.9	33	76		1.6 (55)	
Kerwin 2011	FP 250 µg bid	52	318	39.6	43	82	Y/10	2.3 (68)	Not required
	FP/SAL 250/50 µg bid		310	40.9	40	82		2.2 (69)	
Kerwin 2020	FF 100 µg qd	24	143	49.3	26	92	Y/10	2.1 (68)	Not required
	FF 100 µg + UMEC 62.5 µg qd		139	48.5	29	93		2.2 (69)	
Lee 2020	FF/VI 100/25 µg qd	24-52	407	53.3	38	80	Y/10	1.7 (58)	Not required
	FF/VI 200/25 µg qd		406	53.9	38	78		1.7 (59)	
Lin 2015	FP 500 µg bid	12	154	48.8	44	0	Y/10	1.8 (68)	Not required
	FF/VI 200/25 µg qd		155	46.9	38	0		1.8 (68)	
Mansfield 2017	FP 100 µg bid (MDPI)	26	127	41.5	39	87	Y/10	2.5 (NR)	Not required
	FP 220 µg bid		42	38.4	38	62		2.7 (NR)	
	FP 200 µg bid (MDPI)		126	42	37	79		2.6 (NR)	
	FP 440 µg bid		41	43.6	39	88		2.4 (NR)	
	FP/SAL 100/12.5 bid (MDPI)		120	43.9	30	83		2.5 (NR)	
	FP/SAL 250/50 bid		41	45.9	51	78		2.4 (NR)	
	FP/SAL 200/12.5 bid (MDPI)		133	46.1	46	71		2.3 (NR)	
	FP/SAL 500/50 bid		44	45.6	48	70		2.5 (NR)	
Murphy 2015	BUD 320 µg bid	12	72	42.7	51	79	N/10	2.2 (NR)	Not required
	BUD/FM BA 320/9 µg bid		71	42.6	34	89		2.0 (NR)	
	BUD/FM pMDI 320/9 µg bid		71	42.8	48	80		2.2 (NR)	
Nathan 2010	MF 200 µg bid	26	192	42.8	42	70	Y/10	2.4 (73)	Not required
	MF/FM 200/10 µg bid		191	42.9	49	71		2.4 (72)	
O'Byrne 2014	FP 500 µg bid	24	195	47.3	41	83	Y/10	2.1 (68)	Not required
	FF 200 µg qd		194	44.6	42	85		2.2 (67)	
	FF/VI 200/25 µg qd		197	46.6	41	84		2.1 (67)	
Paggiaro 2016b	xf-BDP 800 µg qd	12	175	49.1	36	NR	Y/5	1.9 (64)	Not required
	xf-BDP/FM 800/24 µg qd		184	49.5	46	NR		2.1 (65)	

Pedersen 2017	CIC 160 µg bid	52	122	44.7	37	94	N/NR*	NR (75)	Not required
	CIC 320 µg bid		125	45.3	35	91		NR(72)	
Pertseva 2013	FP 250 µg bid	12	289	42.5	33	76	Y/10	1.9 (63)	Not required
	FP/FM 250/10 µg bid		145	41.2	40	78		2.0 (64)	
Peters 2008	BUD 640 µg bid	52	133	39.8	32	87	Y/20	2.4 (73)	Not required
	BUD/FM 320/9 µg bid		132	38.6	41	89		2.4 (72)	
	BUD/FM 640/18 µg bid		443	41	37	87		2.4 (75)	
Peters 2016	BUD 320 µg bid	26	4201	44.7	34	68	N/10	NR	Required
	BUD/FM 160/4.5 µg bid		1645	39.3	37	70		NR	
	BUD/FM 320/9 µg bid		4201	45.1	33	69		NR	
Sher 2017	FP 100 µg bid (MDPI)	12	146	45.7	36	76	Y/10	2.1 (66)	Not required
	FP 200 µg bid (MDPI)		146	44.4	40	79		2.1 (64)	
	FP/SAL 100/12.5 µg bid (MDPI)		145	44.3	46	77		2.2 (65)	
	FP/SAL 200/12.5 µg bid (MDPI)		146	44.7	40	86		2.1 (65)	
Spector 2012	BUD 360 µg bid	12	148	39.8	41	0	N/NR	2.1 (70)	Not required
	BUD/FM 320/9 µg bid		153	38.6	29	0		2.0 (69)	
Stempel 2016	FP 250 µg bid	26	578	43.4	33	75	Y/10	NR (PEF>=50%)	Required
	FP 500 µg bid		988					NR (PEF>=50%)	
	FP/SAL 250/50 bid		580	43.4	34	75		NR (PEF>=50%)	
	FP/SAL 500/50 bid		982					NR (PEF>=50%)	
Stirbulov 2012	BUD 400 µg bid	12	90	NR	NR	NR	Y/20	2.3 (76)	Not required
	BUD/FM 400/12 µg bid		85					2.3 (77)	
van Zyl-Smit 2020	MF 400 µg qd	26-52	444	48.7	39	70	Y/10	2.1 (67)	Not required
	MF 400 µg bid		442	47.5	43	72		2.1 (68)	
	MF/IND 320/150 qd		445	47.1	41	70		2.1 (67)	
	MF/IND 160/150 qd		439	47.4	42	71		2.1 (67)	
	FP/SAL 500/50 bid		446	48.9	43	68		2.1 (67)	
Weinstein 2010	MF 400 µg bid	12	240	47.8	43	90	Y/10	2.0 (67)	Not required
	MF/FM 200/10 bid		233	48.4	42	90		2.1 (67)	
	MF/FM 400/10 bid		255	47.7	46	89		2.0 (66)	
Woodcock 2013	FF/VI 100/25 qd	24	403	43.8	39	60	Y/10	2.0 (68)	Not required
	FP/SAL 250/50 bid		403	41.9	39	58		2.0 (69)	
Woodcock 2014	FF 100 µg qd	24	119	46.6	32	85	Y/10	2.0 (68)	Not required
	FF 200 µg qd		119	45.1	34	84		2.1 (68)	
Zangrilli 2011	BUD 320 µg bid	12	123	37.0.	35	NR	Y/10	2.2 (71)	Not required
	BUD/FM 320/9 µg bid		127	39.8	34	NR		2.2 (73)	

***** 87% of participants were never-smokers and 0.8% of them were current smokers. Abbreviations: bid= twice daily; BDP= beclomethasone dipropionate; BUD=budesonide; FEV1= forced expiratory volume in the first second; FF=fluticasone furoate; FM=formoterol; FP=fluticasone propionate; GLY= glycopyrronium; IND=indacaterol; MDPI= multidose dry powder inhaler; MF=mometasone furoate; NR= not reported; PEF=peak expiratory flow; PY= pack-year; qd=once daily; SAL=salmeterol; Tio=tiotropium; UMEC= umeclidinium; VI=vilanterol.

Table 2

Study characteristics of participants across the treatment groups for clinical heterogeneity assessment

Treatment arm	No. of patients included	Mean age	Male %	White %	Maximum pack years allowed for smokers	Baseline FEV1 L (% predicted)	History asthma exacerbation (%)
MD-ICS	11472	43.3	37	69	10-20	2.2 (69)	53
HD-ICS	3944	44.8	38	76	5-20	2.2 (70)	32
LD-ICS/LABA	1991	39.3	37	70	10	2.4 (NR)	83

MD-ICS/LAMA	1434	39.0	44	53	10	2.3 (78)	1
MD-ICS/LABA	13211	44.3	40	72	10-20	2.1 (68)	51
HD-ICS/LABA	5418	47.8	38	77	5-20	1.9 (63)	51

Abbreviations: FEV1: forced expiratory volume in the first second; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; NR: not reported.

Table 3

Hazard Ratios (HRs) for Severe Exacerbations using a random-effects model

Comparison	Median HR (95% CrI)
HD-ICS vs. MD-ICS	1.280 (0.465, 4.222)
LD-ICS/LABA vs. MD-ICS	0.646 (0.072, 6.177)
MD-ICS/LAMA vs. MD-ICS	0.409 (0.010, 8.620)
MD-ICS/LABA vs. MD-ICS	1.003 (0.496, 2.337)
HD-ICS/LABA vs. MD-ICS	1.288 (0.521, 3.982)
LD-ICS/LABA vs. HD-ICS	0.501 (0.047, 4.980)
MD-ICS/LAMA vs. HD-ICS	0.313 (0.006, 7.641)
MD-ICS/LABA vs. HD-ICS	0.782 (0.268, 2.208)
HD-ICS/LABA vs. HD-ICS	1.002 (0.372, 2.828)
MD-ICS/LAMA vs. LD-ICS/LABA	0.614 (0.008, 26.070)
MD-ICS/LABA vs. LD-ICS/LABA	1.557 (0.198, 12.89)
HD-ICS/LABA vs. LD-ICS/LABA	2.001 (0.217, 20.64)
MD-ICS/LABA vs. MD-ICS/LAMA*	2.489 (0.111, 114.00)
HD-ICS/LABA vs. MD-ICS/LAMA*	3.242 (0.136, 159.70)
HD-ICS/LABA vs. MD-ICS/LABA	1.282 (0.537, 3.322)

The second named treatment is the baseline intervention. Hazard Ratios less than one favour the first named treatment. * The HRs for these comparisons are extremely uncertain due to sparsity in the network and should be treated with caution. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 4

Mean and median ranks, with the corresponding 95% CrIs for severe exacerbations sorted by mean rank (random-effects model)

Treatments	Mean Rank	Median Rank	95% CrI
MD-ICS/LAMA	2.50	1.0	(1.0, 6.0)
LD-ICS/LABA	3.14	2.0	(1.0, 6.0)
HD-ICS/LABA	3.43	3.0	(1.0, 6.0)
HD-ICS	3.71	4.0	(1.0, 6.0)
MD-ICS	3.77	4.0	(1.0, 6.0)
MD-ICS/LABA	4.45	5.0	(2.0, 6.0)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 5

Thresholds for severe exacerbations

	Lower Threshold		Upper Threshold	
Comparison	New Optimal Treatment	Change in lnHR	New Optimal Treatment	Change in lnHR
HD-ICS vs. MD-ICS	HD-ICS	-1.31	N/A	Inf
MD-ICS/LAMA vs. MD-ICS	N/A	-Inf	LD-ICS/LABA	0.70
MD-ICS/LABA vs. MD-ICS	LD-ICS/LABA	-0.84	MD-ICS	19.14
HD-ICS/LABA vs. MD-ICS	HD-ICS/LABA	-14.95	N/A	Inf
MD-ICS/LABA vs. HD-ICS	LD-ICS/LABA	-14.12	HD-ICS	7.60
HD-ICS/LABA vs. HD-ICS	HD-ICS/LABA	-2.83	HD-ICS	7.47
MD-ICS/LABA vs. LD-ICS/LABA	N/A	-Inf	LD-ICS/LABA	0.68
HD-ICS/LABA vs. MD-ICS/LABA	HD-ICS/LABA	-1.29	LD-ICS/LABA	19.63

HD: high dose; ICS: inhaled corticosteroids; Inf: Infinity; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; lnHR: log hazard ratio; MD: medium dose; N/A: Not Applicable.

Table 6

Asthma exacerbations- pairwise comparisons

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Intervention/control: Any comparison of the following two arms: MD-ICS, HD-ICS, LD-ICS/LABA, MD-ICS/LAMA, MD-ICS/LABA, and HD-ICS/LABA

Outcome: Asthma exacerbation

Setting: Outpatient

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of the evidence	What happens
		With control	With experimental	Difference		
1.1.1 Severe exacerbations - HD-ICS vs MD-ICS № of participants: 3003 (4 studies) Follow up: 6 to 12 months	**RR 1.14** (0.31 to 4.25)	6.5%	**7.4%** (2 to 27.7)	**0.9% more** (4.5 fewer to 21.2 more)	⨁⨁⨁◯ Moderate[a]	HD-ICS likely results in little to no difference in severe exacerbations compared to MD-ICS.
1.1.2 Severe exacerbations - MD-ICS/LAMA vs MD-ICS № of participants: 282 (1 study) Follow up: 6 months	**RR 0.51** (0.05 to 5.61)	1.4%	**0.7%** (0.1 to 7.8)	**0.7% fewer** (1.3 fewer to 6.4 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that MD-ICS/LAMA results in little to no difference in severe exacerbations compared to MD-ICS.
1.1.3 Severe exacerbations - MD-ICS/LABA vs MD-ICS № of participants: 15651 (10 studies) Follow up: 3 to 12 months	**RR 1.02** (0.57 to 1.84)	1.7%	**1.7%** (1 to 3.1)	**0.0% fewer** (0.7 fewer to 1.4 more)	⨁⨁⨁◯ Moderate[b, d]	MD-ICS/LABA likely results in little to no difference in severe exacerbations compared to MD-ICS.
1.1.4 Severe exacerbations - HD-ICS/LABA vs MD-ICS № of participants: 3319 (3 studies) Follow up: 6 to 12 months	**RR 2.12** (0.22 to 20.50)	7.1%	**15.0%** (1.6 to 100)	**7.9% more** (5.5 fewer to 137.9 more)	⨁⨁◯◯ Low[a, e]	The evidence suggests that HD-ICS/LAMA results in little to no difference in severe exacerbations compared to MD-ICS.
1.1.5 Severe exacerbations - MD-ICS/LABA vs HD-ICS № of participants: 2954 (4 studies) Follow up: 6 to 12 months	**RR 0.68** (0.28 to 1.68)	4.3%	**2.9%** (1.2 to 7.3)	**1.4% fewer** (3.1 fewer to 2.9 more)	⨁⨁◯◯ Low[b, g]	The evidence suggests MD-ICS/LABA reduces severe exacerbations compared to HD-ICS.
1.1.6 Severe exacerbations - HD-ICS/LABA vs HD-ICS № of participants: 5028 (6 studies) Follow up: 3 to 12 months	**RR 0.92** (0.55 to 1.53)	3.3%	**3.1%** (1.8 to 5.1)	**0.3% fewer** (1.5 fewer to 1.8 more)	⨁⨁⨁◯ Moderate[b, h]	HD-ICS/LABA likely results in little to no difference in severe exacerbations compared to HD-ICS.
1.1.7 Severe exacerbations - MD-ICS/LABA vs LD-ICS/LABA № of participants: 694 (1 study) Follow up: 3 months	**RR 1.49** (0.42 to 5.24)	1.2%	**1.7%** (0.5 to 6.1)	**0.6% more** (0.7 fewer to 4.9 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that MD-ICS/LABA results in little to no difference in severe exacerbations compared to LD-ICS/LABA.
1.1.8 Severe exacerbations - HD-ICS/LABA vs MD-ICS/LABA № of participants: 4612 (5 studies) Follow up: 6 to 12 months	**RR 1.12** (0.51 to 2.48)	3.1%	**3.5%** (1.6 to 7.7)	**0.4% more** (1.5 fewer to 4.6 more)	⨁⨁⨁◯ Moderate[b]	HD-ICS/LABA likely results in little to no difference in severe exacerbations compared to MD-ICS/LABA.
1.1.9 Severe exacerbations - ICS-LAMA vs ICS № of participants: 282 (1 study) Follow up: 6 months	**RR 0.51** (0.05 to 5.61)	1.4%	**0.7%** (0.1 to 7.8)	**0.7% fewer** (1.3 fewer to 6.4 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that ICS/LAMA results in little to no difference in severe exacerbations compared to ICS/LABA.
1.1.10 Severe exacerbations - ICS-LABA vs ICS № of participants: 19664 (11 studies) Follow up: 3 to 12 months	**RR 1.01** (0.64 to 1.61)	2.2%	**2.2%** (1.4 to 3.5)	**0.0% fewer** (0.8 fewer to 1.3 more)	⨁⨁⨁◯ Moderate[a, d, e]	ICS/LABA likely results in little to no difference in severe exacerbations compared to ICS.
1.2.1 Moderate to severe exacerbations - HD-ICS vs MD-ICS № of participants: 1685 (4 studies) Follow up: 6 to 12 months	**RR 0.81** (0.67 to 0.98)	19.6%	**15.8%** (13.1 to 19.2)	**3.7% fewer** (6.5 fewer to 0.4 fewer)	⨁◯◯◯ Very low[b, g, i]	The evidence is very uncertain about the effect of HD-ICS on moderate to severe exacerbations compared to MD-ICS.
1.2.2 Moderate to severe exacerbations - MD-	**RR 0.48** (0.24 to	7.1%	**3.4%** (1.7 to 6.8)	**3.7% fewer** (5.4 fewer to	⨁⨁◯◯ Low[b, c]	The evidence suggests MD-ICS/LAMA reduces moderate to severe

ICS/LAMA vs MD-ICS № of participants: 679 (2 studies) Follow up: 6 months	0.95)			0.4 fewer)		exacerbations compared to MD-ICS
1.2.3 Moderate to severe exacerbations - MD-ICS/LABA vs MD-ICS № of participants: 7569 (12 studies) Follow up: 3 to 12 months	**RR 0.68** (0.56 to 0.83)	15.0%	**10.2%** (8.4 to 12.4)	**4.8% fewer** (6.6 fewer to 2.5 fewer)	⨁⨁⨁◯ Moderate[i]	MD-ICS/LABA probably reduces moderate to severe exacerbations compared to MD-ICS.
1.2.4 Moderate to severe exacerbations - HD-ICS/LABA vs MD-ICS № of participants: 1759 (2 studies) Follow up: 6 to 12 months	**RR 0.71** (0.33 to 1.56)	22.4%	**15.9%** (7.4 to 35)	**6.5% fewer** (15 fewer to 12.6 more)	⨁⨁◯◯ Low[a, e]	The evidence suggests that HD-ICS/LABA results in little to no difference in moderate to severe exacerbations compared to MD-ICS.
1.2.5 Moderate to severe exacerbations - MD-ICS/LABA vs HD-ICS № of participants: 1357 (3 studies) Follow up: 6 to 12 months	**RR 0.66** (0.52 to 0.83)	23.6%	**15.6%** (12.3 to 19.6)	**8.0% fewer** (11.3 fewer to 4 fewer)	⨁⨁⨁◯ Moderate[g]	MD-ICS/LABA probably reduces moderate to severe exacerbations compared to HD-ICS
1.2.6 Moderate to severe exacerbations - HD-ICS/LABA vs HD-ICS № of participants: 3434 (6 studies) Follow up: 3 to 12 months	**RR 0.64** (0.53 to 0.77)	11.4%	**7.3%** (6 to 8.7)	**4.1% fewer** (5.3 fewer to 2.6 fewer)	⨁⨁⨁◯ Moderate[b]	HD-ICS/LABA probably reduces moderate to severe exacerbations compared to HD-ICS
1.2.7 Moderate to severe exacerbations - MD-ICS/LABA vs LD-ICS/LABA № of participants: 694 (1 study) Follow up: 3 months	**RR 1.62** (0.68 to 3.85)	2.3%	**3.7%** (1.6 to 8.9)	**1.4% more** (0.7 fewer to 6.6 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that MD-ICS/LABA results in little to no difference in moderate to severe exacerbations compared to LD-ICS/LABA.
1.2.8 Moderate to severe exacerbations - HD-ICS/LABA vs MD-ICS/LABA № of participants: 4880 (5 studies) Follow up: 6 to 12 months	**RR 0.91** (0.74 to 1.12)	21.1%	**19.2%** (15.6 to 23.6)	**1.9% fewer** (5.5 fewer to 2.5 more)	⨁⨁⨁◯ Moderate[b]	HD-ICS/LABA likely results in little to no difference in moderate to severe exacerbations compared to MD-ICS/LABA.
1.2.9 Moderate to severe exacerbations - ICS-LABA vs ICS № of participants: 11141 (16 studies) Follow up: 3 to 12 months	**RR 0.69** (0.60 to 0.79)	14.0%	**9.6%** (8.4 to 11)	**4.3% fewer** (5.6 fewer to 2.9 fewer)	⨁⨁⨁◯ Moderate[i]	ICS-LABA probably reduces moderate to severe exacerbations compared to ICS.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose; RCT: randomised controlled trial; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level for imprecision: Confidence interval includes a clinically important difference

b. Downgraded one level for imprecision: Optimal information size is not met

c. Downgraded one level: Total size of less than 1000 patients may suggest small study effect (Dechartres 2013)

d. Sensitivity analysis using the imputation methods for missing data suggested in Guyatt 2017 did not affect the interpretation of results

e. Downgraded one level for substantial heterogeneity I2>= 50% to 90% in the relative risk or risk difference.

f. No events were reported

g. Downgraded one level: The null effect was detected when van

van Zyl-Smit 2020 was removed.

h. The proportion of information from study(ies) at high risk of bias is not sufficient to affect the interpretation of results.

i. Downgraded one level : The 95% CI crossed the line of no effect when missing data were imputed by the methods suggested in Guyatt 2017.

Table 7

Hazard Ratios (HRs) for moderate-severe exacerbations using a fixed-effects model

Comparison	Median HR (95% CrI)
HD-ICS vs. MD-ICS	0.936 (0.700, 1.243)
LD-ICS/LABA vs. MD-ICS	0.425 (0.150, 1.114)
MD-ICS/LAMA vs. MD-ICS	**0.559 (0.378, 0.818)**
MD-ICS/LABA vs. MD-ICS	**0.698 (0.587, 0.820)**
HD-ICS/LABA vs. MD-ICS	**0.587 (0.457, 0.756)**
LD-ICS/LABA vs. HD-ICS	0.454 (0.157, 1.222)
MD-ICS/LAMA vs. HD-ICS	**0.597 (0.370, 0.950)**
MD-ICS/LABA vs. HD-ICS	**0.745 (0.560, 0.989)**
HD-ICS/LABA vs. HD-ICS	**0.628 (0.469, 0.843)**
MD-ICS/LAMA vs. LD-ICS/LABA	1.312 (0.463, 3.959)
MD-ICS/LABA vs. LD-ICS/LABA	1.642 (0.632, 4.581)
HD-ICS/LABA vs. LD-ICS/LABA	1.382 (0.519, 3.944)
MD-ICS/LABA vs. MD-ICS/LAMA	1.248 (0.843, 1.863)
HD-ICS/LABA vs. MD-ICS/LAMA	1.050 (0.680, 1.655)
HD-ICS/LABA vs. MD-ICS/LABA	0.841 (0.677, 1.059)

The second named treatment is the baseline intervention. Hazard Ratios less than one favour the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 8

Mean and median ranks, with the corresponding 95% CrIs for moderate-severe exacerbations sorted by mean rank (random-effects model)

Treatments	Mean Rank	Median Rank	95% CrI
LD-ICS/LABA	1.816	1.0	(1.0, 6.0)
MD-ICS/LAMA	2.256	2.0	(1.0, 4.0)
HD-ICS/LABA	2.394	2.0	(1.0, 4.0)
MD-ICS/LABA	3.674	4.0	(2.0, 4.0)
HD-ICS	5.223	5.0	(4.0, 6.0)
MD-ICS	5.638	6.0	(5.0, 6.0)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 9

Thresholds and new optimum treatments for moderate-severe exacerbations

	Lower Threshold		Upper Threshold	
Comparison	New Optimal Treatment	Change in lnHR	New Optimal Treatment	Change in lnHR
HD-ICS vs. MD-ICS	HD-ICS	-2.22	MD-ICS/LAMA	4.93
MD-ICS/LAMA vs. MD-ICS	MD-ICS/LAMA	-0.46	MD-ICS	32.13
MD-ICS/LABA vs. MD-ICS	N/A	-Inf	MD-ICS/LAMA	0.55
HD-ICS/LABA vs. MD-ICS	HD-ICS/LABA	-2.24	MD-ICS/LAMA	6.27
MD-ICS/LABA vs. HD-ICS	MD-ICS/LABA	-124.00	HD-ICS	2.84
HD-ICS/LABA vs. HD-ICS	HD-ICS/LABA	-1.97	HD-ICS	2.37
MD-ICS/LABA vs. LD-ICS/LABA	MD-ICS/LAMA	-0.28	N/A	Inf
MD-ICS/LABA vs. MD-ICS/LAMA	N/A	Inf	MD-ICS/LAMA	0.66
HD-ICS/LABA vs. MD-ICS/LABA	HD-ICS/LABA	-0.48	N/A	Inf

HD: high dose; ICS: inhaled corticosteroids; Inf: Infinity; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; lnHR: log hazard ratio; MD: medium dose; N/A: Not Applicable.

Table 10

Relative effects change from baseline in ACQ scores at 3 months using a fixed-effects model

Comparison	Median Mean Difference (95% CrI)
HD-ICS vs. MD-ICS	-0.061 (-0.148, 0.026)
LD-ICS/LABA vs. MD-ICS	0.015 (-0.131, 0.160)
MD-ICS/LABA vs. MD-ICS	**-0.205 (-0.266, -0.144)**
HD-ICS/LABA vs. MD-ICS	**-0.187 (-0.266, -0.110)**
LD-ICS/LABA vs. HD-ICS	0.076 (-0.078, 0.229)
MD-ICS/LABA vs. HD-ICS	**-0.144 (-0.223, -0.066)**
HD-ICS/LABA vs. HD-ICS	**-0.127 (-0.202, -0.051)**
MD-ICS/LABA vs. LD-ICS/LABA	**-0.220 (-0.351, -0.088)**
HD-ICS/LABA vs. LD-ICS/LABA	**-0.202 (-0.351, -0.053)**
HD-ICS/LABA vs. MD-ICS/LABA	0.018 (-0.052, 0.088)

Mean differences less than zero favour the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose

Table 11

NMA Summary of Findings for change from baseline in ACQ score at 3 months

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, LD-ICS/LABA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: Change from baseline in ACQ scores at 3 months

Setting: Outpatient

Total studies: 4 RCTs **Total Participants: 5261**	**Relative effect (95% CrI)**	**Anticipated absolute effect** (95% CrI)**		**Certainty of the evidence**	**Ranking*** (95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS[1]**			
HD-ICS (Direct evidence; 1 RCT; 829 participants)	**-0.06** (-0.15 to 0.03)	**0.80** (0.71 to 0.89)	Change from baseline in ACQ score was 0.06 higher (0.03 lower to 0.15 higher)	⨁⨁⨁⨁ **High**	**3.0** (3.0 to 5.0)	HD-ICS results in little to no difference in ACQ score at 3 months compared to MD-ICS
LD-ICS/LABA (Direct evidence; 0 RCTs; 0 participants)	**0.02** (-0.13 to 0.16)	**0.72** (0.58 to 0.87)	Change from baseline in ACQ score was 0.02 lower (0.16 lower to 0.13 higher)	⨁⨁⨁◯ **Moderate** Due to imprecision[2]	**5.0** (3.0 to 5.0)	LD-ICS/LABA probably result in little to no difference in ACQ scores at 3 months compared to MD-ICS
MD-ICS/LABA (Direct evidence; 2 RCTs; 2700 participants)	**-0.21** (-0.14 to -0.27)	**0.94** (0.88 to 1.00)	Change from baseline in ACQ score was 0.21 higher (0.14 higher to 0.27 higher)	⨁⨁⨁⨁ **High**	**1.0** (1.0 to 2.0)	MD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 3 months compared to MD-ICS [3]
HD-ICS/LABA (Direct evidence; 1 RCT; 1255 participants)	**-0.19** (-0.11 to -0.27)	**0.93** (0.85 to 1.00)	Change from baseline in ACQ score was 0.19 higher (0.11 higher to 0.27 higher)	⨁⨁⨁⨁ **High**	**2.0** (1.0 to 2.0)	HD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 3 months compared to MD-ICS [3]
MD-ICS	Reference Comparator[1]	**0.74**	Reference Comparator	Reference Comparator	**4.0** (3.0 to 5.0)	Reference Comparator

NMA-SoF table definitions

** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

1 The mean change from baseline in ACQ score was 0.74 with MD-ICS

2 Downgraded one level for serious imprecision: Small sample sizes in the direct and/or indirect estimate(s).

3 Minimal clinically important difference is 0.5.

CQ: Asthma Control Questionnaire; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose; RCT: randomised controlled trial.

Table 12

Mean and median ranks (with corresponding 95% CrIs) for change from baseline in ACQ scores at 3 months sorted by mean rank (fixed-effect model)

Treatments	**Mean Rank**	**Median Rank**	**95% CrI**
MD-ICS/LABA	1.31	1.00	(1.00, 2.00)
HD-ICS/LABA	1.69	2.00	(1.00, 2.00)
HD-ICS	3.25	3.00	(3.00, 5.00)
MD-ICS	4.34	4.00	(3.00, 5.00)
LD-ICS/LABA	4.41	5.00	(3.00, 5.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose.

Table 13

Relative effects change from baseline in ACQ scores at 6 months using fixed-effect model

Comparison	Median Mean Difference (95% CrI)
HD-ICS vs. MD-ICS	-0.055 (-0.154, 0.044)
MD-ICS/LAMA vs. MD-ICS	**-0.132 (-0.197, -0.067)**
MD-ICS/LABA vs. MD-ICS	**-0.168 (-0.218, -0.118)**
HD-ICS/LABA vs. MD-ICS	**-0.221 (-0.286, -0.155)**
MD-ICS/LAMA vs. HD-ICS	-0.077 (-0.190, 0.036)
MD-ICS/LABA vs. HD-ICS	**-0.113 (-0.209, -0.018)**
HD-ICS/LABA vs. HD-ICS	**-0.166 (-0.260, -0.072)**
MD-ICS/LABA vs. MD-ICS/LAMA	-0.036 (-0.105, 0.033)
HD-ICS/LABA vs. MD-ICS/LAMA	**-0.089 (-0.171, -0.005)**
HD-ICS/LABA vs. MD-ICS/LABA	-0.053 (-0.105, 0.0004)

Mean differences less than zero favour the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose

Table 14

NMA Summary of Findings for change from baseline in ACQ score at 6 months

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, MD-ICS/LAMA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: Change from baseline in ACQ scores at 6 months

Setting: Outpatient

Total studies: 9 RCTs **Total Participants: 9298**	**Relative effect** **(95% CrI)**	**Anticipated absolute effect** (95% CrI)**		**Certainty of the evidence**	**Ranking*** (95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS[1]**			
HD-ICS (Direct evidence; 1 RCT; 798 participants)	**-0.06** (-0.15 to 0.04)	**0.80** (0.70 to 0.90)	Change from baseline in ACQ score was 0.19 higher (0.11 lower to 0.27 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**4.0** (3.0 to 5.0)	HD-ICS probably does not improve ACQ scores at 6 months compared to MD-ICS.
MD-ICS/LAMA (Direct evidence; 4 RCTs; 2116 participants)	**-0.13** (-0.20 to -0.07)	**0.88** (0.81 to 0.94)	Change from baseline in ACQ score was 0.06 higher (0.04 lower to 0.15 higher)	⊕⊕⊕⊕ **High**	**3.0** (2.0 to 4.0)	MD-ICS/LAMA does not result in clinically meaningful improvement in ACQ scores at 6 months compared to MD-ICS [3]
MD-ICS/LABA (Direct evidence; 5 RCTs; 3909 participants)	**-0.17** (-0.22 to -0.12)	**0.91** (0.86 to 0.96)	Change from baseline in ACQ score was 0.17 higher (0.12 higher to 0.22 higher)	⊕⊕⊕⊕ **High**	**2.0** (2.0 to 3.0)	MD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 6 months compared to MD-ICS [3]
HD-ICS/LABA (Direct evidence; 1 RCT; 1210 participants)	**-0.22** (-0.29 to -0.16)	**0.97** (0.90 to 1.03)	Change from baseline in ACQ score was 0.22 higher (0.16 higher to 0.29 higher)	⊕⊕⊕⊕ **High**	**1.0** (1.0 to 2.0)	HD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 6 months compared to MD-ICS [3]
MD-ICS	Reference Comparator[1]	**0.75**	Reference Comparator	Reference Comparator	**5.0** (4.0 to 5.0)	Reference Comparator

NMA-SoF table definitions

** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

1 The mean change from baseline in ACQ score was 0.75 with MD-ICS.

2 Downgraded one level for serious imprecision due to small sample sizes in the direct and/or indirect estimate(s).

3 Minimal clinically important difference is 0.5.

ACQ: Asthma Control Questionnaire; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; RCT: randomised controlled trial.

Table 15

Mean and median ranks for change from baseline in ACQ scores at 6 months sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
HD-ICS/LABA	1.05	1.00	(1.00, 2.00)
MD-ICS/LABA	2.14	2.00	(2.00, 3.00)
MD-ICS/LAMA	2.92	3.00	(2.00, 4.00)
HD-ICS	4.04	4.00	(3.00, 5.00)
MD-ICS	4.86	5.00	(4.00, 5.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 16

Relative effects change from baseline in ACQ scores at 12 months using both fixed-effect and random-effects models

	Median Mean Difference (95% CrI)	
Comparison	**Fixed-Effect Model**	**Random-Effects Model**
HD-ICS vs. MD-ICS	-0.053 (-0.148, 0.043)	-0.071 (-0.394, 0.215)
MD-ICS/LABA vs. MD-ICS	**-0.178 (-0.263, -0.094)**	-0.196 (-0.541, 0.125)
HD-ICS/LABA vs. MD-ICS	**-0.198 (-0.261, -0.135)**	**-0.210 (-0.498, 0.058)**
MD-ICS/LABA vs. HD-ICS	**-0.126 (-0.227, -0.025)**	-0.126 (-0.485, 0.246)
HD-ICS/LABA vs. HD-ICS	**-0.145 (-0.235, -0.056)**	-0.140 (-0.469, 0.207)
HD-ICS/LABA vs. MD-ICS/LABA	-0.020 (-0.087, 0.048)	-0.014 (-0.301, 0.278)

Mean differences less than zero favour the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 17

Mean and median ranks (with 95% CrI) for change from baseline in ACQ scores at 12 months sorted by mean rank for the fixed-effect and random-effects model

Fixed-Effect Model			
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**
HD-ICS/LABA	1.29	1.00	(1.00, 2.00)
MD-ICS/LABA	1.72	2.00	(1.00, 2.00)
HD-ICS	3.13	3.00	(3.00, 4.00)
MD-ICS	3.86	4.00	(3.00, 4.00)
Random-Effects Model			
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**
HD-ICS/LABA	1.58	1.00	(1.00, 3.00)
MD-ICS/LABA	1.78	2.00	(1.00, 4.00)
HD-ICS	2.96	3.00	(1.00, 4.00)
MD-ICS	3.68	4.00	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose

Table 18

Asthma Control Questionnaire: change from baseline - pairwise comparisons ‡

Should experimental vs. active comparator be used for improving ACQ scores? **Setting: outpatient**					
Outcome **№ of participants (studies)**	**Relative effect (95% CI)**	**Anticipated absolute effects (95% CI)**		**Certainty of the evidence**	**What happens**
		With active control	**Difference**		
2.1.1 CFB in ACQ at 3 months - HD-ICS vs MD-ICS № of participants: 829 (1 RCT)	-	-0.68	MD **0.1 lower** (0.22 lower to 0.01 higher)	⨁⨁◯◯ Low[a, b]	The evidence suggests HD-ICS results in little to no difference in ACQ score at 3 months compared to MD-ICS.
2.1.2 CFB in ACQ at 3 months - MD-ICS/LABA vs MD-ICS № of participants: 2700 (2 RCTs)	-	-0.74	MD **0.2 lower** (0.27 lower to 0.14 lower)	⨁⨁⨁⨁ High	MD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 3 months compared to MD-ICS (MICD 0.5).
2.1.3 CFB in ACQ at 3 months - HD-ICS/LABA vs MD-ICS	-	-0.68	MD **0.2 lower** (0.3 lower to 0.11 lower)	⨁⨁⨁⨁ High	HD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 3 months compared to MD-ICS (MICD 0.5).

№ of participants: 1255 (1 RCT)					
2.1.4 CFB in ACQ at 3 months - MD-ICS/LABA vs HD-ICS № of participants: 1247 (2 RCTs)	-	-0.66	MD **0.16 lower** (0.24 lower to 0.07 lower)	⨁⨁⨁⨁ High	MD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 3 months compared to HD-ICS (MICD 0.5).
2.1.5 CFB in ACQ at 3 months - HD-ICA/LABA vs HD-ICS № of participants: 1698 (2 RCTs)	-	-0.66	MD **0.13 lower** (0.2 lower to 0.05 lower)	⨁⨁⨁⨁ High	HD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 3 months compared to HD-ICS (MICD 0.5).
2.1.6 CFB in ACQ at 3 months - MD-ICS/LABA vs LD-ICS/LABA № of participants: 658 (1 RCT)	-	-1.08	MD **0.22 lower** (0.35 lower to 0.09 lower)	⨁⨁⨁◯ Moderate[b]	MD-ICS/LABA is unlikely to result in clinically meaningful improvement in ACQ scores at 3 months compared to LD-ICS/LABA (MICD 0.5).
2.1.7 CFB in ACQ at 3 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 1689 (2 RCTs)	-	-0.81	MD **0.03 higher** (0.05 lower to 0.11 higher)	⨁⨁⨁◯ Moderate[a]	HD-ICS/LABA probably does not improve ACQ scores at 3 months compared to MD-ICS/LABA.
2.2.1 CFB in ACQ at 6 months - HD-ICS vs MD-ICS № of participants: 798 (1 RCT)	-	-0.79	MD **0.07 lower** (0.18 lower to 0.04 higher)	⨁⨁◯◯ Low[a, b]	The evidence suggests HD-ICS results in little to no difference in ACQ score at 6 months compared to MD-ICS.
2.2.2 CFB in ACQ at 6 months - MD-ICS/LAMA vs MD-ICS № of participants: 2116 (4 RCTs)	-	-0.71	MD **0.13 lower** (0.2 lower to 0.06 lower)	⨁⨁⨁⨁ High	MD-ICS/LAMA does not result in clinically meaningful improvement in ACQ scores at 6 months compared to MD-ICS (MICD 0.5).
2.2.3 CFB in ACQ at 6 months - MD-ICS/LABA vs MD-ICS № of participants: 3909 (5 RCTs)	-	-0.74	MD **0.18 lower** (0.23 lower to 0.13 lower)	⨁⨁⨁⨁ High	MD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 6 months compared to MD-ICS (MICD 0.5).
2.2.4 CFB in ACQ at 6 months - HD-ICS/LABA vs MD-ICS № of participants: 1210 (1 RCT)	-	-0.79	MD **0.21 lower** (0.31 lower to 0.12 lower)	⨁⨁⨁⨁ High	HD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 6 months compared to MD-ICS (MICD 0.5).
2.2.5 CFB in ACQ at 6 months - MD-ICS/LABA vs HD-ICS № of participants: 812 (1 RCT)	-	-0.86	MD **0.17 lower** (0.29 lower to 0.06 lower)	⨁⨁⨁◯ Moderate[b]	MD-ICS/LABA is unlikely to result in clinically meaningful improvement in ACQ scores at 6 months compared to HD-ICS (MICD 0.5).
2.2.6 CFB in ACQ at 6 months - HD-ICS/LABA vs HD-ICS № of participants: 1222 (1 RCT)	-	-0.86	MD **0.14 lower** (0.24 lower to 0.05 lower)	⨁⨁⨁⨁ High	HD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 6 months compared to HD-ICS (MICD 0.5).
2.2.7 CFB in ACQ at 6 months - MD-ICS/LABA vs MD-ICS/LAMA № of participants: 1483 (2 RCTs)	-	-0.82	MD **0.02 lower** (0.11 lower to 0.06 higher)	⨁⨁⨁◯ Moderate[a]	MD-ICS/LABA probably does not improve ACQ scores at 6 months compared to MD-ICS/LAMA.
2.2.8 CFB in ACQ at 6 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 3762 (3 RCTs)	-	-0.86	MD **0.05 lower** (0.1 lower to 0.01 higher)	⨁⨁⨁◯ Moderate[a]	HD-ICS/LABA probably does not improve ACQ scores at 6 months compared to MD-ICS/LABA.
2.3.1 CFB in ACQ at 12 months - HD-ICS vs MD-ICS № of participants: 1005 (2 RCTs)	-	-0.84	MD **0.09 lower** (0.19 lower to 0.02 higher)	⨁⨁◯◯ Low[a, b, c]	The evidence suggests HD-ICS results in little to no difference in ACQ score at 12 months compared to MD-ICS.
2.3.2 CFB in ACQ at 12 months - MD-ICS/LABA vs MD-ICS № of participants: 774 (1 RCT)	-	-0.85	MD **0.27 lower** (0.38 lower to 0.15 lower)	⨁⨁⨁◯ Moderate[b]	MD-ICS/LABA is unlikely to result in clinically meaningful improvement in ACQ scores at 12 months compared to MD-ICS (MICD 0.5).
2.3.3 CFB in ACQ at 12 months - HD-ICS/LABA vs MD-ICS № of participants: 2863 (2 RCTs)	-	-0.94	MD **0.18 lower** (0.25 lower to 0.11 lower)	⨁⨁⨁⨁ High	HD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 12 months compared to MD-ICS (MICD 0.5).
2.3.4 CFB in ACQ at 12 months - MD-ICS/LABA vs HD-ICS	-	-0.93	MD **0.19 lower** (0.3 lower to 0.08 lower)	⨁⨁⨁◯ Moderate[b]	MD-ICS/LABA is unlikely to result in clinically meaningful improvement in ACQ scores at 12 months compared to HD-ICS (MICD 0.5).

№ of participants: 784 (1 RCT)					
2.3.5 CFB in ACQ at 12 months - HD-ICS/LABA vs HD-ICS № of participants: 1177 (1 RCT)	-	-0.93	MD **0.15 lower** (0.25 lower to 0.05 lower)	⨁⨁⨁⨁ High	HD-ICS/LABA does not result in clinically meaningful improvement in ACQ scores at 12 months compared to HD-ICS (MICD 0.5).
2.3.6 CFB in ACQ at 12 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 2980 (2 RCTs)	-	-1.02	MD **0.03 lower** (0.17 lower to 0.11 higher)	⨁⨁◯◯ Low[a, d]	The evidence suggests HD-ICS/LABA results in little to no difference in ACQ score at 12 months compared to MD-ICS/LABA.

‡ ACQ scores range from 0 to 6 with lower scores indicating better asthma control.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ACQ: Asthma Control Questionnaire; CFB change from baseline; CI: confidence interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: medium dose; MD: mean difference; RCT: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level: Optimal information size is not met (Guyatt 2011)

b. Downgraded one level : Total size of less than 1000 patients may suggest small study effect (Dechartres 2013)

c. Pedersen 2017 had very high attrition rates and is considered at high risk of bias. However, excluding the study did not change the results.

d. Downgraded one level for imprecision for substantial heterogeneity I2>= 50% to 90%.

Table 19

Relative effects change from baseline in AQLQ scores at 3 months using a fixed-effect model

Comparison	Median Mean Difference (95% CrI)
HD-ICS vs. MD-ICS	0.053 (-0.079, 0.184)
MD-ICS/LABA vs. MD-ICS	**0.193 (0.088, 0.299)**
HD-ICS/LABA vs. MD-ICS	0.123 (-0.008, 0.254)
MD-ICS/LABA vs. HD-ICS	**0.141 (0.038, 0.242)**
HD-ICS/LABA vs. HD-ICS	0.070 (-0.011, 0.152)
HD-ICS/LABA vs. MD-ICS/LABA	-0.070 (-0.172, 0.031)

Mean differences less than zero favour the first named treatment. Treatment comparisons **in bold** do not include the “null” effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose.

Table 20

NMA Summary of Findings for change from baseline in AQLQ score at 3 months

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: Change from baseline in AQLQ scores at 3 months

Setting: Outpatient

Total studies: 6 RCTs Total Participants: 2585	Relative effect (95% CrI)	Anticipated absolute effect** (95% CrI)		Certainty of the evidence	Ranking*** (95% CrI)	Interpretation of Findings
		With intervention	Difference compared to MD-ICS[1]			
HD-ICS (Direct evidence; 1 RCT; 265 participants)	0.05 (-0.08 to 0.18)	0.57 (0.43 to 0.70)	Change from baseline in AQLQ score was 0.05 higher (0.08 lower to 0.18 higher)	⨁⨁◯◯ Low Due to imprecision[2]	3.0 (2.0 to 4.0)	The evidence suggests that HD-ICS results in little to no difference in CFB in AQLQ at 3 months compared to MD-ICS
MD-ICS/LABA (Direct evidence; 3 RCTs; 880 participants)	0.19 (0.09 to 0.30)	0.71 (0.60 to 0.81)	Change from baseline in AQLQ score was 0.19 higher (0.09 higher to 0.30 higher)	⨁⨁◯◯ Low Due to imprecision[2]	1.0 (1.0 to 2.0)	The evidence suggests that MD-ICS/LABA results in no clinically important difference in CFB in AQLQ at 3 months compared to MD-ICS[3]
HD-ICS/LABA	0.12 (-0.01 to 0.25)	0.64 (0.50 to 0.77)	Change from baseline in AQLQ score was	⨁⨁◯◯ Low	2.0 (1.0 to 3.0)	The evidence suggests that HD-ICS/LABA results in no clinically important difference in CFB in

(Direct evidence;1 RCT; 264 participants)			0.12 higher (0.01 lower to 0.25 higher)	Due to imprecision[2]		AQLQ at 3 months compared to MD-ICS[3]
MD-ICS	Reference Comparator[1]	0.51	Reference Comparator	Reference Comparator	4.0 (2.0 to 4.0)	Reference Comparator

NMA-SoF table definitions
** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.
*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
1 The mean change from baseline in AQLQ score was 0.53 with MD-ICS.
2 Downgraded two levels for very serious imprecision due to small sample sizes in the direct and/or indirect estimate(s).
3 Minimal clinically important difference is 0.5.

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose; RCT: randomised controlled trial.

Table 21

Mean and median ranks (with corresponding 95% CrI) for change from baseline in AQLQ scores at 3 months sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
MD-ICS/LABA	1.09	1.00	(1.00, 2.00)
HD-ICS/LABA	1.99	2.00	(1.00, 3.00)
HD-ICS	3.17	3.00	(2.00, 4.00)
MD-ICS	3.75	4.00	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose.

Table 22

Relative effects change from baseline in AQLQ scores at 6 months using fixed- and random-effects models

	Median Mean Difference (95% CrI)	
Comparison	Fixed-Effect Model	Random-Effects Model
HD-ICS vs MD-ICS	0.024 (-0.199, 0.246)	0.025 (-0.642, 0.699)
LD-ICS/LABA vs MD-ICS	**0.184 (0.082, 0.286)**	0.179 (-0.078, 0.430)
MD-ICS/LABA vs MD-ICS	**0.124 (0.016, 0.232)**	0.127 (-0.126, 0.386)
HD-ICS/LABA vs MD-ICS	0.071 (-0.069, 0.210)	0.073 (-0.425, 0.576)
LD-ICS/LABA vs HD-ICS	0.161 (-0.064, 0.385)	0.154 (-0.537, 0.830)
MD-ICS/LABA vs HD-ICS	0.100 (-0.094, 0.295)	0.102 (-0.522, 0.720)
HD-ICS/LABA vs HD-ICS	0.047 (-0.126, 0.220)	0.048 (-0.405, 0.494)
MD-ICS/LABA vs LD-ICS/LABA	-0.060 (-0.173, 0.052)	-0.052 (-0.332, 0.239)
HD-ICS/LABA vs LD-ICS/LABA	-0.113 (-0.257, 0.030)	-0.106 (-0.615, 0.415)
HD-ICS/LABA vs MD-ICS/LABA	-0.053 (-0.142, 0.036)	-0.054 (-0.484, 0.377)

Mean differences less than zero favour the first named treatment. Treatment comparisons **in bold** do not include the “null” effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose.

Table 23

Mean and median ranks (with corresponding 95% CrI) for change from baseline in AQLQ scores at 6 months sorted by mean rank for the fixed- and random-effects models

Fixed-effect Model			
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**
LD-ICS/LABA	1.29	1	(1.00, 3.00)
MD-ICS/LABA	2.14	2	(1.00, 4.00)
HD-ICS/LABA	3.27	3	(2.00, 5.00)
HD-ICS	3.88	4	(1.00, 5.00)
MD-ICS	4.41	5	(3.00, 5.00)
Random-effects Model			
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**
LD-ICS/LABA	1.88	1	(1.00, 4.00)
MD-ICS/LABA	2.43	2	(1.00, 4.00)
HD-ICS/LABA	3.11	3	(1.00, 5.00)
HD-ICS	3.52	4	(1.00, 5.00)
MD-ICS	4.06	4	(2.00, 5.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 24

Asthma Quality of Life Questionnaire: change from baseline-pairwise comparisons ‡

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Intervention/control: Any comparison of the following two arms: MD-ICS, HD-ICS, LD-ICS/LABA, MD-ICS/LABA, and HD-ICS/LABA

Outcome: Change from baseline in AQLQ scores

Setting: Outpatient

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty of the evidence	What happens
		With active control	Difference		
3.1.1 CFB in AQLQ at 3 months - HD-ICS vs MD-ICS № of participants: 265 (1 study)	-	0.51	MD **0.04 higher** (0.16 lower to 0.25 higher)	⨁⨁◯◯ Low[a, b]	The evidence suggests HD-ICS results in little to no difference in AQLQ score at 3 months compared to MD-ICS.
3.1.2 CFB in AQLQ at 3 months - MD-ICS/LABA vs MD-ICS № of participants: 880 (3 studies)	-	0.51	MD **0.19 higher** (0.08 higher to 0.3 higher)	⨁⨁◯◯ Low[a, b, c]	The evidence suggest that MD-ICS/LABA does not result in clinically meaningful improvement in AQLQ scores at 3 months compared to MD-ICS (MICD 0.5).
3.1.3 CFB in AQLQ at 3 months - HD-ICS/LABA vs MD-ICS № of participants: 264 (1 study)	-	0.51	MD **0.19 higher** (0.01 lower to 0.4 higher)	⨁⨁◯◯ Low[a, b]	The evidence suggests HD-ICS/LABA results in little to no difference in AQLQ score at 3 months compared to MD-ICS.
3.1.4 CFB in AQLQ at 3 months - MD-ICS/LABA vs HD-ICS № of participants: 680 (2 studies)	-	0.59	MD **0.14 higher** (0.03 higher to 0.25 higher)	⨁⨁◯◯ Low[a, b]	The evidence suggests MD-ICS/LABA results in little to no difference in AQLQ score at 3 months compared to HD-ICS.
3.1.5 CFB in AQLQ at 3 months - HD-ICS/LABA vs HD-ICS № of participants: 1500 (4 studies)	-	0.59	MD **0.07 higher** (0.01 lower to 0.15 higher)	⨁⨁⨁◯ Moderate[a, c]	HD-ICS/LABA probably does not improve AQLQ scores at 3 months compared to HD-ICS.
3.1.6 CFB in AQLQ at 3 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 694 (2 studies)	-	0.68	MD **0.09 lower** (0.2 lower to 0.02 higher)	⨁⨁◯◯ Low[a, b]	The evidence suggests HD-ICS/LABA results in little to no difference in AQLQ score at 3 months compared to MD-ICS/LABA
3.2.1 CFB in AQLQ at 6 months - LD-ICS/LABA vs MD-ICS № of participants: 1719 (3 RCTs)	-	0.65	MD **0.18 higher** (0.04 lower to 0.4 higher)	⨁⨁⨁◯ Moderate[d]	LD-ICS/LABA probably does not improve AQLQ scores at 6 months compared to MD-ICS.
3.2.2 CFB in AQLQ at 6 months - MD-ICS/LABA vs MD-ICS № of participants: 1359 (3 RCTs)	-	0.57	MD **0.16 higher** (0.05 higher to 0.27 higher)	⨁⨁⨁⨁ High	MD-ICS/LABA does not result in clinically meaningful improvement in AQLQ scores at 6 months compared to MD-ICS (MICD 0.5).
3.2.3 CFB in AQLQ at 6 months - HD-ICS/LABA vs HD-ICS № of participants: 463 (1 RCT)	-	0.88	MD **0.05 higher** (0.13 lower to 0.22 higher)	⨁⨁◯◯ Low[a, b, e]	The evidence is very uncertain about the effect of HD-ICS/LABA on AQLQ scores at 6 months compared to HD-ICS.
3.2.4 CFB in AQLQ at 6 months - MD-ICS/LABA vs LD-ICS/LABA № of participants: 1470 (2 RCTs)	-	0.94	MD **0.09 lower** (0.22 lower to 0.03 higher)	⨁⨁⨁◯ Moderate[a]	MD-ICS/LABA probably does not improve AQLQ scores at 6 months compared to LD-ICS/LABA.
3.2.5 CFB in AQLQ at 6 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 1222 (1 RCT)	-	0.77	MD **0.05 lower** (0.14 lower to 0.04 higher)	⨁⨁⨁◯ Moderate[a]	HD-ICS/LABA probably does not improve AQLQ scores at 6 months compared to MD-ICS/LABA.

‡ AQLQ scores range from 1 to 7 with higher scores indicating better asthma control.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). AQLQ: Asthma Quality of Life Questionnaire; CFB change from baseline; CI: confidence interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: medium dose; MD: mean difference; RCT: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level : Optimal information size is not met (Guyatt 2011)

b. Downgraded one level: Total size of less than 1000 patients may suggest small study effect (Dechartres 2013)

c. The proportion of information from study(ies) at high risk of bias is not sufficient to affect the interpretation of results.

d. Downgraded one level for substantial heterogeneity I2>= 50% to 90%

e. Sensitivity analysis using the imputation methods for missing data suggested in Guyatt 2017 did not affect the interpretation of results.

Table 25

Odds Ratios for ACQ responders at 6 months using a fixed-effect model

Comparison	Odds Ratio (95% CrI)
HD-ICS vs. MD-ICS	1.280 (0.971, 1.693)
MD-ICS/LAMA vs. MD-ICS	**1.321 (1.114, 1.570)**
MD-ICS/LABA vs. MD-ICS	**1.473 (1.232, 1.760)**
HD-ICS/LABA vs. MD-ICS	**1.595 (1.307, 1.941)**
MD-ICS/LAMA vs. HD-ICS	1.032 (0.762, 1.394)
MD-ICS/LABA vs. HD-ICS	1.151 (0.884, 1.492)
HD-ICS/LABA vs. HD-ICS	1.246 (0.960, 1.607)
MD-ICS/LABA vs. MD-ICS/LAMA	1.115 (0.919, 1.353)
HD-ICS/LABA vs. MD-ICS/LAMA	1.206 (0.965, 1.507)
HD-ICS/LABA vs. MD-ICS/LABA	1.082 (0.939, 1.247)

The second named treatment is the baseline intervention. Odds Ratios greater than one favour the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 26

Mean and median ranks (with corresponding 95% CrI) for ACQ response at 6 months sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
HD-ICS/LABA	1.24	1.00	(1.00, 3.00)
MD-ICS/LABA	2.15	2.00	(1.00, 4.00)
MD-ICS/LAMA	3.23	3.00	(1.00, 4.00)
HD-ICS	3.42	4.00	(1.00, 5.00)
MD-ICS	4.96	5.00	(4.00, 5.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 27

Asthma Control Questionnaire responders-pairwise comparisons

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Intervention/control: Any comparison of the following two arms: MD-ICS, HD-ICS, MD-ICS/LAMA, MD-ICS/LABA, and HD-ICS/LABA

Outcome: ACQ response

Setting: Outpatient

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of the evidence	What happens
		With active control	With experimental	Difference		
4.1.1 ACQ responder at 6 months - HD-ICS vs MD-ICS № of participants: 798 (1 RCT)	**RR 1.08** (0.99 to 1.19)	66.9%	**72.3%** (66.3 to 79.6)	**5.4% more** (0.7 fewer to 12.7 more)	⨁⨁◯◯ Low[a, b]	The evidence suggests that HD-ICS results in little to no difference in ACQ response at 6 months compared to MD-ICS.
4.1.2 ACQ responder at 6 months - MD-ICS/LAMA vs MD-ICS № of participants: 2219 (3 RCTs)	**RR 1.10** (1.03 to 1.18)	60.0%	**66.0%** (61.8 to 70.8)	**6.0% more** (1.8 more to 10.8 more)	⨁⨁⨁◯ Moderate[a]	MD-ICS/LAMA likely increases ACQ responders at 6 months compared to MD-ICS.
4.1.3 ACQ responder at 6 months - MD-ICS/LABA vs MD-ICS № of participants: 1853 (2 RCTs)	**RR 1.15** (1.07 to 1.22)	61.7%	**70.9%** (66 to 75.3)	**9.3% more** (4.3 more to 13.6 more)	⨁⨁⨁⨁ High	MD-ICS/LABA increases ACQ responders at 6 months compared to MD-ICS.

4.1.4 ACQ responder at 6 months - HD-ICS/LABA vs MD-ICS № of participants: 1210 (1 RCT)	**RR 1.14** (1.05 to 1.23)	66.9%	**76.3%** (70.3 to 82.3)	**9.4% more** (3.3 more to 15.4 more)	⨁⨁⨁⨁ High	HD-ICS/LABA increases ACQ responders at 6 months compared to MD-ICS.
4.1.5 ACQ responder at 6 months - MD-ICS/LABA vs HD-ICS № of participants: 812 (1 RCT)	**RR 1.05** (0.97 to 1.14)	72.3%	**76.0%** (70.2 to 82.5)	**3.6% more** (2.2 fewer to 10.1 more)	⨁⨁◯◯ Low[a, b]	The evidence suggests that MD-ICS/LABA results in little to no difference in ACQ response at 6 months compared to HD-ICS.
4.1.6 ACQ responder at 6 months - HD-ICS/LABA vs HD-ICS № of participants: 1222 (1 RCT)	**RR 1.05** (0.98 to 1.13)	72.3%	**76.0%** (70.9 to 81.8)	**3.6% more** (1.4 fewer to 9.4 more)	⨁⨁⨁◯ Moderate[a]	HD-ICS/LABA likely results in little to no difference in ACQ response at 6 months compared to HD-ICS.
4.1.7 ACQ responder at 6 months - MD-ICS/LABA vs MD-ICS/LAMA № of participants: 1563 (1 RCT)	**RR 1.03** (0.96 to 1.11)	64.4%	**66.3%** (61.8 to 71.5)	**1.9% more** (2.6 fewer to 7.1 more)	⨁⨁⨁◯ Moderate[a]	MD-ICS/LABA likely results in little to no difference in ACQ response at 6 months compared to MD-ICS/LAMA.
4.1.8 ACQ responder at 6 months - HD-ICS/LABA cs MD-ICS/LABA № of participants: 3700 (3 RCTs)	**RR 1.02** (0.98 to 1.07)	66.8%	**68.1%** (65.5 to 71.5)	**1.3% more** (1.3 fewer to 4.7 more)	⨁⨁⨁◯ Moderate[a]	HD-ICS/LABA likely results in little to no difference in ACQ response at 6 months compared to MD-ICS/LABA.
4.2.1 ACQ responder at 12 months - HD-ICS vs MD-ICS № of participants: 1011 (2 RCTs)	**RR 1.01** (0.85 to 1.19)	66.1%	**66.8%** (56.2 to 78.7)	**0.7% more** (9.9 fewer to 12.6 more)	⨁⨁◯◯ Low[a, c, d]	The evidence suggests that HD-ICS results in little to no difference in ACQ response at 12 months compared to MD-ICS.
4.2.2 ACQ responder at 12 months - MD-ICS/LABA vs MD-ICS № of participants: 774 (1 RCT)	**RR 1.19** (1.09 to 1.29)	69.2%	**82.4%** (75.5 to 89.3)	**13.2% more** (6.2 more to 20.1 more)	⨁⨁⨁◯ Moderate[b]	MD-ICS/LABA likely increases ACQ responders at 12 months compared to MD-ICS.
4.2.3 ACQ responder at 12 months - HD-ICS/LABA vs MD-ICS № of participants: 1167 (1 RCT)	**RR 1.12** (1.04 to 1.21)	69.2%	**77.5%** (72 to 83.8)	**8.3% more** (2.8 more to 14.5 more)	⨁⨁⨁⨁ High	HD-ICS/LABA increases ACQ responders at 12 months compared to MD-ICS.
4.2.4 ACQ responder at 12 months - MD-ICS/LABA vs HD-ICS № of participants: 784 (1 RCT)	**RR 1.12** (1.03 to 1.20)	73.6%	**82.5%** (75.9 to 88.4)	**8.8% more** (2.2 more to 14.7 more)	⨁⨁⨁◯ Moderate[b]	MD-ICS/LABA likely increases ACQ responders at 12 months compared to HD-ICS.
4.2.5 ACQ responder at 12 months - HD-ICS/LABA vs HD-ICS № of participants: 1177 (1 RCT)	**RR 1.05** (0.98 to 1.13)	73.6%	**77.3%** (72.2 to 83.2)	**3.7% more** (1.5 fewer to 9.6 more)	⨁⨁⨁◯ Moderate[a]	HD-ICS/LABA likely results in little to no difference in ACQ response at 12 months compared to HD-ICS.
4.2.6 ACQ responder at 12 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 2817 (2 RCTs)	**RR 0.99** (0.90 to 1.07)	77.0%	**76.2%** (69.3 to 82.3)	**0.8% fewer** (7.7 fewer to 5.4 more)	⨁◯◯◯ Very low[a, e]	The evidence is very uncertain about the effect of HD-ICS/LABA on ACQ response at 12 months compared to MD-ICS/LABA.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ACQ: Asthma Control Questionnaire; CFB change from baseline; CI: confidence interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: medium dose; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level : Optimal information size is not met (Guyatt 2011).

b. Downgraded one level: Total size of less than 1000 patients may suggest small study effect (Dechartres 2013).

c. The proportion of information from study(ies) at high risk of bias is not sufficient to affect the interpretation of results.

d. Downgraded one level for substantial heterogeneity I2>= 50% to 90%.

e. Downgraded for two levels for considerable heterogeneity. I2 >:75% to 100%.

Table 28

Odds Ratios for ACQ responders at 12 months for the fixed-effect model

Comparison	Odds Ratio (95% CrI)
HD-ICS vs. MD-ICS	1.089 (0.834, 1.423)
MD-ICS/LABA vs. MD-ICS	**1.614 (1.217, 2.133)**
HD-ICS/LABA vs. MD-ICS	**1.549 (1.196, 2.002)**
MD-ICS/LABA vs. HD-ICS	**1.481 (1.118, 1.958)**
HD-ICS/LABA vs. HD-ICS	**1.422 (1.099, 1.837)**
HD-ICS/LABA vs. MD-ICS/LABA	0.961 (0.796, 1.155)

The second named treatment is the baseline intervention. Odds Ratios greater than one favour the treatment named first in the comparisons. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: medium dose.

Table 29

Mean and median ranks (with corresponding 95% CrI) for ACQ response at 12 months for the fixed-effect model (sorted by mean rank)

Treatments	Mean Rank	Median Rank	95% CrI
MD-ICS/LABA	1.34	1.00	(1.00, 2.00)
HD-ICS/LABA	1.67	2.00	(1.00, 2.00)
HD-ICS	3.26	3.00	(3.00, 4.00)
MD-ICS	3.73	4.00	(3.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: medium dose.

Table 30

Odds Ratios for asthma-related SAEs using a fixed-effect and random-effects model

Comparison	Odds Ratio (95% CrI)	
	Fixed-Effect Model	Random-Effects Model
HD-ICS vs. MD-ICS	0.831 (0.407, 1.629)	0.806 (0.297, 2.074)
LD-ICS/LABA vs. MD-ICS	0.255 (0.089, 0.734)	0.257 (0.042, 1.563)
MD-ICS/LAMA vs. MD-ICS	0.723 (0.201, 2.501)	0.724 (0.160, 3.319)
MD-ICS/LABA vs. MD-ICS	0.757 (0.491, 1.170)	0.750 (0.402, 1.454)
HD-ICS/LABA vs. MD-ICS	1.132 (0.683, 1.888)	1.201 (0.586, 3.040)
LD-ICS/LABA vs. HD-ICS	0.308 (0.095, 1.008)	0.319 (0.046, 2.277)
MD-ICS/LAMA vs. HD-ICS	0.872 (0.208, 3.568)	0.899 (0.154, 5.310)
MD-ICS/LABA vs. HD-ICS	0.909 (0.470, 1.855)	0.938 (0.369, 2.535)
HD-ICS/LABA vs. HD-ICS	1.361 (0.726, 2.681)	1.503 (0.643, 4.297)
MD-ICS/LAMA vs. LD-ICS/LABA	2.826 (0.561, 13.856)	2.814 (0.285, 28.143)
MD-ICS/LABA vs. LD-ICS/LABA	**2.966 (1.130, 7.780)**	2.931 (0.547, 16.204)
HD-ICS/LABA vs. LD-ICS/LABA	**4.437 (1.530, 12.905)**	4.700 (0.817, 33.543)
MD-ICS/LABA vs. MD-ICS/LAMA	1.050 (0.294, 3.880)	1.030 (0.219, 5.181)
HD-ICS/LABA vs. MD-ICS/LAMA	1.568 (0.421, 6.102)	1.679 (0.338, 9.632)
HD-ICS/LABA vs. MD-ICS/LABA	1.495 (0.953, 2.371)	1.601 (0.826, 3.679)

The second named treatment is the baseline intervention. Odds Ratios less than one favour the treatment named first in the comparisons. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; SAE: serious adverse event.

Table 31

NMA Summary of Findings for asthma-related SAEs

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, LD-ICS/LABA, MD-ICS/LAMA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: Asthma-related serious adverse event

Setting: Outpatient

Total studies: 24 RCTs Total Participants: 22752	Relative risk** (95% CrI)	Anticipated absolute effect*** (95% CrI)		Certainty of the evidence	Ranking**** (95% CrI)	Interpretation of Findings
		With intervention	Difference compared to MD-ICS			
HD-ICS (Direct evidence; 5 RCTs; 3324 participants)	0.81 (0.30 to 2.07)	5 per 1000	1 per 1000 fewer (from 4 fewer to 7 more)	⊕⊕⊕◯ Moderate Due to heterogeneity[1]	3.0 (1.0 to 6.0)	HD-ICS likely results in little to no difference in asthma-related SAEs compared to MD-ICS
LD-ICS/LABA (Direct evidence; 0 RCTs; 0 participants)	0.26 (0.04 to 1.56)	2 per 1000	4 per 1000 fewer (from 6 fewer to 4 more)	⊕◯◯◯ Very low Due to imprecision[2] and paucity of data[3]	1.0 (1.0 to 5.0)	The evidence is very uncertain

MD-ICS/LAMA (Direct evidence; 4 RCTs; 2238 participants)	0.72 (0.16 to 3.32)	5 per 1000	1 per 1000 fewer (from 5 fewer to 15 more)	⊕⊕⊕⊕ High	3.0 (1.0 to 6.0)	MD-ICS/LAMA results in little to no difference in asthma-related SAEs compared to MD-ICS
MD-ICS/LABA (Direct evidence; 15 RCTs; 11971 participants)	0.75 (0.40 to 1.45)	5 per 1000	1 per 1000 fewer (from 3 fewer to 3 more)	⊕⊕⊕⊕ High	3.0 (2.0 to 5.0)	MD-ICS/LABA results in little to no difference in asthma-related SAEs compared to MD-ICS
HD-ICS/LABA (Direct evidence; 4 RCTs; 3610 participants)	1.20 (0.59 to 3.04)	8 per 1000	2 per 1000 more (from 2 fewer to 13 more)	⊕⊕⊕⊕ High	5.0 (3.0 to 6.0)	HD-ICS/LABA results in little to no difference in asthma-related SAEs compared to MD-ICS
MD-ICS	Reference Comparator	6 per 1000[4]	Reference Comparator	Reference Comparator	5.0 (2.0 to 6.0)	Reference Comparator

NMA-SoF table definitions

** Network Meta-Analysis estimates of **random-effects model** are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

1 Downgraded one level for substantial heterogeneity I^2>= 50% to 90% in the direct estimate.
2 Downgraded for two levels for very serious imprecision due suboptimal sample size in the direct and/or indirect estimate(s).
3 Downgraded one level: Only one study (CHIESI 2009) provided evidence for LD-ICS/LABA to the network and no asthma-related adverse events were observed in the LD-ICS/LABA arm
4 Based on the average rate in patients treated with MD-ICS in the included studies.

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; RCT: randomised controlled trial.

Table 32

Mean and median ranks (with 95% CrIs) for asthma-related SAEs sorted by mean rank (fixed-effect and random-effects model)

Fixed-Effect Model			
Treatments	**Mean Rank**	**Median**	**95% CrI**
LD-ICS/LABA	1.15	1.00	(1.00, 2.00)
MD-ICS/LABA	3.05	3.00	(2.00, 5.00)
MD-ICS/LAMA	3.34	3.00	(1.00, 6.00)
HD-ICS	3.63	4.00	(2.00, 6.00)
MD-ICS	4.61	5.00	(3.00, 6.00)
HD-ICS/LABA	5.22	5.00	(3.00, 6.00)
Random-Effects Model			
Treatments	**Mean Rank**	**Median**	**95% CrI**
LD-ICS/LABA	1.44	1.00	(1.00, 5.00)
MD-ICS/LABA	3.12	3.00	(2.00, 5.00)
MD-ICS/LAMA	3.35	3.00	(1.00, 6.00)
HD-ICS	3.48	3.00	(1.00, 6.00)
MD-ICS	4.43	5.00	(2.00, 6.00)
HD-ICS/LABA	5.17	5.00	(3.00, 6.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; SAE: serious adverse event.

Table 33

Serious adverse events, adverse events, and dropouts due to adverse events-pairwise comparisons

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Intervention/control: Any comparison of the following two arms: MD-ICS, HD-ICS, LD-ICS/LABA, MD-ICS/LAMA, MD-ICS/LABA, and HD-ICS/LABA

Outcome: Various safety outcomes

Setting: Outpatient

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of the evidence	What happens
		With active control	With experimental	Difference		
5.1.1 Asthma-related SAEs - HD-ICS vs MD-ICS № of participants: 3324 (5 RCTs) Follow up: 3 to 12 months	**RR 0.74** (0.21 to 2.67)	1.2%	**0.9%** (0.3 to 3.3)	**0.3% fewer** (1 fewer to 2.1 more)	⨁⨁⨁◯ Moderate[a, b]	HD-ICS probably does not reduce asthma-related SAEs compared to MD-ICS.
5.1.2 Asthma-related SAEs - MD-ICS/LAMA vs MD-ICS № of participants: 2238 (4 RCTs) Follow up: 6 months	**RR 0.63** (0.18 to 2.16)	0.6%	**0.4%** (0.1 to 1.3)	**0.2% fewer** (0.5 fewer to 0.7 more)	⨁⨁⨁◯ Moderate[c]	MD-ICS/LAMA probably does not reduce asthma-related SAEs compared to MD-ICS.
5.1.3 Asthma-related SAEs - MD-ICS/LABA vs MD-ICS № of participants: 11971 (15 RCTs) Follow up: 3 to 12 months	**RR 0.73** (0.41 to 1.27)	0.7%	**0.5%** (0.3 to 0.9)	**0.2% fewer** (0.4 fewer to 0.2 more)	⨁⨁⨁⨁ High[e]	MD-ICS/LABA results in little to no difference in asthma-related SAEs compared to MD-ICS.
5.1.4 Asthma-related SAEs - HD-ICS/LABA vs MD-ICS № of participants: 3610 (4 RCTs) Follow up: 3 to 12 months	**RR 1.34** (0.33 to 5.44)	1.3%	**1.7%** (0.4 to 6.9)	**0.4% more** (0.8 fewer to 5.6 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that HD-ICS/LABA results in little to no difference in asthma-related SAEs compared to MD-ICS.
5.1.5 Asthma-related SAEs - MD-ICS/LABA vs HD-ICS № of participants: 3422 (5 RCTs) Follow up: 3 to 12 months	**RR 0.65** (0.19 to 2.23)	0.6%	**0.4%** (0.1 to 1.4)	**0.2% fewer** (0.5 fewer to 0.8 more)	⨁⨁⨁◯ Moderate[b]	MD-ICS/LABA likely results in little to no difference in asthma-related SAEs compared to HD-ICS.
5.1.6 Asthma-related SAEs - HD-ICS/LABA vs HD-ICS № of participants: 5063 (7 RCTs) Follow up: 3 to 12 months	**RR 1.16** (0.60 to 2.24)	0.6%	**0.7%** (0.4 to 1.3)	**0.1% more** (0.2 fewer to 0.7 more)	⨁⨁⨁⨁ High[a]	HD-ICS/LABA results in little to no difference in asthma-related SAEs compared to HD-ICS.
5.1.7 Asthma-related SAEs - MD-ICS/LABA vs LD-ICS/LABA № of participants: 695 (1 RCT) Follow up: 3 months	**RR 2.96** (0.12 to 72.34)	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	⨁⨁⨁◯ Moderate[c]	MD-ICS/LABA likely results in little to no difference in asthma-related SAEs compared to LD-ICS/LABA.
5.1.8 Asthma-related SAEs - MD-ICS/LABA vs MD-ICS/LAMA № of participants: 1577 (2 RCTs) Follow up: 6 months	**RR 0.64** (0.10 to 4.04)	0.4%	**0.2%** (0 to 1.6)	**0.1% fewer** (0.3 fewer to 1.2 more)	⨁⨁⨁◯ Moderate[c]	MD-ICS/LABA likely results in little to no difference in asthma-related SAEs compared to MD-ICS/LAMA.
5.1.9 Asthma-related SAEs - HD-ICS/LABA vs MD-ICS/LABA № of participants: 6652 (7 RCTs) Follow up: 3 to 12 months	**RR 1.51** (0.92 to 2.46)	0.9%	**1.4%** (0.8 to 2.2)	**0.5% more** (0.1 fewer to 1.3 more)	⨁⨁⨁⨁ High	HD-ICS/LABA results in little to no difference in asthma-related SAEs compared to MD-ICS/LABA.
5.2.1 All cause SAEs - HD-ICS vs MD-ICS № of participants: 3775 (7 RCTs) Follow up: 3 to 12 months	**RR 0.87** (0.56 to 1.36)	4.1%	**3.5%** (2.3 to 5.5)	**0.5% fewer** (1.8 fewer to 1.5 more)	⨁⨁⨁◯ Moderate[a, b]	HD-ICS likely results in little to no difference in all cause SAEs compared to MD-ICS.
5.2.2 All cause SAEs - MD-ICS/LAMA vs MD-ICS № of participants: 2238 (4 RCTs) Follow up: 6 months	**RR 0.83** (0.42 to 1.65)	2.6%	**2.2%** (1.1 to 4.3)	**0.4% fewer** (1.5 fewer to 1.7 more)	⨁⨁⨁◯ Moderate[c]	MD-ICS/LAMA likely results in little to no difference in all cause SAEs compared to MD-ICS.
5.2.3 All cause SAEs - MD-ICS/LABA vs MD-ICS № of participants: 14588 (21 RCTs) Follow up: 3 to 12 months	**RR 0.91** (0.73 to 1.14)	2.7%	**2.5%** (2.0 to 3.1)	**0.2% fewer** (0.7 fewer to 0.4 more)	⨁⨁⨁⨁ High	MD-ICS/LABA results in little to no difference in all cause SAEs compared to MD-ICS.
5.2.4 All cause SAEs - HD-ICS/LABA vs MD-ICS № of participants: 4302 (5 RCTs) Follow up: 3 to 12 months	**RR 1.10** (0.64 to 1.89)	3.5%	**3.9%** (2.2 to 6.6)	**0.4% more** (1.3 fewer to 3.1 more)	⨁⨁⨁◯ Moderate[a, b]	HD-ICS/LABA likely results in little to no difference in all cause SAEs compared to MD-ICS.
5.2.5 All cause SAEs - MD-ICS/LABA vs HD-ICS	**RR 0.90** (0.62 to	3.1%	**2.7%** (1.9 to 4)	**0.3% fewer** (1.2 fewer to	⨁⨁⨁⨁ High	MD-ICS/LABA results in little to no difference in all cause SAEs

№ of participants: 4027 (6 RCTs) Follow up: 3 to 12 months	1.30)			0.9 more)		compared to HD-ICS.
5.2.6 All cause SAEs - HD-ICS/LABA vs HD-ICS № of participants: 5503 (8 RCTs) Follow up: 3 to 12 months	**RR 1.29** (0.95 to 1.74)	2.6%	**3.4%** (2.5 to 4.5)	**0.8% more** (0.1 fewer to 1.9 more)	⨁⨁⨁⨁ High[a]	HD-ICS/LABA results in little to no difference in all cause SAEs compared to HD-ICS.
5.2.7 All cause SAEs - MD-ICS/LABA vs LD-ICS/LABA № of participants: 695 (1 RCT) Follow up: 3 months	**RR 0.49** (0.04 to 5.41)	0.6%	**0.3%** (0 to 3.1)	**0.3% fewer** (0.6 fewer to 2.6 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that MD-ICS/LABA results in little to no difference in all cause SAEs compared to LD-ICS/LABA.
5.2.8 All cause SAEs - MD-ICS/LABA vs MD-ICS/LAMA № of participants: 1577 (2 RCTs) Follow up: 6 months	**RR 0.93** (0.35 to 2.49)	2.2%	**2.1%** (0.8 to 5.5)	**0.2% fewer** (1.4 fewer to 3.3 more)	⨁⨁⨁◯ Moderate[c]	MD-ICS/LABA likely results in little to no difference in all cause SAEs compared to MD-ICS/LAMA.
5.2.9 All cause SAEs - HD-ICS/LABA vs MD-ICS/LABA № of participants: 7919 (9 RCTs) Follow up: 3 to 12 months	**RR 1.23** (0.95 to 1.58)	3.9%	**4.8%** (3.7 to 6.2)	**0.9% more** (0.2 fewer to 2.3 more)	⨁⨁⨁⨁ High[a]	HD-ICS/LABA results in little to no difference in all cause SAEs compared to MD-ICS/LABA.
5.3.1 All cause AEs - HD-ICS vs MD-ICS № of participants: 2208 (6 RCTs) Follow up: 3 to 12 months	**RR 1.00** (0.88 to 1.14)	47.0%	**47.0%** (41.4 to 53.6)	**0.0% fewer** (5.6 fewer to 6.6 more)	⨁⨁⨁⨁ High[a]	HD-ICS results in little to no difference in all cause AEs compared to MD-ICS.
5.3.2 All cause AEs - MD-ICS/LAMA vs MD-ICS № of participants: 2238 (4 RCTs) Follow up: 6 months	**RR 0.86** (0.77 to 0.96)	39.6%	**34.0%** (30.5 to 38)	**5.5% fewer** (9.1 fewer to 1.6 fewer)	⨁⨁⨁◯ Moderate[f]	MD-ICS/LAMA probably reduces all cause AEs compared to MD-ICS.
5.3.3 All cause AEs - MD-ICS/LABA vs MD-ICS № of participants: 13430 (20 RCTs) Follow up: 3 to 12 months	**RR 1.05** (0.93 to 1.19)	38.4%	**40.3%** (35.7 to 45.7)	**1.9% more** (2.7 fewer to 7.3 more)	⨁⨁⨁◯ Moderate[a, b, e]	MD-ICS/LABA likely results in little to no difference in all cause AEs compared to MD-ICS.
5.3.4 All cause AEs - HD-ICS/LABA vs MD-ICS № of participants: 2742 (4 RCTs) Follow up: 3 to 12 months	**RR 0.87** (0.72 to 1.05)	42.4%	**36.9%** (30.5 to 44.5)	**5.5% fewer** (11.9 fewer to 2.1 more)	⨁⨁⨁◯ Moderate[f]	HD-ICS/LABA likely results in little to no difference in all cause AEs compared to MD-ICS.
5.3.5 All cause AEs - MD-ICS/LABA vs HD-ICS № of participants: 2148 (5 RCTs) Follow up: 3 to 12 months	**RR 0.93** (0.87 to 1.00)	44.4%	**41.3%** (38.7 to 44.4)	**3.1% fewer** (5.8 fewer to 0 fewer)	⨁⨁⨁◯ Moderate[f]	MD-ICS/LABA probably reduces all cause AEs compared to HD-ICS for the fixed-effect model but not for the random-effects model.
5.3.6 All cause AEs - HD-ICS/LABA vs HD-ICS № of participants: 3909 (8 RCTs) Follow up: 3 to 12 months	**RR 0.91** (0.85 to 0.97)	37.3%	**33.9%** (31.7 to 36.1)	**3.4% fewer** (5.6 fewer to 1.1 fewer)	⨁⨁⨁◯ Moderate[g]	HD-ICS/LABA probably results in little to no difference in all cause AEs compared to HD-ICS.
5.3.7 All cause AEs - MD-ICS/LABA vs LD-ICS/LABA № of participants: 695 (1 RCT) Follow up: 3 months	**RR 0.92** (0.75 to 1.13)	36.5%	**33.6%** (27.4 to 41.3)	**2.9% fewer** (9.1 fewer to 4.7 more)	⨁⨁⨁◯ Moderate[c]	MD-ICS/LABA likely results in little to no difference in all cause AEs compared to LD-ICS/LABA.
5.3.8 All cause AEs - MD-ICS/LABA vs MD-ICS/LAMA № of participants: 1577 (2 RCTs) Follow up: 6 months	**RR 1.01** (0.87 to 1.17)	33.9%	**34.2%** (29.5 to 39.6)	**0.3% more** (4.4 fewer to 5.8 more)	⨁⨁⨁⨁ High	MD-ICS/LABA results in little to no difference in all cause AEs compared to MD-ICS/LAMA.
5.3.9 All cause AEs - HD-ICS/LABA vs MD-ICS/LABA № of participants: 6357 (8RCTs) Follow up: 3 to 12 months	**RR 1.01** (0.96 to 1.05)	42.4%	**42.9%** (40.7 to 44.6)	**0.4% more** (1.7 fewer to 2.1 more)	⨁⨁⨁⨁ High[a]	HD-ICS/LABA results in little to no difference in all cause AEs compared to MD-ICS/LABA.
5.4.1 Dropouts due to adverse events - HD-ICS vs MD-ICS № of participants: 2211	**RR 1.29** (0.48 to 3.48)	0.8%	**1.0%** (0.4 to 2.6)	**0.2% more** (0.4 fewer to 1.9 more)	⨁⨁⨁⨁ High	HD-ICS results in little to no difference in dropouts due to adverse events compared to MD-ICS.

(6 RCTs) Follow up: 3 to 12 months						
5.4.2 Dropouts due to adverse events - LD-ICS/LABA vs MD-ICS № of participants: 5846 (1 RCT) Follow up: 6 months	**RR 0.66** (0.38 to 1.14)	1.5%	**1.0%** (0.6 to 1.7)	**0.5% fewer** (0.9 fewer to 0.2 more)	⨁⨁⨁⨁ High	LD-ICS/LABA results in little to no difference in dropouts due to adverse events compared to MD-ICS.
5.4.3 Dropouts due to adverse events - MD-ICS/LAMA vs MD-ICS № of participants: 2239 (4 RCTs) Follow up: 6 months	**RR 0.51** (0.26 to 0.99)‡	2.1%	**1.1%** (0.5 to 2.1)	**1.0% fewer** (1.6 fewer to 0 fewer)	⨁⨁⨁◯ Moderate[c]	MD-ICS/LAMA probably results in a slight reduction in dropouts due to adverse events compared to MD-ICS.
5.4.4 Dropouts due to adverse events - MD-ICS/LABA vs MD-ICS № of participants: 20326 (21 RCTs) Follow up: 3 to 20 months	**RR 0.98** (0.74 to 1.31)	1.7%	**1.7%** (1.3 to 2.2)	**0.0% fewer** (0.4 fewer to 0.5 more)	⨁⨁⨁⨁ High	MD-ICS/LABA results in little to no difference in dropouts due to adverse events compared to MD-ICS.
5.4.5 Dropouts due to adverse events - HD-ICS/LABA vs MD-ICS № of participants: 2750 (4 RCTs) Follow up: 3 to 12 months	**RR 0.84** (0.31 to 2.27)	0.8%	**0.6%** (0.2 to 1.7)	**0.1% fewer** (0.5 fewer to 1 more)	⨁⨁⨁⨁ High	HD-ICS/LABA results in little to no difference in dropouts due to adverse events compared to MD-ICS.
5.4.6 Dropouts due to adverse events - MD-ICS/LABA vs HD-ICS № of participants: 2465 (5 RCTs) Follow up: 3 to 12 months	**RR 1.27** (0.67 to 2.40)	1.3%	**1.7%** (0.9 to 3.2)	**0.4% more** (0.4 fewer to 1.9 more)	⨁⨁⨁⨁ High	MD-ICS/LABA results in little to no difference in dropouts due to adverse events compared to HD-ICS.
5.4.7 Dropouts due to adverse events - HD-ICS/LABA vs HD-ICS № of participants: 3916 (8 RCTs) Follow up: 3 to 12 months	**RR 1.22** (0.68 to 2.17)	1.2%	**1.5%** (0.8 to 2.7)	**0.3% more** (0.4 fewer to 1.5 more)	⨁⨁⨁⨁ High	HD-ICS/LABA results in little to no difference in dropouts due to adverse events compared to HD-ICS.
5.4.8 Dropouts due to adverse events - MD-ICS/LABA vs LD-ICS/LABA № of participants: 6542 (2 RCTs) Follow up: 3 to 6 months	**RR 1.03** (0.62 to 1.70)	1.2%	**1.2%** (0.7 to 2)	**0.0% fewer** (0.4 fewer to 0.8 more)	⨁⨁⨁⨁ High	MD-ICS/LABA results in little to no difference in dropouts due to adverse events compared to LD-ICS/LABA.
5.4.9 Dropouts due to adverse events - MD-ICS/LABA vs MD-ICS/LAMA № of participants: 1577 (2 RCTs) Follow up: 6 months	**RR 1.27** (0.19 to 8.66)	1.5%	**2.0%** (0.3 to 13.4)	**0.4% more** (1.3 fewer to 11.8 more)	⨁⨁⨁◯ Moderate[b]	MD-ICS/LABA likely results in little to no difference in dropouts due to adverse events compared to MD-ICS/LAMA.
5.4.10 Dropouts due to adverse events - HD-ICS/LABA vs MD-ICS/LABA № of participants: 6380 (8 RCTs) Follow up: 3 to 12 months	**RR 0.81** (0.56 to 1.19)	2.7%	**2.2%** (1.5 to 3.2)	**0.5% fewer** (1.2 fewer to 0.5 more)	⨁⨁⨁⨁ High	HD-ICS/LABA results in little to no difference in dropouts due to adverse events compared to MD-ICS/LABA.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

‡ fixed-effect model. AE: adverse event; CFB change from baseline; CI: confidence interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio; SAE: serious adverse event.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. The proportion of information from study(ies) at high risk of bias is not sufficient to affect the interpretation of results.

b. Downgraded one level for substantial heterogeneity I2>= 50% to 90% in the relative risk or risk difference.

c. Downgraded one level for imprecision: Confidence interval is either wide or include the null effect in the relative risk or risk difference.

d. Downgraded one level: Total size of less than 1000 patients may suggest small study effect (Dechartres 2013)

e. Sensitivity analysis using the imputation methods for missing data suggested in Guyatt 2017 did not affect the interpretation of results.

f. Downgraded one level: Optimal information size is not met (Guyatt 2011)

g. Downgraded one level: A significant difference was observed with a fixed-effect analysis.

Table 34

Odds Ratios for all-cause SAEs using a fixed-effect and random-effects model

	Odds Ratio (95% CrI)	
Comparison	**Fixed-Effect Model**	**Random-Effects Model**
HD-ICS vs. MD-ICS	0.824 (0.599, 1.124)	0.764 (0.461, 1.204)
LD-ICS/LABA vs. MD-ICS	**2.430 (0.186, 78.864)**	**2.517 (0.168, 85.719)**
MD-ICS/LAMA vs. MD-ICS	0.922 (0.553, 1.533)	0.959 (0.485, 1.917)
MD-ICS/LABA vs. MD-ICS	0.988 (0.816, 1.198)	1.033 (0.767, 1.428)
HD-ICS/LABA vs. MD-ICS	1.034 (0.811, 1.320)	1.033 (0.668, 1.572)
LD-ICS/LABA vs. HD-ICS	**2.958 (0.222, 96.576)**	**3.309 (0.217, 115.371)**
MD-ICS/LAMA vs. HD-ICS	1.120 (0.624, 2.015)	1.253 (0.569, 2.917)
MD-ICS/LABA vs. HD-ICS	1.200 (0.887, 1.638)	1.352 (0.869, 2.264)
HD-ICS/LABA vs. HD-ICS	1.255 (0.936, 1.700)	1.347 (0.857, 2.220)
MD-ICS/LAMA vs. LD-ICS/LABA	0.378 (0.011, 5.215)	0.379 (0.011, 6.180)
MD-ICS/LABA vs. LD-ICS/LABA	0.406 (0.013, 5.283)	0.412 (0.012, 6.089)
HD-ICS/LABA vs. LD-ICS/LABA	0.425 (0.013, 5.578)	0.409 (0.012, 6.190)
MD-ICS/LABA vs. MD-ICS/LAMA	1.072 (0.639, 1.801)	1.080 (0.536, 2.196)
HD-ICS/LABA vs. MD-ICS/LAMA	1.122 (0.650, 1.941)	1.079 (0.489, 2.327)
HD-ICS/LABA vs. MD-ICS/LABA	1.046 (0.848, 1.292)	1.001 (0.663, 1.447)

The second named treatment is the baseline intervention. Odds Ratios less than one favour the treatment named first in the comparisons. Odds ratios in bold are extremely uncertain due to network sparsity and should be treated with caution. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; SAE: serious adverse event.

Table 35

NMA Summary of Findings for all-cause SAEs

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, LD-ICS/LABA, MD-ICS/LAMA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: All-cause serious adverse event

Setting: Outpatient

Total studies: 33 RCTs **Total Participants: 26875**	**Risk ratio** (95% CrI)**	**Anticipated absolute effect*** (95% CrI)**		**Certainty of the evidence**	**Ranking**** (95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS**			
HD-ICS (Direct evidence; 7 RCTs; 3775 participants)	**0.76** (0.47 to 1.19)	21 per 1000	6 per 1000 fewer (from 14 fewer to 5 more)	⊕⊕⊕◯ **Moderate** Due to heterogeneity[1]	**2.0** (1.0 to 5.0)	HD-ICS likely results in little to no difference in all cause AEs compared to MD-ICS
LD-ICS/LABA (Direct evidence; 0 RCTs; 0 participants)	**2.42** (0.17 to 26.08)	65 per 1000	38 per 1000 more (from 22 fewer to 678 more)	⊕⊕◯◯ **Low** Due to imprecision[2]	**6.0** (1.0 to 6.0)	The evidence suggests that LD-ICS/LABA results in little to no difference in all cause AEs compared to MD-ICS
MD-ICS/LAMA (Direct evidence; 4 RCTs; 2238 participants)	**0.96** (0.49 to 1.87)	26 per 1000	1 per 1000 fewer (from 14 fewer to 24 more)	⊕⊕⊕⊕ **High**	**2.0** (1.0 to 6.0)	MD-ICS/LAMA results in little to no difference in all cause SAEs compared to MD-ICS
MD-ICS/LABA (Direct evidence; 21 RCTs; 14588 participants)	**1.03** (0.77 to 1.41)	28 per 1000	1 per 1000 more (from 6 fewer to 11 more)	⊕⊕⊕⊕ **High**	**4.0** (1.0 to 6.0)	MD-ICS/LABA results in little to no difference in all cause SAEs compared to MD-ICS
HD-ICS/LABA (Direct evidence; 5 RCTs; 4302 participants)	**1.03** (0.68 to 1.55)	28 per 1000	1 per 1000 more (from 9 fewer to 15 more)	⊕⊕⊕⊕ **High**	**4.0** (2.0 to 6.0)	HD-ICS/LABA results in little to no difference in all cause SAEs compared to MD-ICS
MD-ICS	Reference Comparator	27 per 1000[3]	Reference Comparator	Reference Comparator	**4.0**	Reference Comparator

					(2.0 to 6.0)	

NMA-SoF table definitions

** Network Meta-Analysis estimates of **random-effects model** are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

1 Downgraded one level for substantial heterogeneity I^2>= 50% to 90% in the direct estimate.
2 Downgraded for two levels for very serious imprecision due to suboptimal sample size and wide confidence intervals in the direct and/or indirect estimate(s).
3 Based on the average rate in patients treated with MD-ICS in the included studies.

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; RCT: randomised controlled trial; SAE: serious adverse event

Table 36

Mean and median ranks (with corresponding 95% CrIs) for all-cause SAEs sorted by mean rank (fixed-effect and random-effects model)

Fixed-Effect Model			
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**
HD-ICS	1.85	2.00	(1.00, 5.00)
MD-ICS/LAMA	2.99	2.00	(1.00, 6.00)
MD-ICS/LABA	3.52	4.00	(1.00, 6.00)
MD-ICS	3.70	4.00	(2.00, 6.00)
HD-ICS/LABA	4.13	4.00	(2.00, 6.00)
LD-ICS/LABA	4.81	6.00	(1.00, 6.00)
Random-Effects Model			
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**
HD-ICS	1.85	2.00	(1.00, 5.00)
MD-ICS/LAMA	2.99	2.00	(1.00, 6.00)
MD-ICS/LABA	3.52	4.00	(1.00, 6.00)
MD-ICS	3.70	4.00	(2.00, 6.00)
HD-ICS/LABA	4.13	4.00	(2.00, 6.00)
LD-ICS/LABA	4.81	6.00	(1.00, 6.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; SAE: serious adverse event.

Table 37

Odds Ratios for all-cause AEs using a random-effects model

Comparison	Odds Ratio (95% CrI)
HD-ICS vs. MD-ICS	1.117 (0.829, 1.511)
LD-ICS/LABA vs. MD-ICS	1.180 (0.522, 2.671)
MD-ICS/LAMA vs. MD-ICS	0.882 (0.601, 1.294)
MD-ICS/LABA vs. MD-ICS	1.042 (0.867, 1.252)
HD-ICS/LABA vs. MD-ICS	0.954 (0.718, 1.272)
LD-ICS/LABA vs. HD-ICS	1.056 (0.451, 2.461)
MD-ICS/LAMA vs. HD-ICS	0.790 (0.489, 1.270)
MD-ICS/LABA vs. HD-ICS	0.933 (0.689, 1.260)
HD-ICS/LABA vs. HD-ICS	0.855 (0.637, 1.148)
MD-ICS/LAMA vs. LD-ICS/LABA	0.747 (0.307, 1.823)
MD-ICS/LABA vs. LD-ICS/LABA	0.883 (0.399, 1.954)
HD-ICS/LABA vs. LD-ICS/LABA	0.809 (0.350, 1.874)
MD-ICS/LABA vs. MD-ICS/LAMA	1.181 (0.792, 1.764)
HD-ICS/LABA vs. MD-ICS/LAMA	1.082 (0.681, 1.727)
HD-ICS/LABA vs. MD-ICS/LABA	0.916 (0.700, 1.203)

The second named treatment is the baseline intervention. Odds Ratios less than one favour the treatment named first in the comparisons.
CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 38

NMA Summary of Findings for all-cause adverse events

Population: Adolescents and adults with uncontrolled asthma, despite being on medium-dose ICS

Interventions: HD-ICS, LD-ICS/LABA, MD-ICS/LAMA, MD-ICS/LABA, or HD-ICS/LABA

Control: MD-ICS

Outcome: All-cause adverse event

Setting: Outpatient

-ATotal studies: 33 RCTs Total Participants: 24122	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI) With intervention Difference compared to MD-ICS		Certainty of the evidence	Ranking**** (95% CrI)	Interpretation of Findings
HD-ICS (Direct evidence; 6 RCTs; 2208 participants)	**1.07** (0.89 to 1.27)	407 per 1000	27 per 1000 more (from 42 fewer to 103 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**2.0** (1.0 to 6.0)	HD-ICS likely results in little to no difference in all cause AEs compared to MD-ICS.
LD-ICS/LABA (Direct evidence; 0 RCTs; 0 participants)	**1.10** (0.64 to 1.63)	418 per 1000	38 per 1000 more (from 137 fewer to 239 more)	⊕⊕◯◯ **Low** Due to imprecision[2] and heterogeity[3]	**1.0** (1.0 to 6.0)	The evidence suggests that LD-ICS/LABA results in little to no difference in all cause AEs compared to MD-ICS.
MD-ICS/LAMA (Direct evidence; 4 RCTs; 2238 participants)	**0.92** (0.71 to 1.16)	350 per 1000	30 per 1000 fewer (from 110 fewer to 61 more)	⊕◯◯◯ **Very low** Due to imprecision[2,3] and heterogeneity[4]	**5.0** (1.0 to 6.0)	The evidence is very uncertain
MD-ICS/LABA (Direct evidence; 20 RCTs; 13430 participants)	**1.02** (0.92 to 1.14)	388 per 1000	8 per 1000 more (from 30 fewer to 53 more)	⊕⊕◯◯ **Low** Due to imprecision[2] and heterogeity[4]	**3.0** (1.0 to 5.0)	The evidence suggests that MD-ICS/LABA results in little to no difference in all cause AEs compared to MD-ICS
HD-ICS/LABA (Direct evidence; 4 RCTs; 2742 participants)	**0.97** (0.81 to 1.15)	369 per 1000	11 per 1000 fewer (from 72 fewer to 57 more)	⊕⊕◯◯ **Low** Due to imprecision[1] and heterogeity[4]	**5.0** (1.0 to 6.0)	The evidence suggests that HD-ICS/LABA results in little to no difference in all cause AEs compared to MD-ICS
MD-ICS	Reference Comparator	380 per 1000[5]	Reference Comparator	Reference Comparator	**4.0** (1.0 to 6.0)	Reference Comparator

NMA-SoF table definitions

** Network Meta-Analysis estimates are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

1 Downgraded one level for serious imprecision due to a wide confidence interval in the direct and/or indirect estimate(s).
2 Downgraded one level for serious imprecision due to suboptimal sample size in the direct and/or indirect estimate(s).
3 Downgraded one level for serious imprecision due to credible intervals crossing the line of no effect in the fixed- and random- effect(s) NMA estimates while the confidence interval of direct estimate does not.
4 Downgraded one level for substantial heterogeneity I^2>= 50% to 90% in the direct and/or indirect estimate(s).
5 Based on the average rate in patients treated with MD-ICS in the included studies.

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; RCT: randomised controlled trial.

Table 39

Mean and median ranks (with corresponding 95% CrI) for all-cause AEs sorted by mean rank (random-effects model)

Treatments	Mean Rank	Median Rank	95% CrI
HD-ICS	2.41	2.00	(1.00, 6.00)
LD-ICS/LABA	2.73	1.00	(1.00, 6.00)
MD-ICS/LABA	3.09	3.00	(1.00, 5.00)

MD-ICS	3.73	4.00	(1.00, 6.00)
HD-ICS/LABA	4.28	5.00	(1.00, 6.00)
MD-ICS/LAMA	4.76	5.00	(1.00, 6.00)

AE: adverse event; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 40

Odds Ratios for drop-outs due to AEs using fixed-effect and random-effects models

Comparison	Odds Ratio (95% CrI)	
	Fixed-Effect Model	Random-Effects Model
HD-ICS vs. MD-ICS	0.737 (0.429, 1.238)	0.750 (0.412, 1.374)
LD-ICS/LABA vs. MD-ICS	0.815 (0.492, 1.296)	0.852 (0.429, 1.713)
MD-ICS/LAMA vs. MD-ICS	0.570 (0.296, 1.067)	0.535 (0.242, 1.091)
MD-ICS/LABA vs. MD-ICS	0.967 (0.783, 1.194)	0.971 (0.728, 1.289)
HD-ICS/LABA vs. MD-ICS	0.822 (0.551, 1.225)	0.816 (0.480, 1.338)
LD-ICS/LABA vs. HD-ICS	1.104 (0.553, 2.198)	1.139 (0.471, 2.711)
MD-ICS/LAMA vs. HD-ICS	0.773 (0.342, 1.736)	0.710 (0.264, 1.776)
MD-ICS/LABA vs. HD-ICS	1.311 (0.800, 2.213)	1.293 (0.719, 2.313)
HD-ICS/LABA vs. HD-ICS	1.116 (0.664, 1.903)	1.087 (0.592, 1.954)
MD-ICS/LAMA vs. LD-ICS/LABA	0.700 (0.318, 1.532)	0.629 (0.218, 1.623)
MD-ICS/LABA vs. LD-ICS/LABA	1.186 (0.751, 1.956)	1.139 (0.572, 2.221)
HD-ICS/LABA vs. LD-ICS/LABA	1.009 (0.566, 1.848)	0.957 (0.420, 2.119)
MD-ICS/LABA vs. MD-ICS/LAMA	1.698 (0.903, 3.279)	1.809 (0.888, 4.008)
HD-ICS/LABA vs. MD-ICS/LAMA	1.444 (0.701, 3.032)	1.520 (0.654, 3.804)
HD-ICS/LABA vs. MD-ICS/LABA	0.850 (0.595, 1.210)	0.838 (0.527, 1.317)

The second named treatment is the baseline intervention. Odds Ratios less than one favour the treatment named first in the comparisons. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Table 41

Mean and median ranks (with corresponding 95% CrIs) for drop-outs due to AEs sorted by mean rank (fixed-effect and random-effects models)

Fixed-effect Model			
Treatments	Mean Rank	Median Rank	95% CrI
MD-ICS/LAMA	1.70	1	(1.00, 6.00)
HD-ICS	2.73	2	(1.00, 6.00)
LD-ICS/LABA	3.35	3	(1.00, 6.00)
HD-ICS/LABA	3.36	3	(1.00, 6.00)
MD-ICS/LABA	4.76	5	(3.00, 6.00)
MD-ICS	5.09	5	(3.00, 6.00)
Random-effects Model			
Treatments	Mean Rank	Median Rank	95% CrI
MD-ICS/LAMA	1.66	1	(1.00, 5.00)
HD-ICS	2.90	3	(1.00, 6.00)
HD-ICS/LABA	3.32	3	(1.00, 6.00)
LD-ICS/LABA	3.65	3	(1.00, 6.00)
MD-ICS/LABA	4.62	5	(2.00, 6.00)
MD-ICS	4.84	5	(2.00, 6.00)

AE: adverse event; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Figure 1

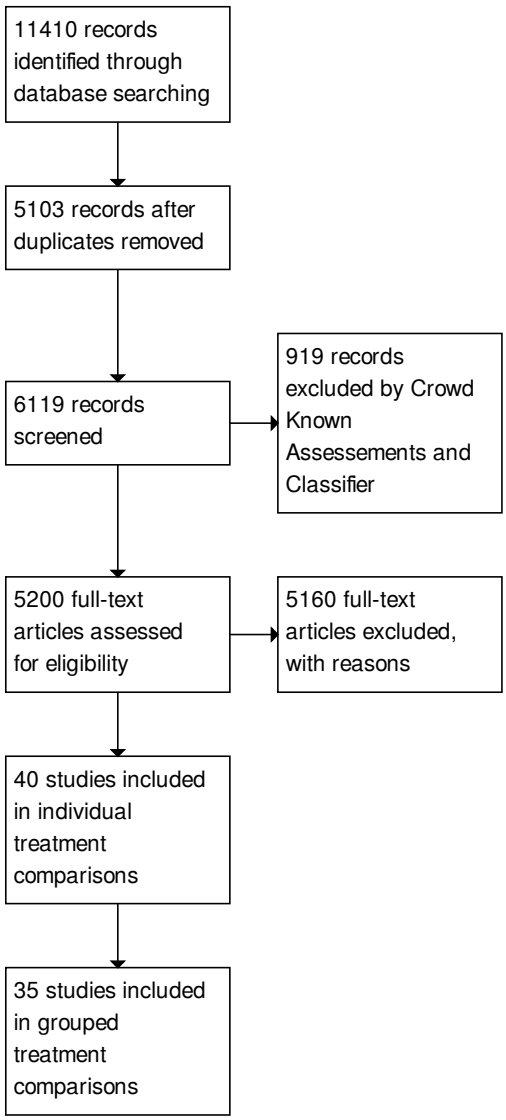
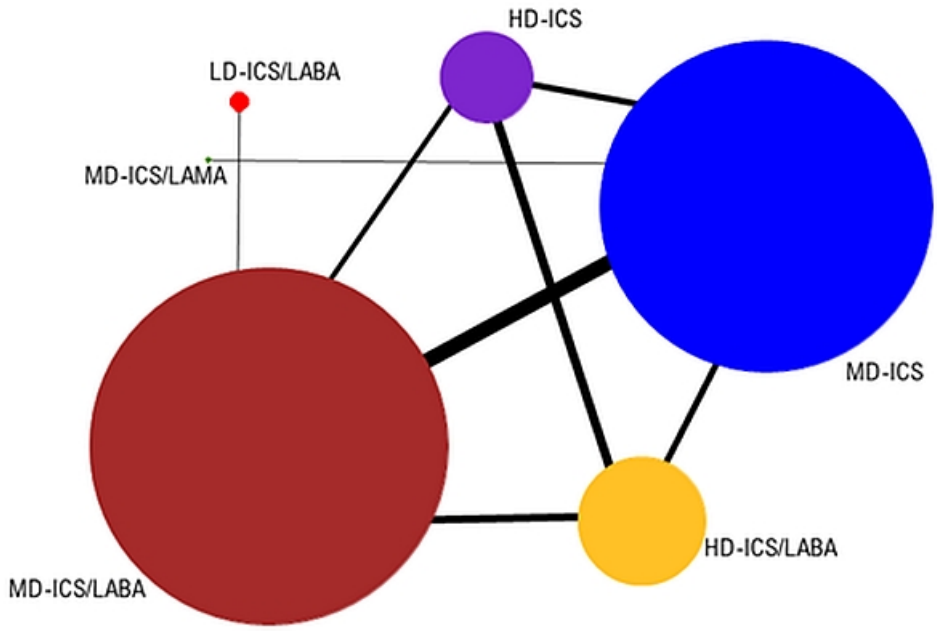


Figure 2

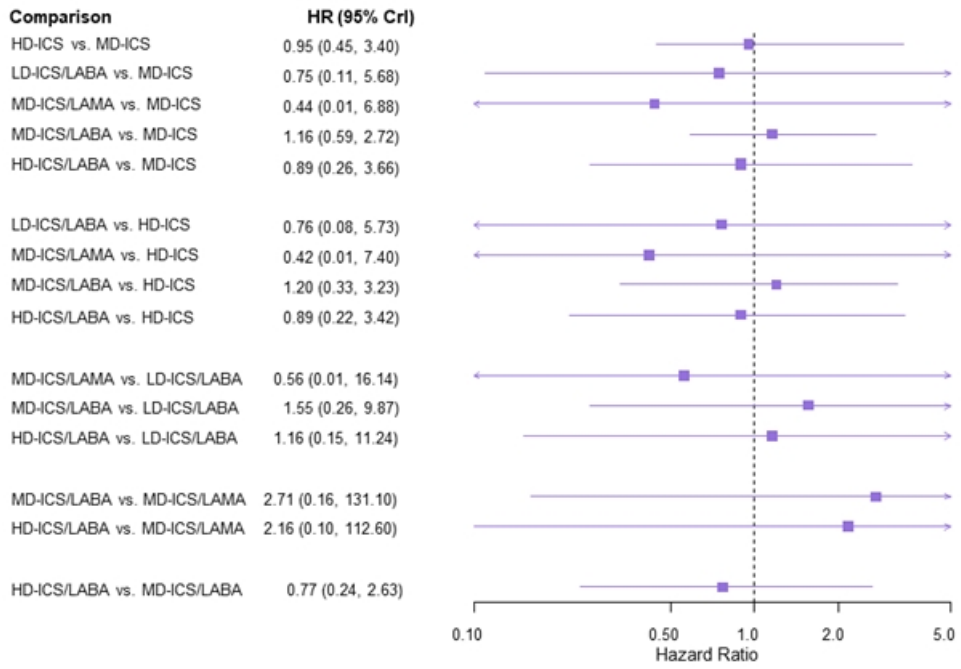


Network diagram for severe exacerbations.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on

that comparison. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

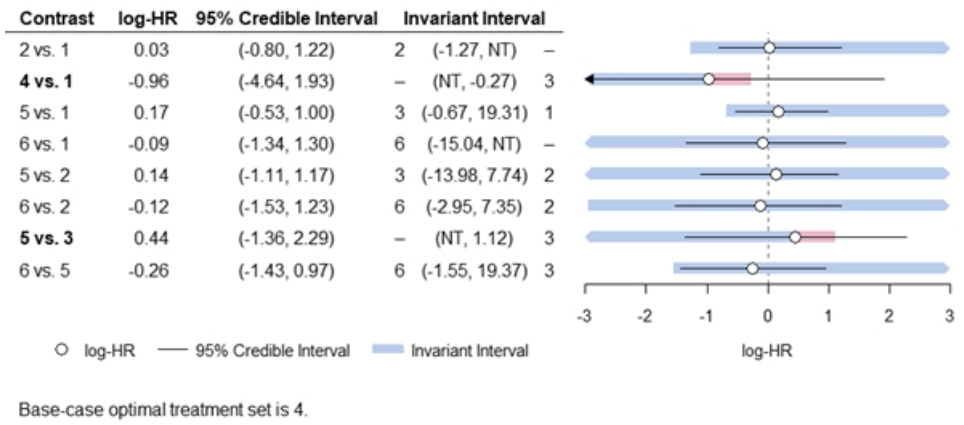
Figure 3



Plot of hazard ratios (HRs) relative for severe exacerbations.

Hazard Ratios less than one favour the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose

Figure 4

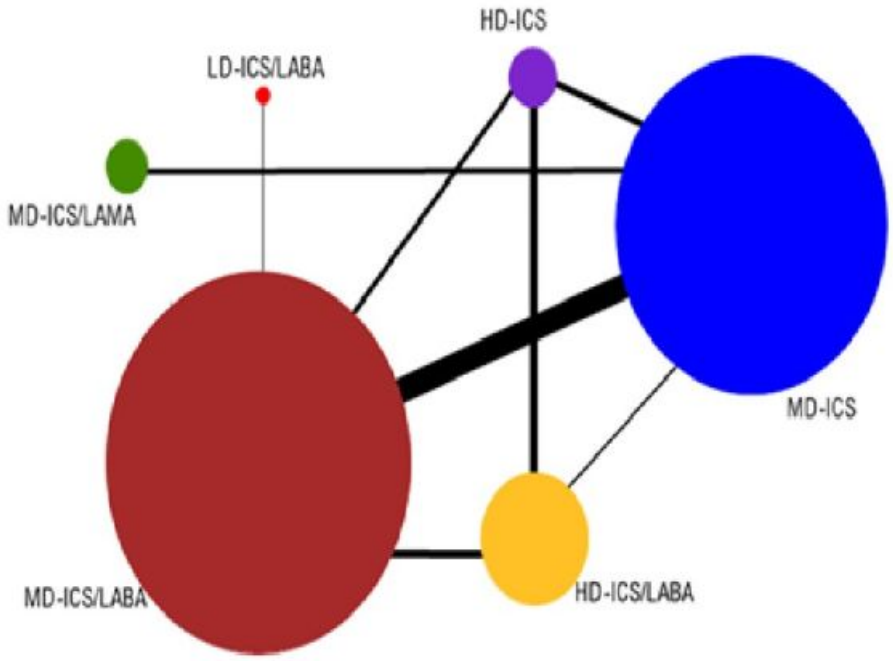


Base-case optimal treatment set is 4.

Forest plot for threshold analysis for severe exacerbations (random-effects model).

Treatment Codes: 1=MD-ICS, 2= HD-ICS, 3= LD-ICS/LABA, 4= MD-ICS/LAMA, 5= MD-ICS/LABA, 6= HD-ICS/LABA. The optimum treatment for this analysis was MD-ICS/LAMA. HD: high dose; HR: hazard ratio; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

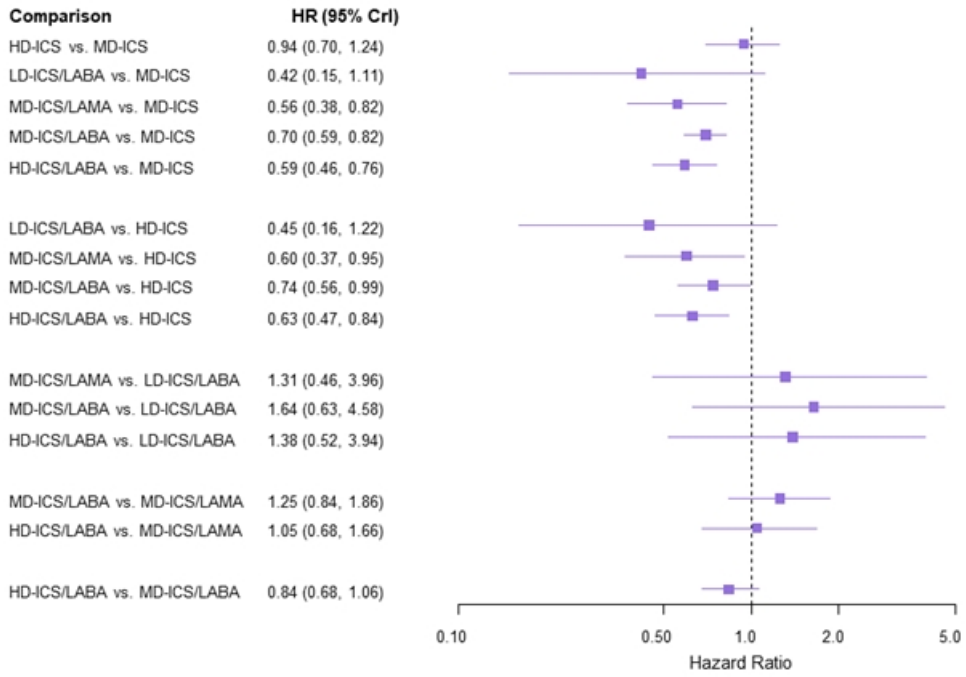
Figure 5



Network diagram for moderate to severe exacerbations.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Figure 6

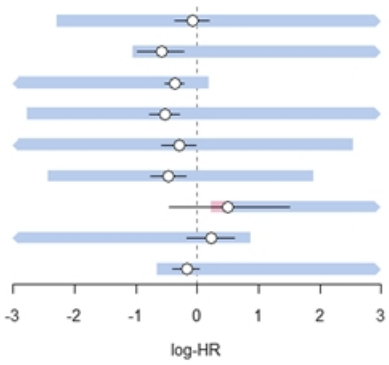


Plot of hazard ratios (HRs) relative for moderate to severe exacerbations.

Hazard Ratios less than one favour the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

Figure 7

Contrast	log-HR	95% Credible Interval	Invariant Interval	
2 vs. 1	-0.07	(-0.36, 0.22)	2 (-2.28, 4.86)	4
4 vs. 1	-0.58	(-0.97, -0.20)	4 (-1.05, NT)	–
5 vs. 1	-0.36	(-0.53, -0.20)	– (NT, 0.19)	4
6 vs. 1	-0.53	(-0.78, -0.28)	6 (-2.77, 5.73)	4
5 vs. 2	-0.29	(-0.58, -0.01)	– (NT, 2.54)	2
6 vs. 2	-0.47	(-0.76, -0.17)	6 (-2.43, 1.91)	2
5 vs. 3	0.50	(-0.46, 1.52)	4 (0.23, NT)	–
5 vs. 4	0.22	(-0.17, 0.62)	– (NT, 0.88)	4
6 vs. 5	-0.17	(-0.39, 0.06)	6 (-0.65, NT)	–

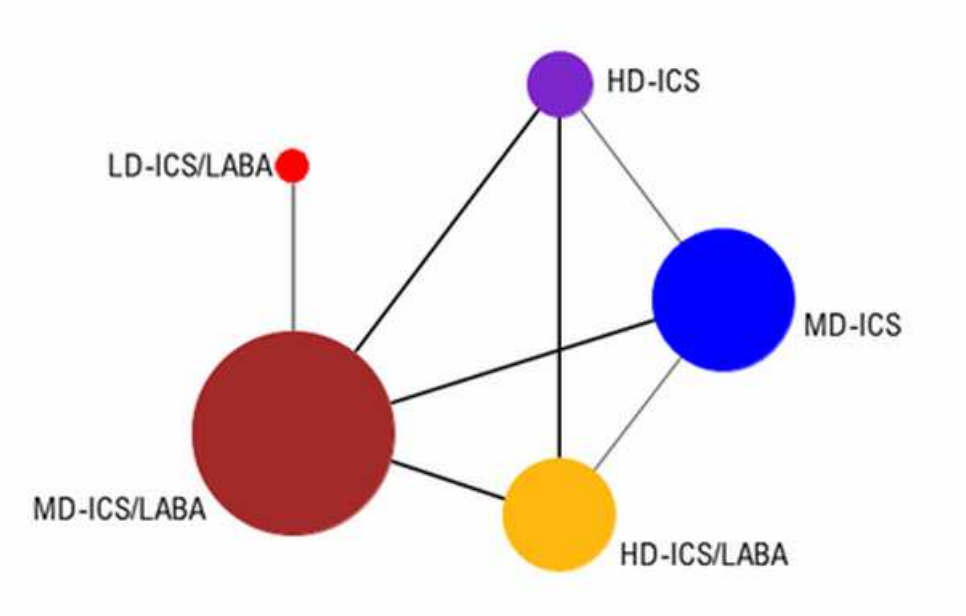


Base-case optimal treatment set is 3.

Forest plot for threshold analysis for moderate-severe exacerbations (random-effects model).

Treatment Codes: 1=MD-ICS, 2= HD-ICS, 3= LD-ICS/LABA, 4= MD-ICS/LAMA, 5= MD-ICS/LABA, 6= HD-ICS/LABA. The optimum treatment for this analysis was LD-ICS/LABA. HD: high dose; HR: hazard ratio; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

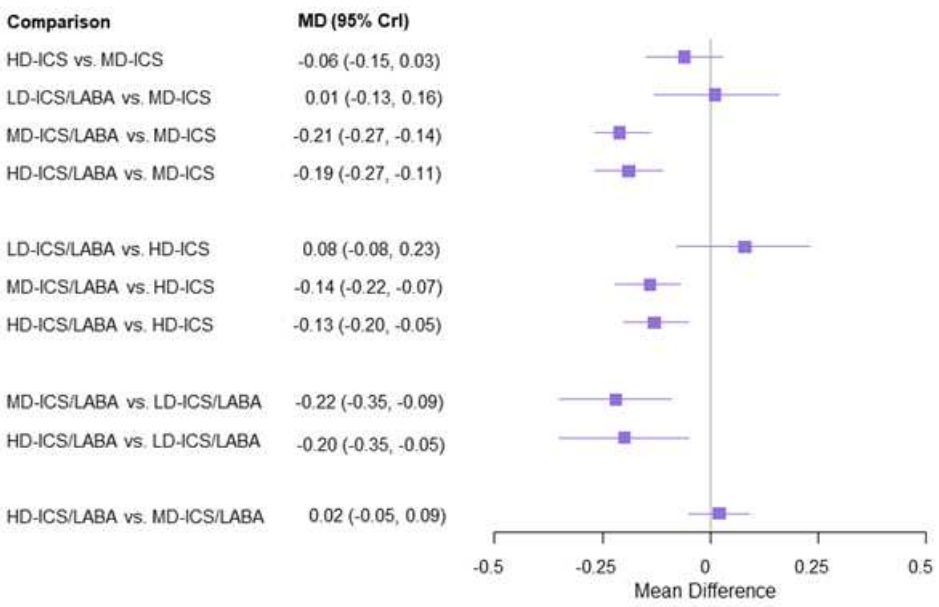
Figure 8



Network diagram for change from baseline ACQ score at 3 months.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose.

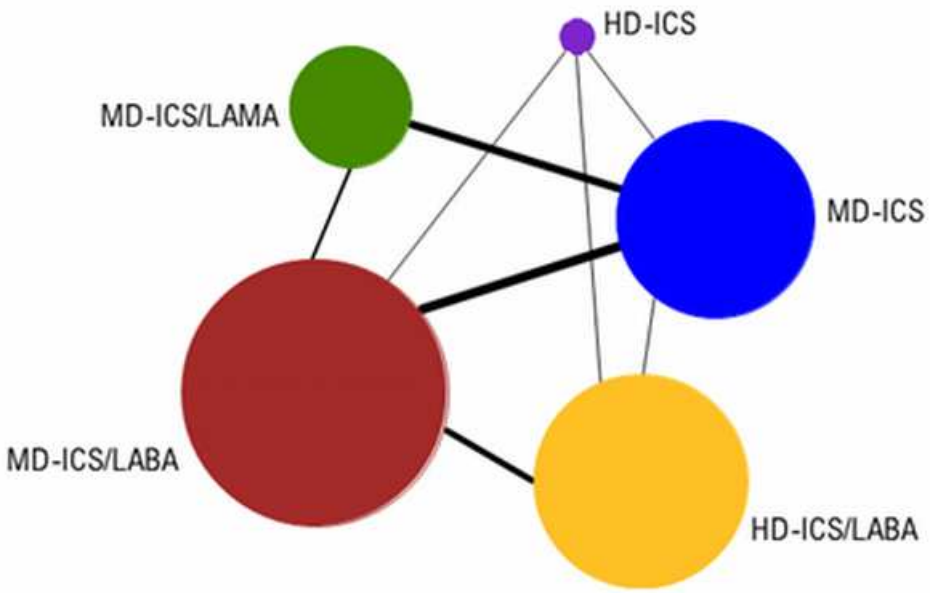
Figure 9



Plot of relative effects for the change from baseline ACQ score at 3 months using a fixed-effects model.

Mean differences less than zero favour the first named treatment. ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonistLD: low dose; MD: medium dose

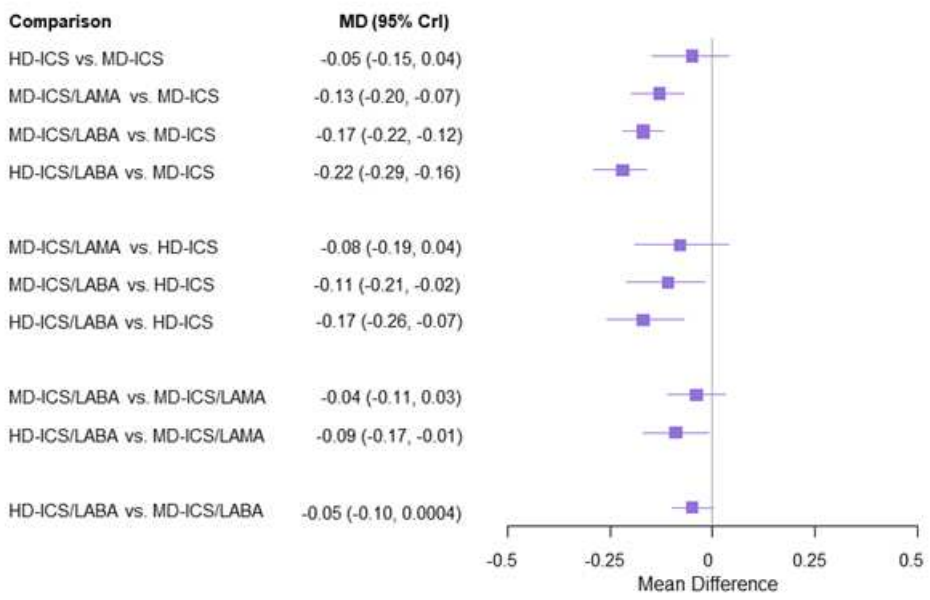
Figure 10



Network diagram for change from baseline ACQ score at 6 months. Nodes colours denote the treatment group.

Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: medium dose.

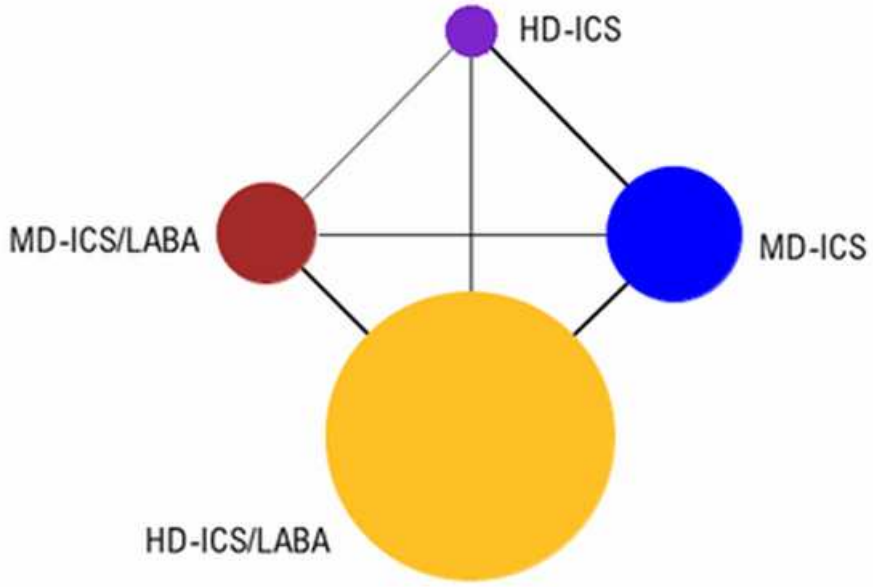
Figure 11



Plot of relative effects for the change from baseline in ACQ score at 6 months using the fixed-effect model.

Mean differences less than zero favour the first named treatment. ACQ: Asthma Control Questionnaire; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: mean difference; MD: medium dose.

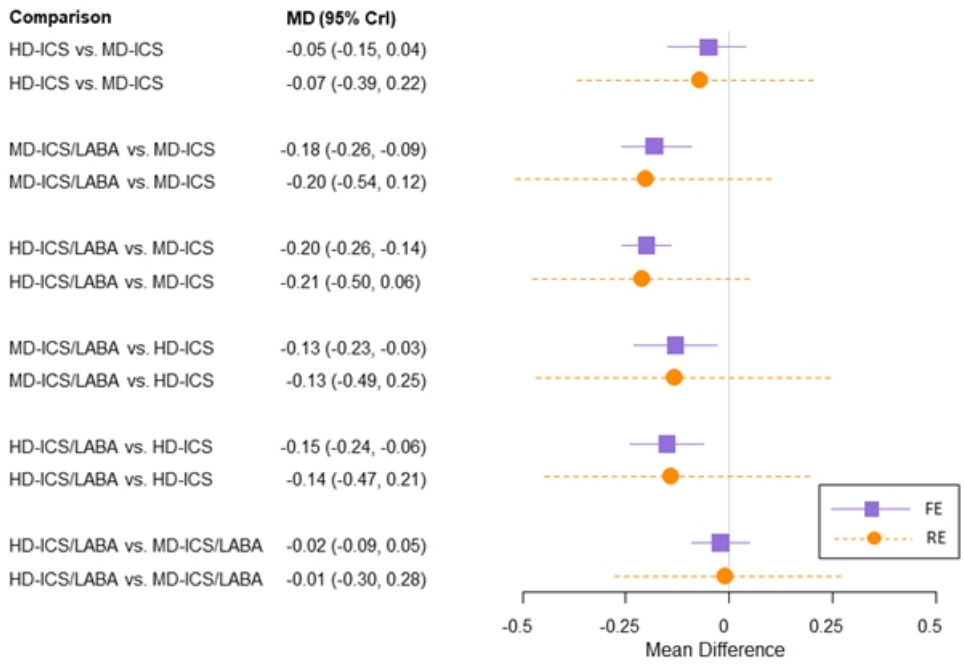
Figure 12



Network diagram for change from baseline ACQ score at 12 months.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose.

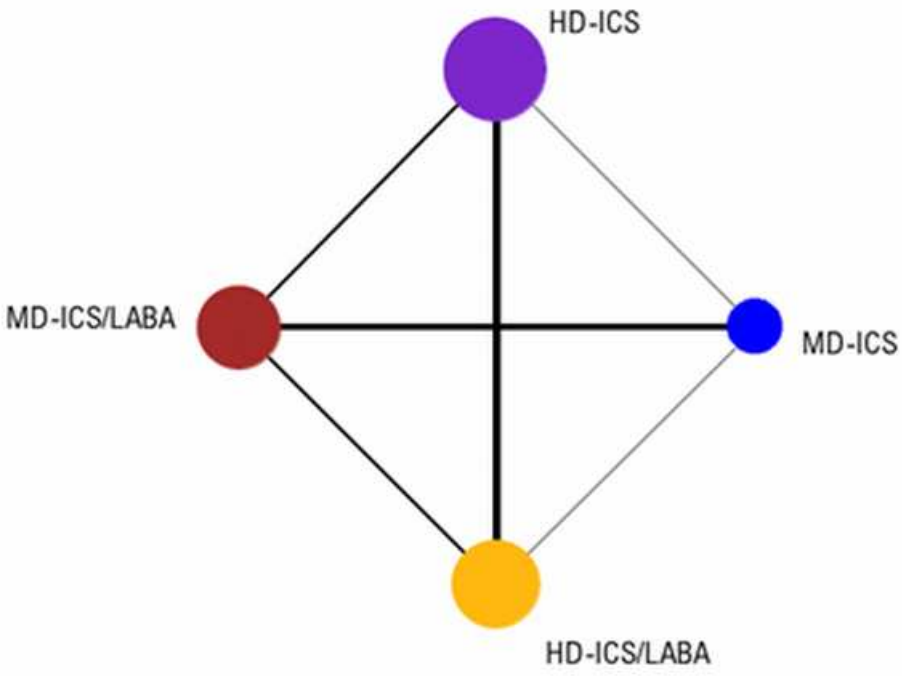
Figure 13



Plot of relative effects for the change from baseline ACQ score at 12 months using a fixed-effect (FE) and a random-effects (RE) model.

Mean differences (MD) less than zero favour the first named treatment. ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose.

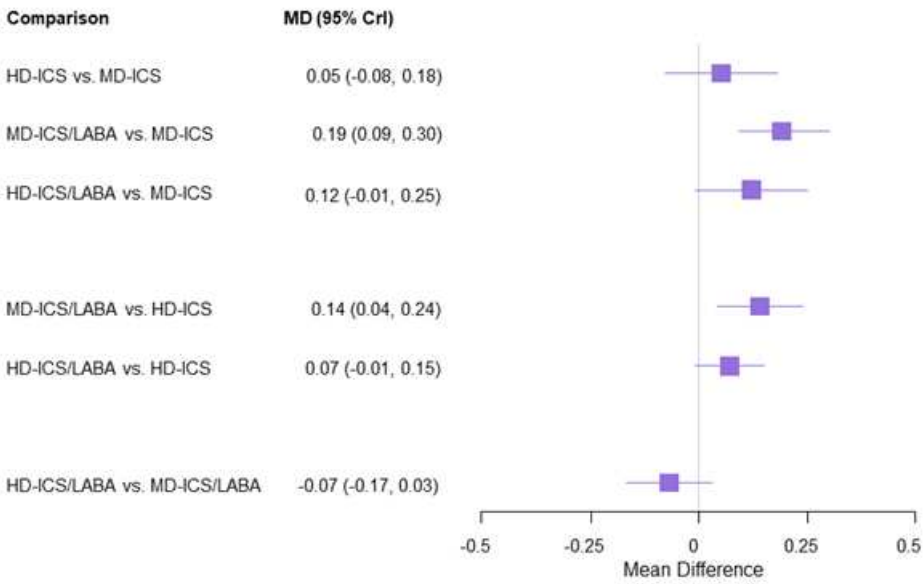
Figure 14



Network diagram for change from baseline AQLQ score at 3 months.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. AQLQ: Asthma Quality of Life Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose.

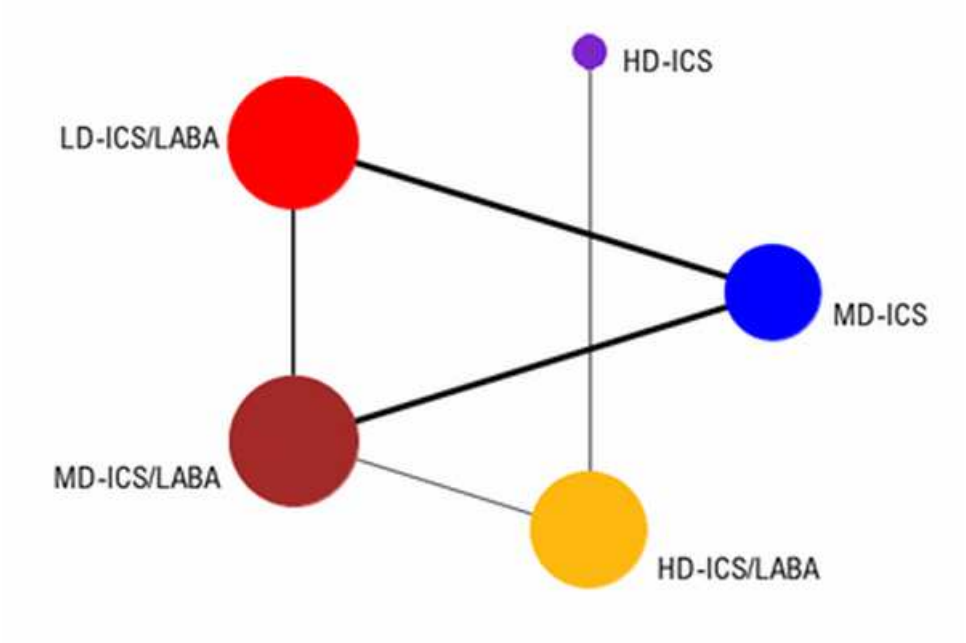
Figure 15



Plot of relative effects for the change from baseline AQLQ score at 3 months using a fixed-effect model.

Mean differences (MDs) greater than zero favour the first named treatment. AQLQ: Asthma Quality of Life Questionnaire; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose.

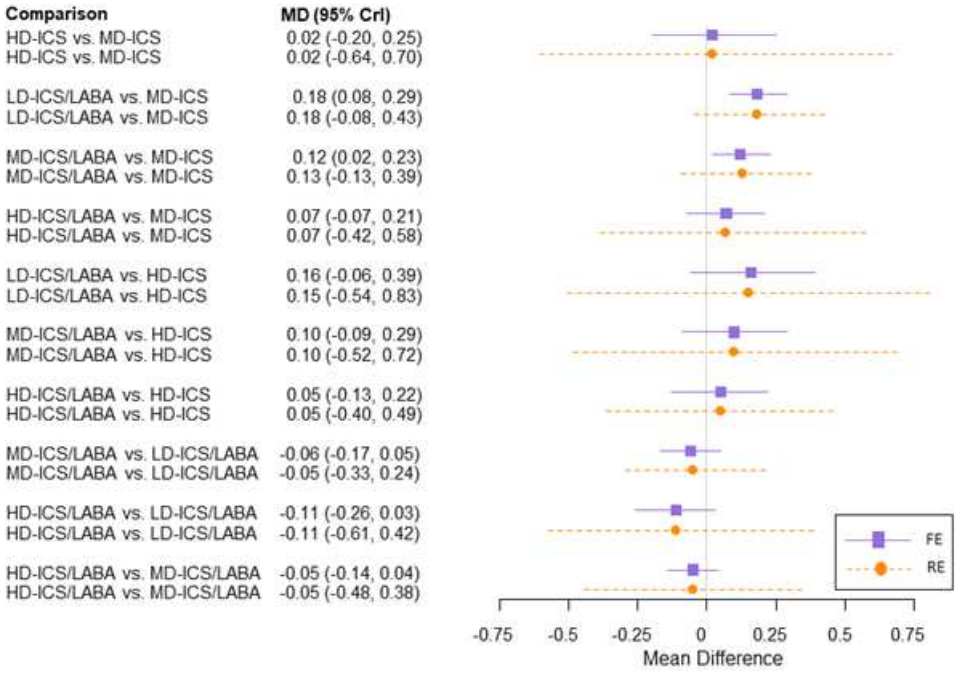
Figure 16



Network diagram for change from baseline AQLQ score at 6 months.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. AQLQ: Asthma Quality of Life Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose.

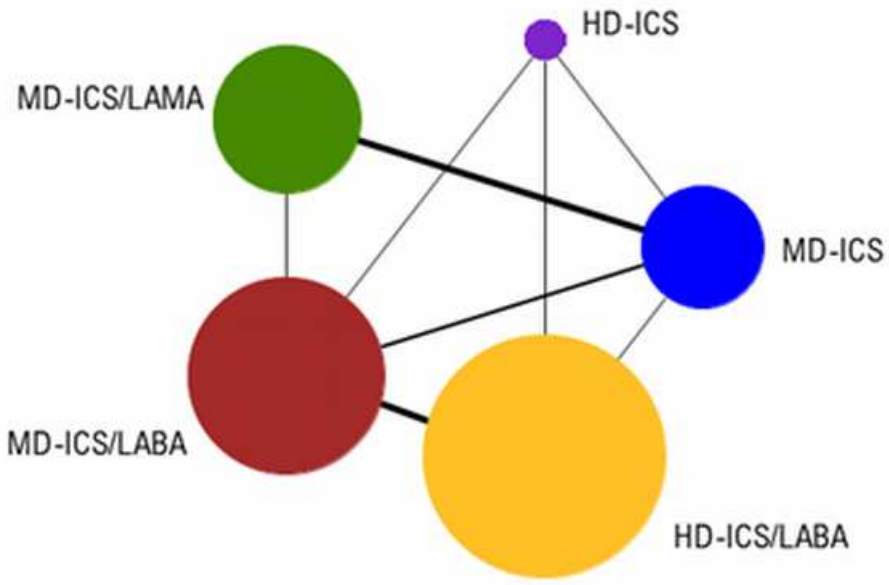
Figure 17



Plot of relative effects for the change from baseline AQLQ score at 6 months using fixed- (FE) and random-effects (RE) model.

Mean differences (MDs) greater than zero favour the first named treatment. AQLQ: Asthma Quality of Life Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LD: low dose; MD: medium dose.

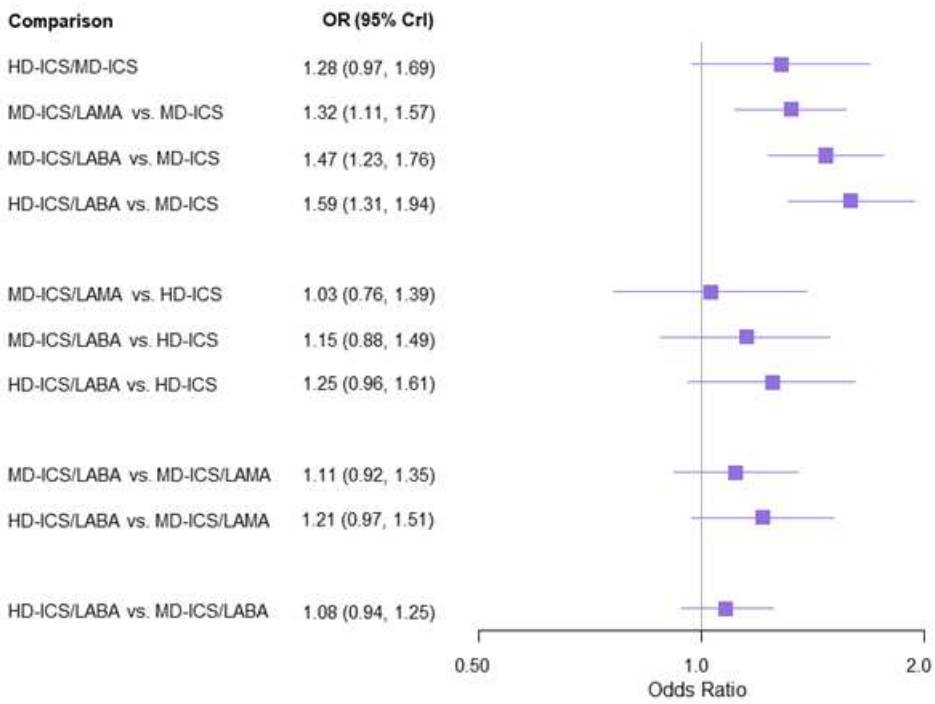
Figure 18



Network diagram for ACQ Response at 6 months.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: medium dose.

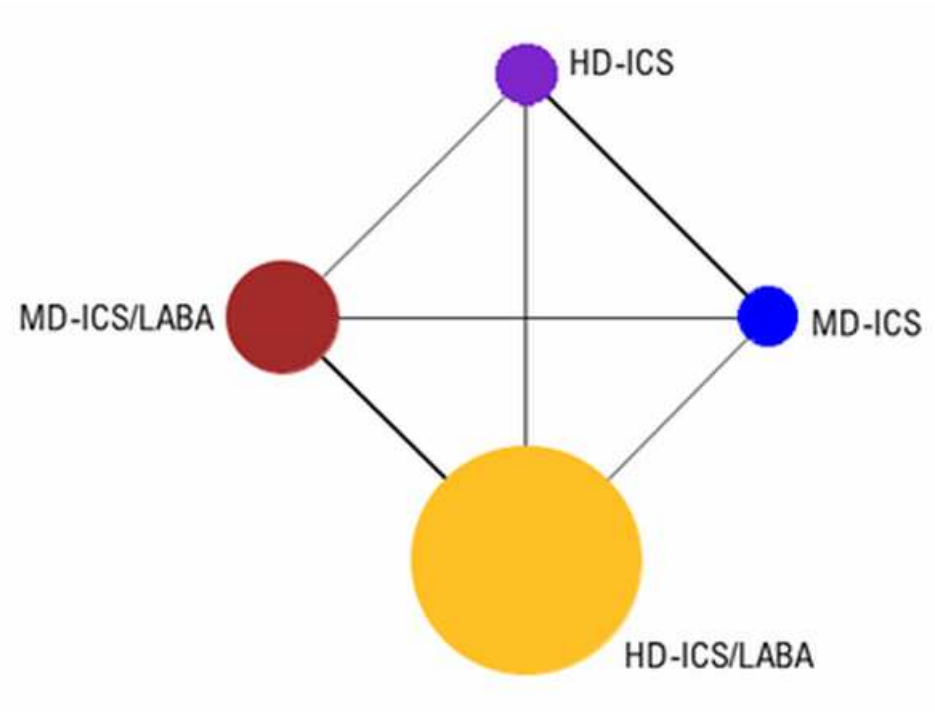
Figure 19



Plot of odds ratios relative for ACQ responders at 6 months (fixed-effect model).

Odds Ratios (ORs) greater than one favour the first named treatment. ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; MD: medium dose.

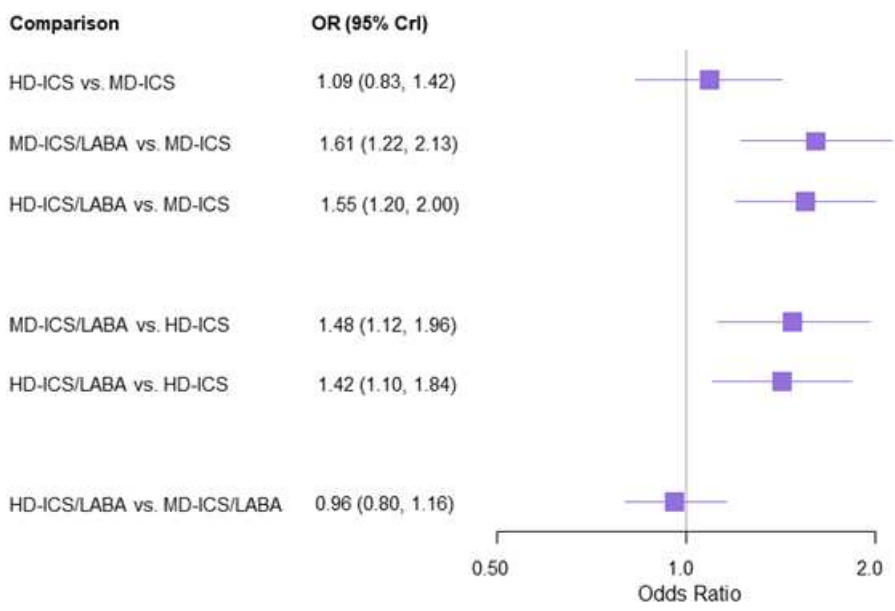
Figure 20



Network diagram for ACQ Response at 12 months.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose.

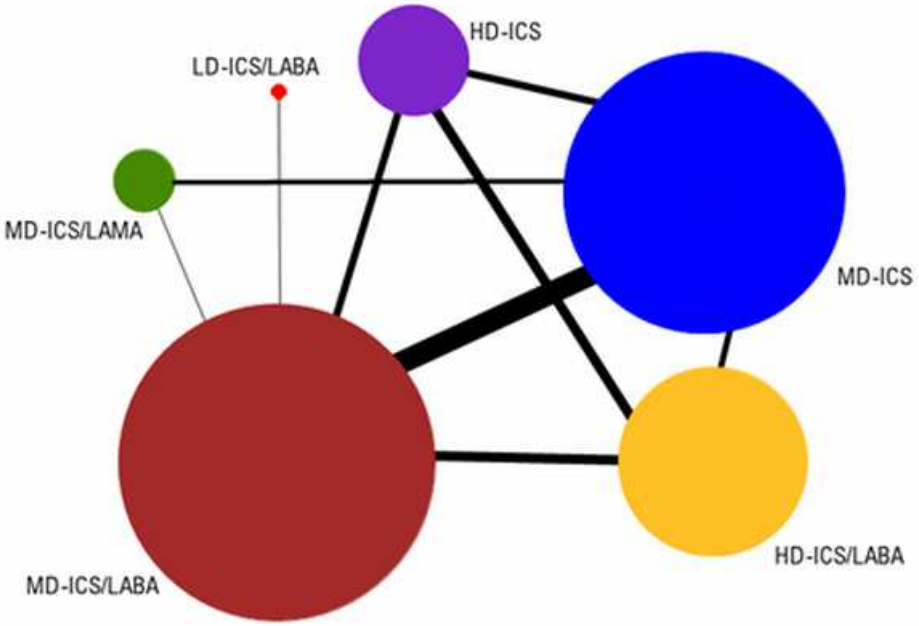
Figure 21



Plot of odds ratios for ACQ responders at 12 months for the fixed-effect model.

Odds Ratios (ORs) greater than one favour the first named treatment. ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose.

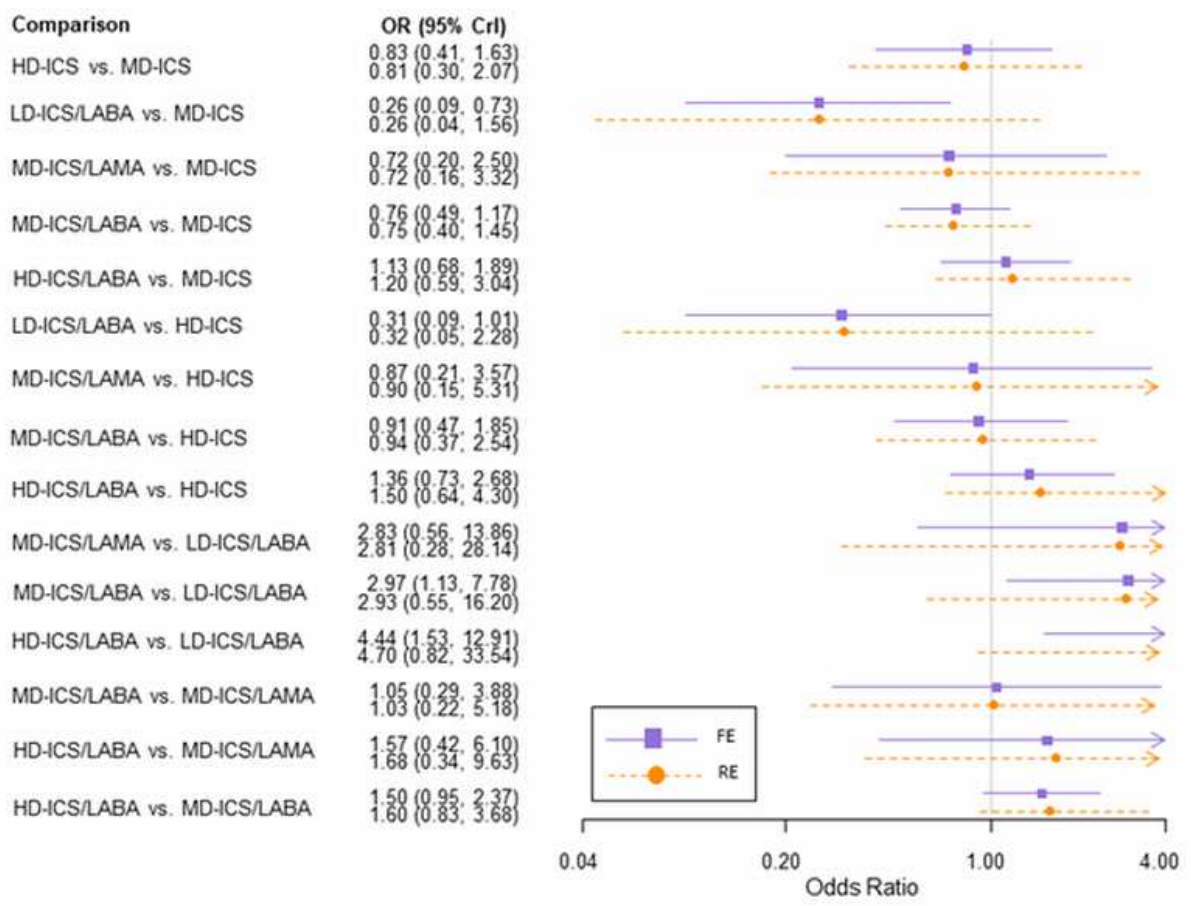
Figure 22



Network diagram for asthma-related SAEs.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; SAE: serious adverse event.

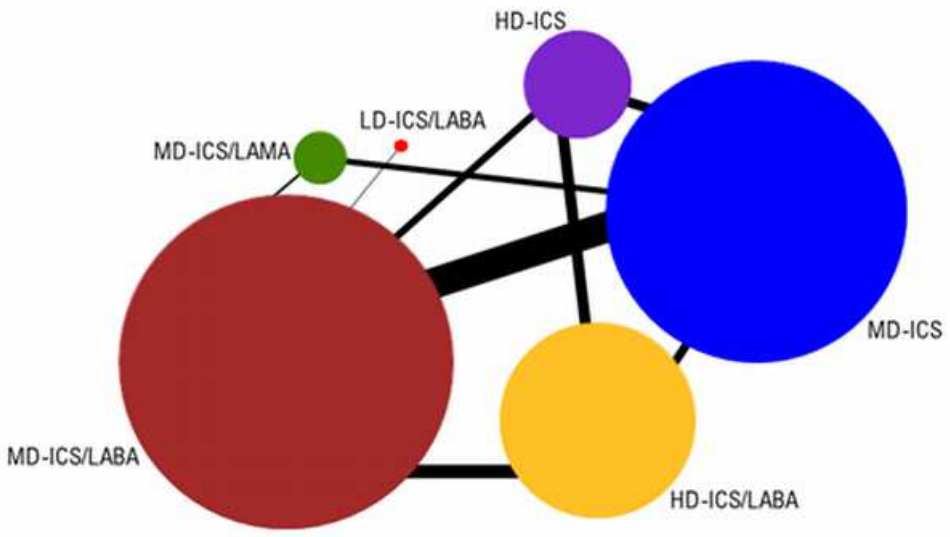
Figure 23



Plots of odds ratios relative for asthma-related SAEs for fixed-effect and random-effects models.

Odds Ratios (ORs) less than one favour the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; SAE: serious adverse event.

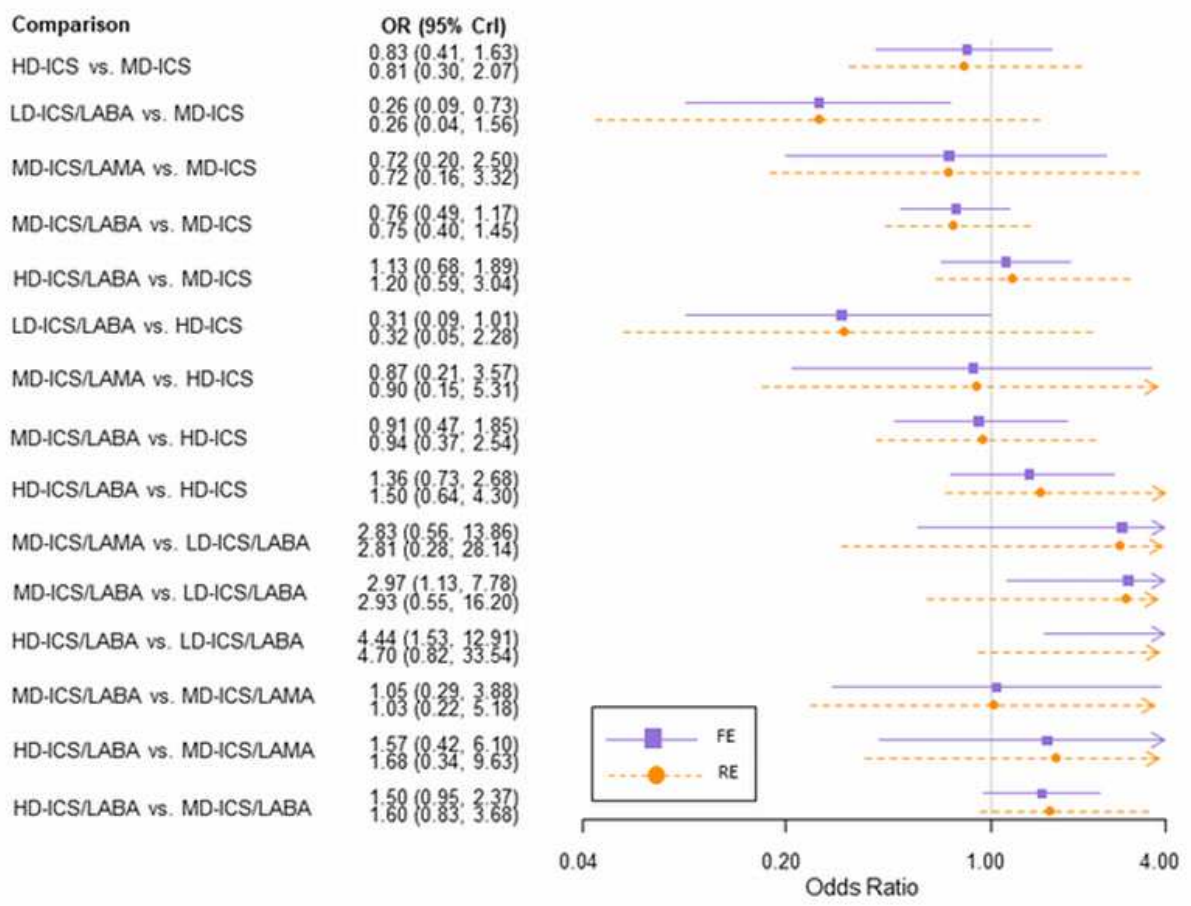
Figure 24



Network diagram for all-cause SAEs.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; SAE: serious adverse event.

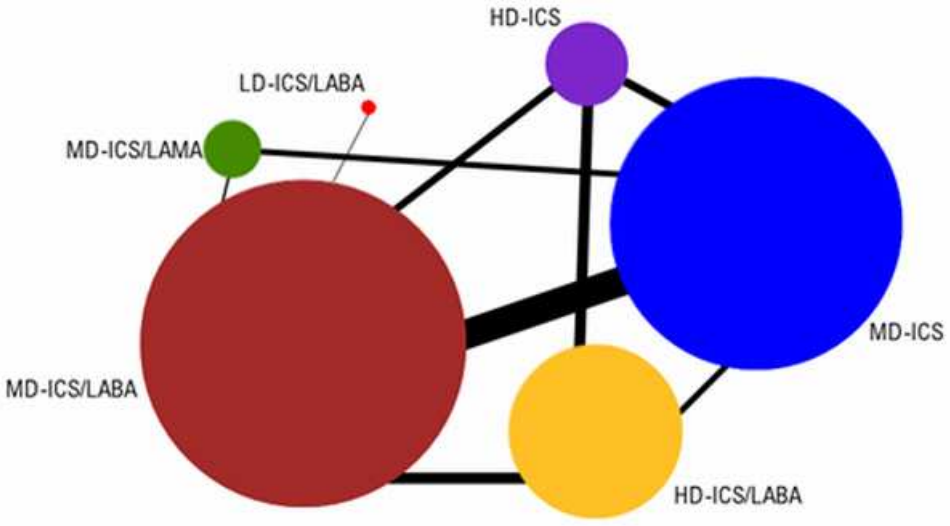
Figure 25



Plots of odds ratios for all-cause SAEs for the fixed-effect (FE) and random-effects (RE) models.

Odds Ratios (ORs) less than one favour the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose; SAE: serious adverse event.

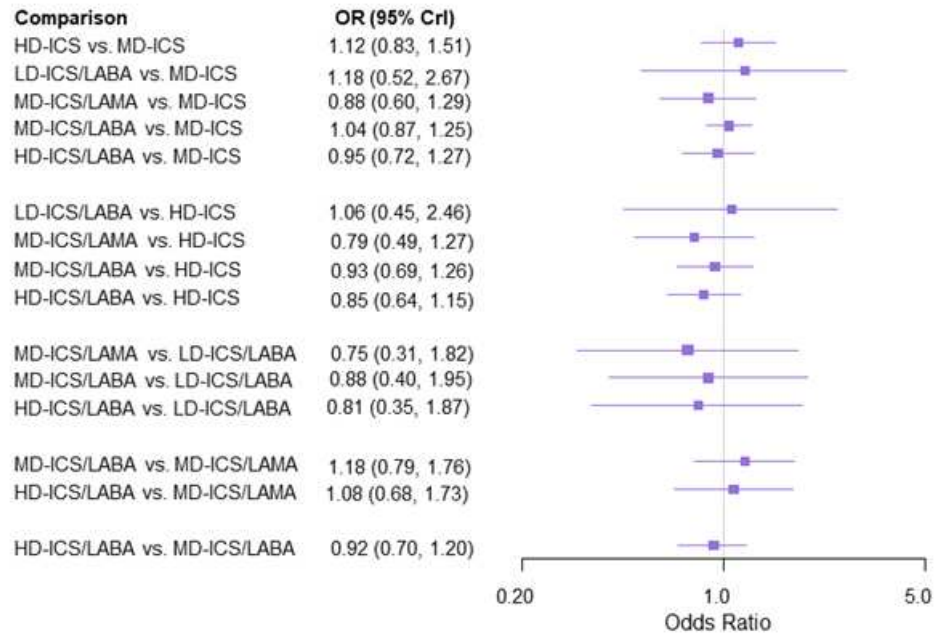
Figure 26



Network diagram for all-cause AEs.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. AE: adverse event; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

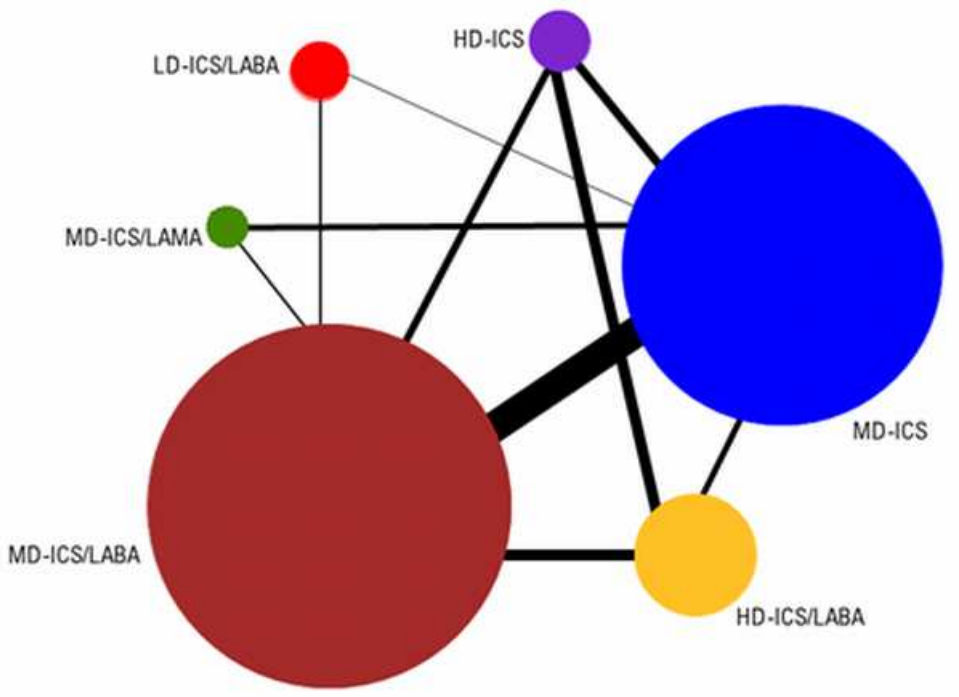
Figure 27



Plots of odds ratios for all-cause AEs (fixed-effect model). Odds Ratios (ORs) less than one favour the first named treatment.

AE: adverse event; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

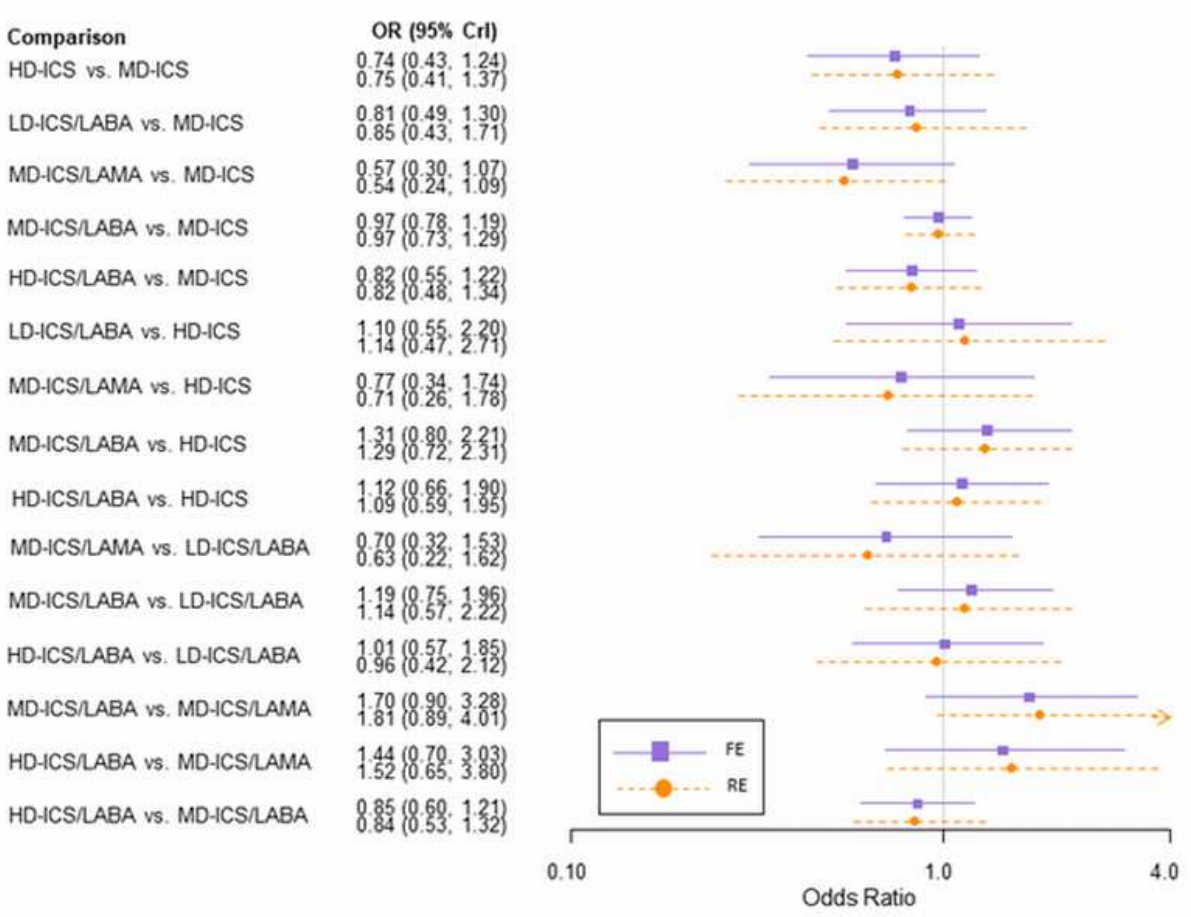
Figure 28



Network diagram for drop-outs due to AEs.

Nodes colours denote the treatment group. Nodes are scaled proportional to the number of patients who receive a particular treatment. The width of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. AE: adverse event; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

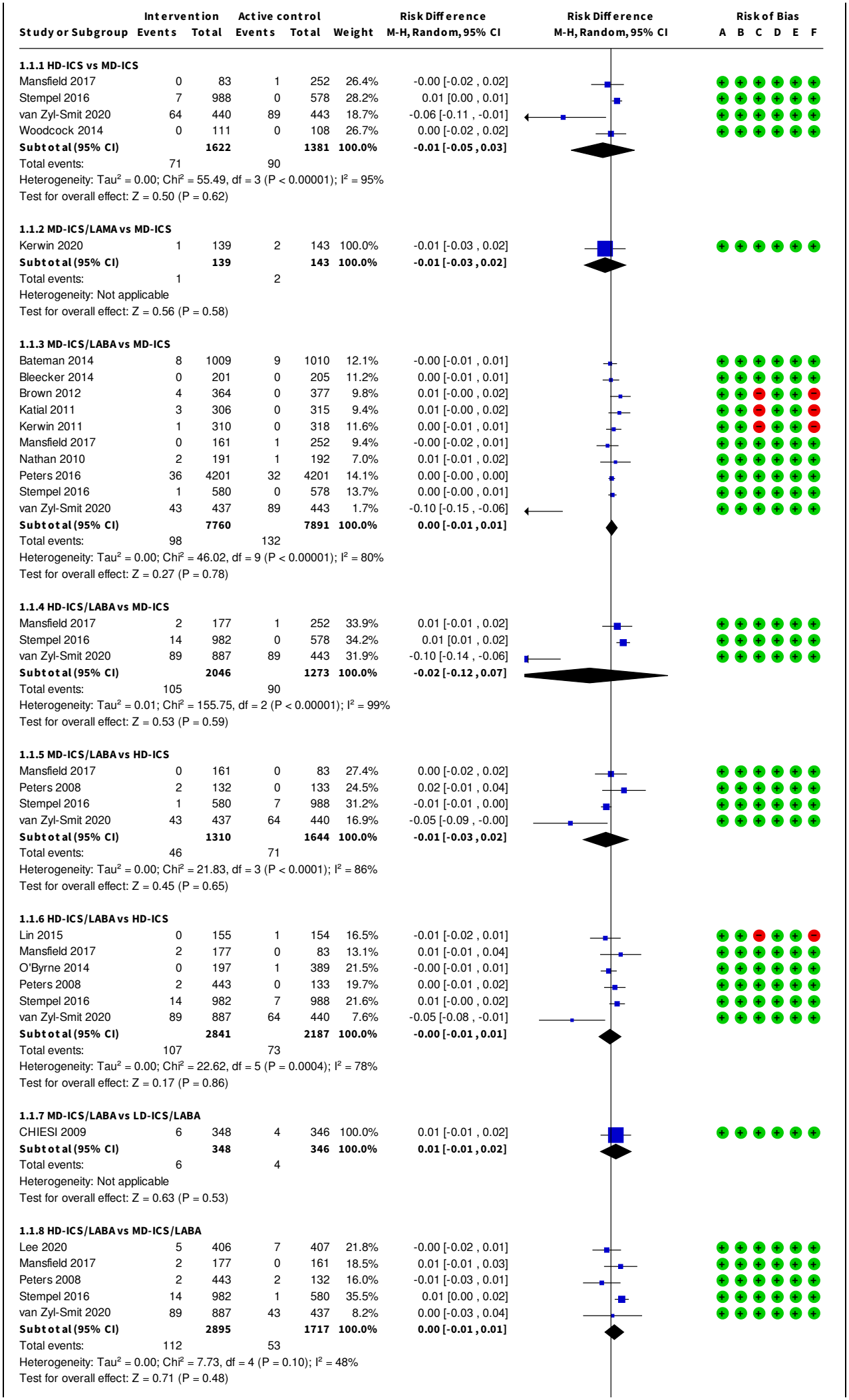
Figure 29



Plots of odds ratios for drop-outs due to AEs (fixed-effect (FE) and random-effects (RE) models).

Odds Ratios (ORs) less than one favour the first named treatment. AE: adverse event; CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LD: low dose; MD: medium dose.

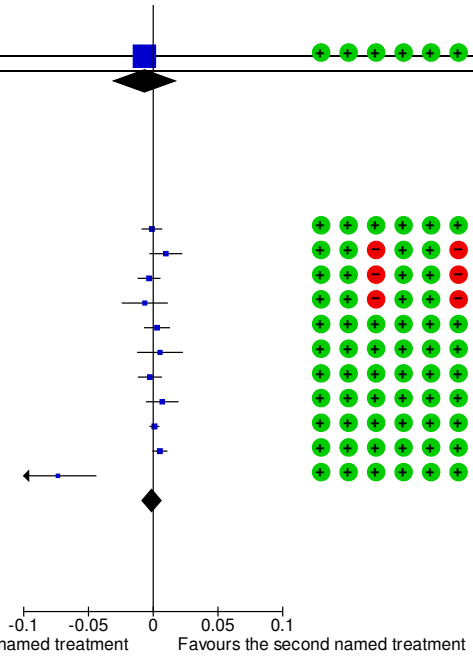
Analysis 1.1


Intervention
Active control
Risk Difference
Risk Difference
Risk of Bias
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI A B C D E F
1.1.1 HD-ICS vs MD-ICS
Mansfield 2017 0 83 1 252 26.4% -0.00 [-0.02 , 0.02]
Stempel 2016 7 988 0 578 28.2% 0.01 [0.00 , 0.01]
van Zyl-Smit 2020 64 440 89 443 18.7% -0.06 [-0.11 , -0.01]
Woodcock 2014 0 111 0 108 26.7% 0.00 [-0.02 , 0.02]
Subtotal (95% CI) 1622 1381 100.0% -0.01 [-0.05 , 0.03]
Total events: 71 90
Heterogeneity: Tau² = 0.00; Chi² = 55.49, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.50 (P = 0.62)
1.1.2 MD-ICS/LAMA vs MD-ICS
Kerwin 2020 1 139 2 143 100.0% -0.01 [-0.03 , 0.02]
Subtotal (95% CI) 139 143 100.0% -0.01 [-0.03 , 0.02]
Total events: 1 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)
1.1.3 MD-ICS/LABA vs MD-ICS
Bateman 2014 8 1009 9 1010 12.1% -0.00 [-0.01 , 0.01]
Bleecker 2014 0 201 0 205 11.2% 0.00 [-0.01 , 0.01]
Brown 2012 4 364 0 377 9.8% 0.01 [-0.00 , 0.02]
Katial 2011 3 306 0 315 9.4% 0.01 [-0.00 , 0.02]
Kerwin 2011 1 310 0 318 11.6% 0.00 [-0.01 , 0.01]
Mansfield 2017 0 161 1 252 9.4% -0.00 [-0.02 , 0.01]
Nathan 2010 2 191 1 192 7.0% 0.01 [-0.01 , 0.02]
Peters 2016 36 4201 32 4201 14.1% 0.00 [-0.00 , 0.00]
Stempel 2016 1 580 0 578 13.7% 0.00 [-0.00 , 0.01]
van Zyl-Smit 2020 43 437 89 443 1.7% -0.10 [-0.15 , -0.06]
Subtotal (95% CI) 7760 7891 100.0% 0.00 [-0.01 , 0.01]
Total events: 98 132
Heterogeneity: Tau² = 0.00; Chi² = 46.02, df = 9 (P < 0.00001); I² = 80%
Test for overall effect: Z = 0.27 (P = 0.78)
1.1.4 HD-ICS/LABA vs MD-ICS
Mansfield 2017 2 177 1 252 33.9% 0.01 [-0.01 , 0.02]
Stempel 2016 14 982 0 578 34.2% 0.01 [0.01 , 0.02]
van Zyl-Smit 2020 89 887 89 443 31.9% -0.10 [-0.14 , -0.06]
Subtotal (95% CI) 2046 1273 100.0% -0.02 [-0.12 , 0.07]
Total events: 105 90
Heterogeneity: Tau² = 0.01; Chi² = 155.75, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.53 (P = 0.59)
1.1.5 MD-ICS/LABA vs HD-ICS
Mansfield 2017 0 161 0 83 27.4% 0.00 [-0.02 , 0.02]
Peters 2008 2 132 0 133 24.5% 0.02 [-0.01 , 0.04]
Stempel 2016 1 580 7 988 31.2% -0.01 [-0.01 , 0.00]
van Zyl-Smit 2020 43 437 64 440 16.9% -0.05 [-0.09 , -0.00]
Subtotal (95% CI) 1310 1644 100.0% -0.01 [-0.03 , 0.02]
Total events: 46 71
Heterogeneity: Tau² = 0.00; Chi² = 21.83, df = 3 (P < 0.0001); I² = 86%
Test for overall effect: Z = 0.45 (P = 0.65)
1.1.6 HD-ICS/LABA vs HD-ICS
Lin 2015 0 155 1 154 16.5% -0.01 [-0.02 , 0.01]
Mansfield 2017 2 177 0 83 13.1% 0.01 [-0.01 , 0.04]
O'Byrne 2014 0 197 1 389 21.5% -0.00 [-0.01 , 0.01]
Peters 2008 2 443 0 133 19.7% 0.00 [-0.01 , 0.02]
Stempel 2016 14 982 7 988 21.6% 0.01 [-0.00 , 0.02]
van Zyl-Smit 2020 89 887 64 440 7.6% -0.05 [-0.08 , -0.01]
Subtotal (95% CI) 2841 2187 100.0% -0.00 [-0.01 , 0.01]
Total events: 107 73
Heterogeneity: Tau² = 0.00; Chi² = 22.62, df = 5 (P = 0.0004); I² = 78%
Test for overall effect: Z = 0.17 (P = 0.86)
1.1.7 MD-ICS/LABA vs LD-ICS/LABA
CHIESI 2009 6 348 4 346 100.0% 0.01 [-0.01 , 0.02]
Subtotal (95% CI) 348 346 100.0% 0.01 [-0.01 , 0.02]
Total events: 6 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
1.1.8 HD-ICS/LABA vs MD-ICS/LABA
Lee 2020 5 406 7 407 21.8% -0.00 [-0.02 , 0.01]
Mansfield 2017 2 177 0 161 18.5% 0.01 [-0.01 , 0.03]
Peters 2008 2 443 2 132 16.0% -0.01 [-0.03 , 0.01]
Stempel 2016 14 982 1 580 35.5% 0.01 [0.00 , 0.02]
van Zyl-Smit 2020 89 887 43 437 8.2% 0.00 [-0.03 , 0.04]
Subtotal (95% CI) 2895 1717 100.0% 0.00 [-0.01 , 0.01]
Total events: 112 53
Heterogeneity: Tau² = 0.00; Chi² = 7.73, df = 4 (P = 0.10); I² = 48%
Test for overall effect: Z = 0.71 (P = 0.48)

Comparison 1: Exacerbations, Outcome 1: Severe exacerbations

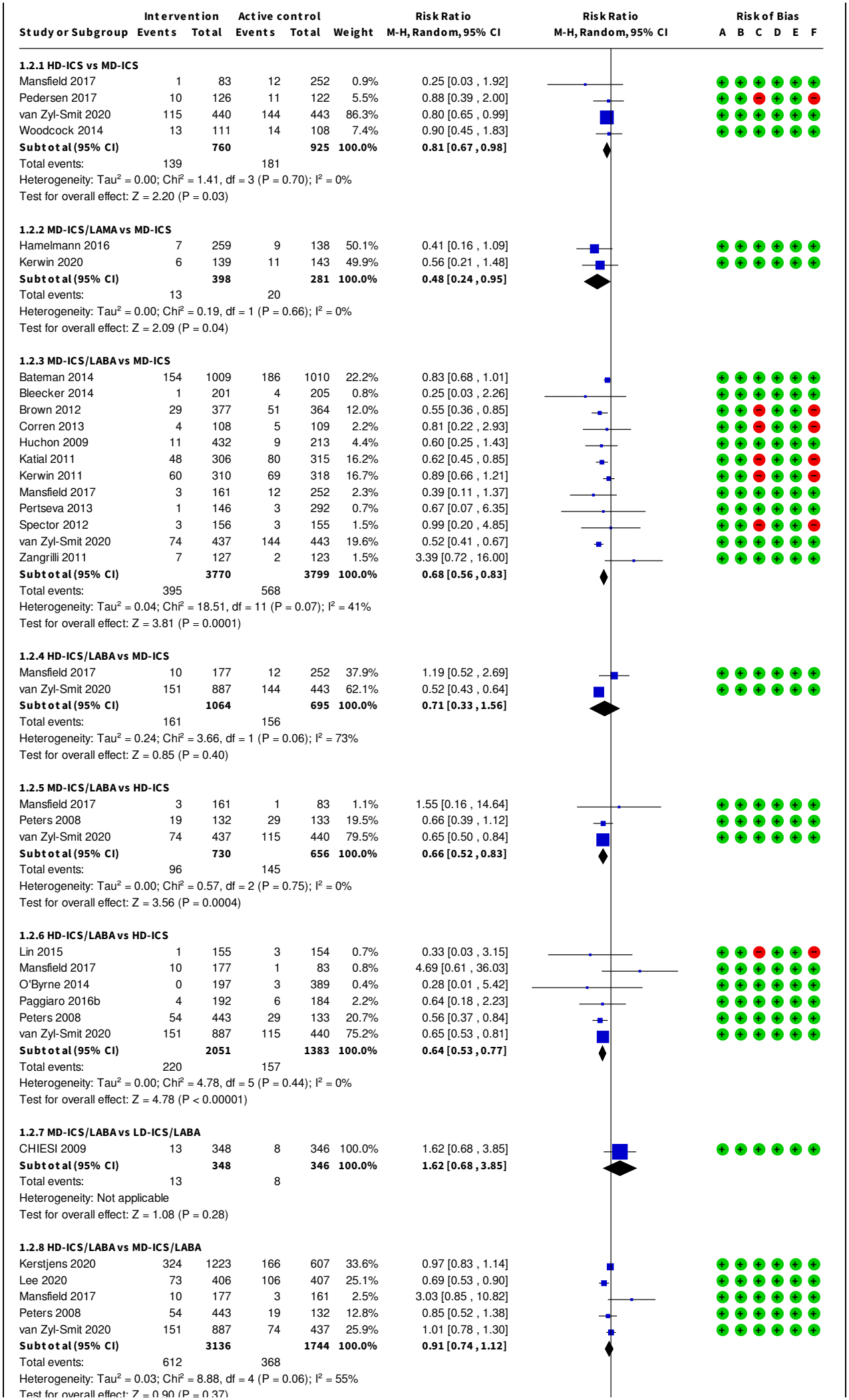
Analysis 1.2

1.1.9 ICS-LAMA vs ICS						
Kerwin 2020	1	139	2	143	100.0%	-0.01 [-0.03 , 0.02]
Subtotal (95% CI)		**139**		**143**	**100.0%**	**-0.01 [-0.03 , 0.02]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
1.1.10 ICS-LABA vs ICS						
Bateman 2014	8	1009	9	1010	10.6%	-0.00 [-0.01 , 0.01]
Katial 2011	3	306	0	315	8.9%	0.01 [-0.00 , 0.02]
Kerwin 2011	0	318	1	310	10.3%	-0.00 [-0.01 , 0.01]
Lin 2015	0	155	1	154	7.1%	-0.01 [-0.02 , 0.01]
Mansfield 2017	2	338	1	335	9.9%	0.00 [-0.01 , 0.01]
Nathan 2010	2	191	1	192	7.1%	0.01 [-0.01 , 0.02]
O'Byrne 2014	0	197	1	389	10.1%	-0.00 [-0.01 , 0.01]
Peters 2008	4	575	0	133	8.9%	0.01 [-0.01 , 0.02]
Peters 2016	36	4201	32	4201	11.7%	0.00 [-0.00 , 0.00]
Stempel 2016	15	1562	7	1566	11.2%	0.01 [-0.00 , 0.01]
van Zyl-Smit 2020	132	1324	153	883	4.1%	-0.07 [-0.10 , -0.04]
Subtotal (95% CI)		**10176**		**9488**	**100.0%**	**-0.00 [-0.01 , 0.01]**
Total events:	202		206			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 68.70$, df = 10 (P < 0.00001); $I^2 = 85\%$						
Test for overall effect: Z = 0.35 (P = 0.73)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 9 (P < 0.00001), $I^2 = 0\%$						

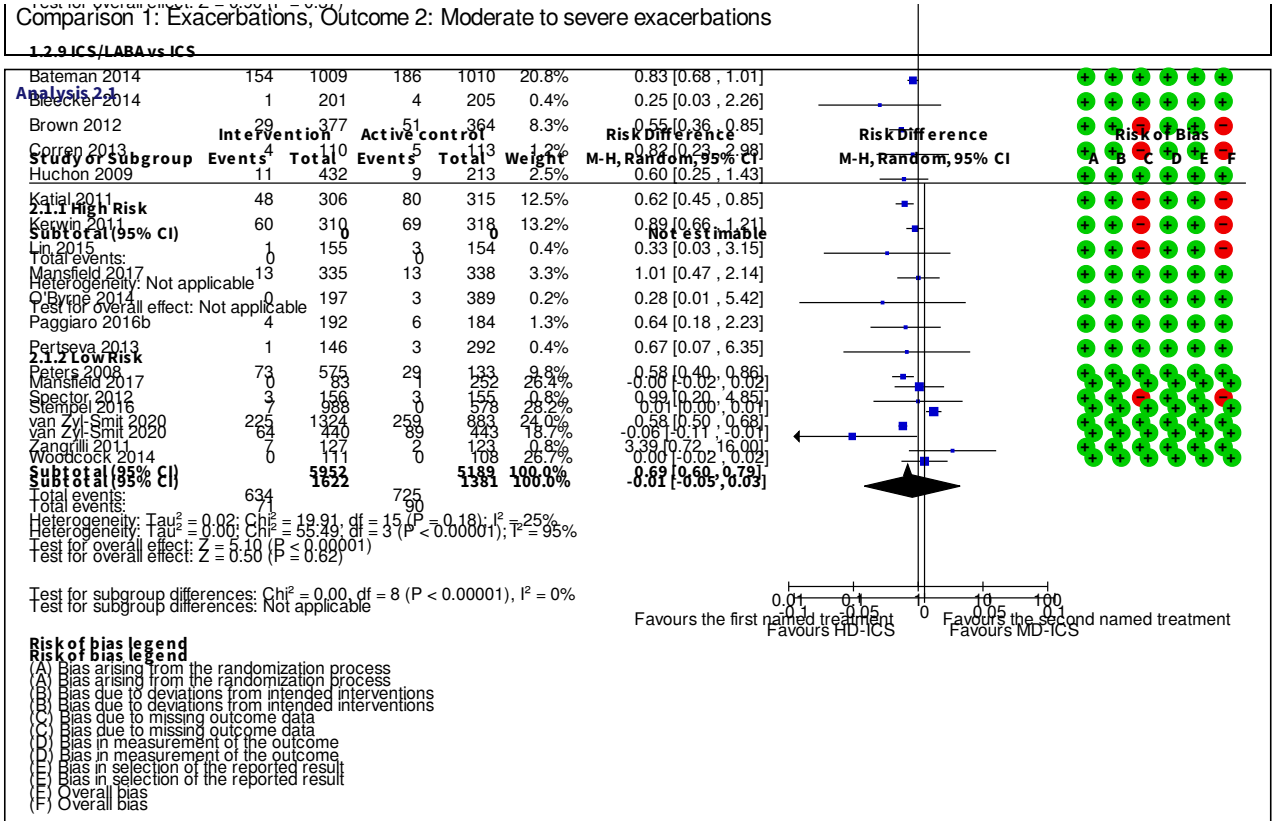


Risk of bias legend

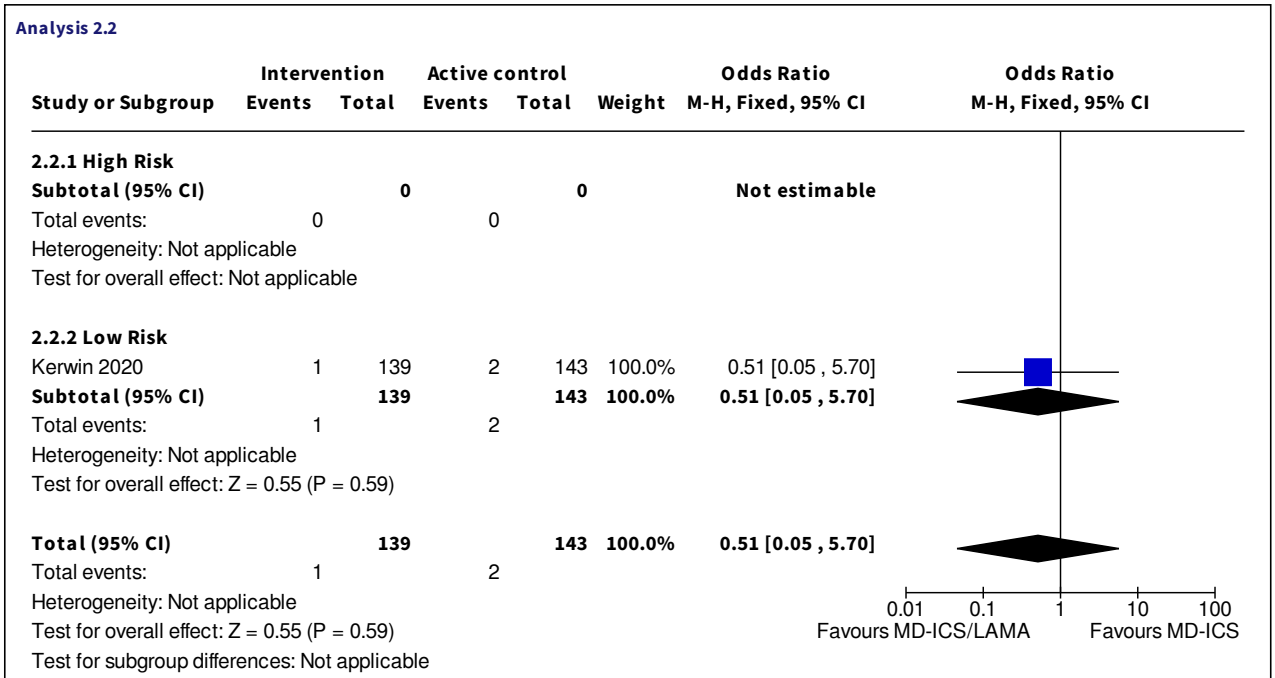
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias


Intervention
Active control
Risk Ratio
Risk Ratio
Risk of Bias
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI A B C D E F
1.2.1 HD-ICS vs MD-ICS
Mansfield 2017 1 83 12 252 0.9% 0.25 [0.03 , 1.92]
Pedersen 2017 10 126 11 122 5.5% 0.88 [0.39 , 2.00]
van Zyl-Smit 2020 115 440 144 443 86.3% 0.80 [0.65 , 0.99]
Woodcock 2014 13 111 14 108 7.4% 0.90 [0.45 , 1.83]
Subtotal (95% CI) 760 925 100.0% 0.81 [0.67 , 0.98]
Total events: 139 181
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 3 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)
1.2.2 MD-ICS/LAMA vs MD-ICS
Hamelmann 2016 7 259 9 138 50.1% 0.41 [0.16 , 1.09]
Kerwin 2020 6 139 11 143 49.9% 0.56 [0.21 , 1.48]
Subtotal (95% CI) 398 281 100.0% 0.48 [0.24 , 0.95]
Total events: 13 20
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)
1.2.3 MD-ICS/LABA vs MD-ICS
Bateman 2014 154 1009 186 1010 22.2% 0.83 [0.68 , 1.01]
Bleecker 2014 1 201 4 205 0.8% 0.25 [0.03 , 2.26]
Brown 2012 29 377 51 364 12.0% 0.55 [0.36 , 0.85]
Corren 2013 4 108 5 109 2.2% 0.81 [0.22 , 2.93]
Huchon 2009 11 432 9 213 4.4% 0.60 [0.25 , 1.43]
Katial 2011 48 306 80 315 16.2% 0.62 [0.45 , 0.85]
Kerwin 2011 60 310 69 318 16.7% 0.89 [0.66 , 1.21]
Mansfield 2017 3 161 12 252 2.3% 0.39 [0.11 , 1.37]
Pertseva 2013 1 146 3 292 0.7% 0.67 [0.07 , 6.35]
Spector 2012 3 156 3 155 1.5% 0.99 [0.20 , 4.85]
van Zyl-Smit 2020 74 437 144 443 19.6% 0.52 [0.41 , 0.67]
Zangrilli 2011 7 127 2 123 1.5% 3.39 [0.72 , 16.00]
Subtotal (95% CI) 3770 3799 100.0% 0.68 [0.56 , 0.83]
Total events: 395 568
Heterogeneity: Tau² = 0.04; Chi² = 18.51, df = 11 (P = 0.07); I² = 41%
Test for overall effect: Z = 3.81 (P = 0.0001)
1.2.4 HD-ICS/LABA vs MD-ICS
Mansfield 2017 10 177 12 252 37.9% 1.19 [0.52 , 2.69]
van Zyl-Smit 2020 151 887 144 443 62.1% 0.52 [0.43 , 0.64]
Subtotal (95% CI) 1064 695 100.0% 0.71 [0.33 , 1.56]
Total events: 161 156
Heterogeneity: Tau² = 0.24; Chi² = 3.66, df = 1 (P = 0.06); I² = 73%
Test for overall effect: Z = 0.85 (P = 0.40)
1.2.5 MD-ICS/LABA vs HD-ICS
Mansfield 2017 3 161 1 83 1.1% 1.55 [0.16 , 14.64]
Peters 2008 19 132 29 133 19.5% 0.66 [0.39 , 1.12]
van Zyl-Smit 2020 74 437 115 440 79.5% 0.65 [0.50 , 0.84]
Subtotal (95% CI) 730 656 100.0% 0.66 [0.52 , 0.83]
Total events: 96 145
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 3.56 (P = 0.0004)
1.2.6 HD-ICS/LABA vs HD-ICS
Lin 2015 1 155 3 154 0.7% 0.33 [0.03 , 3.15]
Mansfield 2017 10 177 1 83 0.8% 4.69 [0.61 , 36.03]
O'Byrne 2014 0 197 3 389 0.4% 0.28 [0.01 , 5.42]
Paggiaro 2016b 4 192 6 184 2.2% 0.64 [0.18 , 2.23]
Peters 2008 54 443 29 133 20.7% 0.56 [0.37 , 0.84]
van Zyl-Smit 2020 151 887 115 440 75.2% 0.65 [0.53 , 0.81]
Subtotal (95% CI) 2051 1383 100.0% 0.64 [0.53 , 0.77]
Total events: 220 157
Heterogeneity: Tau² = 0.00; Chi² = 4.78, df = 5 (P = 0.44); I² = 0%
Test for overall effect: Z = 4.78 (P < 0.00001)
1.2.7 MD-ICS/LABA vs LD-ICS/LABA
CHIESI 2009 13 348 8 346 100.0% 1.62 [0.68 , 3.85]
Subtotal (95% CI) 348 346 100.0% 1.62 [0.68 , 3.85]
Total events: 13 8
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)
1.2.8 HD-ICS/LABA vs MD-ICS/LABA
Kerstjens 2020 324 1223 166 607 33.6% 0.97 [0.83 , 1.14]
Lee 2020 73 406 106 407 25.1% 0.69 [0.53 , 0.90]
Mansfield 2017 10 177 3 161 2.5% 3.03 [0.85 , 10.82]
Peters 2008 54 443 19 132 12.8% 0.85 [0.52 , 1.38]
van Zyl-Smit 2020 151 887 74 437 25.9% 1.01 [0.78 , 1.30]
Subtotal (95% CI) 3136 1744 100.0% 0.91 [0.74 , 1.12]
Total events: 612 368
Heterogeneity: Tau² = 0.03; Chi² = 8.88, df = 4 (P = 0.06); I² = 55%
Test for overall effect: Z = 0.90 (P = 0.37)

Comparison 1: Exacerbations, Outcome 2: Moderate to severe exacerbations

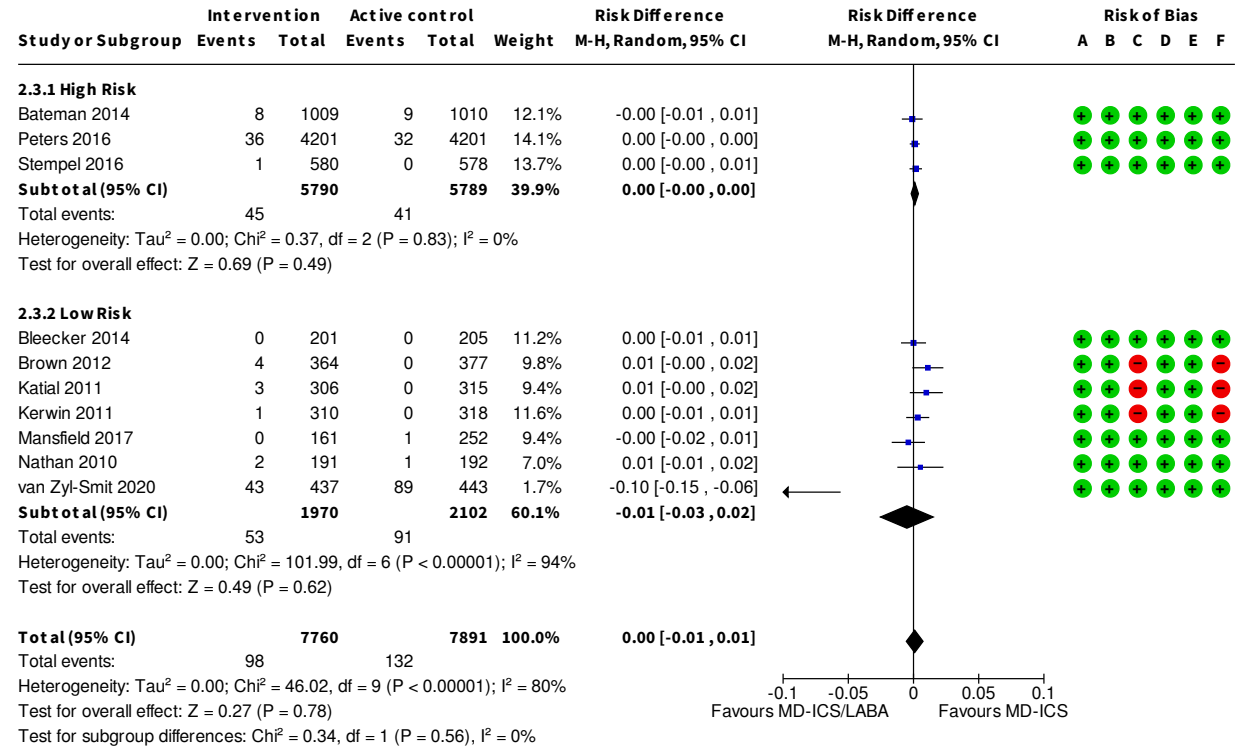


Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 1: HD-ICS vs MD-ICS



Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 2: MD-ICS/LAMA vs MD-ICS

Analysis 2.3

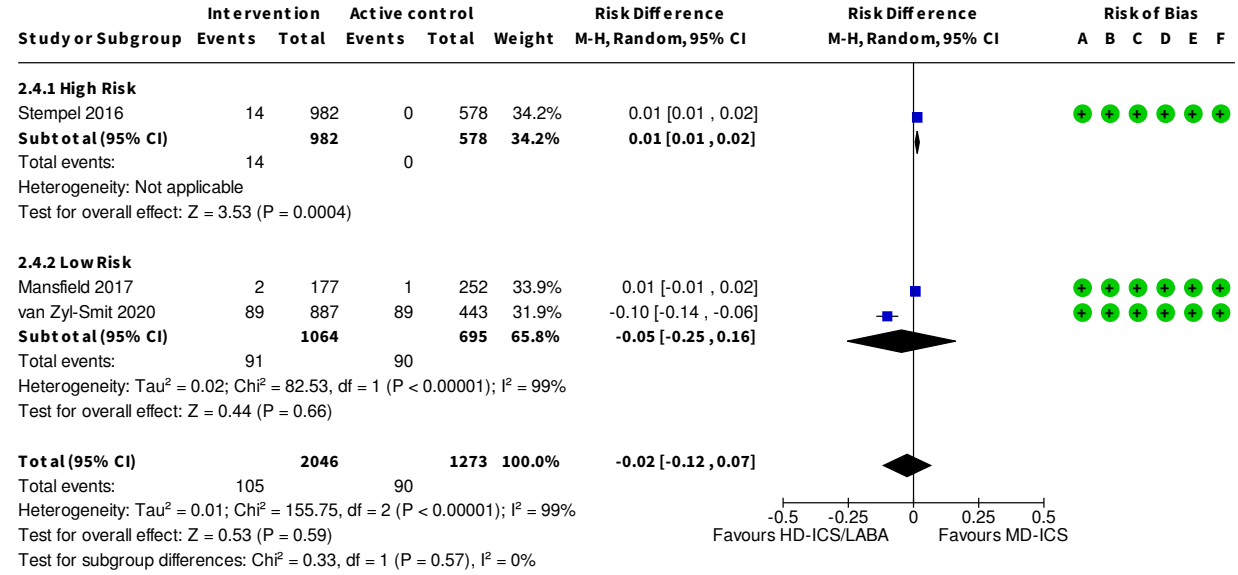


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 3: MD-ICS/LABA vs MD-ICS

Analysis 2.4

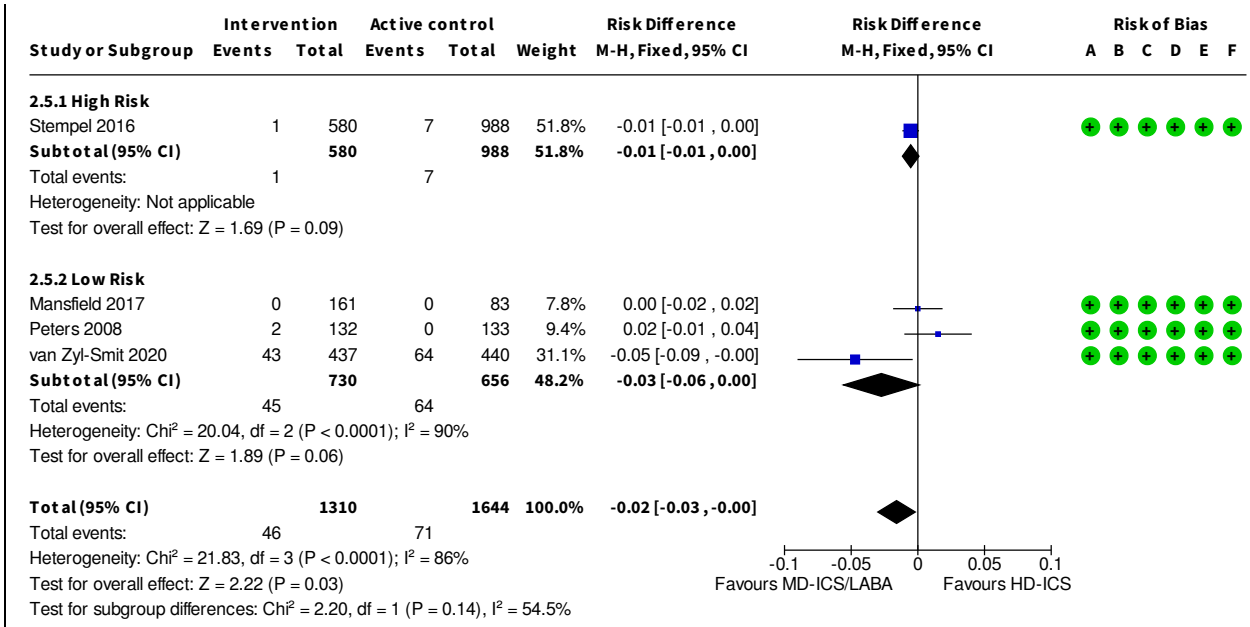


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 4: HD-ICS/LABA vs MD-ICS

Analysis 2.5

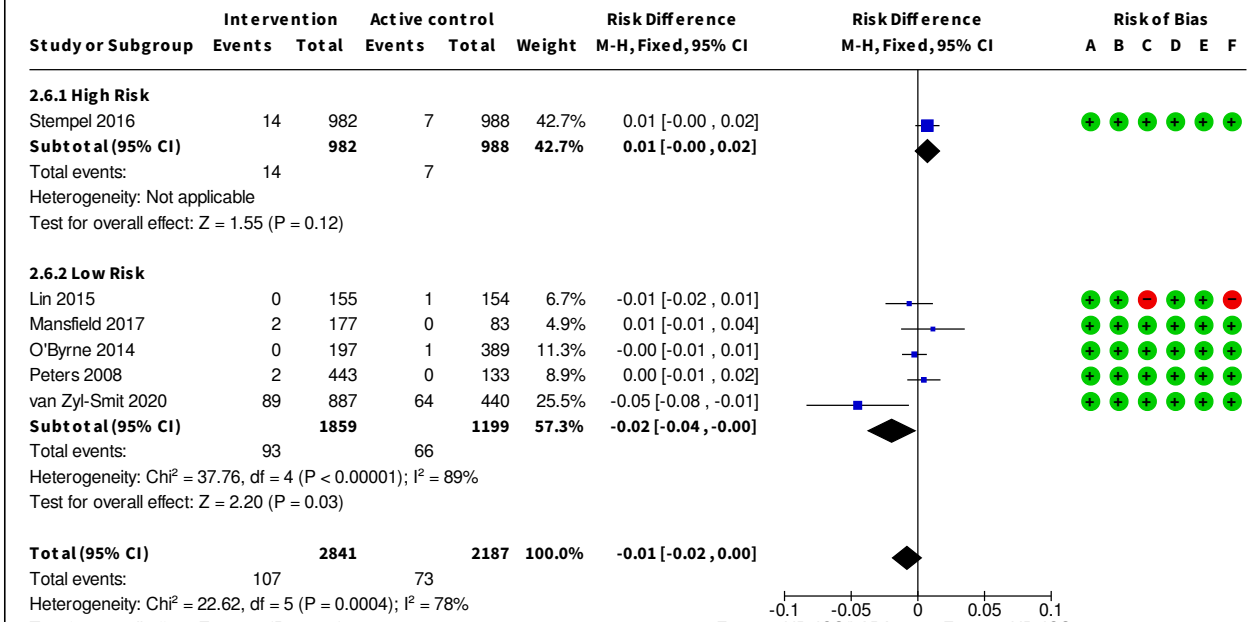


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 5: MD-ICS/LABA vs HD-ICS

Analysis 2.6

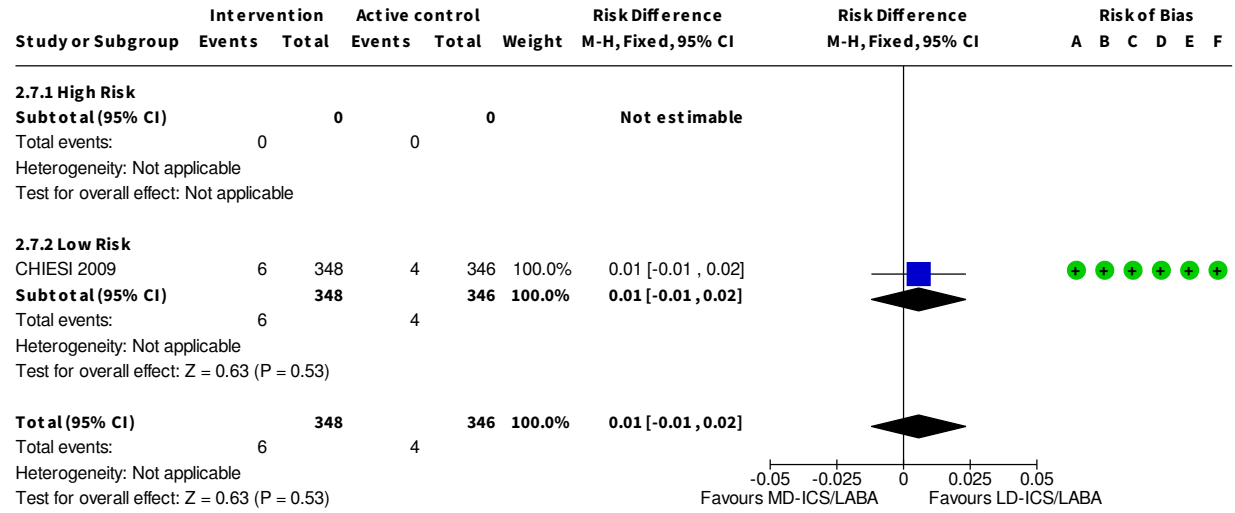


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 6: HD-ICS/LABA vs HD-ICS

Analysis 2.7

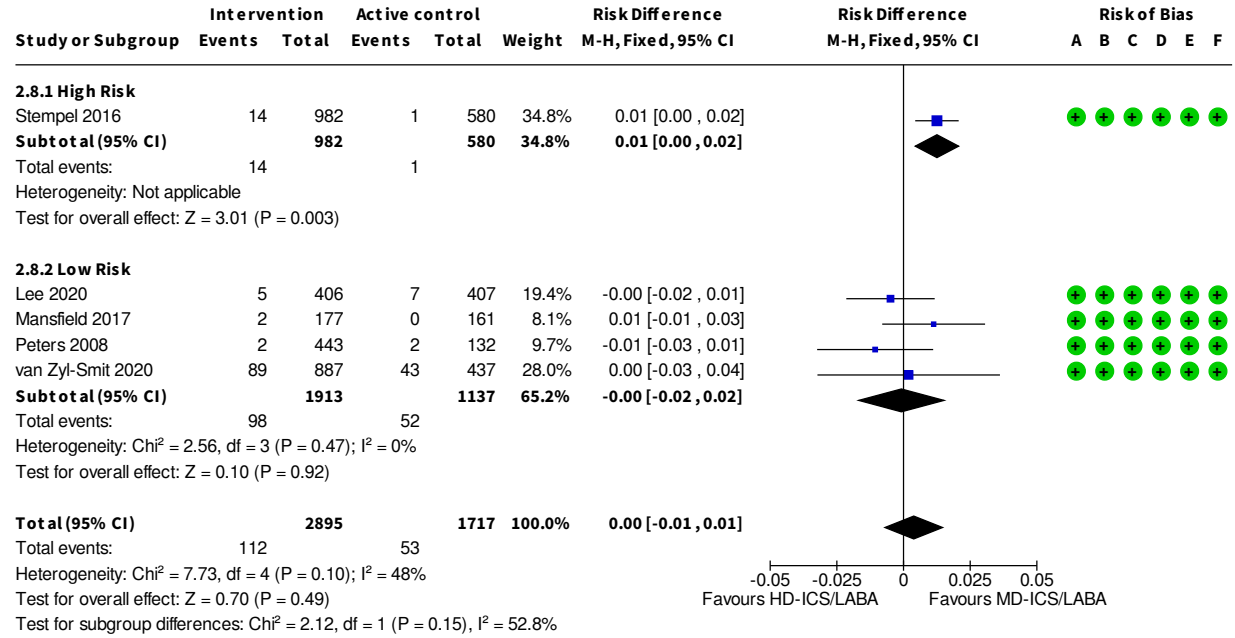


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 7: MD-ICS/LABA vs LD-ICS/LABA

Analysis 2.8

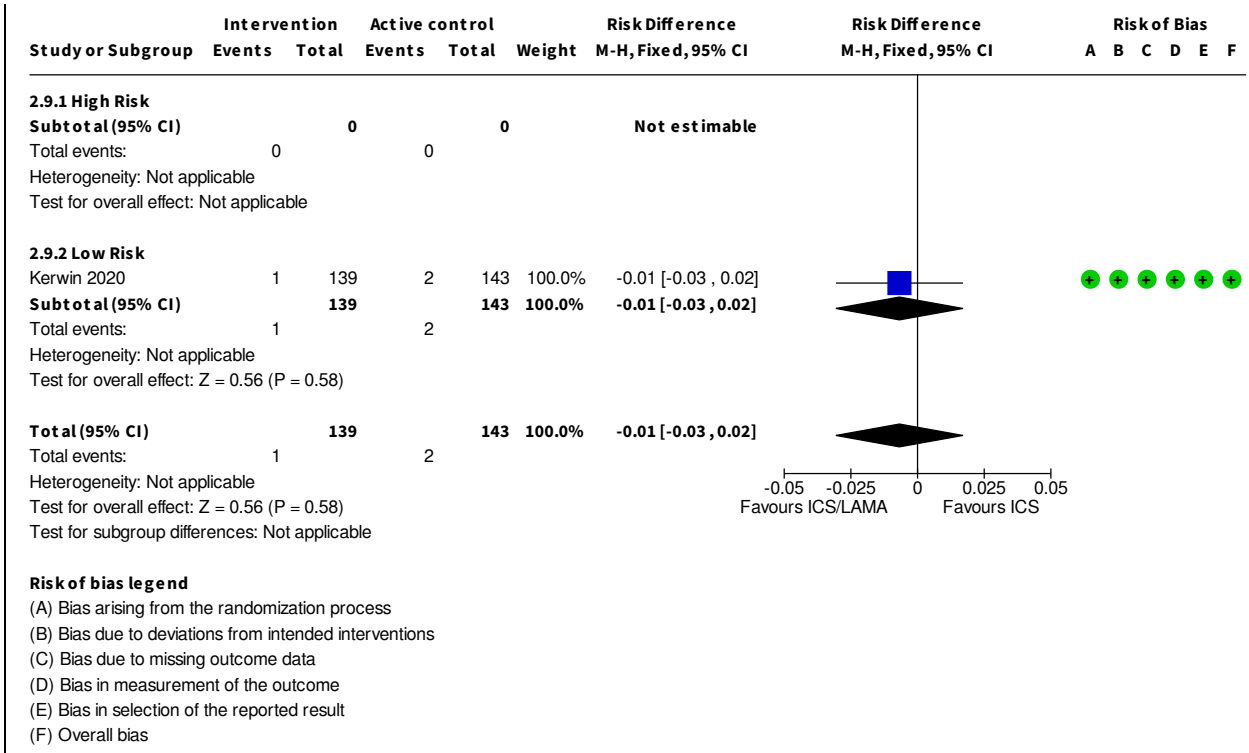


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 8: HD-ICS/LABA vs MD-ICS/LABA

Analysis 2.9

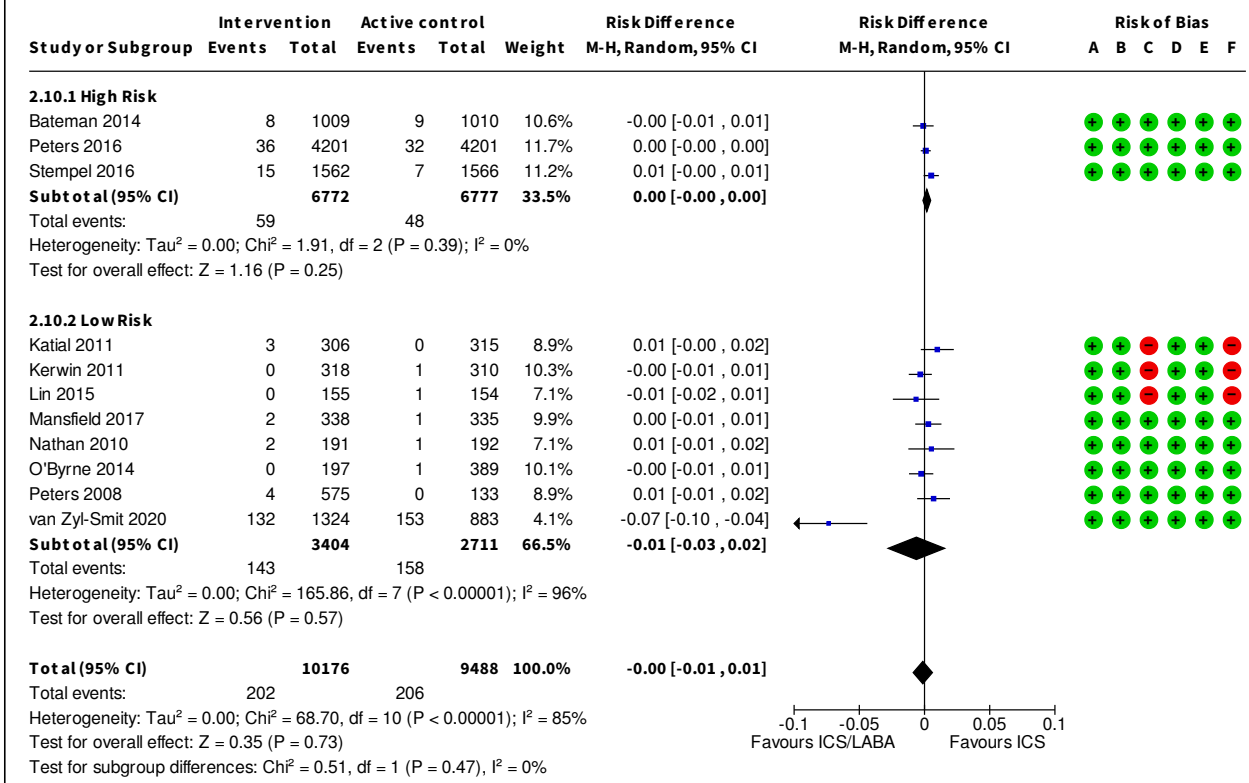


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 9: ICS/LAMA vs ICS

Analysis 2.10

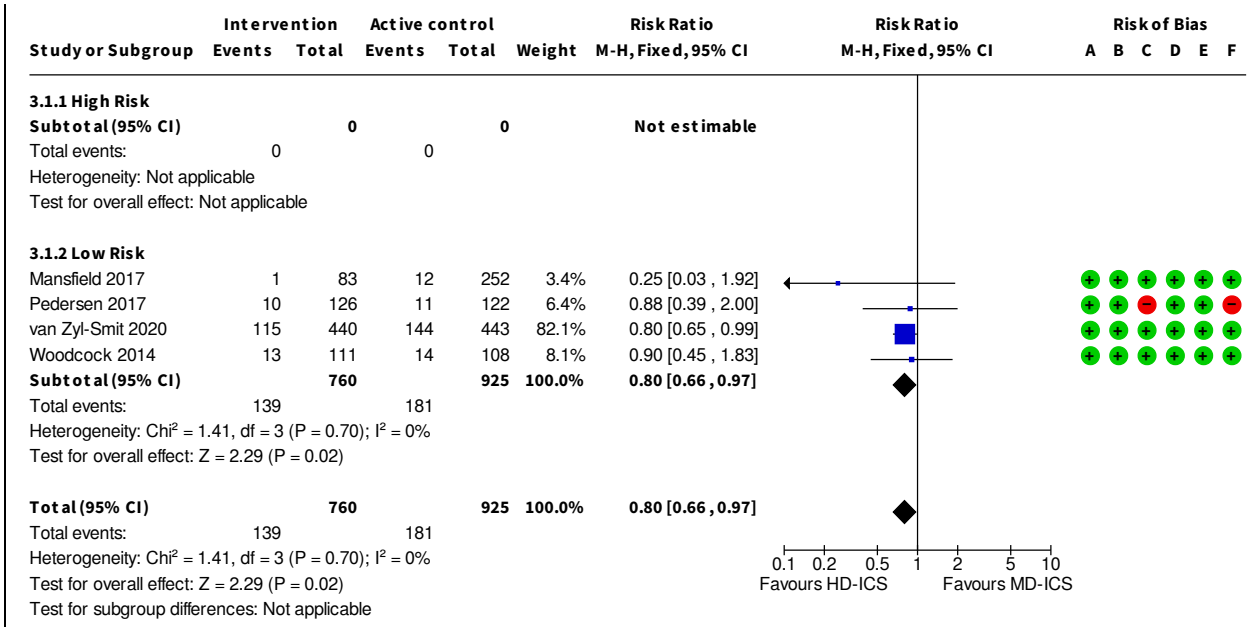


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2: Severe exacerbations (high and low risk subgroups), Outcome 10: ICS/LABA vs ICS

Analysis 3.1

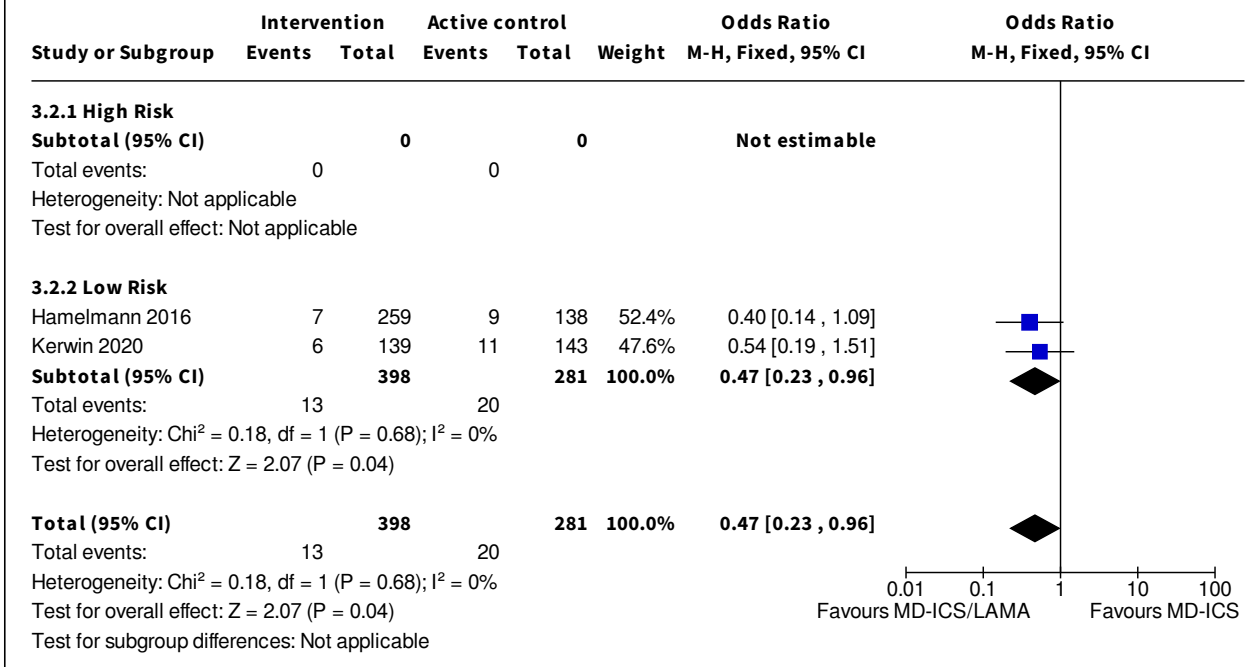


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

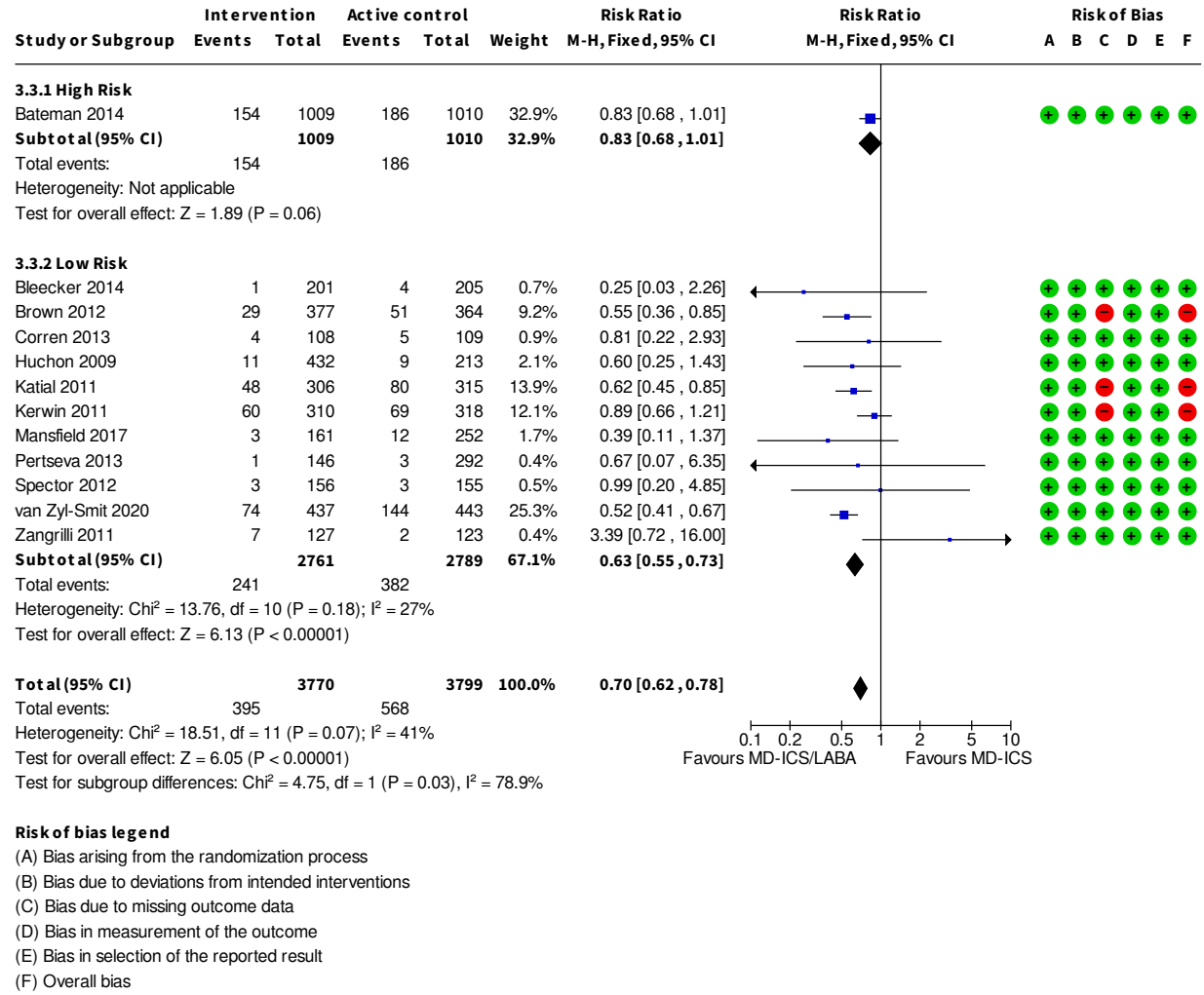
Comparison 3: Moderate to severe exacerbations (high and low risk subgroups), Outcome 1: HD-ICS vs MD-ICS

Analysis 3.2



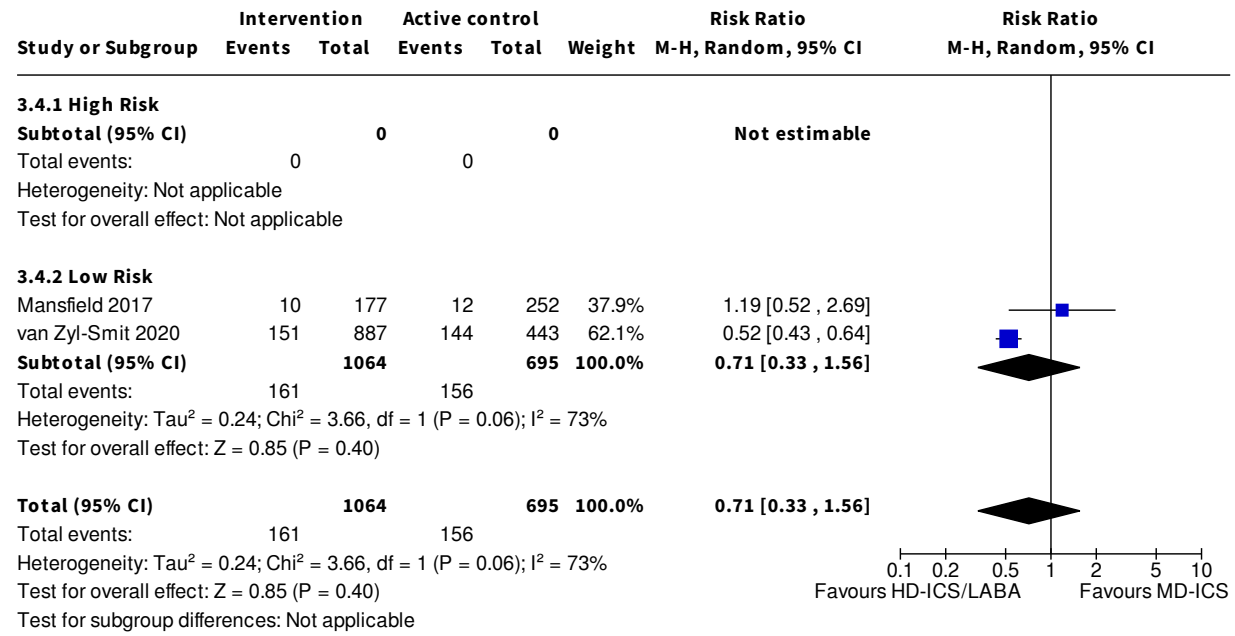
Comparison 3: Moderate to severe exacerbations (high and low risk subgroups), Outcome 2: MD-ICS/LAMA vs MD-ICS

Analysis 3.3



Comparison 3: Moderate to severe exacerbations (high and low risk subgroups), Outcome 3: MD-ICS/LABA vs MD-ICS

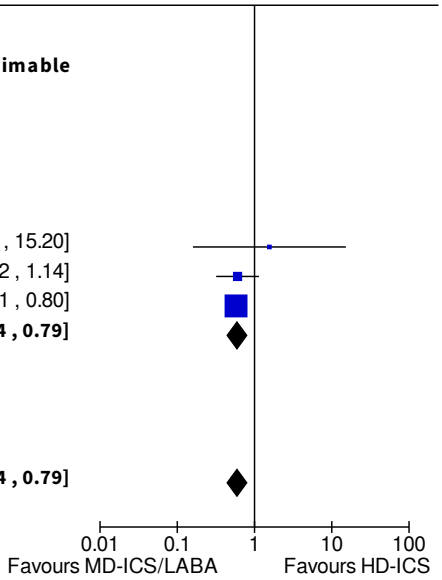
Analysis 3.4



Comparison 3: Moderate to severe exacerbations (high and low risk subgroups), Outcome 4: HD-ICS/LABA vs MD-ICS

Analysis 3.5

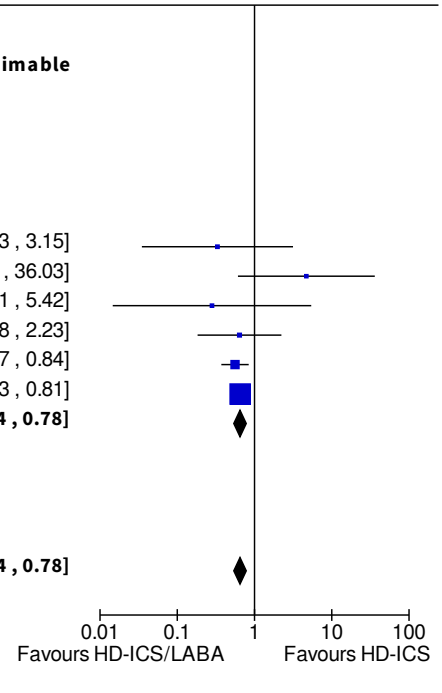
Study or Subgroup	Intervention Events	Total	Active control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.5.1 High Risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.5.2 Low Risk						
Mansfield 2017	3	161	1	83	1.1%	1.56 [0.16 , 15.20]
Peters 2008	19	132	29	133	20.4%	0.60 [0.32 , 1.14]
van Zyl-Smit 2020	74	437	115	440	78.5%	0.58 [0.41 , 0.80]
Subtotal (95% CI)		**730**		**656**	**100.0%**	**0.59 [0.44 , 0.79]**
Total events:	96		145			
Heterogeneity: $Chi^2 = 0.72$, df = 2 (P = 0.70); $I^2 = 0\%$						
Test for overall effect: Z = 3.56 (P = 0.0004)						
Total (95% CI)		**730**		**656**	**100.0%**	**0.59 [0.44 , 0.79]**
Total events:	96		145			
Heterogeneity: $Chi^2 = 0.72$, df = 2 (P = 0.70); $I^2 = 0\%$						
Test for overall effect: Z = 3.56 (P = 0.0004)						
Test for subgroup differences: Not applicable						



Comparison 3: Moderate to severe exacerbations (high and low risk subgroups), Outcome 5: MD-ICS/LABA vs HD-ICS

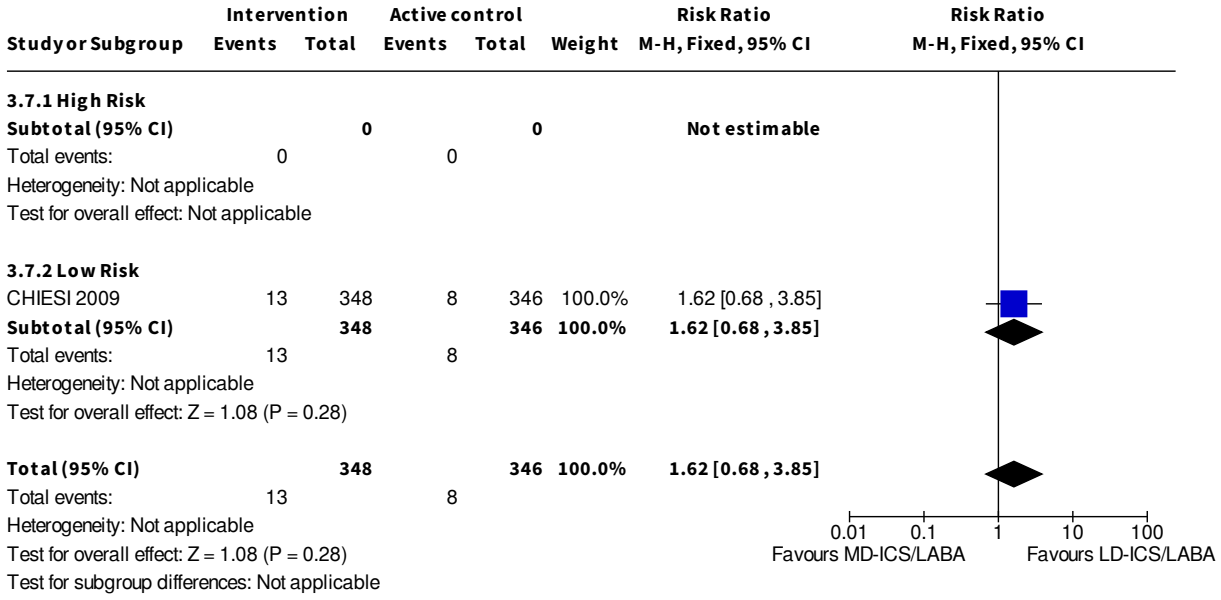
Analysis 3.6

Study or Subgroup	Intervention Events	Total	Active control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 High Risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.6.2 Low Risk						
Lin 2015	1	155	3	154	1.4%	0.33 [0.03 , 3.15]
Mansfield 2017	10	177	1	83	0.6%	4.69 [0.61 , 36.03]
O'Byrne 2014	0	197	3	389	1.1%	0.28 [0.01 , 5.42]
Paggiaro 2016b	4	192	6	184	2.9%	0.64 [0.18 , 2.23]
Peters 2008	54	443	29	133	21.1%	0.56 [0.37 , 0.84]
van Zyl-Smit 2020	151	887	115	440	72.8%	0.65 [0.53 , 0.81]
Subtotal (95% CI)		**2051**		**1383**	**100.0%**	**0.65 [0.54 , 0.78]**
Total events:	220		157			
Heterogeneity: $Chi^2 = 4.78$, df = 5 (P = 0.44); $I^2 = 0\%$						
Test for overall effect: Z = 4.58 (P < 0.00001)						
Total (95% CI)		**2051**		**1383**	**100.0%**	**0.65 [0.54 , 0.78]**
Total events:	220		157			
Heterogeneity: $Chi^2 = 4.78$, df = 5 (P = 0.44); $I^2 = 0\%$						
Test for overall effect: Z = 4.58 (P < 0.00001)						
Test for subgroup differences: Not applicable						



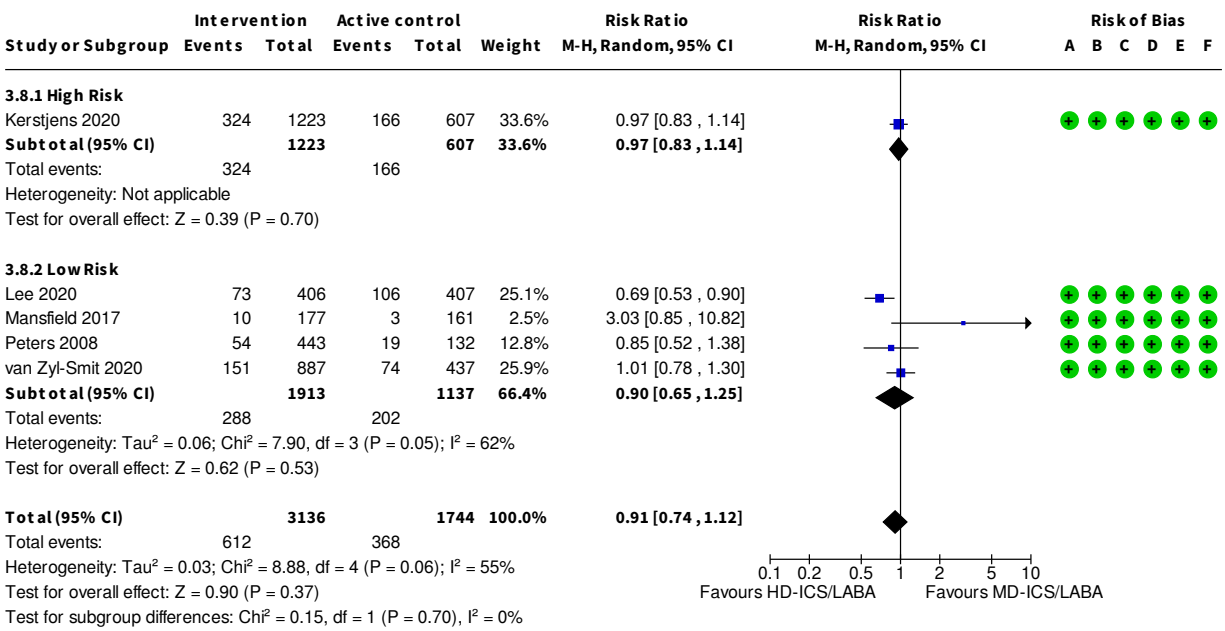
Comparison 3: Moderate to severe exacerbations (high and low risk subgroups), Outcome 6: HD-ICS/LABA vs HD-ICS

Analysis 3.7



Comparison 3: Moderate to severe exacerbations (high and low risk subgroups), Outcome 7: MD-ICS/LABA vs LD-ICS/LABA

Analysis 3.8

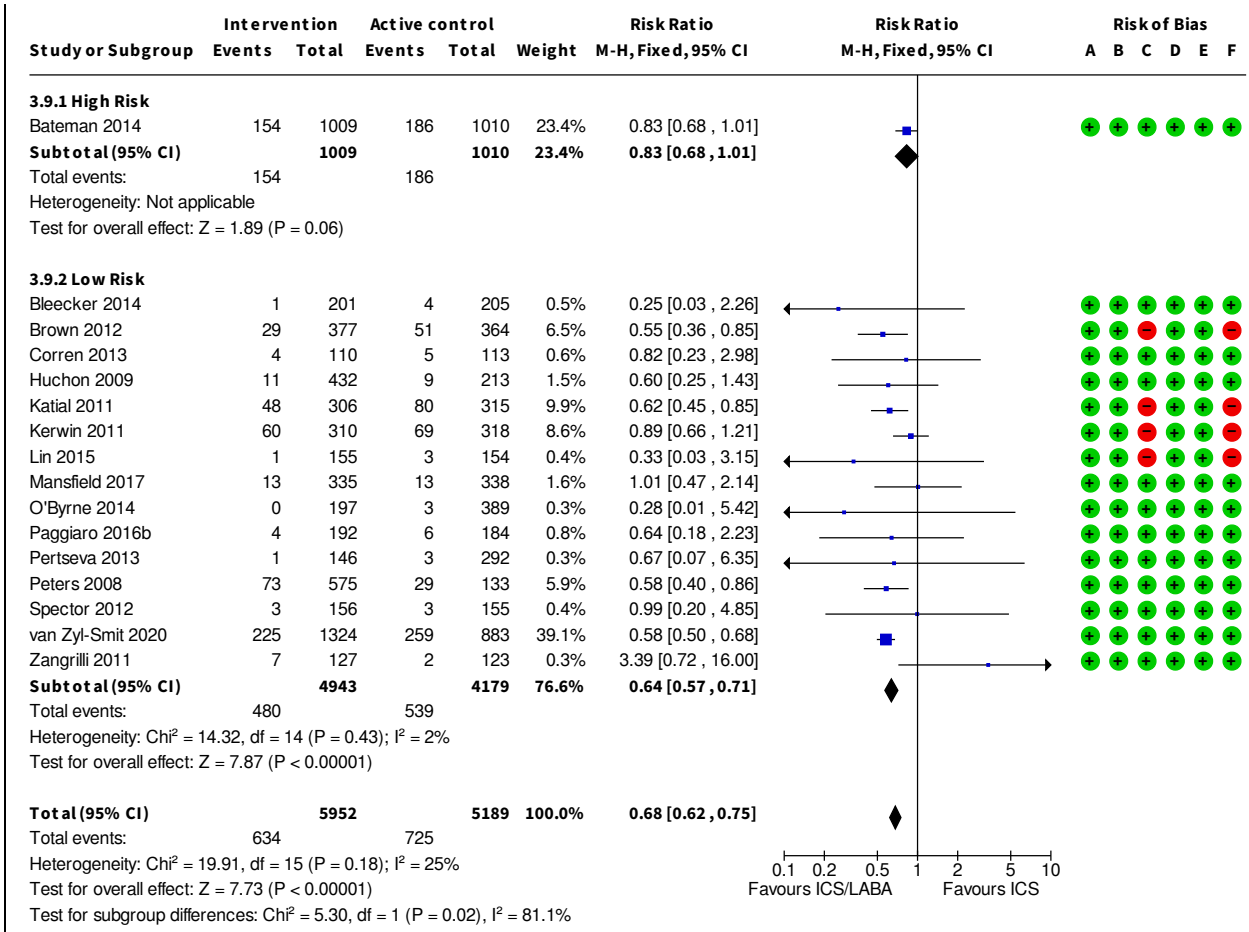


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

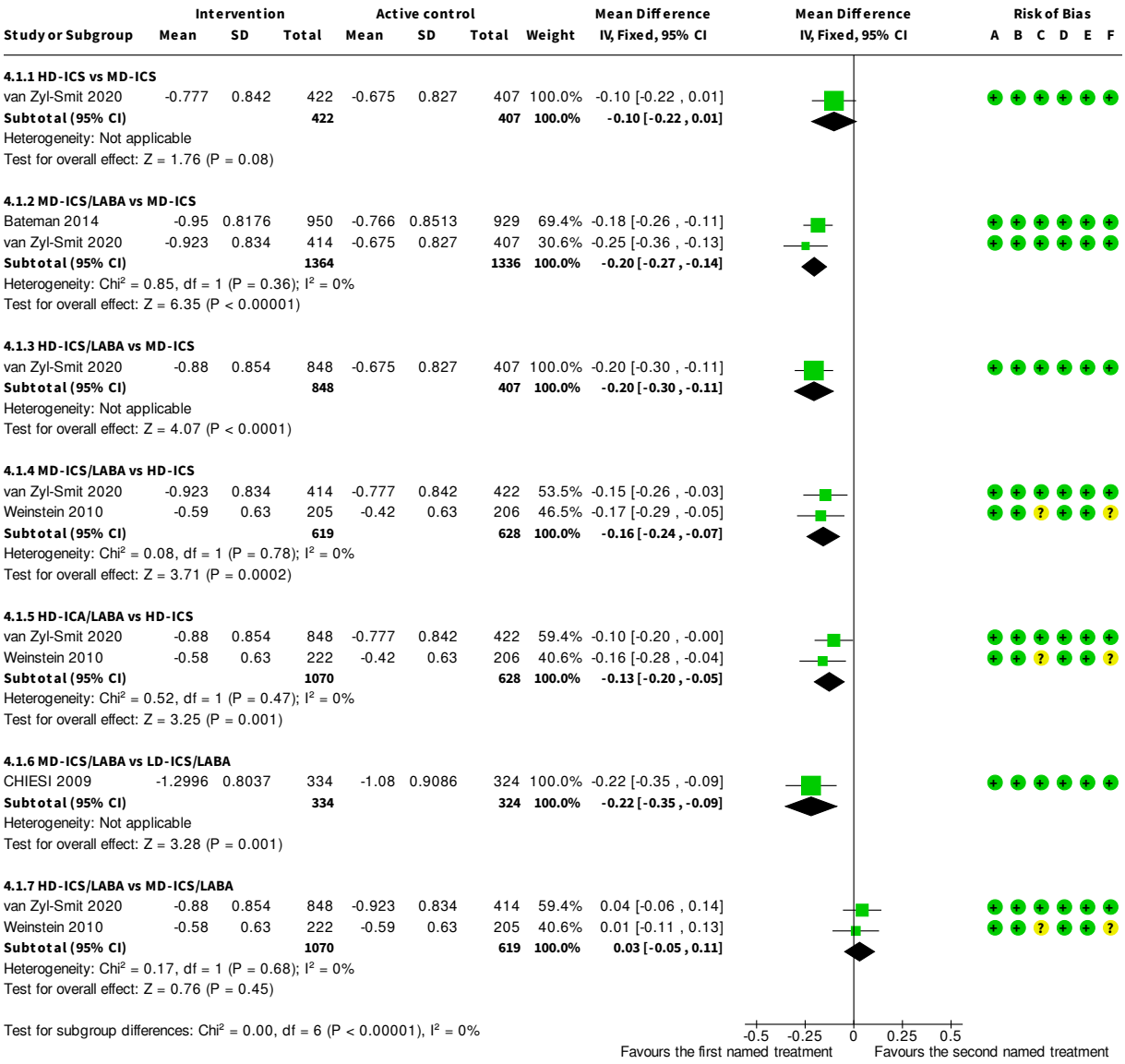
Comparison 3: Moderate to severe exacerbations (high and low risk subgroups), Outcome 8: HD-ICS/LABA vs MD-ICS/LABA

Analysis 3.9



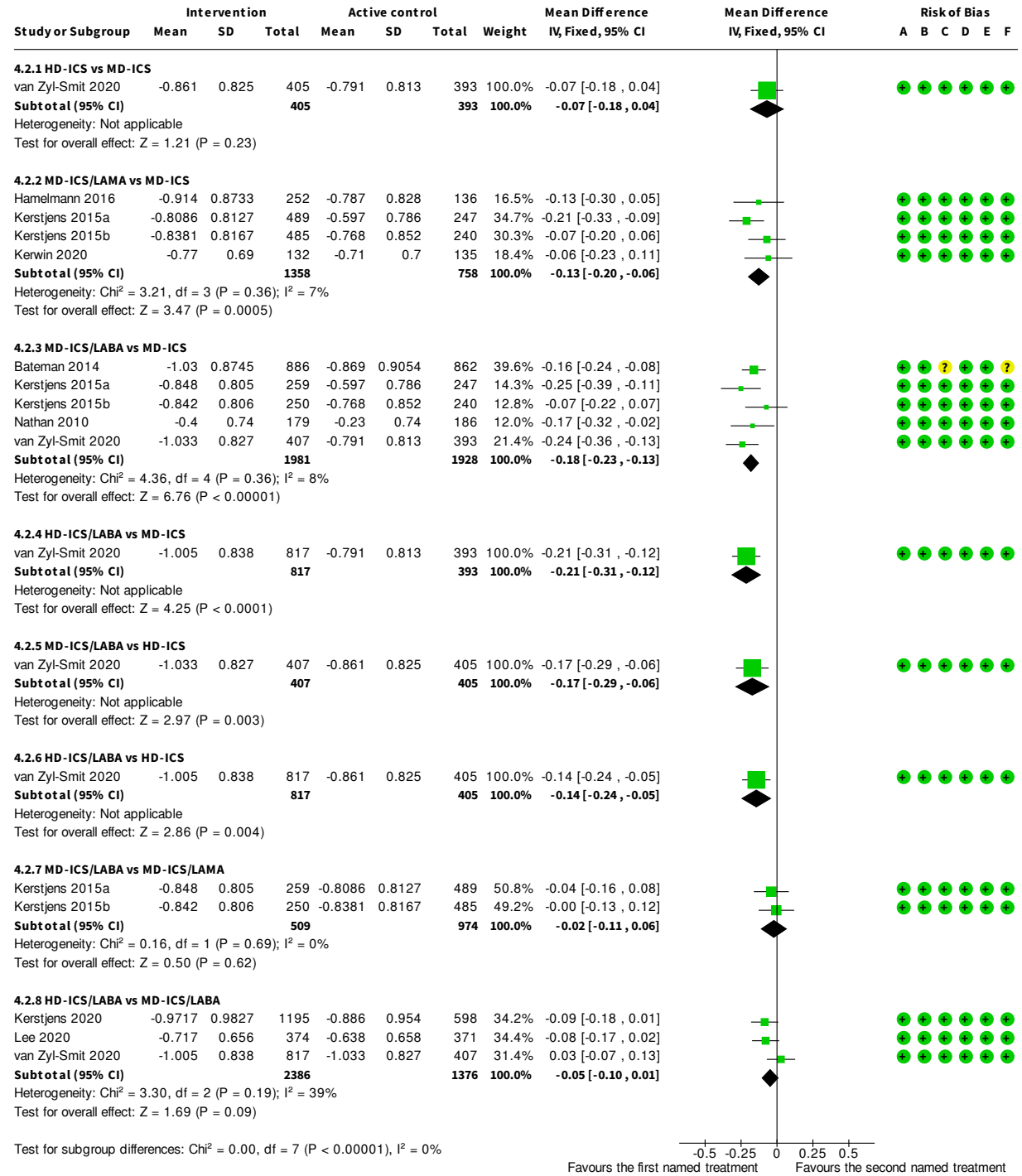
Comparison 3: Moderate to severe exacerbations (high and low risk subgroups), Outcome 9: ICS/LABA vs ICS

Analysis 4.1



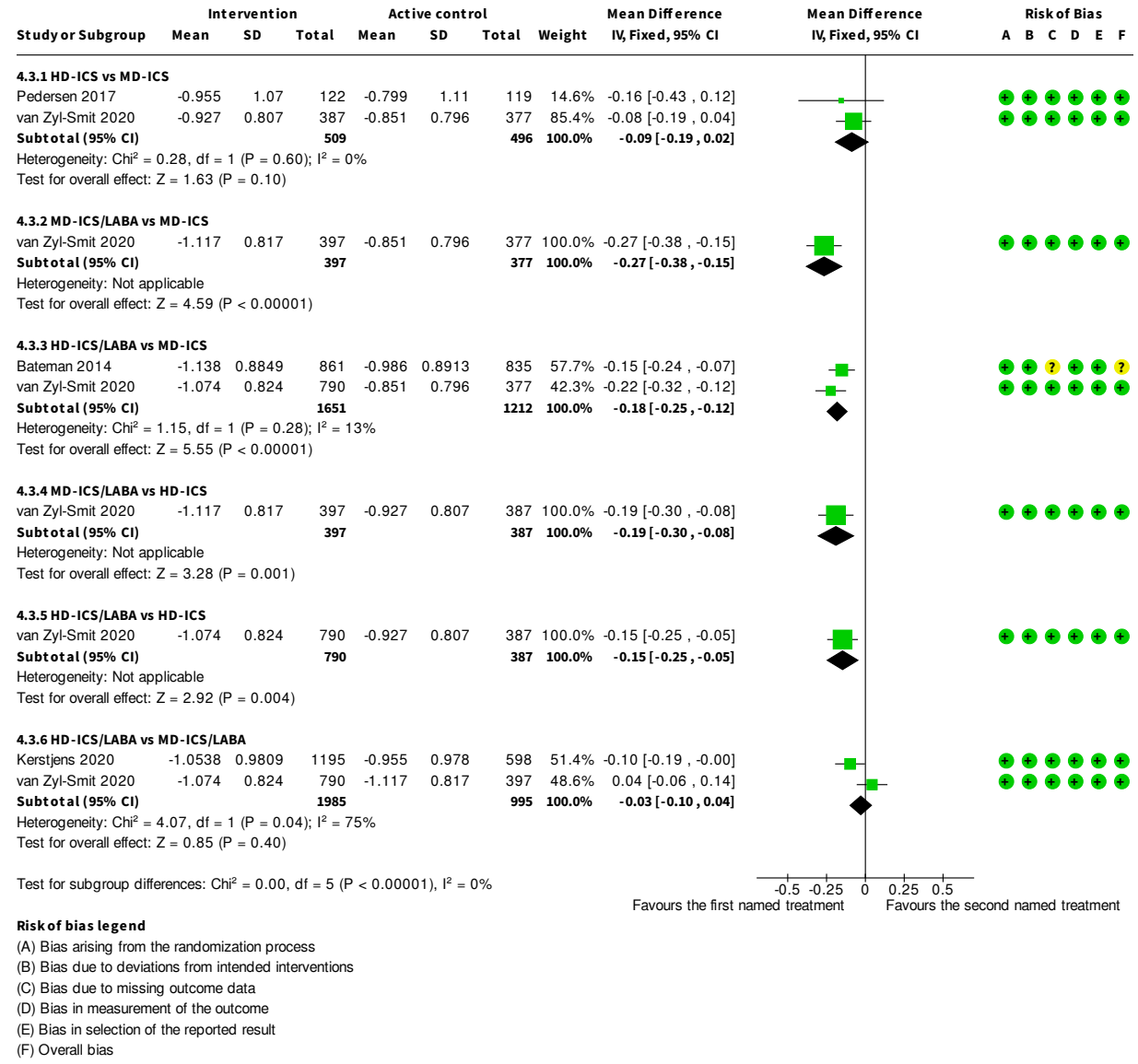
Comparison 4: CFB in ACQ, Outcome 1: CFB in ACQ at 3 months

Analysis 4.2



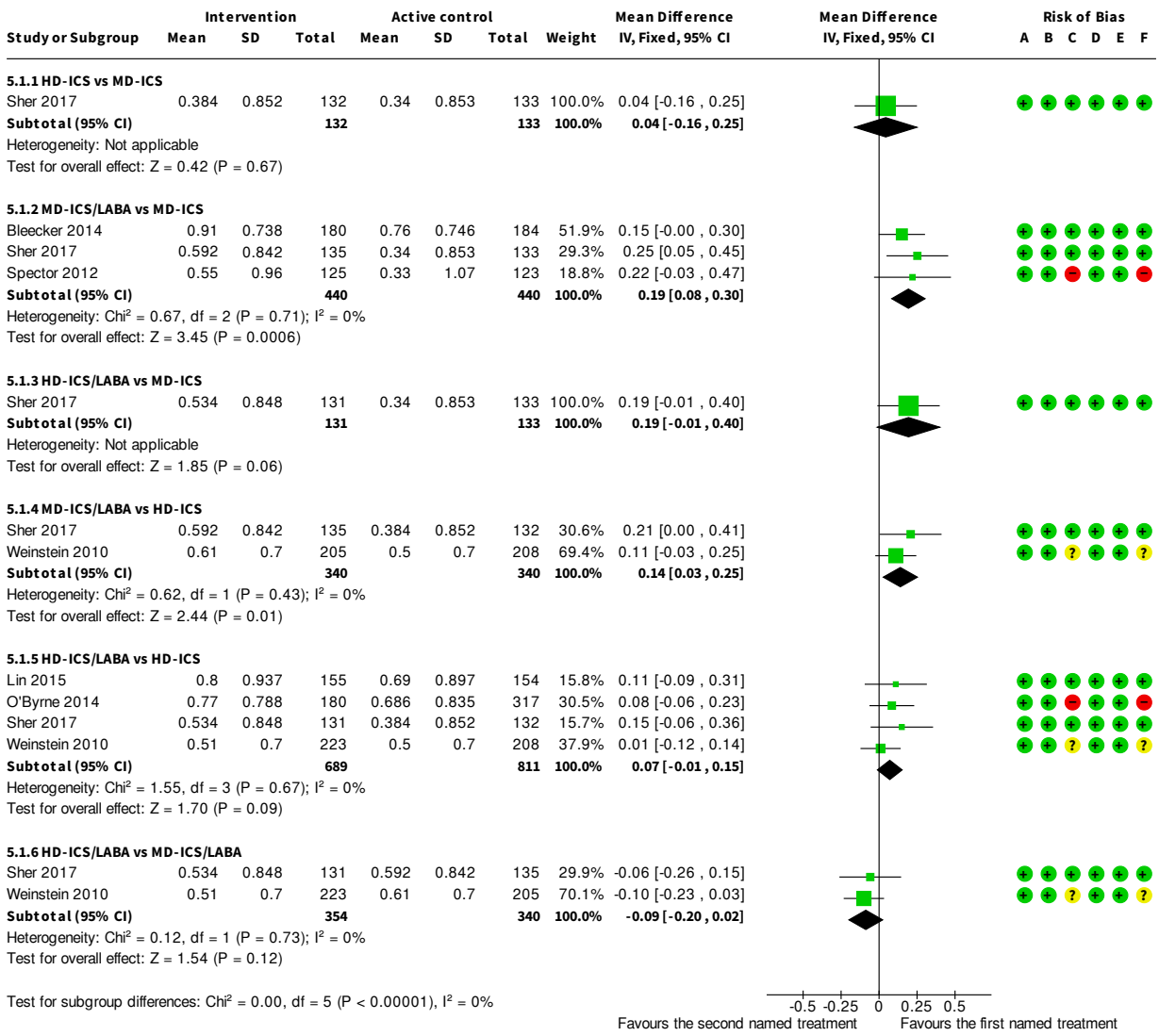
Comparison 4: CFB in ACQ, Outcome 2: CFB in ACQ at 6 months

Analysis 4.3



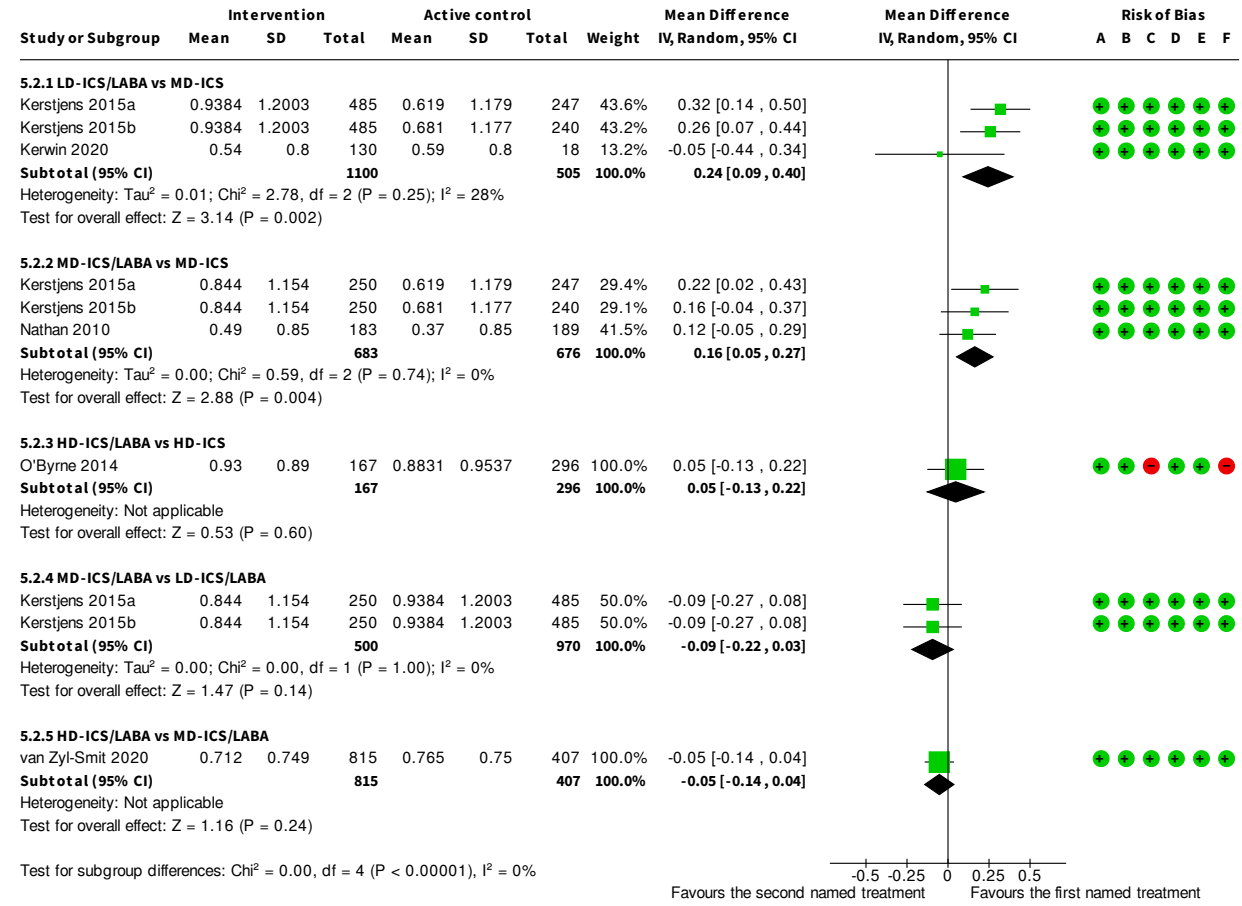
Comparison 4: CFB in ACQ, Outcome 3: CFB in ACQ at 12 months

Analysis 5.1



Comparison 5: CFB in AQLQ, Outcome 1: CFB in AQLQ at 3 months

Analysis 5.2

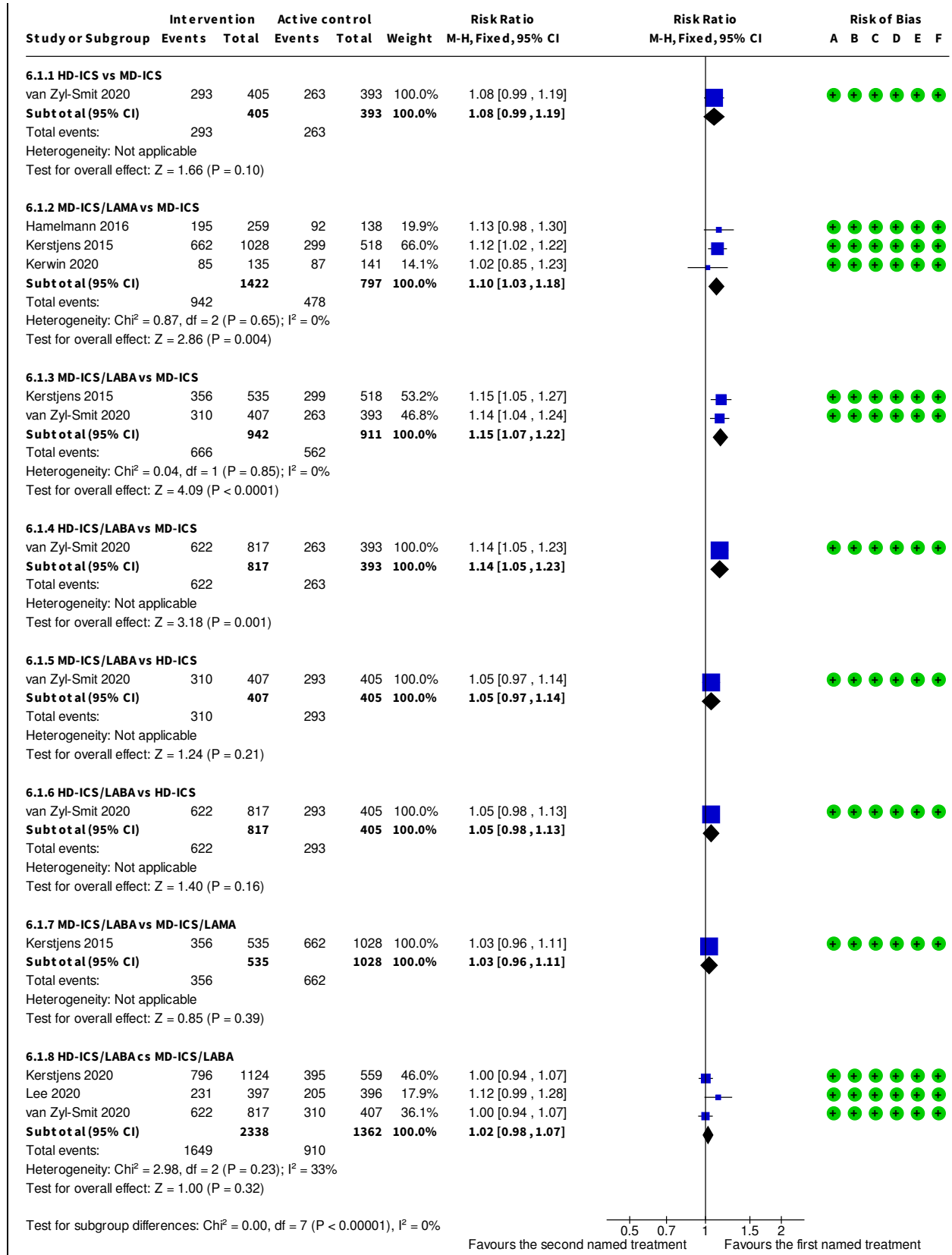


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

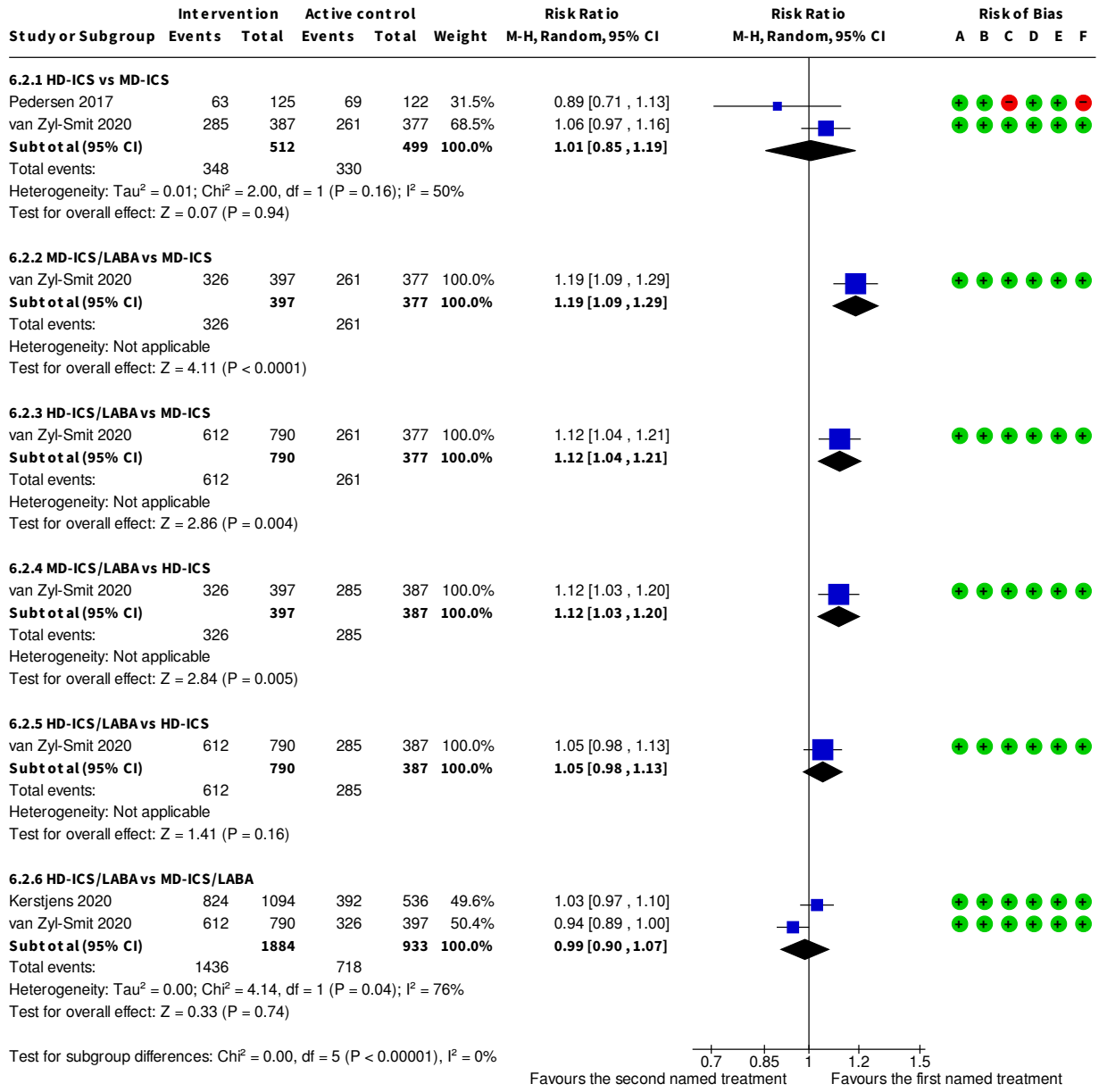
Comparison 5: CFB in AQLQ, Outcome 2: CFB in AQLQ at 6 months

Analysis 6.1



Comparison 6: ACQ responder, Outcome 1: ACQ responder at 6 months

Analysis 6.2

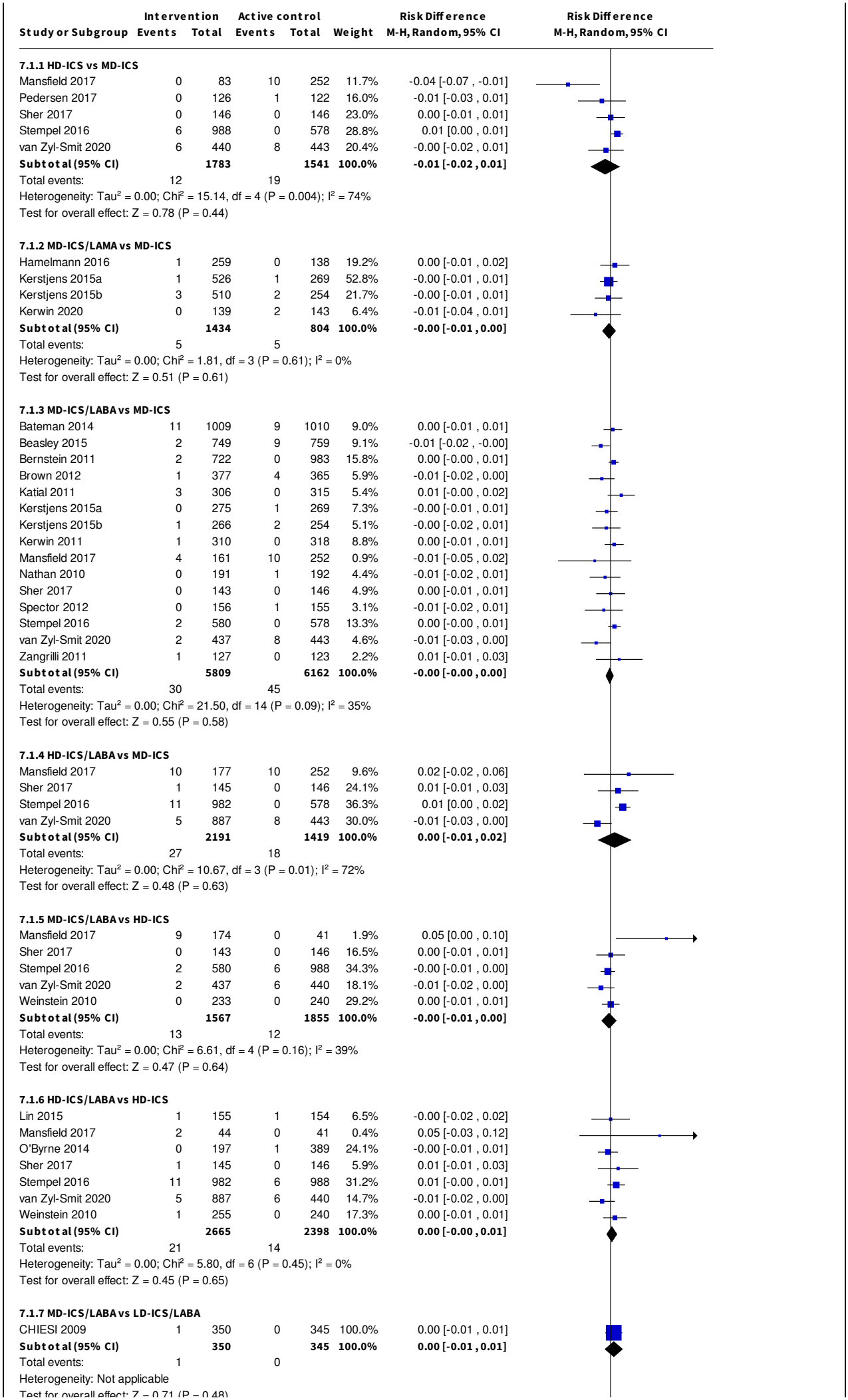


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 6: ACQ responder, Outcome 2: ACQ responder at 12 months

Analysis 7.1


Intervention
Active control
Risk Difference
Risk Difference
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
7.1.1 HD-ICS vs MD-ICS
Mansfield 2017 0 83 10 252 11.7% -0.04 [-0.07 , -0.01]
Pedersen 2017 0 126 1 122 16.0% -0.01 [-0.03 , 0.01]
Sher 2017 0 146 0 146 23.0% 0.00 [-0.01 , 0.01]
Stempel 2016 6 988 0 578 28.8% 0.01 [0.00 , 0.01]
van Zyl-Smit 2020 6 440 8 443 20.4% -0.00 [-0.02 , 0.01]
Subtotal (95% CI) 1783 1541 100.0% -0.01 [-0.02 , 0.01]
Total events: 12 19
Heterogeneity: Tau² = 0.00; Chi² = 15.14, df = 4 (P = 0.004); I² = 74%
Test for overall effect: Z = 0.78 (P = 0.44)
7.1.2 MD-ICS/LAMA vs MD-ICS
Hamelmann 2016 1 259 0 138 19.2% 0.00 [-0.01 , 0.02]
Kerstjens 2015a 1 526 1 269 52.8% -0.00 [-0.01 , 0.01]
Kerstjens 2015b 3 510 2 254 21.7% -0.00 [-0.01 , 0.01]
Kerwin 2020 0 139 2 143 6.4% -0.01 [-0.04 , 0.01]
Subtotal (95% CI) 1434 804 100.0% -0.00 [-0.01 , 0.00]
Total events: 5 5
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
7.1.3 MD-ICS/LABA vs MD-ICS
Bateman 2014 11 1009 9 1010 9.0% 0.00 [-0.01 , 0.01]
Beasley 2015 2 749 9 759 9.1% -0.01 [-0.02 , -0.00]
Bernstein 2011 2 722 0 983 15.8% 0.00 [-0.00 , 0.01]
Brown 2012 1 377 4 365 5.9% -0.01 [-0.02 , 0.00]
Katial 2011 3 306 0 315 5.4% 0.01 [-0.00 , 0.02]
Kerstjens 2015a 0 275 1 269 7.3% -0.00 [-0.01 , 0.01]
Kerstjens 2015b 1 266 2 254 5.1% -0.00 [-0.02 , 0.01]
Kerwin 2011 1 310 0 318 8.8% 0.00 [-0.01 , 0.01]
Mansfield 2017 4 161 10 252 0.9% -0.01 [-0.05 , 0.02]
Nathan 2010 0 191 1 192 4.4% -0.01 [-0.02 , 0.01]
Sher 2017 0 143 0 146 4.9% 0.00 [-0.01 , 0.01]
Spector 2012 0 156 1 155 3.1% -0.01 [-0.02 , 0.01]
Stempel 2016 2 580 0 578 13.3% 0.00 [-0.00 , 0.01]
van Zyl-Smit 2020 2 437 8 443 4.6% -0.01 [-0.03 , 0.00]
Zangrilli 2011 1 127 0 123 2.2% 0.01 [-0.01 , 0.03]
Subtotal (95% CI) 5809 6162 100.0% -0.00 [-0.00 , 0.00]
Total events: 30 45
Heterogeneity: Tau² = 0.00; Chi² = 21.50, df = 14 (P = 0.09); I² = 35%
Test for overall effect: Z = 0.55 (P = 0.58)
7.1.4 HD-ICS/LABA vs MD-ICS
Mansfield 2017 10 177 10 252 9.6% 0.02 [-0.02 , 0.06]
Sher 2017 1 145 0 146 24.1% 0.01 [-0.01 , 0.03]
Stempel 2016 11 982 0 578 36.3% 0.01 [0.00 , 0.02]
van Zyl-Smit 2020 5 887 8 443 30.0% -0.01 [-0.03 , 0.00]
Subtotal (95% CI) 2191 1419 100.0% 0.00 [-0.01 , 0.02]
Total events: 27 18
Heterogeneity: Tau² = 0.00; Chi² = 10.67, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 0.48 (P = 0.63)
7.1.5 MD-ICS/LABA vs HD-ICS
Mansfield 2017 9 174 0 41 1.9% 0.05 [0.00 , 0.10]
Sher 2017 0 143 0 146 16.5% 0.00 [-0.01 , 0.01]
Stempel 2016 2 580 6 988 34.3% -0.00 [-0.01 , 0.00]
van Zyl-Smit 2020 2 437 6 440 18.1% -0.01 [-0.02 , 0.00]
Weinstein 2010 0 233 0 240 29.2% 0.00 [-0.01 , 0.01]
Subtotal (95% CI) 1567 1855 100.0% -0.00 [-0.01 , 0.00]
Total events: 13 12
Heterogeneity: Tau² = 0.00; Chi² = 6.61, df = 4 (P = 0.16); I² = 39%
Test for overall effect: Z = 0.47 (P = 0.64)
7.1.6 HD-ICS/LABA vs HD-ICS
Lin 2015 1 155 1 154 6.5% -0.00 [-0.02 , 0.02]
Mansfield 2017 2 44 0 41 0.4% 0.05 [-0.03 , 0.12]
O'Byrne 2014 0 197 1 389 24.1% -0.00 [-0.01 , 0.01]
Sher 2017 1 145 0 146 5.9% 0.01 [-0.01 , 0.03]
Stempel 2016 11 982 6 988 31.2% 0.01 [-0.00 , 0.01]
van Zyl-Smit 2020 5 887 6 440 14.7% -0.01 [-0.02 , 0.00]
Weinstein 2010 1 255 0 240 17.3% 0.00 [-0.01 , 0.01]
Subtotal (95% CI) 2665 2398 100.0% 0.00 [-0.00 , 0.01]
Total events: 21 14
Heterogeneity: Tau² = 0.00; Chi² = 5.80, df = 6 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
7.1.7 MD-ICS/LABA vs LD-ICS/LABA
CHIESI 2009 1 350 0 345 100.0% 0.00 [-0.01 , 0.01]
Subtotal (95% CI) 350 345 100.0% 0.00 [-0.01 , 0.01]
Total events: 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

Comparison 7: Safety outcomes, Outcome 1: Asthma-related SAEs

Analysis 7.2

7.1.8 MD-ICS/LABA vs MD-ICS/LAMA

Kerstjens 2015a	0	275	1	526	68.2%	-0.00 [-0.01 , 0.00]
Kerstjens 2015b	1	266	3	510	31.8%	-0.00 [-0.01 , 0.01]
Subtotal (95% CI)		**541**		**1036**	**100.0%**	**-0.00 [-0.01 , 0.00]**
Total events:	1		4			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%

Test for overall effect: Z = 0.69 (P = 0.49)

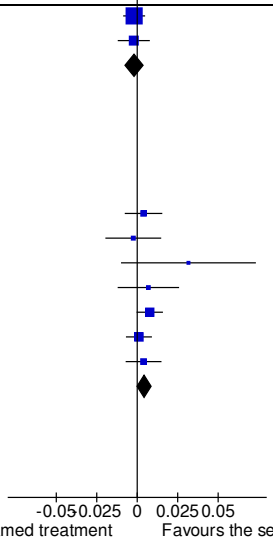
7.1.9 HD-ICS/LABA vs MD-ICS/LABA

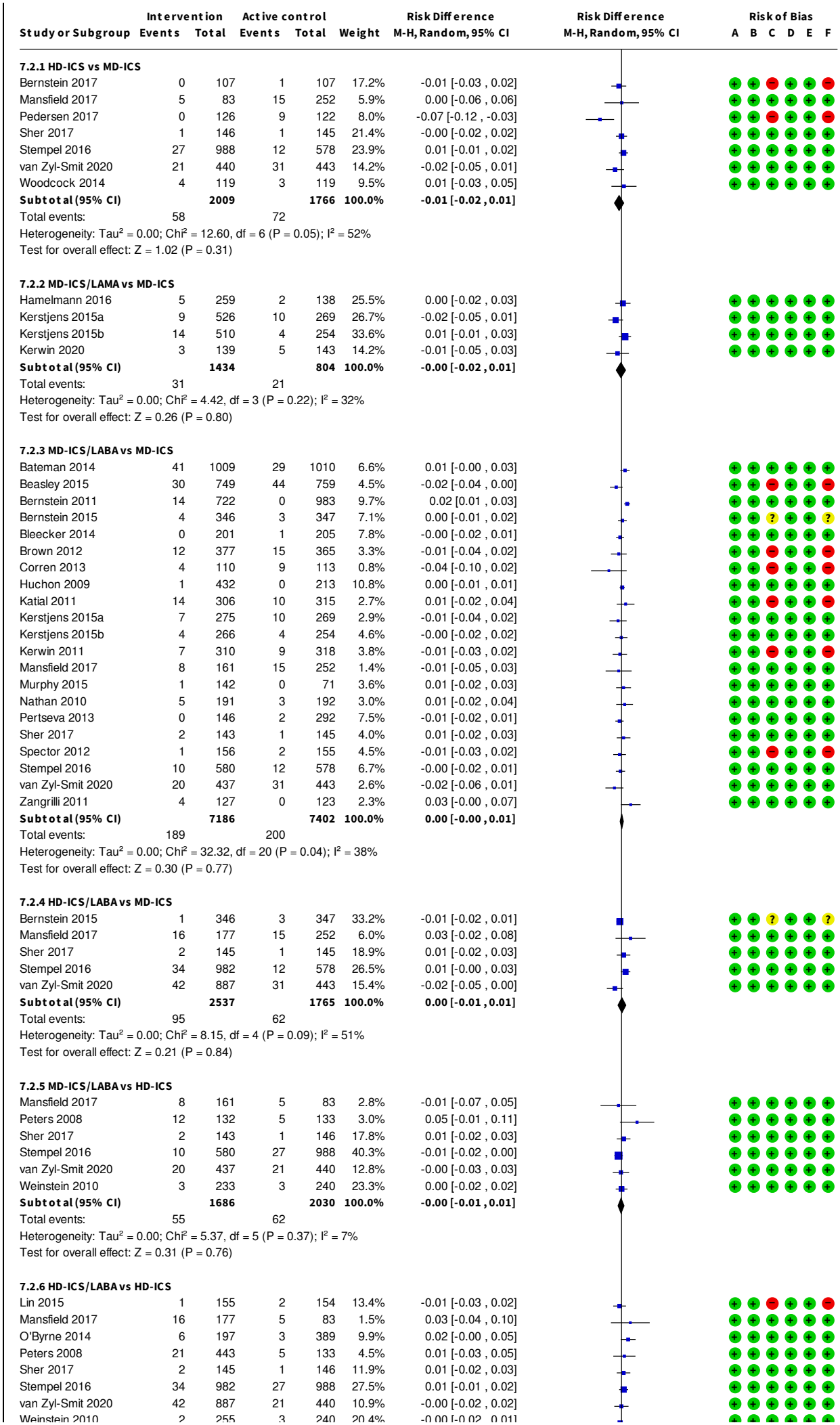
Kerstjens 2020	21	1231	8	608	14.0%	0.00 [-0.01 , 0.02]
Lee 2020	6	406	7	407	6.3%	-0.00 [-0.02 , 0.01]
Mansfield 2017	10	177	4	161	1.1%	0.03 [-0.01 , 0.07]
Sher 2017	1	145	0	143	5.2%	0.01 [-0.01 , 0.03]
Stempel 2016	11	982	2	580	28.5%	0.01 [-0.00 , 0.02]
van Zyl-Smit 2020	5	887	2	437	29.3%	0.00 [-0.01 , 0.01]
Weinstein 2010	1	255	0	233	15.4%	0.00 [-0.01 , 0.01]
Subtotal (95% CI)		**4083**		**2569**	**100.0%**	**0.00 [-0.00 , 0.01]**
Total events:	55		23			

Heterogeneity: Tau² = 0.00; Chi² = 3.79, df = 6 (P = 0.70); I² = 0%

Test for overall effect: Z = 1.91 (P = 0.06)

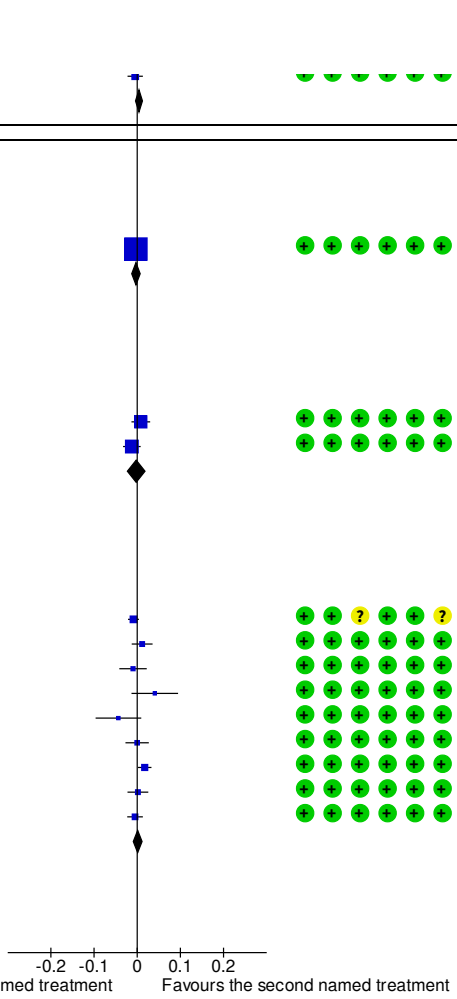
Test for subgroup differences: Chi² = 0.00, df = 8 (P < 0.00001), I² = 0%




Intervention
Active control
Risk Difference
Risk Difference
Risk of Bias
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
A B C D E F
7.2.1 HD-ICS vs MD-ICS
Bernstein 2017 0 107 1 107 17.2% -0.01 [-0.03 , 0.02]
Mansfield 2017 5 83 15 252 5.9% 0.00 [-0.06 , 0.06]
Pedersen 2017 0 126 9 122 8.0% -0.07 [-0.12 , -0.03]
Sher 2017 1 146 1 145 21.4% -0.00 [-0.02 , 0.02]
Stempel 2016 27 988 12 578 23.9% 0.01 [-0.01 , 0.02]
van Zyl-Smit 2020 21 440 31 443 14.2% -0.02 [-0.05 , 0.01]
Woodcock 2014 4 119 3 119 9.5% 0.01 [-0.03 , 0.05]
Subtotal (95% CI) 2009 1766 100.0% -0.01 [-0.02 , 0.01]
Total events: 58 72
Heterogeneity: Tau² = 0.00; Chi² = 12.60, df = 6 (P = 0.05); I² = 52%
Test for overall effect: Z = 1.02 (P = 0.31)
7.2.2 MD-ICS/LAMA vs MD-ICS
Hamelmann 2016 5 259 2 138 25.5% 0.00 [-0.02 , 0.03]
Kerstjens 2015a 9 526 10 269 26.7% -0.02 [-0.05 , 0.01]
Kerstjens 2015b 14 510 4 254 33.6% 0.01 [-0.01 , 0.03]
Kerwin 2020 3 139 5 143 14.2% -0.01 [-0.05 , 0.03]
Subtotal (95% CI) 1434 804 100.0% -0.00 [-0.02 , 0.01]
Total events: 31 21
Heterogeneity: Tau² = 0.00; Chi² = 4.42, df = 3 (P = 0.22); I² = 32%
Test for overall effect: Z = 0.26 (P = 0.80)
7.2.3 MD-ICS/LABA vs MD-ICS
Bateman 2014 41 1009 29 1010 6.6% 0.01 [-0.00 , 0.03]
Beasley 2015 30 749 44 759 4.5% -0.02 [-0.04 , 0.00]
Bernstein 2011 14 722 0 983 9.7% 0.02 [0.01 , 0.03]
Bernstein 2015 4 346 3 347 7.1% 0.00 [-0.01 , 0.02]
Bleecker 2014 0 201 1 205 7.8% -0.00 [-0.02 , 0.01]
Brown 2012 12 377 15 365 3.3% -0.01 [-0.04 , 0.02]
Corren 2013 4 110 9 113 0.8% -0.04 [-0.10 , 0.02]
Huchon 2009 1 432 0 213 10.8% 0.00 [-0.01 , 0.01]
Katial 2011 14 306 10 315 2.7% 0.01 [-0.02 , 0.04]
Kerstjens 2015a 7 275 10 269 2.9% -0.01 [-0.04 , 0.02]
Kerstjens 2015b 4 266 4 254 4.6% -0.00 [-0.02 , 0.02]
Kerwin 2011 7 310 9 318 3.8% -0.01 [-0.03 , 0.02]
Mansfield 2017 8 161 15 252 1.4% -0.01 [-0.05 , 0.03]
Murphy 2015 1 142 0 71 3.6% 0.01 [-0.02 , 0.03]
Nathan 2010 5 191 3 192 3.0% 0.01 [-0.02 , 0.04]
Pertseva 2013 0 146 2 292 7.5% -0.01 [-0.02 , 0.01]
Sher 2017 2 143 1 145 4.0% 0.01 [-0.02 , 0.03]
Spector 2012 1 156 2 155 4.5% -0.01 [-0.03 , 0.02]
Stempel 2016 10 580 12 578 6.7% -0.00 [-0.02 , 0.01]
van Zyl-Smit 2020 20 437 31 443 2.6% -0.02 [-0.06 , 0.01]
Zangrilli 2011 4 127 0 123 2.3% 0.03 [-0.00 , 0.07]
Subtotal (95% CI) 7186 7402 100.0% 0.00 [-0.00 , 0.01]
Total events: 189 200
Heterogeneity: Tau² = 0.00; Chi² = 32.32, df = 20 (P = 0.04); I² = 38%
Test for overall effect: Z = 0.30 (P = 0.77)
7.2.4 HD-ICS/LABA vs MD-ICS
Bernstein 2015 1 346 3 347 33.2% -0.01 [-0.02 , 0.01]
Mansfield 2017 16 177 15 252 6.0% 0.03 [-0.02 , 0.08]
Sher 2017 2 145 1 145 18.9% 0.01 [-0.02 , 0.03]
Stempel 2016 34 982 12 578 26.5% 0.01 [-0.00 , 0.03]
van Zyl-Smit 2020 42 887 31 443 15.4% -0.02 [-0.05 , 0.00]
Subtotal (95% CI) 2537 1765 100.0% 0.00 [-0.01 , 0.01]
Total events: 95 62
Heterogeneity: Tau² = 0.00; Chi² = 8.15, df = 4 (P = 0.09); I² = 51%
Test for overall effect: Z = 0.21 (P = 0.84)
7.2.5 MD-ICS/LABA vs HD-ICS
Mansfield 2017 8 161 5 83 2.8% -0.01 [-0.07 , 0.05]
Peters 2008 12 132 5 133 3.0% 0.05 [-0.01 , 0.11]
Sher 2017 2 143 1 146 17.8% 0.01 [-0.02 , 0.03]
Stempel 2016 10 580 27 988 40.3% -0.01 [-0.02 , 0.00]
van Zyl-Smit 2020 20 437 21 440 12.8% -0.00 [-0.03 , 0.03]
Weinstein 2010 3 233 3 240 23.3% 0.00 [-0.02 , 0.02]
Subtotal (95% CI) 1686 2030 100.0% -0.00 [-0.01 , 0.01]
Total events: 55 62
Heterogeneity: Tau² = 0.00; Chi² = 5.37, df = 5 (P = 0.37); I² = 7%
Test for overall effect: Z = 0.31 (P = 0.76)
7.2.6 HD-ICS/LABA vs HD-ICS
Lin 2015 1 155 2 154 13.4% -0.01 [-0.03 , 0.02]
Mansfield 2017 16 177 5 83 1.5% 0.03 [-0.04 , 0.10]
O'Byrne 2014 6 197 3 389 9.9% 0.02 [-0.00 , 0.05]
Peters 2008 21 443 5 133 4.5% 0.01 [-0.03 , 0.05]
Sher 2017 2 145 1 146 11.9% 0.01 [-0.02 , 0.03]
Stempel 2016 34 982 27 988 27.5% 0.01 [-0.01 , 0.02]
van Zyl-Smit 2020 42 887 21 440 10.9% -0.00 [-0.02 , 0.02]
Weinstein 2010 2 255 3 240 20.4% -0.00 [-0.02 , 0.01]

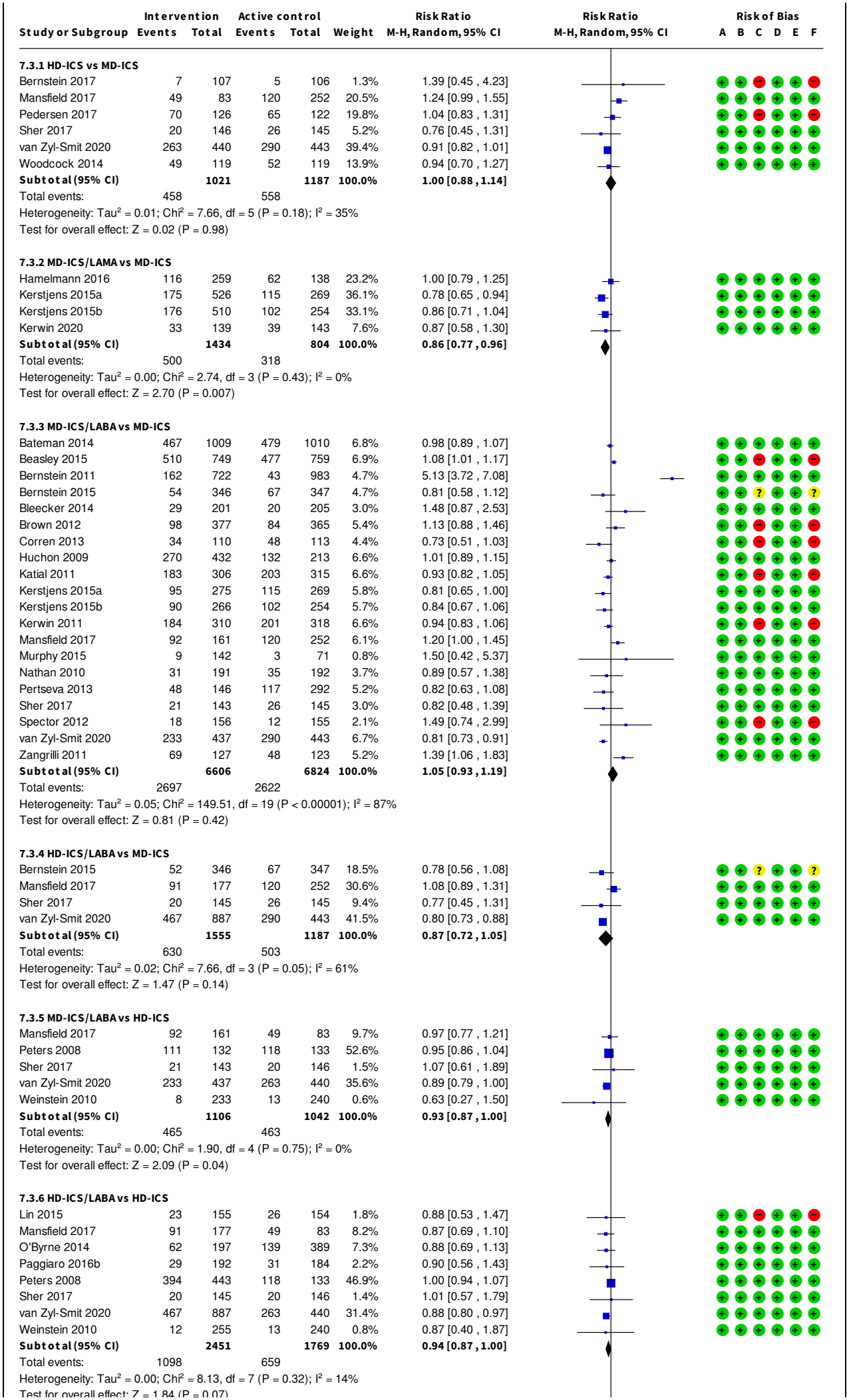
Analysis 7.3

Subtotal (95% CI)		**3241**		**2373**	**100.0%**	**0.00 [-0.00 , 0.01]**
Total events:	124		67			
Heterogeneity: Tau² = 0.00; Chi² = 5.24, df = 7 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
7.2.7 MD-ICS/LABA vs LD-ICS/LABA						
CHIESI 2009	1	350	2	345	100.0%	-0.00 [-0.01 , 0.01]
Subtotal (95% CI)		**350**		**345**	**100.0%**	**-0.00 [-0.01 , 0.01]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
7.2.8 MD-ICS/LABA vs MD-ICS/LAMA						
Kerstjens 2015a	7	275	9	526	48.4%	0.01 [-0.01 , 0.03]
Kerstjens 2015b	4	266	14	510	51.6%	-0.01 [-0.03 , 0.01]
Subtotal (95% CI)		**541**		**1036**	**100.0%**	**-0.00 [-0.02 , 0.02]**
Total events:	11		23			
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 1 (P = 0.17); I² = 47%						
Test for overall effect: Z = 0.23 (P = 0.82)						
7.2.9 HD-ICS/LABA vs MD-ICS/LABA						
Bernstein 2015	1	346	4	346	20.7%	-0.01 [-0.02 , 0.00]
Kerstjens 2020	91	1231	38	608	11.2%	0.01 [-0.01 , 0.04]
Lee 2020	21	406	25	407	7.7%	-0.01 [-0.04 , 0.02]
Mansfield 2017	16	177	8	161	3.2%	0.04 [-0.01 , 0.09]
Peters 2008	21	443	12	132	3.3%	-0.04 [-0.10 , 0.01]
Sher 2017	2	145	2	143	9.6%	-0.00 [-0.03 , 0.03]
Stempel 2016	34	982	10	580	17.7%	0.02 [0.00 , 0.03]
van Zyl-Smit 2020	42	887	20	437	11.2%	0.00 [-0.02 , 0.03]
Weinstein 2010	2	255	3	233	15.5%	-0.01 [-0.02 , 0.01]
Subtotal (95% CI)		**4872**		**3047**	**100.0%**	**0.00 [-0.01 , 0.01]**
Total events:	230		122			
Heterogeneity: Tau² = 0.00; Chi² = 13.52, df = 8 (P = 0.10); I² = 41%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi² = 0.00, df = 8 (P < 0.00001), I² = 0%						



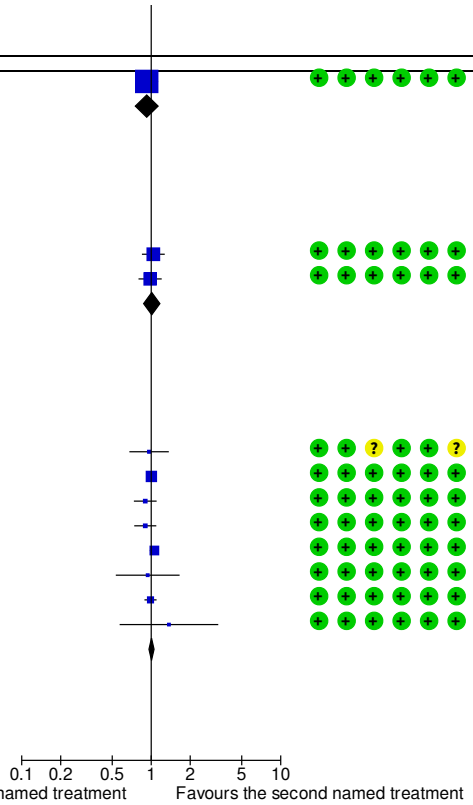
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias


Intervention
Active control
Risk Ratio
Risk Ratio
Risk of Bias
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
A B C D E F
7.3.1 HD-ICS vs MD-ICS
Bernstein 2017 7 107 5 106 1.3% 1.39 [0.45 , 4.23]
Mansfield 2017 49 83 120 252 20.5% 1.24 [0.99 , 1.55]
Pedersen 2017 70 126 65 122 19.8% 1.04 [0.83 , 1.31]
Sher 2017 20 146 26 145 5.2% 0.76 [0.45 , 1.31]
van Zyl-Smit 2020 263 440 290 443 39.4% 0.91 [0.82 , 1.01]
Woodcock 2014 49 119 52 119 13.9% 0.94 [0.70 , 1.27]
Subtotal (95% CI) 1021 1187 100.0% 1.00 [0.88 , 1.14]
Total events: 458 558
Heterogeneity: Tau² = 0.01; Chi² = 7.66, df = 5 (P = 0.18); I² = 35%
Test for overall effect: Z = 0.02 (P = 0.98)
7.3.2 MD-ICS/LAMA vs MD-ICS
Hamelmann 2016 116 259 62 138 23.2% 1.00 [0.79 , 1.25]
Kerstjens 2015a 175 526 115 269 36.1% 0.78 [0.65 , 0.94]
Kerstjens 2015b 176 510 102 254 33.1% 0.86 [0.71 , 1.04]
Kerwin 2020 33 139 39 143 7.6% 0.87 [0.58 , 1.30]
Subtotal (95% CI) 1434 804 100.0% 0.86 [0.77 , 0.96]
Total events: 500 318
Heterogeneity: Tau² = 0.00; Chi² = 2.74, df = 3 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)
7.3.3 MD-ICS/LABA vs MD-ICS
Bateman 2014 467 1009 479 1010 6.8% 0.98 [0.89 , 1.07]
Beasley 2015 510 749 477 759 6.9% 1.08 [1.01 , 1.17]
Bernstein 2011 162 722 43 983 4.7% 5.13 [3.72 , 7.08]
Bernstein 2015 54 346 67 347 4.7% 0.81 [0.58 , 1.12]
Bleecker 2014 29 201 20 205 3.0% 1.48 [0.87 , 2.53]
Brown 2012 98 377 84 365 5.4% 1.13 [0.88 , 1.46]
Corren 2013 34 110 48 113 4.4% 0.73 [0.51 , 1.03]
Huchon 2009 270 432 132 213 6.6% 1.01 [0.89 , 1.15]
Katial 2011 183 306 203 315 6.6% 0.93 [0.82 , 1.05]
Kerstjens 2015a 95 275 115 269 5.8% 0.81 [0.65 , 1.00]
Kerstjens 2015b 90 266 102 254 5.7% 0.84 [0.67 , 1.06]
Kerwin 2011 184 310 201 318 6.6% 0.94 [0.83 , 1.06]
Mansfield 2017 92 161 120 252 6.1% 1.20 [1.00 , 1.45]
Murphy 2015 9 142 3 71 0.8% 1.50 [0.42 , 5.37]
Nathan 2010 31 191 35 192 3.7% 0.89 [0.57 , 1.38]
Pertseva 2013 48 146 117 292 5.2% 0.82 [0.63 , 1.08]
Sher 2017 21 143 26 145 3.0% 0.82 [0.48 , 1.39]
Spector 2012 18 156 12 155 2.1% 1.49 [0.74 , 2.99]
van Zyl-Smit 2020 233 437 290 443 6.7% 0.81 [0.73 , 0.91]
Zangrilli 2011 69 127 48 123 5.2% 1.39 [1.06 , 1.83]
Subtotal (95% CI) 6606 6824 100.0% 1.05 [0.93 , 1.19]
Total events: 2697 2622
Heterogeneity: Tau² = 0.05; Chi² = 149.51, df = 19 (P < 0.00001); I² = 87%
Test for overall effect: Z = 0.81 (P = 0.42)
7.3.4 HD-ICS/LABA vs MD-ICS
Bernstein 2015 52 346 67 347 18.5% 0.78 [0.56 , 1.08]
Mansfield 2017 91 177 120 252 30.6% 1.08 [0.89 , 1.31]
Sher 2017 20 145 26 145 9.4% 0.77 [0.45 , 1.31]
van Zyl-Smit 2020 467 887 290 443 41.5% 0.80 [0.73 , 0.88]
Subtotal (95% CI) 1555 1187 100.0% 0.87 [0.72 , 1.05]
Total events: 630 503
Heterogeneity: Tau² = 0.02; Chi² = 7.66, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 1.47 (P = 0.14)
7.3.5 MD-ICS/LABA vs HD-ICS
Mansfield 2017 92 161 49 83 9.7% 0.97 [0.77 , 1.21]
Peters 2008 111 132 118 133 52.6% 0.95 [0.86 , 1.04]
Sher 2017 21 143 20 146 1.5% 1.07 [0.61 , 1.89]
van Zyl-Smit 2020 233 437 263 440 35.6% 0.89 [0.79 , 1.00]
Weinstein 2010 8 233 13 240 0.6% 0.63 [0.27 , 1.50]
Subtotal (95% CI) 1106 1042 100.0% 0.93 [0.87 , 1.00]
Total events: 465 463
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 4 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)
7.3.6 HD-ICS/LABA vs HD-ICS
Lin 2015 23 155 26 154 1.8% 0.88 [0.53 , 1.47]
Mansfield 2017 91 177 49 83 8.2% 0.87 [0.69 , 1.10]
O'Byrne 2014 62 197 139 389 7.3% 0.88 [0.69 , 1.13]
Paggiaro 2016b 29 192 31 184 2.2% 0.90 [0.56 , 1.43]
Peters 2008 394 443 118 133 46.9% 1.00 [0.94 , 1.07]
Sher 2017 20 145 20 146 1.4% 1.01 [0.57 , 1.79]
van Zyl-Smit 2020 467 887 263 440 31.4% 0.88 [0.80 , 0.97]
Weinstein 2010 12 255 13 240 0.8% 0.87 [0.40 , 1.87]
Subtotal (95% CI) 2451 1769 100.0% 0.94 [0.87 , 1.00]
Total events: 1098 659
Heterogeneity: Tau² = 0.00; Chi² = 8.13, df = 7 (P = 0.32); I² = 14%
Test for overall effect: Z = 1.84 (P = 0.07)

Comparison 7: Safety outcomes, Outcome 3: All cause AEs

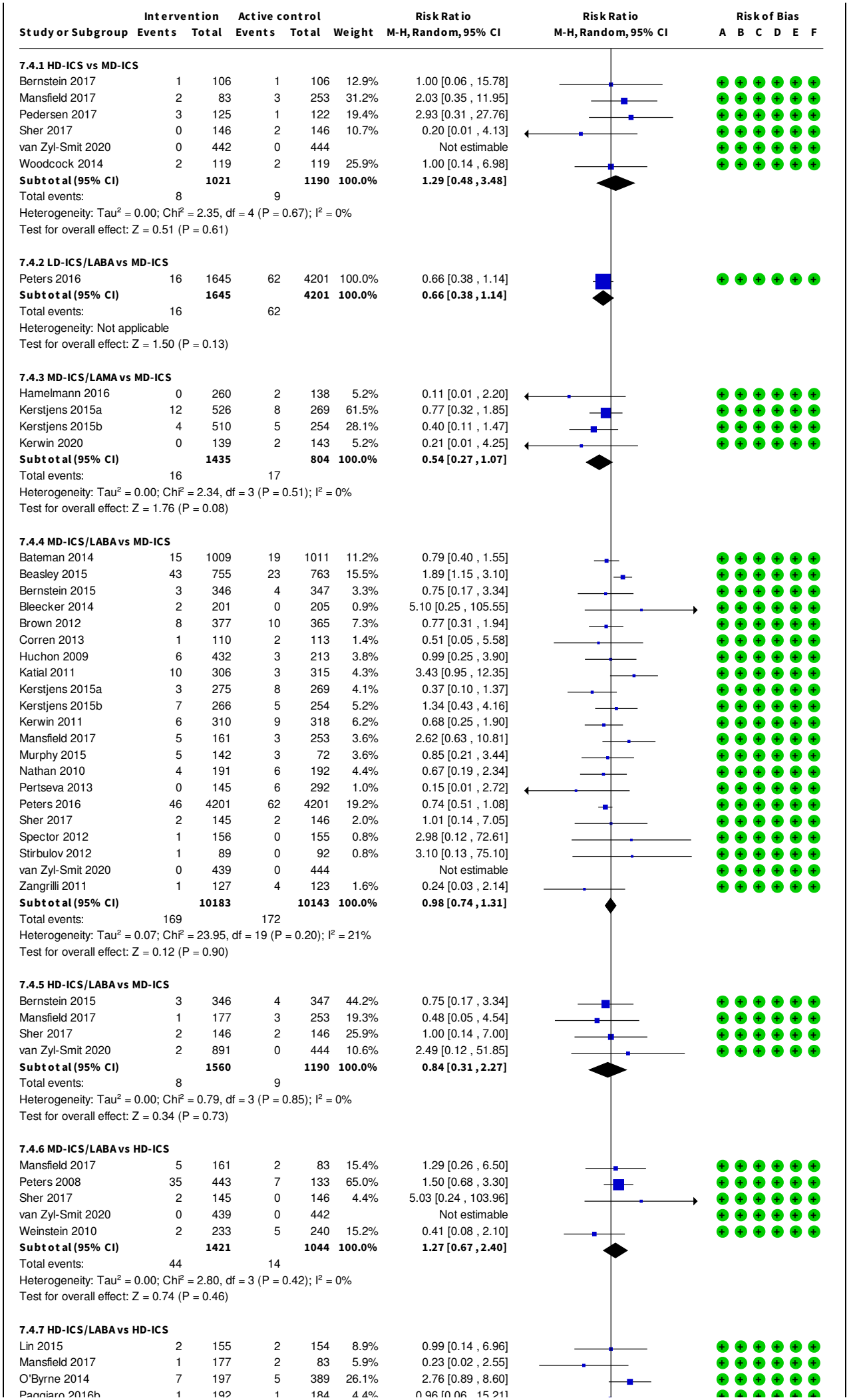
Analysis 7.4

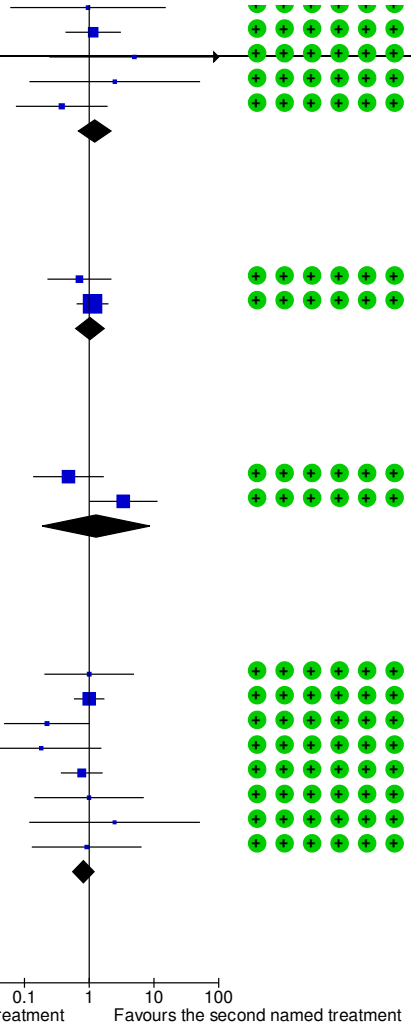


7.3.7 MD-ICS/LABA vs LD-ICS/LABA						
CHIESI 2009	118	350	126	345	100.0%	0.92 [0.75 , 1.13]
Subtotal (95% CI)		**350**		**345**	**100.0%**	**0.92 [0.75 , 1.13]**
Total events:	118		126			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
7.3.8 MD-ICS/LABA vs MD-ICS/LAMA						
Kerstjens 2015a	95	275	175	526	50.8%	1.04 [0.85 , 1.27]
Kerstjens 2015b	90	266	176	510	49.2%	0.98 [0.80 , 1.21]
Subtotal (95% CI)		**541**		**1036**	**100.0%**	**1.01 [0.87 , 1.17]**
Total events:	185		351			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
7.3.9 HD-ICS/LABA vs MD-ICS/LABA						
Bernstein 2015	52	346	54	346	1.6%	0.96 [0.68 , 1.37]
Kerstjens 2020	796	1231	392	608	39.0%	1.00 [0.93 , 1.08]
Lee 2020	122	406	136	407	5.0%	0.90 [0.73 , 1.10]
Mansfield 2017	91	177	92	161	5.3%	0.90 [0.74 , 1.09]
Peters 2008	394	443	111	132	30.7%	1.06 [0.98 , 1.15]
Sher 2017	20	145	21	143	0.6%	0.94 [0.53 , 1.66]
van Zyl-Smit 2020	467	887	233	437	17.5%	0.99 [0.89 , 1.10]
Weinstein 2010	12	255	8	233	0.3%	1.37 [0.57 , 3.29]
Subtotal (95% CI)		**3890**		**2467**	**100.0%**	**1.01 [0.96 , 1.05]**
Total events:	1954		1047			
Heterogeneity: Tau² = 0.00; Chi² = 5.18, df = 7 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.82)						
Test for subgroup differences: Chi² = 0.00, df = 8 (P < 0.00001), I² = 0%						

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias


Intervention
Active control
Risk Ratio
Risk Ratio
Risk of Bias
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
A B C D E F
7.4.1 HD-ICS vs MD-ICS
Bernstein 2017 1 106 1 106 12.9% 1.00 [0.06 , 15.78]
Mansfield 2017 2 83 3 253 31.2% 2.03 [0.35 , 11.95]
Pedersen 2017 3 125 1 122 19.4% 2.93 [0.31 , 27.76]
Sher 2017 0 146 2 146 10.7% 0.20 [0.01 , 4.13]
van Zyl-Smit 2020 0 442 0 444 Not estimable
Woodcock 2014 2 119 2 119 25.9% 1.00 [0.14 , 6.98]
Subtotal (95% CI) 1021 1190 100.0% 1.29 [0.48 , 3.48]
Total events: 8 9
Heterogeneity: Tau² = 0.00; Chi² = 2.35, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
7.4.2 LD-ICS/LABA vs MD-ICS
Peters 2016 16 1645 62 4201 100.0% 0.66 [0.38 , 1.14]
Subtotal (95% CI) 1645 4201 100.0% 0.66 [0.38 , 1.14]
Total events: 16 62
Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)
7.4.3 MD-ICS/LAMA vs MD-ICS
Hamelmann 2016 0 260 2 138 5.2% 0.11 [0.01 , 2.20]
Kerstjens 2015a 12 526 8 269 61.5% 0.77 [0.32 , 1.85]
Kerstjens 2015b 4 510 5 254 28.1% 0.40 [0.11 , 1.47]
Kerwin 2020 0 139 2 143 5.2% 0.21 [0.01 , 4.25]
Subtotal (95% CI) 1435 804 100.0% 0.54 [0.27 , 1.07]
Total events: 16 17
Heterogeneity: Tau² = 0.00; Chi² = 2.34, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)
7.4.4 MD-ICS/LABA vs MD-ICS
Bateman 2014 15 1009 19 1011 11.2% 0.79 [0.40 , 1.55]
Beasley 2015 43 755 23 763 15.5% 1.89 [1.15 , 3.10]
Bernstein 2015 3 346 4 347 3.3% 0.75 [0.17 , 3.34]
Bleecker 2014 2 201 0 205 0.9% 5.10 [0.25 , 105.55]
Brown 2012 8 377 10 365 7.3% 0.77 [0.31 , 1.94]
Corren 2013 1 110 2 113 1.4% 0.51 [0.05 , 5.58]
Huchon 2009 6 432 3 213 3.8% 0.99 [0.25 , 3.90]
Katial 2011 10 306 3 315 4.3% 3.43 [0.95 , 12.35]
Kerstjens 2015a 3 275 8 269 4.1% 0.37 [0.10 , 1.37]
Kerstjens 2015b 7 266 5 254 5.2% 1.34 [0.43 , 4.16]
Kerwin 2011 6 310 9 318 6.2% 0.68 [0.25 , 1.90]
Mansfield 2017 5 161 3 253 3.6% 2.62 [0.63 , 10.81]
Murphy 2015 5 142 3 72 3.6% 0.85 [0.21 , 3.44]
Nathan 2010 4 191 6 192 4.4% 0.67 [0.19 , 2.34]
Pertseva 2013 0 145 6 292 1.0% 0.15 [0.01 , 2.72]
Peters 2016 46 4201 62 4201 19.2% 0.74 [0.51 , 1.08]
Sher 2017 2 145 2 146 2.0% 1.01 [0.14 , 7.05]
Spector 2012 1 156 0 155 0.8% 2.98 [0.12 , 72.61]
Stirbulov 2012 1 89 0 92 0.8% 3.10 [0.13 , 75.10]
van Zyl-Smit 2020 0 439 0 444 Not estimable
Zangrilli 2011 1 127 4 123 1.6% 0.24 [0.03 , 2.14]
Subtotal (95% CI) 10183 10143 100.0% 0.98 [0.74 , 1.31]
Total events: 169 172
Heterogeneity: Tau² = 0.07; Chi² = 23.95, df = 19 (P = 0.20); I² = 21%
Test for overall effect: Z = 0.12 (P = 0.90)
7.4.5 HD-ICS/LABA vs MD-ICS
Bernstein 2015 3 346 4 347 44.2% 0.75 [0.17 , 3.34]
Mansfield 2017 1 177 3 253 19.3% 0.48 [0.05 , 4.54]
Sher 2017 2 146 2 146 25.9% 1.00 [0.14 , 7.00]
van Zyl-Smit 2020 2 891 0 444 10.6% 2.49 [0.12 , 51.85]
Subtotal (95% CI) 1560 1190 100.0% 0.84 [0.31 , 2.27]
Total events: 8 9
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 3 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.73)
7.4.6 MD-ICS/LABA vs HD-ICS
Mansfield 2017 5 161 2 83 15.4% 1.29 [0.26 , 6.50]
Peters 2008 35 443 7 133 65.0% 1.50 [0.68 , 3.30]
Sher 2017 2 145 0 146 4.4% 5.03 [0.24 , 103.96]
van Zyl-Smit 2020 0 439 0 442 Not estimable
Weinstein 2010 2 233 5 240 15.2% 0.41 [0.08 , 2.10]
Subtotal (95% CI) 1421 1044 100.0% 1.27 [0.67 , 2.40]
Total events: 44 14
Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
7.4.7 HD-ICS/LABA vs HD-ICS
Lin 2015 2 155 2 154 8.9% 0.99 [0.14 , 6.96]
Mansfield 2017 1 177 2 83 5.9% 0.23 [0.02 , 2.55]
O'Byrne 2014 7 197 5 389 26.1% 2.76 [0.89 , 8.60]
Paggiaro 2016b 1 192 1 184 4.4% 0.96 [0.06 , 15.21]



Peters 2008	8	132	7	133	34.7%	1.15 [0.43 , 3.08]
Sher 2017	2	146	0	146	3.7%	5.00 [0.24 , 103.25]
van Zyl-Smit 2020	2	891	0	442	3.7%	2.48 [0.12 , 51.61]
Weinstein 2010	2	255	5	240	12.7%	0.38 [0.07 , 1.92]
Subtotal (95% CI)		**2145**		**1771**	**100.0%**	**1.22 [0.68 , 2.17]**
Total events:	25		22			
Heterogeneity: Tau² = 0.00; Chi² = 6.96, df = 7 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
7.4.8 MD-ICS/LABA vs LD-ICS/LABA						
CHIESI 2009	5	350	7	346	19.8%	0.71 [0.23 , 2.20]
Peters 2016	46	4201	16	1645	80.2%	1.13 [0.64 , 1.98]
Subtotal (95% CI)		**4551**		**1991**	**100.0%**	**1.03 [0.62 , 1.70]**
Total events:	51		23			
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
7.4.9 MD-ICS/LABA vs MD-ICS/LAMA						
Kerstjens 2015a	3	275	12	526	49.7%	0.48 [0.14 , 1.68]
Kerstjens 2015b	7	266	4	510	50.3%	3.36 [0.99 , 11.36]
Subtotal (95% CI)		**541**		**1036**	**100.0%**	**1.27 [0.19 , 8.66]**
Total events:	10		16			
Heterogeneity: Tau² = 1.51; Chi² = 4.79, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 0.25 (P = 0.80)						
7.4.10 HD-ICS/LABA vs MD-ICS/LABA						
Bernstein 2015	3	346	3	346	5.7%	1.00 [0.20 , 4.92]
Kerstjens 2020	38	1236	19	617	49.4%	1.00 [0.58 , 1.72]
Lee 2020	2	406	9	407	6.2%	0.22 [0.05 , 1.02]
Mansfield 2017	1	177	5	161	3.2%	0.18 [0.02 , 1.54]
Peters 2008	8	132	35	443	26.3%	0.77 [0.36 , 1.61]
Sher 2017	2	146	2	145	3.8%	0.99 [0.14 , 6.96]
van Zyl-Smit 2020	2	891	0	439	1.6%	2.47 [0.12 , 51.26]
Weinstein 2010	2	255	2	233	3.8%	0.91 [0.13 , 6.43]
Subtotal (95% CI)		**3589**		**2791**	**100.0%**	**0.81 [0.56 , 1.19]**
Total events:	58		75			
Heterogeneity: Tau² = 0.00; Chi² = 5.92, df = 7 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.29)						
Test for subgroup differences: Chi² = 0.00, df = 9 (P < 0.00001), I² = 0%						

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias