ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

FINAL CENSORED REPORT

Comparative Safety and Effectiveness of Inhaled Corticosteroids and Beta-agonists for Chronic Asthma: A Rapid Review and Network Meta-Analysis

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Executive Summary

Summary

This rapid review and network meta-analysis was conducted to determine the comparative safety and efficacy of inhaled corticosteroids (ICS) and long-acting beta- agonists (LABA) in treating patients 12 years and older with chronic asthma. A network meta-analysis found that adjustable or fixed dose combined ICS+LABA inhalers had the greatest probability of decreasing the risk of moderate to severe exacerbations in patients with chronic asthma. Only 2 randomized controlled trials included in the review reported on symptoms using the Asthma Control Test (ACT) scale; neither study found a clinically relevant change in symptoms. There were no significant differences in the risk of cardiovascular disease or cardiovascular related mortality across all treatment groups.

Implications

Adjustable or fixed dose combined inhalers with low dosage ICS+LABA, medium dosage ICS+LABA, or high dosage ICS+LABA are likely effective in preventing moderate to severe exacerbations in patients with chronic asthma. These inhalers likely do not increase the risk of cardiovascular disease or cardiovascular related mortality. As this is a rapid review, our results should be interpreted with caution.

What is the current practice in treating asthma with long-acting inhaled agents?

- Evidence suggests that combined therapy with inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) for patients with chronic asthma is promising
- However, it is not clear which combinations of therapies are safest and most effective for these patients

Objective

- The objective of this rapid review and network meta-analysis was to determine the comparative safety and efficacy of long-acting inhaled agents (ICS, LABA) for patients with chronic asthma 12 years of age and older

How was the study conducted?

- The protocol (or plan) for the review was developed and revised with input from researchers, clinicians, industry stakeholders, and the Ontario Ministry of Health and Long Term Care
- A librarian in the group identified the literature by searching studies from previous systematic reviews, including eight Cochrane reviews
- The primary outcome of interest was the proportion of patients with moderate to severe exacerbations and secondary outcomes included symptoms (ACT scale), cardiovascular diseases, and cardiovascular-related mortality
- Screening of literature search results was conducted independently by two reviewers, data abstraction was completed by one reviewer and independently verified by a second reviewer
- Bayesian network meta-analysis (NMA) was conducted to synthesize the available evidence

What did the study find?

- 64 parallel randomized controlled trials (RCTs) including four companion reports were identified for inclusion in the review
- Fixed or adjustable dose combined inhalers with low dosage ICS+LABA , medium dosage ICS+LABA , or high dosage ICS+LABA had the greatest probability of decreasing the risk of moderate to severe exacerbations (46 RCTs)
- There were no significant differences in risk of cardiovascular disease (3 RCTs) or cardiovascular related mortality across all treatment groups (6 RCTs)
- An NMA or MA for symptoms could not be completed as only 2 included RCTs reported on this outcome; neither trial reached a clinically relevant important difference on the ACT scale

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Rationale

Evidence from previous systematic reviews and network meta-analyses suggests that therapy with combined inhaled corticosteroids (ICS), and long-acting β agonists (LABA) for patients with chronic asthma is promising (1-8). However, to date, it is not clear which combinations of therapies are safest and most effective for these patients. This rapid review and network meta-analysis was completed to examine this further, and specifically to determine the comparative safety and efficacy of long-acting inhaled agents (in particular, ICS and LABA) for patients with chronic asthma aged 12 years and older.

Methods

Our rapid review protocol was drafted using guidance from the Preferred Reporting Items for Systematic reviews and Meta-analyses for Protocols (PRISMA-P) (9). The protocol was revised based on feedback from various stakeholders, including policy makers from the Ontario Ministry of Health and Long-term care, industry partners, patients, researchers with the ODPRN, and health care professionals.

Eligibility criteria

We included parallel-group randomised clinical trials (RCTs) examining inhaled ICS, LABA, and combinations of these agents. Studies examining these agents in any combination compared with each other, combinations of each other, LTRA, best practice, or placebo in patients 12 years or older with chronic asthma were included. Concomitant asthma medications were included if both groups received the same interventions (e.g., rescue medication with a short-acting beta-agonist). A full list of included agents can be found in Appendix 1. We excluded studies that did not examine long-acting formulations or inhaler formulations of ICS, LABA, and combination ICS/LABA. A full list of the excluded medications can be found in Appendix 2.

The proportion of patients with moderate to severe exacerbations (e.g., worsening of asthma symptoms that may require hospitalization, emergency department visits, treatment with oral steroids and/or antibiotics, use of rescue medication, unscheduled visits) was the primary outcome of interest. Additional outcomes were selected based on feedback from patients with chronic asthma and other stakeholders, including researchers, healthcare providers, and industry partners. We surveyed 11 patients with asthma and asked them to rate the importance of 28 efficacy and safety outcomes that were reported in RCTs of asthma therapies, as outlined in Appendix 3. The patients indicated that myocardial infarction or angina, ischemic heart disease, arrhythmia and bone mineral density were important patient-related adverse events associated with therapy. We considered patient's preferences (Appendix 4) along with input from other stakeholder groups (such as researchers, healthcare providers, industry partners) and came to a consensus regarding the final outcomes that were chosen.

Studies were included if it examined, patients aged 12 years or greater with chronic asthma, relevant intervention and comparators, at least 24 week treatment duration, and any outcomes of interest. Due to time constraints conference abstracts, trial protocols, and non-English studies were not

included thus this report focuses on data from published studies.

Information sources and literature search

An experienced librarian in our group identified the literature by searching included and excluded studies from previous Cochrane reviews (1-8), as well as systematic reviews published by Loyman (10) and van der Mark (11). The results from the literature search were uploaded onto our online screening software (Sythesi.SR) (12).

Study selection process

To ensure reliability, a training exercise was conducted prior to commencing screening. Using the inclusion and exclusion criteria, a random sample of 75 titles and abstracts from the literature search was screened by all team members during the level 1 screening (screening of titles and abstracts). This training exercise was then repeated for the level 2 screening. Subsequently, two reviewers screened citations for inclusion, independently for level 1 and level 2 screening. Conflicts were resolved by discussion or the involvement of a third reviewer (HA and ACT).

Data items and data abstraction process

We abstracted data on study characteristics (e.g., study design, year of conduct, sample size, setting [e.g., multi-center, single center], country of study conduct, duration of treatment, duration of follow-up), patient characteristics (e.g., number of patients, age mean and standard deviation, severity of asthma, asthma duration, history of medication), and the definitions of outcomes (e.g., number of patients experiencing exacerbations). We abstracted data for 4 outcomes for this report based on feedback from our stakeholders; moderate to severe asthma exacerbations [main efficacy outcome] and symptoms based on the Asthma Control Test (ACT) (13) [secondary efficacy outcome] and cardiovascular-related mortality, and cardiovascular diseases for the safety outcomes. We abstracted the outcome results (e.g. number of patients with exacerbations) for the longest duration of follow-up only, as this is the most conservative approach (14). Prior to data abstraction, we completed a calibration exercise of the data abstraction form on a random sample of 5 articles. Subsequently, all of the included studies were abstracted by a single reviewer and a random sample of the data was verified by another team member (EL).

Synthesis of included studies

Study and patient characteristics were summarised descriptively. All outcomes presented here are dichotomous and the odds ratios (OR) were calculated, with the exception of symptoms (as per the ACT), for which NMA and MA was not possible. Clinical, methodological, and statistical heterogeneity was assessed for each pairwise comparison. We assessed statistical heterogeneity using the I^2 statistic, which measures the percentage of variability that cannot be attributed to random error alone (15). Bayesian meta-analysis was analyzed in Winbugs (16) and the R statistical software (17). When statistical heterogeneity was observed (e.g., I^2 >50%), the random effects model was used.

We performed Bayesian network meta-analysis to synthesise the available evidence from the network of trials for the outcomes considered. Treatments were grouped into nodes based on input

from clinicians, methodologists, and statisticians on the team. Markov Chain Monte Carlo (MCMC) method using non-informative prior was used and a simulation of 5,000 burn-in iterations and a further 20,000 iterations was performed to estimate model parameters. Model convergence was assessed using trace and history plots, as well as the Gelman Rubin statistic.

ORs and 95% credible intervals (CrIs) were calculated. In order to put our results into context, we also calculated the number needed to treat (NNT) or number needed to harm (NNH) for statistically significant results. The NNT and NNH were calculated from the ORs using the following formula:

For OR <1: NNT = (1-[PEER*(1-OR)]) / ([1-PEER]*[PEER]*[1-OR])

For OR >1: NNH = ([PEER*(OR-1)]+1) / [PEER*(OR-1)*(1-PEER)]

where, for a given outcome, PEER represents Patient Expected Event Rate and is calculated as ratio of total number of events across all placebo arms and total sample size across all placebo arms.

To assess the consistency assumption in certain parts of the network, we used the loop-specific method (also known as the node-splitting method) (18, 19). We estimated the ranking probabilities for all treatments and presented this using rankograms, which are used to plot the ranking probabilities for each treatment. A treatment hierarchy was also obtained using the surface under the cumulative ranking curve (SUCRA) (20). All network meta-analysis was done using Winbugs and the R statistical software.

Results

Literature search

The literature search yielded a total of 824 titles and abstracts (Figure 1). Of these, 373 articles were potentially relevant and their full-text was reviewed. Subsequently, 64 parallel RCTs including 4 companion reports fulfilled our eligibility criteria and were included. The list of 64 articles included RCTs can be found in Appendix 5.

Study and patient characteristics

The year of publication ranged from 1994 to 2013 (Appendix 6). All of the RCTs were multi-center, conducted across numerous countries, with the exception of one study. The number of patients included per trial ranged from 44 to 8,424. The duration of treatment with long-acting inhaled agents ranged from 24 weeks to 2 years. The age of included patients ranged from 12 to 80 years and the percent females ranged from 40.2% to 69.6% (Appendix 7).

Primary efficacy outcome

Moderate to severe exacerbations

Fifty-nine RCTs reported on exacerbations but the data was not included for 13 of these studies because they did not specify the type of exacerbation or were mild exacerbations (n=10), examined the

same treatment in all treatment groups (n=2) or reported 0 events in all treatment arms (n=1). Therefore, 46 RCTs with 19 different treatment nodes reported on moderate to severe exacerbations including 35,012 patients were included in NMA (Appendix 8). There was no statistical inconsistency between the direct MA and NMA results so the text focuses on the NMA results. A total of 190 treatment comparisons were made in our NMA, and 26 were statistically significant (see below). Results for all treatment comparisons can be found in Tables 1, 2 and 3.

Lower dosage of ICS versus all comparators

ICS low dosage vs. ICS medium dosage + LABA

ICS low dosage alone increased the risk of exacerbation compared to ICS medium dosage and LABA therapy (NNH 4).

ICS low dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage

ICS low dosage alone increased the risk of exacerbation compared to fixed low dosage ICS and LABA in one inhaler (NNH 5).

ICS low dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage

ICS low dosage alone increased the risk of exacerbation compared to fixed medium dosage ICS and LABA in one inhaler (NNH 5).

ICS low dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage

ICS low dosage alone increased the risk of exacerbation compared to fixed high dosage ICS and LABA in one inhaler (NNH 4).

Medium dosage of ICS versus all comparators

ICS medium dosage vs. ICS medium dosage + LABA

Medium ICS dosage alone increased the risk of exacerbation compared to ICS medium dosage and LABA therapy (NNH 4).

ICS medium dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage

Medium ICS dosage alone increased the risk of exacerbation compared to fixed medium dosage ICS and LABA in one inhaler (NNH 5).

ICS medium dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage

Medium ICS dosage alone increased the risk of exacerbation compared to fixed high dosage ICS and LABA in one inhaler (NNH 4).

Higher dosage of ICS versus all comparators

ICS high dosage vs. Placebo

High ICS dosage decreased the risk of exacerbation compared to placebo (NNT 5).

LABA versus all comparators

LABA vs. ICS low dosage + LABA

LABA increased the risk of exacerbation compared to ICS low dosage and LABA therapy (NNH 3).

LABA vs. ICS medium dosage + LABA

LABA increased the risk of exacerbation compared to ICS medium dosage and LABA therapy (NNH 3).

LABA vs. ICS + LABA Combined in one inhaler, Fixed low dosage

LABA increased the risk of exacerbation compared to fixed low dosage ICS and LABA in one inhaler (NNH 3).

LABA vs. ICS + LABA Combined in one inhaler, Fixed medium dosage

LABA increased the risk of exacerbation compared to fixed medium dosage ICS and LABA in one inhaler (NNH 3).

LABA vs. ICS + LABA Combined in one inhaler, Fixed high dosage

LABA increased the risk of exacerbation compared to fixed high dosage ICS and LABA in one inhaler (NNH 3).

LABA vs. ICS + LABA Combined in one inhaler, Adjustable low dosage

LABA increased the risk of exacerbation compared to adjustable low dosage ICS and LABA in one inhaler (NNH 2).

LABA vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage

LABA increased the risk of exacerbation to adjustable medium dosage ICS and LABA in one inhaler (NNH 3).

LABA vs. ICS + LABA Combined in one inhaler, Adjustable high dosage

LABA increased the risk of exacerbation to adjustable high dosage ICS and LABA in one inhaler (NNH 3).

Lower dosage of ICS + LABA versus all comparators

ICS low dosage + LABA vs. Placebo

Low ICS dosage plus LABA decreased the risk of exacerbation compared to placebo (NNT 4).

Medium dosage of ICS + LABA versus all comparators

ICS medium dosage + LABA vs. Placebo

Medium ICS dosage plus LABA decreased the risk of exacerbation compared to placebo (NNT 3).

ICS medium dosage + LABA vs. LTRA

Medium ICS dosage plus LABA decreased the risk of exacerbation compared to LTRA (NNT 4).

Higher dosage of ICS + LABA versus all comparators

No statistically significant differences were observed for high dosage ICS plus LABA versus all comparators.

Combined ICS + LABA in one inhaler, Fixed low dosage versus all comparators

ICS + LABA Combined in one inhaler, Fixed low dosage vs. Placebo

Fixed low dosage ICS and LABA in one inhaler decreased the risk of exacerbation compared to placebo (NNT 3).

Combined ICS + LABA in one inhaler, Fixed medium dosage versus all comparators

ICS + LABA Combined in one inhaler, Fixed medium dosage vs. Placebo

Fixed medium dosage ICS and LABA in one inhaler decreased the risk of exacerbation compared to placebo (NNT 3).

Combined ICS + LABA in one inhaler, Fixed high dosage versus all comparators

ICS + LABA Combined in one inhaler, Fixed high dosage vs. Placebo

Fixed high dosage ICS and LABA in one inhaler decreased the risk of exacerbation compared to placebo (NNT 3).

ICS + LABA Combined in one inhaler, Fixed high dosage vs. LTRA

Fixed high dosage ICS and LABA in one inhaler decreased the risk of exacerbation compared to LTRA (NNT 4).

Combined ICS + LABA in one inhaler, Adjustable low dosage versus all comparators

ICS + LABA Combined in one inhaler, Adjustable low dosage vs. Placebo

Adjustable low dosage ICS and LABA in one inhaler decreased the risk of exacerbation compared to placebo (NNT 3).

Combined ICS + LABA in one inhaler, Adjustable medium dosage versus all comparators

ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. Placebo

Adjustable medium dosage ICS and LABA in one inhaler decreased the risk of exacerbation compared to placebo (NNT 3).

Combined ICS + LABA in one inhaler, Adjustable high dosage versus all comparators

ICS + LABA Combined in one inhaler, Adjustable high dosage vs. Placebo

Adjustable high dosage ICS and LABA in one inhaler decreased the risk of exacerbation compared to placebo (NNT 4).

Combined ICS + LABA in one inhaler, Maintenance medium dosage versus all comparators

No statistically significant differences were observed for maintenance medium dosage for combined ICS plus LABA in one inhaler versus all comparators.

Combined ICS + LABA in one inhaler, Maintenance medium dosage + LABA versus all

No statistically significant differences were observed for maintenance medium dosage for combined ICS plus LABA in one inhaler plus LABA versus all comparators

Results of our ranking analysis

Our ranking analysis was based on statistically calculating the rankograms and surface under the cumulative ranking curve. We found that the following inhalers had the greatest probability of being the most effective regarding exacerbations overall: low dosage of ICS plus LABA combined in one inhaler, adjustable dosage (82% probability of being the best), high dosage ICS plus LABA combined in one inhaler, fixed dosage (78% probability of being the best), medium dosage of ICS plus LABA combined in one inhaler, adjustable dosage (71% probability of being the best), medium dosage ICS plus LABA combined in one inhaler, fixed dosage (70% probability of being the best), low dosage ICS plus LABA in one inhaler, and fixed dosage (69% probability of being the best). Table 2 shows the probability of interventions that are most efficacious in the moderate to severe exacerbations network meta-analysis.

Secondary efficacy outcome

Symptoms

Two RCTs reported on symptoms assessed using the ACT scale. The first included 621 patients and found that patients receiving Fluticasone/Salmeterol (250/50 µg) had a mean change of 4.5 on the ACT (no measure of variance was reported) versus those receiving Fluticasone (250 µg) alone who experienced a mean change of 3.5 on the ACT after 52 weeks of follow-up. The second RCT included 628 patients and found that those receiving fixed dosage ICS medium plus LABA in one inhaler had a mean difference of -0.8 (95% confidence interval of -1.51 to -0.09) demonstrating a significant reduction of symptoms compared to ICS medium alone after 52 weeks of follow-up (table 3).

Secondary safety outcomes

Cardiovascular diseases

Seven RCTs reported on cardiovascular diseases but 2 were excluded because they reported 0 events across all treatment arms and another 2 were excluded because the treatment was not connected to the network. Therefore, 3 RCTs with 5 different treatment nodes including 1,527 patients were included in an NMA on cardiovascular diseases. Across the 5 treatment comparisons, nothing was statistically significant. See Appendix 9 for a list of studies that reported cardiovascular diseases as an adverse event.

Cardiovascular-related mortality

Twenty-four RCTs reported on cardiovascular-related mortality but 16 were excluded because they reported 0 events across all treatment arms and another 2 RCTs were excluded because the treatment was not connected to the network (Appendix 10). A NMA was attempted with 6 RCTs but the results were not reliable so we were only able to conduct a meta-analysis comparing ICS versus fixed dosage ICS plus LABA combined in one inhaler; the results were not statistically significant. See Appendix 10 for a list of studies that reported cardiovascular-related mortality adverse events.

Discussion

We found that low dosage of ICS plus LABA combined in one inhaler (adjustable dosage), high dosage ICS plus LABA combined in one inhaler (fixed dosage), medium dosage of ICS plus LABA combined in one inhaler (adjustable), medium dosage ICS plus LABA combined in one inhaler (fixed dosage), and low dosage ICS plus LABA in one inhaler (fixed dosage) as having the largest probability of being the most effective for decreasing risk of moderate to severe exacerbation in patients with chronic asthma. Other long-acting inhaler agents that were used as comparisons included ICS, LTRA and LABAs (either alone or in combination). The NMA was consistent overall and didn't show evidence of statistical inconsistency between direct and indirect evidence.

Some of our results should be interpreted with caution because **few studies** contributed head-to-head data to the treatment comparisons. Examples for the exacerbation outcome include the results for ICS low dosage vs. ICS high dosage plus LABA and ICS medium dosage vs. ICS plus LABA Combined in one inhaler using a fixed low dosage for which no direct evidence was included. Similarly, some of the treatments only had 1 trial providing data, such as the results for high dosage ICS plus LABA in separate inhalers, medium dosage combination ICS plus LABA in one inhaler, maintenance therapy, and medium dosage combination ICS plus LABA in one inhaler plus LABA (Appendix 12).

Our results are similar to the previous NMA published by Loyman and colleagues, who found that combined ICS and LABA in one inhaler as maintenance treatment and fixed dosage ICS and LABA combined in one inhaler had the greatest probability of being the most effective for exacerbations. However, we included fewer studies because we focused on moderate to severe exacerbations, excluded studies with 0 events in all treatment arms, excluded studies with the same treatment administered in all arms, and excluded studies comparing a long-acting inhaler to a SABA on its own. As well, we classified maintenance, fixed, and adjustable therapy in a slightly different manner than Loyman et al., due to clinician input from team members (Appendix 11). This is likely why our results are slightly different.

We also analyzed cardiovascular disease and cardiovascular-related mortality and found no statistically significant differences in NMA. We were unable to conduct a NMA or MA for symptoms as per the ACT, due to only identifying 2 studies for inclusion on this outcome. However, neither study reached the clinically relevant important difference on the ACT.

The results of our rapid review must be interpreted with caution for several reasons. First, because of the tight timelines, we were only able to include published literature. This is a very common practice when conducting a rapid review. As such, the results for treatments with many trials included in the network will likely be more stable than those for treatments with fewer studies, which is usually the case for newer drugs. Second, because of the limited timelines we were unable to appraise the risk of bias of the included RCTs so are unsure whether our results are influenced by a high risk of bias. Third, as this is a rapid review, we were unable to conduct meta-regression analyses to determine the impact of important effect modifiers, such as duration of treatment administration, and definition of outcomes.

Fourth, we were unable to conduct a specific drug review and were forced to conduct a drug class review due to the dearth of the included studies.

Key messages:

- For patients with chronic asthma aged 12 years or greater, low dosage of ICS plus LABA combined in one inhaler (adjustable or fixed), medium dosage ICS plus LABA combined in one inhaler (adjustable or fixed), high dosage of ICS plus LABA combined in one inhaler (adjustable or fixed), as having the largest probability of being the most effective for decreasing risk of moderate to severe exacerbations.
- No conclusions can be made on symptom control as per the ACT, due to a lack of data.
- There were no significant differences in risk of cardiovascular disease across the compared agents.
- There were no significant differences in risk of cardiovascular-related mortality across the compared agents.

Our results should be interpreted with caution, as our review was conducted in a very short period of time.

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Exhibits:

Exhibit 1: Study Flow

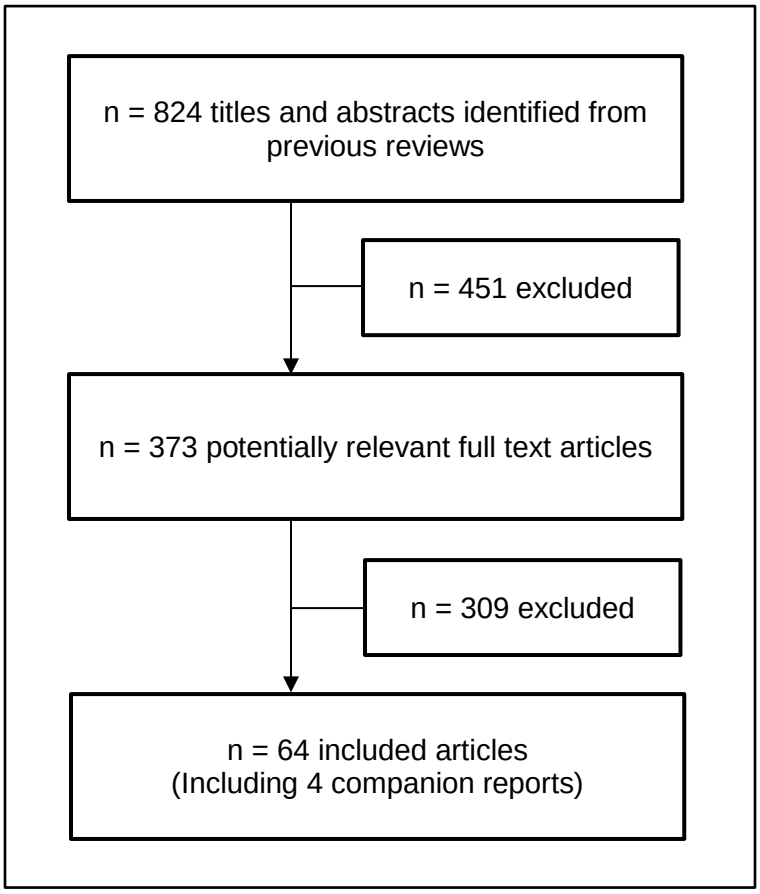

Exhibit 2: Results of network meta-analysis by outcome

Treatment comparison	Exacerbations	CVD
Placebo versus all comparators		
Placebo vs. Best Practice	NS	NS
Placebo vs. LTRA	NS	NS
Placebo vs. LABA	NS	NS
Placebo vs. ICS low dosage	NS	NS
Placebo vs. ICS low dosage + LTRA	NS	NS
Placebo vs. ICS medium dosage	NS	NS
Placebo vs. ICS high dosage	NNH: 4	NS
Placebo vs. ICS low dosage + LABA	NNH: 4	NS
Placebo vs. ICS medium dosage + LABA	NNH: 3	NS
Placebo vs. ICS high dosage + LABA	NS	NS
Placebo vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NNH: 3	NS
Placebo vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NNH: 3	NS
Placebo vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NNH: 3	NS
Placebo vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NNH: 2	NS
Placebo vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NNH: 3	NS

Treatment comparison	Exacerbations	CVD
Placebo vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NNH: 3	NS
Placebo vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
Placebo vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Best Practice versus all comparators		
Best Practice vs. Placebo	NS	NS
Best Practice vs. LTRA	NS	NS
Best Practice vs. LABA	NS	NS
Best Practice vs. ICS low dosage	NS	NS
Best Practice vs. ICS low dosage + LTRA	NS	NS
Best Practice vs. ICS medium dosage	NS	NS
Best Practice vs. ICS high dosage	NS	NS
Best Practice vs. ICS low dosage + LABA	NS	NS
Best Practice vs. ICS medium dosage + LABA	NS	NS
Best Practice vs. ICS high dosage + LABA	NS	NS
Best Practice vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
Best Practice vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
Best Practice vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS

Treatment comparison	Exacerbations	CVD
Best Practice vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
Best Practice vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
Best Practice vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
Best Practice vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
Best Practice vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
LTRA versus all comparators		
LTRA vs. Placebo	NS	NS
LTRA vs. Best Practice	NS	NS
LTRA vs. LABA	NNH: 3	NS
LTRA vs. ICS low dosage	NS	NS
LTRA vs. ICS low dosage + LTRA	NS	NS
LTRA vs. ICS medium dosage	NS	NS
LTRA vs. ICS high dosage	NS	NS
LTRA vs. ICS low dosage + LABA	NS	NS
LTRA vs. ICS medium dosage + LABA	NS	NS
LTRA vs. ICS high dosage + LABA	NS	NS
LTRA vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
LTRA vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS

Treatment comparison	Exacerbations	CVD
LTRA vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NNH: 3	NS
LTRA vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
LTRA vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
LTRA vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
LTRA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
LTRA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
LABA versus all comparators		
LABA vs. Placebo	NS	NS
LABA vs. Best Practice	NS	NS
LABA vs. LTRA	NS	NS
LABA vs. ICS low dosage	NS	NS
LABA vs. ICS low dosage + LTRA	NS	NS
LABA vs. ICS medium dosage	NS	NS
LABA vs. ICS high dosage	NS	NS
LABA vs. ICS low dosage + LABA	NNH:3	NS
LABA vs. ICS medium dosage + LABA	NNH: 3	NS
LABA vs. ICS high dosage + LABA	NS	NS
LABA vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NNH: 3	NS
LABA vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NNH: 3	NS

Treatment comparison	Exacerbations	CVD
LABA vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NNH: 3	NS
LABA vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NNH: 2	NS
LABA vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NNH: 3	NS
LABA vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NNH: 3	NS
LABA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
LABA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Lower dosage of ICS versus all comparators		
ICS low dosage vs. Placebo	NS	NS
ICS low dosage vs. Best Practice	NS	NS
ICS low dosage vs. LTRA	NS	NS
ICS low dosage vs. LABA	NS	NS
ICS low dosage vs. ICS low dosage + LTRA	NS	NS
ICS low dosage vs. ICS medium dosage	NS	NS
ICS low dosage vs. ICS high dosage	NS	NS
ICS low dosage vs. ICS low dosage + LABA	NS	NS
ICS low dosage vs. ICS medium dosage + LABA	NNH:4	NS
ICS low dosage vs. ICS high dosage + LABA	NS	NS
ICS low dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NNH:5	NS

Treatment comparison	Exacerbations	CVD
ICS low dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NNH:5	NS
ICS low dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NNH:4	NS
ICS low dosage vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS low dosage vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS low dosage vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS low dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS low dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Lower dosage of ICS + LTRA versus all comparators		
ICS low dosage + LTRA vs. Placebo	NS	NS
ICS low dosage + LTRA vs. Best Practice	NS	NS
ICS low dosage + LTRA vs. LTRA	NS	NS
ICS low dosage + LTRA vs. LABA	NS	NS
ICS low dosage + LTRA vs. ICS low dosage + LTRA	NS	NS
ICS low dosage + LTRA vs. ICS medium dosage	NS	NS
ICS low dosage + LTRA vs. ICS high dosage	NS	NS
ICS low dosage + LTRA vs. ICS low dosage + LABA	NS	NS

Treatment comparison	Exacerbations	CVD
ICS low dosage + LTRA vs. ICS medium dosage + LABA	NS	NS
ICS low dosage + LTRA vs. ICS high dosage + LABA	NS	NS
ICS low dosage + LTRA vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS low dosage + LTRA vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS low dosage + LTRA vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS low dosage + LTRA vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS low dosage + LTRA vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS low dosage + LTRA vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS low dosage + LTRA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS low dosage + LTRA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Medium dosage of ICS versus all comparators		
ICS medium dosage vs. Placebo	NS	NS
ICS medium dosage vs. Best Practice	NS	NS
ICS medium dosage vs. LTRA	NS	NS
ICS medium dosage vs. LABA	NS	NS
ICS medium dosage vs. ICS low dosage	NS	NS

Treatment comparison	Exacerbations	CVD
ICS medium dosage vs. ICS low dosage + LTRA	NS	NS
ICS medium dosage vs. ICS high dosage	NS	NS
ICS medium dosage vs. ICS low dosage + LABA	NS	NS
ICS medium dosage vs. ICS medium dosage + LABA	NNH: 4	NS
ICS medium dosage vs. ICS high dosage + LABA	NS	NS
ICS medium dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS medium dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NNH: 5	NS
ICS medium dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NNH: 4	NS
ICS medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS medium dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS medium dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Higher dosage of ICS versus all comparators		
ICS high dosage vs. Placebo	NNT:5	NS
ICS high dosage vs. Best Practice	NS	NS

Treatment comparison	Exacerbations	CVD
ICS high dosage vs. LTRA	NS	NS
ICS high dosage vs. LABA	NS	NS
ICS high dosage vs. ICS low dosage	NS	NS
ICS high dosage vs. ICS low dosage + LTRA	NS	NS
ICS high dosage vs. ICS medium dosage	NS	NS
ICS high dosage vs. ICS low dosage + LABA	NS	NS
ICS high dosage vs. ICS medium dosage + LABA	NS	NS
ICS high dosage vs. ICS high dosage + LABA	NS	NS
ICS high dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS high dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS high dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS high dosage vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS high dosage vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS high dosage vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS high dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS high dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS

Treatment comparison	Exacerbations	CVD
Lower dosage of ICS + LABA versus all comparators		
ICS low dosage + LABA vs. Placebo	NNT: 4	NS
ICS low dosage + LABA vs. Best Practice	NS	NS
ICS low dosage + LABA vs. LTRA	NS	NS
ICS low dosage + LABA vs. LABA	NNT: 4	NS
ICS low dosage + LABA vs. ICS low dosage	NS	NS
ICS low dosage + LABA vs. ICS low dosage + LTRA	NS	NS
ICS low dosage + LABA vs. ICS medium dosage	NS	NS
ICS low dosage + LABA vs. ICS high dosage	NS	NS
ICS low dosage + LABA vs. ICS medium dosage + LABA	NS	NS
ICS low dosage + LABA vs. ICS high dosage + LABA	NS	NS
ICS low dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS low dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS low dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS low dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS low dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS low dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS

Treatment comparison	Exacerbations	CVD
ICS low dosage + LABA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS low dosage + LABA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Medium dosage of ICS + LABA versus all comparators		
ICS medium dosage + LABA vs. Placebo	NNT: 3	NS
ICS medium dosage + LABA vs. Best Practice	NS	NS
ICS medium dosage + LABA vs. LTRA	NNT: 4	NS
ICS medium dosage + LABA vs. LABA	NNT: 3	NS
ICS medium dosage + LABA vs. ICS low dosage	NNT: 5	NS
ICS medium dosage + LABA vs. ICS low dosage + LTRA	NS	NS
ICS medium dosage + LABA vs. ICS medium dosage	NNT: 5	NS
ICS medium dosage + LABA vs. ICS high dosage	NS	NS
ICS medium dosage + LABA vs. ICS low dosage + LABA	NS	NS
ICS medium dosage + LABA vs. ICS high dosage + LABA	NS	NS
ICS medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS

Treatment comparison	Exacerbations	CVD
ICS medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Higher dosage of ICS + LABA versus all comparators		
ICS high dosage + LABA vs. Placebo	NS	NS
ICS high dosage + LABA vs. Best Practice	NS	NS
ICS high dosage + LABA vs. LTRA	NS	NS
ICS high dosage + LABA vs. LABA	NS	NS
ICS high dosage + LABA vs. ICS low dosage	NS	NS
ICS high dosage + LABA vs. ICS low dosage + LTRA	NS	NS
ICS high dosage + LABA vs. ICS medium dosage	NS	NS
ICS high dosage + LABA vs. ICS high dosage	NS	NS
ICS high dosage + LABA vs. ICS low dosage + LABA	NS	NS
ICS high dosage + LABA vs. ICS medium dosage + LABA	NS	NS
ICS high dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS high dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS

Treatment comparison	Exacerbations	CVD
ICS high dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS high dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS high dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS high dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS high dosage + LABA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS high dosage + LABA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Combined ICS + LABA in one inhaler, Fixed low dosage versus all comparators		
ICS + LABA Combined in one inhaler, Fixed low dosage vs. Placebo	NNT:3	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. Best Practice	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. LTRA	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. LABA	NNT:3	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS low dosage	NNT: 5	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS low dosage + LTRA	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS high dosage	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS low dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS medium dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS high dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed low dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Combined ICS + LABA in one inhaler, Fixed medium dosage versus all comparators		
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. Placebo	NNT: 3	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. Best Practice	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. LTRA	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. LABA	NNT: 3	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS low dosage	NNT: 5	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS low dosage + LTRA	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS medium dosage	NNT: 6	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS high dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS low dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS medium dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS high dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed medium dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Combined ICS + LABA in one inhaler, Fixed high dosage versus all comparators		
ICS + LABA Combined in one inhaler, Fixed high dosage vs. Placebo	NNT: 3	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. Best Practice	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. LTRA	NNT: 4	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. LABA	NNT: 3	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS low dosage	NNT: 4	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS low dosage + LTRA	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS medium dosage	NNT: 5	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS high dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS low dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS medium dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS high dosage + LABA	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Fixed high dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Combined ICS + LABA in one inhaler, Adjustable low dosage versus all comparators		
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. Placebo	NNT:3	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. Best Practice	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. LTRA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. LABA	NNT:3	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS low dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS low dosage + LTRA	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS high dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS low dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS medium dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS high dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable low dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Combined ICS + LABA in one inhaler, Adjustable medium dosage versus all comparators		

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. Placebo	NNT:3	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. Best Practice	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. LTRA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. LABA	NNT:3	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS low dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS low dosage + LTRA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS high dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS low dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS medium dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS high dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable medium dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Combined ICS + LABA in one inhaler, Adjustable high dosage versus all comparators		
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. Placebo	NNT: 4	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. Best Practice	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. LTRA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. LABA	NNT: 4	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS low dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS low dosage + LTRA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS high dosage	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS low dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS medium dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS high dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Adjustable high dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Combined ICS + LABA in one inhaler, Maintenance medium dosage versus all comparators		
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. Placebo	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. Best Practice	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. LTRA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. LABA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS low dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS low dosage + LTRA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS high dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS low dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS medium dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS high dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA	NS	NS
Combined ICS + LABA in one inhaler, Maintenance medium dosage + LABA versus all comparators		
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. Placebo	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. Best Practice	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. LTRA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. LABA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS low dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS low dosage + LTRA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS high dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS low dosage + LABA	NS	NS

Treatment comparison	Exacerbations	CVD
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS medium dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS high dosage + LABA	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed low dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Fixed high dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable low dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable medium dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Adjustable high dosage	NS	NS
ICS + LABA Combined in one inhaler, Maintenance medium dosage + LABA vs. ICS + LABA Combined in one inhaler, Maintenance medium dosage	NS	NS

Exhibit 3: Probability that each intervention is the most efficacious intervention in the moderate to severe exacerbations network meta-analysis

Intervention	Probability best intervention
Low dosage of ICS plus LABA combined in one inhaler, adjustable dosage	82%
High dosage ICS plus LABA combined in one inhaler, fixed dosage	78%
Medium dosage of ICS plus LABA combined in one inhaler, adjustable dosage	71%
Medium dosage ICS plus LABA combined in one inhaler, fixed dosage	70%
Low dosage ICS plus LABA in one inhaler, fixed dosage	69%

Exhibit 4: Results of Meta-analysis for risk of exacerbation

Intervention	Comparison	NNT
ICS + LABA Combined in one inhaler, Fixed dosage		
Low dosage ICS + LABA combined in one inhaler, Fixed dosage	Placebo	3
Medium dosage ICS + LABA combined in one inhaler, Fixed dosage	Medium dosage ICS	9

Exhibit 5: Results of Point Estimate of Symptoms

Intervention	Comparison	NNT
ICS + LABA Combined in one inhaler, Fixed dosage		
ICS + LABA Combined in one inhaler, Fixed dosage	ICS	Not applicable (no meta-analysis conducted)

Appendix 1: Medications included in the rapid review

Generic name(s)*	Trade name(s)*
Inhaled corticosteroids (ICS)	
beclomethasone	QVAR, Clenil
budesonide	Pulmicort
fluticasone or GW685698	Flovent, FloventDiskus, Flixotide
mometasone	Asmanex Twisthaler
ciclesonide	Alvesco
Inhaled long-acting beta$_2$-agonists (LABA)	
formoterol or eformoterol	Foradil, Oxeze, Oxis
indacaterol	Arcapta
olodaterol	Striverdi
salmeterol	Serevent, Serevent Diskus
vilanterol or GW642444	
Combo LABA plus ICS in one inhaler**	
budesonide/ formoterol	Symbicort
mometasone /formoterol	Zenhale
fluticasone/salmeterol	Advair, AdvairDiskus, Seretide
fluticasone/ vilanterol	BreoEllipta

Note: *This is not an exhausitve list. **Combination therapy could also be given in multiple inhalers.

Appendix 2: Medications excluded in the rapid review

Generic name(s)*	Trade name(s)*
Long-acting beta$_2$-agonists (LABA) in nebulizer and transdermal form	
formoterol (when in nebulizer form)	
arformoterol	
tulobuterol	
Inhaled corticosteroids (ICS) in nebulizer form	
beclomethasone (when in nebulizer form)	
budesonide (when in nebulizer form)	
We will exclude ALL of the following agents:	
Short-acting beta2-agonists (SABA) (inhaled, nebulizer, oral, injection)†	
fenoterol	
levosalbutamol or levalbuterol	Xopenex
salbutamol or albuterol	Ventolin
terbutaline	Bricanyl
Short-acting muscarinic anticholinergics (SAMA) (inhaler, nebulizer)	
ipratropium bromide	Combivent, Atrovent
oxitropium bromide	
Combo SABA plus anticholinergic in one inhaler (inhaler, nebulizer)	
fenoterol/ipratropium	
salbutamol/ipratropium	
Methylxanthines (oral, injection)	
aminophylline	
theophylline	
Systemic corticosteroids (oral)	
prednisone	
methyl-prednisolone	
Phosphodiesterase-4 (PDE4) inhibitors (oral)	
roflumilast	
Inhaled long-acting muscarinic anticholinergics (LAMA)	
aclidinium bromide	Tudorza Genuai
glycopyrronium bromide	Seebri
tiotropium bromide	Spiriva
umeclidinium bromide or GSK573719	
Combo LAMA plus LABA in one inhaler (MABA)	
GSK961081 (formerly TD5959)	

Note: *This is not an exhaustive list.

† Although SABAs were excluded as drug comparators, they may have been used as rescue medications.

Appendix 3: All efficacy and safety outcomes considered

Efficacy outcomes

1. Proportion of patients with exacerbations (primary outcome of interest)
2. Number of hospitalizations (overall and due to exacerbations)
3. Number of emergency room visits (overall and due to exacerbations)
4. Number of corticosteroids use (overall and due to exacerbation)
5. Number of awakening (overall and due to exacerbation)
6. Number of change of medication (overall and due to exacerbation)
7. Number of rescue medication (overall and due to exacerbation)
8. Number of unscheduled visits (overall and due to exacerbation)
9. Symptoms (measured via Asthma Control Test)

Safety outcomes

Deaths due to cardiovascular diseases outcomes:

1. Acute cardiac failure
2. Aortic aneurysm
3. Cardiac arrest
4. Cardiac arrest due to arrhythmia
5. Cardiac arrhythmia due to cardiomegaly
6. Cardiac deaths
7. Cardiac disorders
8. Cardiopulmonary failure
9. Cardiorespiratory arrest
10. Cardiovascular causes.
11. Circulatory collapse
12. Congestive heart failure
13. Congestive heart failure (CHF)
14. Death due to cardiovascular disease
15. Myocardial infarction (MI)
16. Ruptured aortic aneurysm
17. Stroke
18. Sudden cardiac/cardiovascular death

Cardiovascular disease outcomes:

1. Acute cardiac failure
2. Angina
3. Aortic aneurysm
4. Cardiac disorders
5. Cardiac/Cardiopulmonary failure
6. Cardiac/Cardiorespiratory arrest
7. Chest Pain

8. Circulatory collapse
9. Congestive heart failure (CHF)
10. Coronary heart disease
11. Heart decompensation
12. Heart failure
13. Ischemic heart disease
14. Myocardial failure
15. Myocardial infarction (MI)
16. Myocardial ischemia
17. Ruptured aortic aneurysm
18. Stroke

Appendix 4: Patient ratings of relevant outcomes

TOP 4 - MOST important effectiveness outcomes:

1. Help reduce the amount of limitations put on my physical activity (8/11 rated this outcome in their top 4)
2. Improve my quality of life (6/11 rated this outcome in their top 4)
3. Decrease the frequency of symptoms experienced during such as coughing, wheezing, chest tightness, or shortness of breath (6/11 rated this outcome in their top 4)
4. Decrease the severity of my asthma (5/11 rated this outcome in their top 4)

TOP 4 - LEAST important effectiveness outcomes:

1. Improve my scores on asthma symptom scales, which are used to measure my overall asthma symptoms e.g., 30 second asthma control test, Juniper's Asthma Control Questionnaire (9/11 rated this in their bottom 4)
2. Improve my forced expiratory volume (FEV1), which is the volume of air that can be forced out when taking a deep breath (8/11 rated this in their bottom 4)
3. Improve my peak expiratory flow, which is the volume of air you breathe when you exhale (7/11 rated this in their bottom 4)
4. Reduce work or school absenteeism related to my asthma (6/11 rated this in their bottom 4)

TOP 4 - MOST important safety/side effects:

1. Heart attack or chest pain (9/11 rated this outcome in their top 4)
2. Ischemic heart disease (4/11 rated this outcome in their top 4)
3. Arrhythmia (3/11 rated this outcome in their top 4)
4. Bone mineral density (1/11 rated this outcome in their top 4)

TOP 4 - LEAST important safety/side effects:

1. Slowed growth in children (7/11 rated this in their bottom 4)
2. Cataracts(5/11 rated this in their bottom 4)
3. Dry mouth (5/11 rated this in their bottom 4)
4. Dyspnea (4/11 rated this in their bottom 4)

Appendix 5: List of included studies

1. Aalbers R. Fixed or adjustable maintenance-dose budesonide/formoterol compared with fixed maintenance-dose salmeterol/fluticasone propionate in asthma patients aged >or=16 years: post hoc analysis of a randomized, double-blind/open-label extension, parallel-group study. Clin Drug Investig. 2010;30(7):439-51.
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Appendix 6: Study Characteristics

Study	Country of conduct	Study design	Study period	Setting	Sample size	Treatment duration (weeks)	Intervention	Outcomes
Aalbers R, 2004 (CR: Aalbers R, 2010)	Denmark, Finland, Germany, Norway, Sweden, and The Netherlands	parallel RCT - double dummy	2001-2002	Multi-center	658	26	BUD/FM (160 µg/4.5µg 2X bid) vs. BUD/FM (160 µg/4.5µg 2X bid) vs. FP/SM (250 µg/ 50µg 1X bid)	Exacerbation
Aubier M, 1999	France	parallel RCT - double dummy	NR	Multi-center	503	28	SM/FP (50/500 µg) + Placebo vs. SM (50 µg) + FP (500 µg) vs. FP (500 µg) + Placebo	Exacerbation
Aubier M, 2010	France	parallel RCT	2007 - 2008	Multi-center	8424	26	BUD/FM (160/4.5 µg 1X bid) + BUD/FM (160/4.5 µg p.r.n.) vs. BUD/FM (160/4.5 µg 2X bid) + BUD/FM (160/4.5 µg p.r.n.)	Exacerbation, Mortality, CVD
Bailey W, 2008	USA	parallel RCT	NR	Multi-center	475	52	FP/SM (100/50 µg 1X bid) vs. FP (100 µg 1X bid) vs. FP (500 µg) + Placebo	Exacerbation, Mortality
Bateman E, 2004 (CR: Bousquet J, 2004)	UK	parallel RCT	NR	Multi-center	3416	52	FP (100 µg - 500 µg 1X bid) vs. SM/FP (50/100 µg - 50/500 µg 1X bid)	Exacerbation
Bjemer L, 2003 (CR: Bousquet J, 2005)	Sweden (37 countries)	parallel RCT - double dummy	2000-2001	Multi-center	1490	48	FP (100 µg 1X bid) + ML (10 mg 1X od) vs. FP (100 µg 1X bid) + SM (50 µg 1X bid)	Exacerbation
Brown R, 2012	US	parallel RCT	2007-2009	Multi-center	742	52	BUD/FM (160/4.5 µg 1X bid) vs. BUD (160 µg 1X bid)	Exacerbation, Mortality

Study	Country of conduct	Study design	Study period	Setting	Sample size	Treatment duration (weeks)	Intervention	Outcomes
Busse W, 2001	USA	parallel RCT - double dummy	NR	Multi-center	533	24	FP (88 µg 1X bid) vs. ML (10 mg 1X od)	Exacerbation, Mortality
Busse W, 2008	US	parallel RCT	NR	Multi-center	1222	30	BUD/FM (160/4.5 µg 1X bid) vs. BUD/FM (160/4.5 µg NR) vs. FP/SM (250/50 µg 2X bid)	Exacerbation
Busse W, 2013	USA, Germany, Ukraine, Thailand	parallel RCT - double dummy	2009 - 2011	Multi-center	503	52	FP/vilanterol (100 µg/ 25µg 1X od) vs. FP/ vilanterol (200 µg/ 25µg 1X od) vs. FP (500 µg/ 25µg 1X bid)	Exacerbation, Mortality
Champman KR, 1999	Canada	parallel RCT - double dummy	NR	Multi-center	371	28	SM/FP (50/250 ug) + placebo vs. SM (50 ug) + FP (250 ug) +placebo	Exacerbation,
Chuchalin A, 2008	Russia (28 countries worldwide)	parallel RCT - double dummy	NR	Multi-center	2258	52	Placebo (NA 1X bid) vs. FP (100 µg 1X bid) vs. FP/SM (100/50 µg 1X od)	Exacerbation, Mortality
Condemi J, 1999	USA	parallel RCT - double dummy	NR	Multi-center	437	24	FP (44 µg 2X bid) + SM (21 µg 2X bid) vs. FP (110 µg 2X bid) + Placebo	Exacerbation
D'Urzo A, 2001		parallel RCT	NR	Multi-center	911	24	Placebo (NA 1X bid) vs. SM (50 µg 1X bid)	Exacerbation, Mortality
Dahl R, 2006	Denmark (18 countries)	parallel RCT - double dummy	NR	Multi-center	1391	24	BUD/FM (6/200 µg 2X bid) + Placebo vs. SM/FP (50/250 µg 1X bid) + Placebo	Exacerbation, Mortality
Fitzgerald J, 2005	Canada, Multinational	parallel RCT - double dummy	2002 - 2004	Multi-center	688	52	FP/SM (250 µg/ 50µg 1X bid) + placebo vs. BUD/FM (200 µg/ 6µg 2X bid)	Exacerbation

Study	Country of conduct	Study design	Study period	Setting	Sample size	Treatment duration (weeks)	Intervention	Outcomes
Godard P, 2008	France	parallel RCT	NR	Multi-center	475	24	SM/FP (250/50 µg 1X bid) vs. SM/FP (100/50 µg 1X bid) vs. FP (250 µg 1X bid)	Exacerbation, Mortality, CVD
Greening A, 1994	UK	parallel RCT - double dummy	1991-1993	Multi-center	429	26	BDP (200 µg 1X bid) + SM (50 µg 1X bid) vs. BDP (500 µg 1X bid) + Placebo	Exacerbation, CVD
Haahtela T, 2006	Finland	parallel RCT	NR	Multi-center	92	24	BUD/FM (160/4.5 µg p.r.n.) vs. FM (4.5 µg p.r.n.)	Exacerbation, Mortality
Huchon G, 2009	Belgium, France, Hungary, Poland, Romania, and Russia	parallel RCT - double dummy	NR	Multi-center	645	24	BDP/FM (250/12 µg 2X bid) + placebo vs. BDP (100/6 µg 2X bid) + FM (250 µg 1X bid) vs. BDP (250 µg 2X bid) + placebo	Exacerbation
Ilowite J, 2004	USA	parallel RCT - double dummy	NR	Multi-center	1473	48	FP (110 µg 1X bid) + ML (10 mg 1X od) vs. FP (110 µg 1X bid) + SM (42 µg 1X bid)	Exacerbation, Mortality
Ind P, 2003	United Kingdom, Italy, Canada, Denmark, Iceland and the Republic of Ireland	parallel RCT - double dummy	1995-1996	Multi-center	502	24	FP/SM (250 µg/50 µg 1X bid) vs. FP (500 µg 1X bid) vs. FP (250 µg 1X bid)	Exacerbation
Jenkins C, 2000	Australia	parallel RCT - double dummy	NR	Multi-center	353	24	FP/SM (250 µg/50 µg 1X bid) + Placebo vs. BUD (800 µg 1X bid) + Placebo	Exacerbation

Study	Country of conduct	Study design	Study period	Setting	Sample size	Treatment duration (weeks)	Intervention	Outcomes
Juniper E, 2002	Belgium, the Netherlands, Australia and South Africa	parallel RCT - double dummy	NR	Multi-center	113	24	SM/FP (50/250 µg) + placebo vs. BUD (800 µg) + placebo	Exacerbation,
Kaital R, 2011	Argentina, Brazil, United States, Canada, Philippines	parallel RCT	NR	Multi-center	621	52	FP/SM (250/50 µg 1X bid) vs. FP (250 µg 1X bid)	Exacerbation, Symptom, Mortality
Kelsen S, 1999	USA	parallel RCT - double dummy	NR	Multi-center	483	24	BDP (168 µg 1X bid) + SM (42 µg 1X bid) vs. BDP (336 µg 1X bid) + Placebo (NA)	Exacerbation
Kerwin E, 2011	USA, Canada, Argentina, Brazil, and the Philippines	parallel RCT	NR	Multi-center	628	52	FP/SM (250 µg 1X bid) vs. FP (250 µg 1X bid)	Exacerbation, Symptom, Mortality
Kips J, 2000	Canada, UK, Belgium	parallel RCT	NR	Multi-center	60	52	BUD (100 µg 1X bid) + FM (12 µg 1X bid) vs. BUD (400 µg 1X bid)	Exacerbation
Koenig S, 2008	US, Latin America, Latvia	parallel RCT	NR	Multi-center	466	40	FP/SM (100/50 µg - 500/50 µg 1X bid) vs. FP (100 µg - 500 µg 1X bid) vs. FP (100 µg 1X bid)	Exacerbation, Mortality
Kuna P, 2007 (CR: Kuna P, 2010)	Poland	parallel RCT - double dummy	2003-2005	NR	2228	24	FP/SM (125/25 µg 2X bid) + Terbutaline vs. BUD/FM (320/9 µg 1X bid) + Terbutaline	Exacerbation, Mortality
Louis R, 2009	Belgium, Luxembourg	parallel RCT	2004-2006	Multi-center	908	26	BUD/FM (160 µg 1X bid) vs. Conventional best practice	Exacerbation, Mortality

Study	Country of conduct	Study design	Study period	Setting	Sample size	Treatment duration (weeks)	Intervention	Outcomes
Lundback B, 2006	Sweden	parallel RCT	1997-2000	NR	282	52	SM/FP (50/250 µg 1X bid) vs. FP (250 µg 1X bid) vs. SM (50 µg 1X bid)	Exacerbation, CVD
Maspero J, 2010	Argentina, Peru, Ecuador, Guatemala, Chile, and Mexico	parallel RCT	NR	Multi-center	404	52	MOM/FM (200/10 µg 2X bid) vs. FP/SM (250/50 µg 2X bid) vs. MOM/FM (400/10 µg 2X bid) vs. FP/SM (500/50 µg 2X bid)	Exacerbation, Mortality
Meltzer E, 2002	USA	parallel RCT - double dummy	1998-2000	Multi-center	522	24	FP (44 µg 2X bid) + placebo vs. ML (10 mg 1X od) + placebo	Exacerbation
Meltzer E, 2012	North America, Latin America, Europe and Asia	parallel RCT - double dummy	NR	Multi-center	746	26	Placebo vs. FM (10 µg 1X bid) vs. MOM(100 µg 1X bid) vs. MOM/FM (100 µg/ 10µg 1X bid)	Exacerbation, Mortality
Murray J, 1999	USA	parallel RCT - double dummy	NR	Multi-center	514	24	BDP (168 µg 1X bid) + SM (42 µg 1X bid) vs. BDP (336 µg 1X bid) + Placebo	Exacerbation
Nathan R, 1999	US	parallel RCT - double dummy	NR	Multi-center	386	26	SM (42 µg 1X bid) vs. BDP (84 µg 1X qid) vs. Placebo	Exacerbation
Nathan R, 2010	USA (North America, Latin America, Europe, and Asia)	parallel RCT - double dummy	NR	Multi-center	781	26	MOM/FM (200 µg 1X bid) vs. MOM (200 µg 1X bid) vs. FM (10 µg 1X bid) vs. Placebo	Exacerbation, CVD

Study	Country of conduct	Study design	Study period	Setting	Sample size	Treatment duration (weeks)	Intervention	Outcomes
O'Byrne P, 2001	Canada (17 countries)	parallel RCT	NR	Multi-center	1970	52	Placebo vs. BUD (100 µg 1X bid) vs. BUD (100 µg 1X bid) + FM (4.5 µg 1X bid) vs. BUD (100 µg 1X bid) vs. BUD (200 µg 1X bid) vs. BUD (100 µg 1X bid) + FM (4.5 µg 1X bid) vs. BUD (200 µg 1X bid) + FM (4.5 µg 1X bid)	Exacerbation
Pauwels R, 1997	Belgium, Canada, the Netherlands, Israel, Italy, Luxembourg, Norway, Spain, and the United Kingdom	parallel RCT	1994-1995	Multi-center	852	52	BUD (100 µg 1X bid) + placebo vs. BUD (100 µg 1X bid) + FM (12 µg 1X bid) vs. BUD (400 µg 1X bid) + placebo vs. BUD (400 µg 1X bid) + FM (12 µg 1X bid)	Exacerbation
Peters S, 2008	US	parallel RCT - double dummy	NR	Multi-center	708	52	BUD/FM (160 µg/4.5µg 4X bid) vs. BUD/FM (160 µg/4.5µg 2X bid) vs. BUD (160 µg 4X bid)	Exacerbation, Mortality
Postma D, 2011	Netherlands	parallel RCT - double dummy	NR	Multi-center	652	52	Ciclesonide (160 µg 1X od) vs. Placebo vs. FP/SM (100 µg 1X bid)	Exacerbation
Price D, 2002	UK, Republic of Ireland	parallel RCT	NR	Multi-center	663	4	BUD (400 µg 1X bid) + FM (9 µg 1X bid) vs. BUD (400 µg 1X bid) + placebo	Exacerbation
Price D, 2011	UK	parallel RCT	2002-2007	Multi-center	306	104	ICS vs. LTRA	Exacerbation
Quirce S, 2011	Spain	parallel RCT	2006 -2008	Multi-center	654	26	BUD/FM (160 µg 1X bid) vs. Conventional Best Practicel	Exacerbation, Mortality

Study	Country of conduct	Study design	Study period	Setting	Sample size	Treatment duration (weeks)	Intervention	Outcomes
Rabe K, 2006	Belgium, Bulgaria, China, Czech Republic, Germany, Greece, Hungary, Indonesia, Italy, Malaysia, The Netherlands, Norway, the Philippines, Poland, Romania, Russia, Slovakia, South Africa, South Korea, Vietnam	parallel RCT	NR	Multi-center	2253	52	BUD/FM (160/4.5 µg 1X bid) + BUD/FM (160/4.5 µg p.r.n.) vs. BUD/FM (160/4.5 µg 1X bid) + FM (4.5 µg p.r.n.)	Exacerbation, Mortality
Reddel H, 2008	Australia	parallel RCT	NR	Single center	44	48	FP (125 µg 1X bid) vs. Placebo	Exacerbation
Reddel H, 2010	Australia	parallel RCT	NR	Multi-center	82	52	SM/FP (0 od to 50/500 µg 1X od/bid) vs. FP (0 od to 500 µg 1X od/bid)	Exacerbation, CVD
Renzi P, 2010	Canada	parallel RCT	2002-2004	Multi-center	532	24	FP/SM (100 µg 1X bid) vs. FP (100 µg 1X bid)	Exacerbation

Study	Country of conduct	Study design	Study period	Setting	Sample size	Treatment duration (weeks)	Intervention	Outcomes
Riemersma R, 2012	The Netherlands	parallel RCT	NR	Multi-center	102	52	BUD/FM (80/4.5 µg 2X od) + BUD/FM (80/4.5 µg p.r.n.) vs. Usual Care: guidelines directed asthma treatment	Exacerbation
Rosenhall L, 2002	Sweden, Norway, Finland, & Denmark	parallel RCT	NR	Multi-center	586	26	BUD/FM (160 µg/4.5µg 2X bid) vs. BUD (160 µg 2X bid) + FM (4.5 µg 2X bid)	Exacerbation
Rosenthal R, 1999	US	parallel RCT	NR	Multi-center	408	24	SM (42 µg 1X bid) vs. Placebo (NA 1X bid)	Exacerbation
Sears M, 2008	Canada	parallel RCT	NR	Multi-center	1538	26	BUD/FM (160/4.5 µg 1X bid) + BUD/FM (160/4.5 µg p.r.n.) vs. Conventional best practice	Exacerbation, Mortality
Soes Petersen U, 2011	Denmark, Finland and Norway	parallel RCT	NR	Multi-center	1854	26	BUD/FM (160/4.5 µg 1X bid) + BUD/FM (160/4.5 µg p.r.n.) vs. Current Best Practice	Exacerbation, Mortality
Stallberg B, 2003	Sweden	parallel RCT	NR	Multi-center	1034	26	BUD/FM (161 µg/4.5µg or 80 µg/4.5µg 2X bid) vs. BUD/FM (160 µg/4.5µg or 80 µg/4.5µg 1-4X bid) vs. BUD/FM (80/4.5ug or 160/4.5 µg 1-4X bid) vs. BUD/FM (80/4.5 ug or 160/4.5 µg 2X bid)	Exacerbation, Mortality
Stallberg B, 2008	Sweden	parallel RCT	NR	NR	889	52	BUD (100-400 µg NR) + FM (4.5 or 9 µg NR) vs. BUD/FM (160/4.5 µg or 80/4.5 µg 2X bid) + Terbutaline (0.25 or 0.5 µg p.r.n.)	Exacerbation

Study	Country of conduct	Study design	Study period	Setting	Sample size	Treatment duration (weeks)	Intervention	Outcomes
Ställberg B, 2008	Sweden	parallel RCT	2004-2007	Multi-center	885	52	BUD (100-400 µg NR) + FM (4.5 or 9 µg NR) vs. BUD/FM (160/4.5 or 80/4.5 µg 2X bid) + Terbutaline (0.25 or 0.5 mg p.r.n.)	Exacerbation
Strand A, 2004	Denmark	parallel RCT	NR	Multi-center	150	24	FP/SM (100/50 µg 1X bid) vs. FP (100 µg 1X bid)	Exacerbation
van der Molen T, 1997	Canada and the Netherlands	parallel RCT	1992-1994	Multi-center	239	24	FM (12 µg 2X bid) vs. Placebo	Exacerbation
Woolcock A, 1996	Australia (14 countries)	parallel RCT	NR	Multi-center	738	24	BDP (500 µg 1X bid) + SM (50 µg 1X bid) vs. BDP (1000 µg 1X bid) vs. BDP (500 µg 1X bid) + SM (100 µg 1X bid)	Exacerbation

Appendix 7: Patient Characteristics

Study	Age range (years)	Asthma definition	Classified by	Asthma severity	Asthma duration (months)	% Female	Medical History
Aalbers R, 2004 (CR: Aalbers R, 2010)	≥12	NR	ATS Guidelines	NR	≥6	54.6	ICS, SABA, LABA
Aubier M, 1999	≥ 12	Steroid dependent asthma (reversible airway disease)	NR	NR	1 to ≥10	46.5	ICS
Aubier M, 2010	≥ 18	Symptomatic asthma	ATS Guidelines	Moderate-to-Severe	≥6	62.0	ICS, LABA, SABA
Bailey W, 2008	12-65	Persistent asthma	NR	NR	≥ 6	61.7	ICS
Bateman E, 2004 (CR: Bousquet J, 2004)	12-80	Uncontrolled asthma.	NR	NR	≥ 6	58.0	ICS, ß2agonists
Bjermer L, 2003 (CR: Bousquet J, 2005)	15 - 72	Chronic asthma	NR	NR	≥ 12	54.9	ICS, LABA
Brown R, 2012	≥12	Stable asthma	ATS Guidelines	moderate-to-severe	≥ 6	64.8	ICS
Busse W, 2001	≥ 15	Asthma	ATS Guidelines	NR	≥ 6	55.2	SABA
Busse W, 2008	≥12	Documented diagnosis of asthma	ATS Guidelines	moderate-to-severe	≥6	59.7	ICS, ICS + LABA, SABA
Busse W, 2013	≥12	NR	NIH	NR	NR	62.8	NR

Study	Age range (years)	Asthma definition	Classified by	Asthma severity	Asthma duration (months)	% Female	Medical History
Champman KR, 1999	≥ 12	Symptomatic asthma despite inhaled corticosteroids; documented clinical history of reversible airways obstruction and treatment with Beclomethasone (BDP), budesonide or fluticasone for at least 4 weeks before starting treatment	NR	NR	NR	53.1	ICS
Chuchalin A, 2008	12-79	Persistent asthma	NR	mild	≥ 6	57.6	NR
Condemi J, 1999	≥ 12	Persistent asthma	ATS Guidelines	NR	≥ 6	61.1	SABA
D'Urzo A, 2001	30-62*	Documented history of asthma	ATS Guidelines		NR	54.0	ICS, SABA
Dahl R, 2006	≥18	Documented clinical history of asthma	NR	NR	≥ 6	57.5	ICS, SABA
Fitzgerald J, 2005	18 - 70	Documented clinical history of asthma (confirmed by the medical record)	NR	NR	NR	61.1	ICS, LABA, SABA
Godard P, 2008	≥18	Documented history of asthma	NR	NR	> 6	48.5	ICS, LABA, SABA, ICS + LABA
Greening A, 1994	≥ 18	Symptomatic asthma	NR	NR	NR	NR	ICS

Study	Age range (years)	Asthma definition	Classified by	Asthma severity	Asthma duration (months)	% Female	Medical History
Haahtela T, 2006	15-63*	Global Initiative for Asthma (GINA) guidelines on functional criteria for mild intermittent asthma [3] and had a documented need of short-acting inhaled b2-agonists for relief of asthma symptoms. The need for reliever medication during the preceding months was a maximum of 2 doses?Week-1, which was within the limits stated in GINA guidelines at the time of planning the study	GINA	Mild	NR	69.6	SABA
Houchon G, 2009	18 - 70	Persistent asthma	GINA	moderate-to-severe	NR	64.3	ICS, LABA, SABA, ICS + LABA
Ilowite J, 2004	14 - 73	Chronic asthma	NR	moderate-to-severe	≥ 12	60.6	ICS
Ind P, 2003	16 - 75	Symptomatic asthma	NR	moderate-to-severe	NR	53.6	ICS
Jenkins C, 2000	≥ 12	Reversible airways obstruction	NR	moderate-to-severe	NR	50.0	ICS
Juniper E, 2002	≥ 12 years	Persistent asthma	NR	moderate-to-severe	NR	46.0	ICS, SABA
Kaital R, 2011	≥12	Clinical diagnosis of asthma	ATS Guidelines	NR	≥6	63.0	SABA, ICS + LABA, ICS
Kelsen S, 1999	≥ 18	Symptomatic asthma	NR	NR	NR	61.0	ICS
Kerwin E, 2011	≥ 12	Persistent asthma	ATS Guidelines	NR	≥ 6	58.5	ICS, ICS + LABA, SABA, LTRA
Kips J, 2000	18-70	Established diagnosis of asthma	NR	NR	≥ 6	60.0	ICS, SABA
Koenig S, 2008	≥ 12	NR	NR	NR	≥ 3	59.0	SABA, ICS

Study	Age range (years)	Asthma definition	Classified by	Asthma severity	Asthma duration (months)	% Female	Medical History
Kuna P, 2007 (CR: Kuna P, 2010)	≥ 12	NR	ATS Guidelines	NR	≥ 6	58.0	ICS
Louis R, 2009	≥12	Asthma symptoms while on treatment with ICS, or who were symptomatic or asymptomatic on ICS and LABA therapy with or without additional controller therapy	NR	NR	≥3	57.5	ICS, LABA, LTRA
Lundback B, 2006	18-70	Persistent asthma, with symptoms at least twice a week	NR	Mild-to-Moderate	NR	66.3	SABA, LABA
Maspero J, 2010	≥ 12	Persistent asthma	NR	NR	≥ 12	63.0	ICS, ICS + LABA
Meltzer E, 2002	≥ 15	Persistent asthma	ATS Guidelines	NR	-	53.6	SABA
Meltzer E, 2012	≥12	NR	NR	NR	≥12	55.4	ICS + LABA
Murray J, 1999	≥ 18	NR	NR	NR	NR	57.0	NR
Nathan R, 1999	≥12	Diagnosis of asthma	ATS Guidelines	persistent	≥3	53.6	NR
Nathan R, 2010	≥ 12	Persistent asthma	NR	NR	≥ 12	58.9	ICS, ICS + LABA
O'Byrne P, 2001	≥ 12	Persistent asthma	NR	mild	NR	58.1	ICS
Pauwels R, 1997	18 - 70	NR	NR	NR	≥ 6	51.2	ICS
Peters S, 2008	≥12	Documented clinical diagnosis of asthma	ATS Guidelines	NR	≥6	63.3	ICS, ICS + LABA, SABA

Study	Age range (years)	Asthma definition	Classified by	Asthma severity	Asthma duration (months)	% Female	Medical History
Postma D, 2011	12-75	Clinical diagnosis of mild persistent asthma (FEV1 > 80% predicted at least 4 h after rescue medication use; only short-acting b -agonists as required for 2 months before the start of the study).	NR	mild or intermittent	NR	58.0	SABA
Price D, 2002	≥12	Diagnosis of asthma confirmed in the clinical record	NR	NR	≥3	57.8	SABA, ICS
Price D, 2011	12-80	Physicians' diagnosis of asthma, requiring regular control medication	Mini Asthma Quality of Life Questionnaire or Asthma Control Questionnaire	NR	NR	51.0	ICS, LABA
Quirce S, 2011	≥18	Suboptimally controlled persistent asthma currently treated with an ICS either with or without a LABA	NR	persistent	NR	64.3	ICS, LABA, SABA
Rabe K, 2006	≥ 12	Persistent asthma	NR	moderate-to-severe	≥ 6	-	NR, ICS + LABA, ICS

Study	Age range (years)	Asthma definition	Classified by	Asthma severity	Asthma duration (months)	% Female	Medical History
Reddel H, 2008	18 - 80	Established history of asthma -- documented either by historical evidence of bronchodilator reversibility within the previous year (increase in FEV1 by >180mls and/or >12%, or in peak expiratory flow (PEF) by >12%), or by confirmation by two independent physicians on a case-by-case basis that the subject had a clinical history of reversible symptoms which were consistent with asthma	NR	mild or intermittent	≥12	63.6	SABA, ICS
Reddel H, 2010	18-80	Clinical diagnosis of asthma	ATS Guidelines	NR	≥6	54.5	ICS + LABA
Renzi P, 2010	≥ 12	Persistent uncontrolled asthma	NR	mild	NR	64.0	SABA
Riemersma R, 2012	≥18	Persistent asthma	NR	mild-to-moderate	NR	62.0	ICS
Rosenhall L, 2002	≥18	Diagnosis of perennial asthma	NR	moderate	≥6	56.1	ICS + SABA
Rosenthal R, 1999	≥12	Diagnosis of asthma	NR	moderate	NR	40.9	SABA
Sears M, 2008	≥ 12	Persistent asthma	ATS Guidelines	NR as inclusion (mild to severe with various proportions were included)	≥ 3	60.2	ICS, ICS + LABA
Soes Petersen U, 2011	≥ 12	Persistent asthma	ATS Guidelines	NR	≥ 3	59.7	ICS, ICS + LABA
Stallberg B, 2003	≥ 12	Asthma according to ATS criteria	ATS Guidelines	NR	≥6	40.2	ICS + LABA, ICS + SABA, ICS

Study	Age range (years)	Asthma definition	Classified by	Asthma severity	Asthma duration (months)	% Female	Medical History
Stallberg B, 2008	≥ 12	Persistent asthma.	ATS Guidelines	NR	NR	57.5	ICS, ICS + LABA
Ställberg B, 2008	≥12	Persistent asthma	ATS Guidelines	NR	NR	58.3	ICS, ICS+LABA
Strand A, 2004	≥ 18	Persistent asthma	ATS Guidelines	NR	≥ 3	56.8	SABA
van der Molen T, 1997	26-59*	NR	ATS Guidelines	mild to moderate	NR	51.0	ICS, SABA
Woolcock A, 1996	≥ 17	NR	NR	NR	NR	47.8	ICS
***no target age range reported; range taken from baseline data**							

Appendix 8: Definitions of exacerbations

Study	Exacerbation definition
Aalbers R, 2004 (CR: Aalbers R, 2010)	Exacerbations, defined as oral steroid treatment for ≥ 3 days, emergency room (ER) visits and/or hospitalization were recorded. If patients needed to use oral steroids for > 10 consecutive days, the eleventh day was considered to be a second exacerbation.
Aubier M, 1999	Exacerbation is defined as asthma reported under adverse events
Aubier M, 2010	Exacerbation was defined as deterioration in asthma leading to a need for oral or systemic corticosteroids either for ≥3days, and/or associated with hospitalization, an emergency room visit or other patient-initiated unscheduled visit to a health-care centre
Aubier M, 2010	Severe exacerbations are those leading to hospitalization or an ER visit because of asthma, requiring treatment with systemic corticosteroids.
Bailey W, 2008	An asthma exacerbation during this period was defined as any of the following: (1) worsening of asthma that required treatment with an oral corticosteroid; (2) hospitalization for the treatment of asthma; (3) unscheduled urgent care for acute asthma symptoms that required intervention (e.g., unscheduled clinic visit, physician office visit, emergency room [ER] visit); (4) 30% decrease in FEV1 from the baseline obtained at the randomization visit; or (5) morning peak expiratory flow (AM PEF) below the AM PEF Stability Limit on any 2 consecutive days.
Bateman E, 2004 (CR: Bousquet J, 2004)	Deterioration in asthma requiring treatment with an oral corticosteroid or an emergency department visit or hospitalization (withdrawal due to exacerbation during 52 weeks of phase I and II)
Bjemer L, 2003 (CR: Bousquet J, 2005)	Asthma exacerbation, defined as worsening asthma requiring an unscheduled visit to a doctor, emergency department, or hospital or treatment with oral, intravenous, or intramuscular corticosteroids.
Brown, 2012	Asthma exacerbations were defined as requirement of oral/parenteral corticosteroids and/or emergency department visit and/or urgent care visit and/or hospitalization for asthma. Patients who experienced more than 2 exacerbations within 3 months or more than 5 exacerbations within 1 year during randomized treatment were discontinued from the study.
Busse W, 2001	Asthma exacerbation was defined as any event that required an emergency department visit and/or hospitalization, an unscheduled doctor visit, or treatment with oral or parenteral corticosteroids. Patients who had an asthma exacerbation that required treatment with oral or parenteral corticosteroids were withdrawn from the study.
Busse W, 2008	An asthma exacerbation was defined as worsening asthma requiring oral corticosteroid treatment; if a second course of corticosteroids was required, it was considered a second exacerbation.
Busse W, 2013	A severe asthma exacerbation was defined according to American Thoracic Society/European Respiratory Society taskforce guidelines as deterioration of asthma requiring the use of systemic corticosteroids for ≥3 days, or an inpatient hospitalization or emergency room visit due to asthma that required systemic corticosteroids.

Study	Exacerbation definition
Champman KR, 1999	Exacerbation is defined as asthma reported under adverse events
Chuchalin A, 2004	Severe asthma exacerbations were defined as the need for an oral steroid course or hospitalization due to asthma.
Chuchalin A, 2008	Severe exacerbations were defined as deterioration in asthma requiring hospital admission.
Condemi J, 1999	All exacerbations were defined as asthma symptoms requiring the use of oral or parenteral steroids, and none of the exacerbations resulted in hospitalization.
D'Urzo A, 2001	Asthma exacerbations, defined as an exacerbation requiring hospitalization, emergency department visit, or use of oral prednisone during the treatment period.
Dahl, 2006	Exacerbations were defined as severe if requiring hospitalization
Dennis S, 2000	Exacerbation rate defined as: use of oral corticosteroids, or an exacerbation rate defined as: use of oral corticosteroids, or an increase in the dose of inhaled corticosteroids, or at least two of the following three criteria on 2 consecutive days; (i) fall in PEF to less than 80% of median baseline level; (ii) bronchodilator inhalations per 24 h increased by three or more over baseline level; (iii) symptom-score increased during the day or at night, by two or more over median baseline level.
FitzGerald J, 1998	"Exacerbation days," each defined as a 24-hour period during which more than 8 puffs of rescue albuterol were inhaled and/or any asthma symptom score equaled 4.
Fitzgerald J, 2005	An asthma exacerbation was defined as a worsening of asthma requiring hospital treatment or treatment with oral corticosteroids, either in the opinion of the investigator or based on a morning PEF <70% of the mean of the last 7 days in weeks 1 through 4 for >2 consecutive days.
Godard P, 2008	Moderate exacerbation = worsening of asthma leading to a prescription for a short use of oral corticosteroids. Severe exacerbation=worsening of asthma leading to hospitalization.
Greening A, 1994	The severity of asthma exacerbations was defined as severe (requiring hospital admission).
Houchon G, 2009	Severe exacerbation: need for oral corticosteroid; asthma-related unscheduled medical visit or visit to an emergency department; hospital admission for asthma; diurnal PEF variability >30% or SABA inhalation of more than eight puffs per day during at least two consecutive days; or nocturnal awakening due to asthma during at least three consecutive 24-hour periods.
Ilowite J, 2004	Component of an asthma attack, including unscheduled physician's office visit, emergency department visit, hospitalization, and treatment with oral, intravenous, or intramuscular corticosteroids
Ind P, 2003	Exacerbations were assessed by the physician and categorized severe (requiring emergency hospital treatment).
Jenkins C, 2000	A severe exacerbation of asthma was deemed as deterioration in asthma requiring emergency hospital treatment.
Juniper E, 2002	No definition provided for exacerbation

Study	Exacerbation definition
Kaital R, 2011	Asthma exacerbation defined as the requirement for treatment with an oral or parenteral corticosteroid, or an unscheduled urgent care visit (e.g., unscheduled clinic visit, physician office visit, emergency room visit, or hospitalization) for acute asthma symptoms requiring intervention.
Kelsen S, 1999	Asthma exacerbation was defined as any event requiring treatment with oral or parenteral corticosteroids or any other asthma medication not allowed as concurrent therapy during study participation.
Kerwin E, 2011	Asthma exacerbation defined by the requirement for treatment with an oral or parenteral corticosteroid, or an unscheduled urgent care (e.g. Unscheduled clinic visit, physician office visit, emergency room visit, hospitalization) for acute asthma symptoms requiring intervention per subject per year.
Kips J, 2000	Severe exacerbations was defined based on whether oral glucocorticoids were required either as judged by the investigator, or after a decrease in morning or evening peak flow by more than 30% below baseline on two consecutive days
Koenig S, 2008	Defined as worsening asthma for which treatment with medication other than the double-blind study drugs or study-provided albuterol was necessary, and was treated with the same dosing regimen for prednisone as above
Kuna P, 2007 (CR: Kuna P, 2010)	Severe asthma exacerbations were defined as a deterioration in asthma resulting in hospitalization/emergency room treatment, oral steroid treatment (or an increase in ICS [via a separate inhaler] and/or other additional treatment for children aged 4–11 years), or morning peak expiratory flow (PEF) of 70% or less of baseline on 2 consecutive days. Severe exacerbations confined to those requiring medical intervention were also analyzed separately.
Louis R, 2009	Severe asthma exacerbation defined as deterioration in asthma leading to at least hospitalization ⁄ emergency room (or equivalent) or oral glucocorticoid treatment for at least 3 days
Maspero J, 2010	Deterioration resulting in emergency treatment, hospitalization, or treatment with additional asthma medications
Meltzer E, 2002	Asthma exacerbation was defined as any event that required an emergency department visit and/or hospitalization, an unscheduled physician visit, or treatment with inhaled, oral, or parenteral corticosteroids. Patients who experienced an asthma exacerbation that required treatment with oral or parenteral corticosteroids were withdrawn from the study.
Meltzer E, 2012	An asthma deterioration was defined as a clinically judged deterioration (i.e. Asthma attack resulting in emergency treatment, hospitalization or treatment with additional, excluded asthma medication (i.e. Systemic corticosteroids)) or a meaningful reduction in lung function (i.e. A decrease in FEV1 of >20% from baseline at any study visit or a decrease in PEF of >30% from baseline foro2 days consecutively at any time during the treatment period).
Murray J, 1999	Asthma exacerbations were assessed throughout the study and were defined as events requiring treatment with any asthma medication excluded during study participation, including oral and parenteral corticosteroids.

Study	Exacerbation definition
Nathan R, 1999	Asthma exacerbation treated with oral steroids within 2 weeks, or other asthma exacerbation within 5 days. Patients who experienced three asthma exacerbations, defined as asthma symptoms requiring drug therapy in addition to study medication (blinded study medication and albuterol as needed), were withdrawn from the study.
Nathan R, 2010	An asthma deterioration was defined as any one of the three following events: (1) an occurrence of any clinically judged deterioration that resulted in emergency treatment, hospitalization due to asthma, or treatment with additional excluded asthma medication (i.e., systemic corticosteroids); (2) a 20% decrease from the average of the two pre-dose FEV1 measurements taken just before the first dose of randomized study medication; or (3) a 30% decrease from the respective average A.M. or P.M. PEF baseline measurements (obtained over the 7 days immediately before receiving the first dose of randomized study medication) for at least 2 consecutive days.
O'Byrne P, 2001	Severe asthma exacerbation, defined as need for treatment with oral corticosteroids, as judged by the investigator, or hospital admission or emergency treatment for worsening asthma, or a decrease in morning PEF 25% from baseline (the mean values during the last 14 d of the run-in) on two consecutive days.
Pauwels R, 1997	A severe exacerbation was defined as one requiring treatment with oral glucocorticoids, as judged by the investigator, or a decrease in the peak expiratory flow as measured in the morning to more than 30 percent below the base-line value on two consecutive days.
Peters S, 2008	Asthma exacerbations (defined as the use of oral or systemic corticosteroids, hospitalization, or an emergency department [ED] or urgent care visit caused by an asthma exacerbation),
Postma D, 2011	Severe asthma exacerbation was the primary efficacy variable and defined as a >30% decrease in PEF from baseline on 2 consecutive days or the need for oral corticosteroids, hospitalization, or emergency treatment of worsening asthma. Following an exacerbation, patients were treated with an additional 7-day course of oral corticosteroids (0.5 mg/kg body weight).
Price D, 2002	A severe exacerbation was defined in both parts I and II as requiring oral corticosteroid treatment or as a decrease in morning/evening PEF >30% of baseline on two consecutive days. A maximum of three severe exacerbations requiring additional treatment was allowed during the whole study. Patients exceeding these criteria were withdrawn.
Price D, 2011	Asthma exacerbations, which were defined as the need for an oral course of glucocorticoids or hospitalization for asthma.
Quirce S, 2011	Severe asthma exacerbation was defined as deterioration in asthma leading to at least hospitalization or emergency room treatment for asthma or treatment with oral corticosteroids for at least three consecutive days.
Rabe K, 2006	A severe exacerbation was defined as deterioration in asthma resulting in emergency treatment or hospitalization or the need for oral steroids for 3 days or more (as judged by the investigator).

Study	Exacerbation definition
Reddel H, 2008	Severe exacerbations were defined by use of oral corticosteroids. Oral prednisolone 50mg/day was given for 7-10 days if PEF fell by ≥30% baseline for ≥2 of three consecutive days, or at investigator discretion. Subjects were withdrawn if they required prednisolone for more than four weeks, or additional ICS for more than eight weeks, or if they experienced three exacerbations.
Renzi P, 2010	Severe exacerbations were defined as deterioration in asthma requiring emergency hospital treatment/admission or according to investigator opinion. A patient was withdrawn if he or she required hospitalization or more than 3 exacerbations requiring treatment with oral corticosteroids.
Riemersma, 2012	Severe asthma exacerbations deterioration in asthma resulting in hospitalization or emergency room treatment or need for oral glucocorticoid treatment for at least 3 days
Rosenhall L, 2002	Exacerbations were defined by first use of oral steroids
Rosenthal R, 1999	Exacerbations were defined as asthma symptoms requiring treatment with medications other than albuterol MDI and the blinded study drug.
Sears M, 2008	Severe asthma exacerbation, defined as hospitalization or emergency room (ER) visit and/or use of oral corticosteroid for ≥3 days due to asthma.
Soes Petersen U, 2011	A severe asthma exacerbation was defined as deterioration in asthma leading to hospitalization, emergency room visits (or equivalent) or treatment with oral corticosteroids for at least 3 days.
Stallberg B, 2003	Exacerbations were defined as one or more of the following (as judged by the investigator): use of oral corticosteroids for treatment due to worsening of asthma; treatment at a medical care unit due to worsening of asthma; asthma related SAE; withdrawal due to a need to use non-study asthma medication.
Stallberg B, 2008	An exacerbation was defined as deterioration in asthma resulting in a hospitalization/emergency room visit or the use of oral corticosteroids due to asthma.
Stallberg B, 2008	Deterioration in asthma resulting in a hospitalization/emergency room visit or the use of oral corticosteroids due to asthma
Strand A, 2004	A severe asthma exacerbation was defined as deterioration in asthma requiring emergency hospital treatment.
van der Molen T, 1997	Initiated an oral prednisolone course for treatment of the exacerbation.
Woolcock A, 1996	An exacerbation of asthma was defined as any worsening of asthma symptoms requiring a change in prescribed therapy, other than increased use of rescue medication.

Appendix 9: Definitions of Cardiovascular Diseases

Study	Intervention	Type of CVD	# of patients
Godard P, 2008	SM/FP (250/50 µg 1X bid)	chest pain - reported as serious adverse event	1
Greening A, 1994	BDP (500 µg 1X bid) + Placebo	chest pain	1
Greening A, 1994	BDP (500 µg 1X bid) + Placebo	myocardial infarction	1
Lundback B, 2006	SM/FP (50/250 µg 1X bid)	chest symptoms	1
Lundback B, 2006	FP (250 µg 1X bid)	chest symptoms	5
Lundback B, 2006	SM (50 µg 1X bid)	chest symptoms	4
Nathan R, 2010	MOM/FM (200 µg 1X bid)	chest pain	2
Nathan R, 2010	MOM (200 µg 1X bid)	chest pain	2
Nathan R, 2010	FM (10 µg 1X bid)	chest pain	1
Nathan R, 2010	Placebo	chest pain	4
Papi A, 2007	BDP (250 µg 1X bid) + Albuterol (100µg 1X bid)	myocardial ischemia	1

Appendix 10: Definitions of Cardiovascular Related Mortalities

Study	Intervention	Type of mortality	# of patients
Aubier M, 2010	BUD/FM (160/4.5 µg 1X bid) + BUD/FM (160/4.5 µg p.r.n.)	Intracranial hemorrhage	1
Aubier M, 2010	BUD/FM (160/4.5 µg 2X bid) + BUD/FM (160/4.5 µg p.r.n.)	colon cancer + acute heart failure	1
Busse W, 2001	ML (10 mg 1X od)	myocardial infarction	1
D'Urzo A, 2001	SM (50 µg 1X bid)	congestive heart failure	1
Kerwin E, 2011	FP/SM (250 µg 1X bid)	cardiac disease	1
Koenig S, 2008	FP (100 µg - 500 µg 1X bid)	cardiac arrest and convulsions following deep vein thrombosis	1
Kuna P, 2007 (CR: Kuna P, 2010)	FP/SM (125/25 µg 2X bid)	cardiac failure	1
Louis R, 2009	BUD/FM (160 µg 1X bid)	myocardial infarction	1
Renzi P, 2010	FP (100 µg 1X bid)	cardiac arrest	1
Sears M, 2008	Conventional best practice	myocardial infarction	1

Appendix 11: Treatment Strategies for Asthma

Type of intervention	Definition
Placebo	Non treatment
Best practice	Patients treated according to current or local asthma treatment guidelines
ICS	Inhaled corticosteroids
Beclometasone	-
Budesonide	-
Ciclesonide	-
Fluticasone	-
Mometasone	-
ICS + LABA	Combination of inhaled corticosteroids and long acting β agents, in separate inhalers
ICS + LTRA	Combination of inhaled corticosteroids and leukotriene receptor antagonist, in separate inhalers
ICS Low dosage*	Low dosage is defined as ≤250 µg/day of fluticasone or equivalent*
ICS Medium dosage*	Medium dosage defined as 251-500 µg/day of fluticasone or equivalent*
ICS High dosage*	High dosage is defined as >500 µg/day of fluticasone or equivalent*
Combined in one inhaler	Combination of inhaled corticosteroids and long acting β agents, in the same inhaler
Budesonide/Formoterol	-
Fluticasone/Salmeterol	-
Beclomethason/Formoterol	-
Fluticasone/Vilanterol	-
Mometason/Formoterol	-
ICS+LABA Combined in one inhaler, Fixed low dosage	Combination of inhaled corticosteroids and long acting β agents, in single inhaler at a fixed dose of ≤250µg/day of fluticasone or equivalent
ICS+LABA Combined in one inhaler, Fixed medium dosage	Combination of inhaled corticosteroids and long acting β agents, in single inhaler at a fixed dose of 251-500 µg/day of fluticasone or equivalent
ICS+LABA Combined in one inhaler, Fixed high dosage	Combination of inhaled corticosteroids and long acting β agents, in single inhaler at a fixed dose of >500 µg/day of fluticasone or equivalent
ICS+LABA Combined in one inhaler, Adjustable low dosage	Combination of inhaled corticosteroids and long acting β agents, in single inhaler, but dose (≤250 µg/day of fluticasone or equivalent) regularly adapted by physician or patient, guided by symptoms

Type of intervention	Definition
ICS+LABA Combined in one inhaler, Adjustable medium dosage	Combination of inhaled corticosteroids and long acting β agents, in single inhaler, but dose (251-500 µg/day of fluticasone or equivalent) regularly adapted by physician or patient, guided by symptoms
ICS+LABA Combined in one inhaler, Adjustable high dosage	Combination of inhaled corticosteroids and long acting β agents, in single inhaler, but dose (>500 µg/day of fluticasone or equivalent) regularly adapted by physician or patient, guided by symptoms
ICS+LABA Combined in one inhaler, Maintenance therapy medium dosage	Maintenance combination of inhaled corticosteroids and long acting β agents, in single inhaler. Medium dosage defined as 251-500 µg/day of fluticasone or equivalent
ICS+LABA Combined in one inhaler, Maintenance therapy medium dosage	Maintenance combination of inhaled corticosteroids and long acting β agents, in single inhaler and short acting β agents, in separate inhalers. Medium dosage defined as 251-500 µg/day of fluticasone or equivalent.
LABA	Long acting β agents
LTRA	Leukotriene receptor antagonist
Adjustable	Dose regularly adapted by physician or patient, guided by symptoms (reported as adjustable dosage in study or reported as a range of dosages, or dosage titration, or taken as needed)
Fixed	A fixed daily dose without any variation (reported as fixed dosage in the study or patient is given a specific dosage on a regular basis)
Maintenance:	Maintenance daily dose or regular controlled therapy (reported as maintenance in study)

* Lougheed MD, Leniere C, Ducharme FM, Licskai C, Dell SD, Rowe BH, FitzGerald M, Leigh R, Watson W, Boulet LP. Canadian Thoracic Society Asthma Clinical Assemby. Canadian Thoracic Society 2012 guideline update: Diagnosis and management of asthma in preschoolers, children and adults: executive summary. Can Respir J. (2012).19(6):e81-8.

Appendix 12: Frequencies of different asthma therapies

Treatment Node	Treatments	Frequency
Exacerbation		
Placebo	Placebo	7
Best practice	Best practice	5
ICS+LABA Combined in one inhaler, Adjustable high dosage	Budesonide/Formoterol Fluticasone/Salmeterol	3
ICS+LABA Combined in one inhaler, Adjustable low dosage	Budesonide/Formoterol Fluticasone/Salmeterol	3
ICS+LABA Combined in one inhaler, Adjustable medium dosage	Budesonide/Formoterol+ Budesonide/Formoterol Budesonide/Formoterol	6
ICS+LABA Combined in one inhaler, Fixed high dosage	Fluticasone/Salmeterol Beclomethason/Formoterol Budesonide/Formoterol Mometasone/Formoterol	4
ICS+LABA Combined in one inhaler, Fixed low dosage	Fluticasone/Salmeterol Fluticasone/Vilanterol Budesonide/Formoterol Mometasone/Formoterol	7
ICS+LABA Combined in one inhaler, Fixed medium dosage	Budesonide/Formoterol Fluticasone/Salmeterol Mometasone/Formoterol	11
ICS+LABA Combined in one inhaler, Maintenance therapy medium dosage	Budesonide/Formoterol	1
ICS+LABA Combined in one inhaler, Maintenance therapy medium dosage + LABA	Budesonide/Formoterol + Formoterol	1

Treatment Node	Treatments	Frequency
ICS high dosage	Budesonide + Placebo Budesonide Beclomethasone + Placebo Beclomethasone Fluticasone	9
ICS low dosage	Mometasone Fluticasone Fluticasone + Placebo Budesonide Budesonide + Placebo Ciclesonide	12
ICS medium dosage	Budesonide + Placebo Fluticasone + Placebo Fluticasone Beclomethasone + Placebo Mometasone Budesonide ICS	12
ICS + LABA high dosage	Beclomethasone + Salmeterol	1
ICS + LABA low dosage	Fluticasone + Salmeterol + Placebo Fluticasone + Salmeterol Budesonide + Formoterol	6
ICS + LABA medium dosage	Budesonide + Formoterol Beclomethasone + Salmeterol Beclomethasone + Formoterol + Placebo	10
ICS + LTRA low dosage	Fluticasone + Montelukast Fluticasone + Montelukast + Placebo	2
LABA	Salmeterol Formoterol	4
LTRA	Montelukast + Placebo LTRA	3

Treatment Node	Treatments	Frequency
Symptoms		
ICS+LABA Combined in one inhaler, Fixed medium dosage	Fluticasone/Salmeterol	2
ICS Medium	Fluticasone	2
CVD's		
Placebo	Placebo	1
ICS high dosage	Beclomethasone + Placebo	1
ICS medium dosage	Mometasone Fluticasone	3
ICS + LABA medium dosage	Beclomethasone + Salmeterol	1
LABA	Formoterol Salemterol	2
ICS+LABA Combined in one inhaler, Fixed medium dosage ICS+LABA Combined in one inhaler, Fixed low dosage	Mometasone/Formoterol Fluticasone/Salmeterol Fluticasone/Salmeterol	3 1
CV related mortality		
Placebo	Placebo	1
Best practice	Best practice	2
ICS+LABA Combined in one inhaler, Adjustable high dosage	Fluticasone/Salmeterol	1
ICS+LABA Combined in one inhaler, Adjustable medium dosage	Budesonide/Formoterol	1
ICS+LABA Combined in one inhaler, Fixed low dosage	Fluticasone/Salmeterol	1
ICS+LABA Combined in one inhaler, Fixed medium dosage	Fluticasone/Salmeterol	1
ICS+LABA Combined in one inhaler, Maintenance therapy medium dosage	Budesonide/Formoterol	1

Treatment Node	Treatments	Frequency
ICS high dosage	Fluticasone	1
ICS low dosage	Fluticasone + Placebo Fluticasone	3
ICS medium dosage	Fluticasone	1
LABA	Salmeterol	1
LTRA	Montelukast + Placebo	1

Appendix 13: Abbreviations

Abbreviated	Definition
General	
CR	companion report
CI	confidence interval
CrI	credibility interval
CVD	cardiovascular disease
NA	not applicable
NMA	network meta-analysis
NNT	number needed to treat
NNH	number needed to harm
NR	not reported
NS	not significant
OR	odds ratio
RCT	randomized controlled trial
vs.	versus
Drug Class	
ICS	inhaled corticosteroid
BDP	beclomethasone dipropionate
BUD	budesonide
FP	fluticasone propionate
LABA	long-acting beta-agonist
FM	formoterol/formeterol
SM	salmeterol
MOM	mometasone
LTRA	leukotriene receptor antagonist
ML	montelukast
Drug Dose	
od	once daily
bid	twice daily
qid	four times a day
prn	as needed
µg	microgram
Organizations	
GINA	Global Initiative for Asthma
ATS	American Thoracic Society
NIH	National Institute of Health